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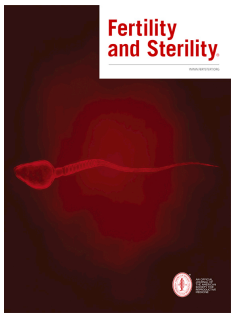

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Linzagolix with and without hormonal add-back therapy for symptomatic uterine fibroids: PRIMROSE 1 & 2 long-term extension and withdrawal study

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Abstract

Objectives: To evaluate 1) whether oral linzagolix administered once daily for up to 52 weeks (extension study) at a dose of 100 mg or 200 mg with or without hormonal add-back therapy (ABT) (1.0 mg estradiol; 0.5 mg norethisterone acetate) can maintain the efficacy and tolerability seen at 6 months of therapy, and 2) whether there is any recurrence of symptoms (bleeding and pain) after cessation of therapy (withdrawal study).

Study design:

PRIMROSE 1 and PRIMROSE 2 were essentially identical, randomized, parallel, double-blind, placebo-controlled phase 3 trials conducted in women with uterine fibroid-associated heavy menstrual bleeding (menstrual blood loss of more than 80 ml per cycle over 2 menstrual cycles). Eligible women with uterine fibroid-associated heavy menstrual bleeding were randomly assigned at a 1:1:1:1:1 ratio to one of five masked daily treatments: (1) placebo, (2) 100 mg linzagolix alone, (3) 100 mg linzagolix with hormonal ABT (1 mg estradiol and 0.5 mg norethisterone acetate), (4) 200 mg linzagolix alone (with ABT after 24 weeks), or (5) 200 mg linzagolix with hormonal ABT (1 mg estradiol and 0.5 mg norethisterone acetate).

After 24 weeks, patients assigned to the placebo or 200 mg linzagolix alone groups were switched to 200 mg linzagolix with ABT, except in PRIMROSE 1, where 50% of subjects on a placebo continued with the placebo (random selection) until week 52. All other women continued on the original study medication. Efficacy and safety were evaluated at week 52 (extension study) as well as week 64 (withdrawal study). Bone mineral density was also assessed at week 76 (6 months after cessation of therapy).

Setting: A total of 94 clinical sites in the USA (PRIMROSE 1) and 95 in Europe and the USA (PRIMROSE 2).

Participants:

In PRIMROSE 1 and 2, 1,012 women were included in the full analysis set. Eligible subjects were women aged 18 years or older with ultrasound-confirmed fibroids and heavy menstrual bleeding of at least 80 ml blood loss per cycle for a minimum of two cycles, as determined by the alkaline haematin method. Eligible participants had to have at least one fibroid measuring 2 cm in diameter or more (or multiple small fibroids with overall uterine volume exceeding 200 cm^3), but no fibroids greater than 12 cm in diameter.

Main outcomes measures: The primary endpoint was decreased menstrual blood loss to less than 80 ml and a reduction of more than 50% from baseline. Specifically, this study sought to determine whether the reduction in menstrual blood loss and other secondary outcomes, such as uterine volume and pain, observed at 24 weeks could be maintained over an extended (52 weeks) treatment period and further withdrawal period.

Main results:

In the pooled data from PRIMROSE 1 and PRIMROSE 2 extension studies, the significantly higher proportion of women showing a reduction in heavy menstrual bleeding in all linzagolix (with or without ABT) treatment groups observed at week 24, was maintained until week 52. Percentages of women with reduced menstrual blood loss at week 52 (based on the pooled week 52 full analysis set) were 55.0% in the 100 mg group, 86.1% in the 100 mg with ABT group, 76.7% in the 200 mg group/200 mg with ABT, and 89.9% in the 200 mg with ABT group.

Of subjects previously treated with linzagolix and in amenorrhoea by week 52, 88.8% reported their first bleed or heavy bleeding between weeks 52 and 64.

In both PRIMROSE studies, the most common adverse events up to week 52 were hot flushes. Their incidence had returned to baseline values by week 64. Bone mineral density was well preserved in all groups at week 52. In women treated with 200 mg linzagolix alone up to week 24, initial BMD loss (lumbar spine) recovered by week 52 after adding ABT from week 24 onwards.

Conclusions: Findings at 52 weeks confirmed the benefits of treatment observed at 24 weeks. At 52 weeks, linzagolix (100 mg or 200 mg) with or without ABT was found to reduce heavy menstrual bleeding, which is a burden for women with uterine fibroids. Their quality of life was improved. Risks of bone loss and vasomotor symptoms were minimized as a result of ABT administration.

Partial suppression with once daily linzagolix (100 mg) without ABT potentially provides a unique option for chronic treatment of symptomatic uterine fibroids in women who do not wish to have ABT or in whom it is contraindicated. The relatively fast recurrence of uterine fibroid-associated symptoms after cessation of therapy is an argument in favour of long-term continuation of treatment.

Keywords: Uterine fibroids; oral GnRH antagonist; linzagolix; heavy menstrual bleeding; bone mineral density; amenorrhoea; quality of life.

Introduction

Uterine fibroids are common, non-cancerous uterine neoplasms, which occur in 50–60% of women, increasing to 70% in those aged over 50 years. In 30% of these women, fibroids cause morbidity due to abnormal uterine bleeding (heavy menstrual bleeding inducing anaemia) and pelvic pressure (causing urinary symptoms, constipation and tenesmus) (1-4). Race appears to be associated with the risk of uterine fibroid development. Indeed, the incidence of uterine fibroids is 60% by age 35 years among African-American women, increasing to more than 80% by 50 years (5). Other risk factors were recently reviewed by Dolmans et al (4) and were found to include age, early menarche, parity, obesity, caffeine and, more recently, vitamin D deficiency and endocrine disruptors (2,4,6,7).

Uterine fibroids are managed by surgical and radiological interventions or medical therapies (1,3,8,9). Among existing medical therapies, the most commonly used treatments are progestogens, but their long-term efficacy is questionable because progesterone and progestogens are important factors in growth and development of uterine fibroids (1,3,6,10). Ulipristal acetate previously proved to be a very effective drug for management of symptomatic uterine fibroids, but its use was restricted to very limited indications due to cases of drug-induced liver disease (11,12).

Recently, oral gonadotropin-releasing hormone (GnRH) antagonists (elagolix, relugolix, linzagolix) have demonstrated their efficacy in reducing heavy menstrual bleeding (13-16). For treatment of symptomatic uterine fibroids, elagolix has been approved by the US Food and Drug Administration, while relugolix is authorized in both the USA and Europe. Both are approved for use in a fixed dose combination with hormonal add-back therapy (ABT) (13,14). Linzagolix is approved in Europe and the UK for management of symptomatic uterine fibroids

and was developed with a once-daily dose of 100 mg providing partial hormone suppression and 200 mg providing full suppression (15).

Two large randomized, double-blind, placebo-controlled phase 3 studies (PRIMROSE 1 and PRIMROSE 2) were conducted to investigate the efficacy and safety of linzagolix (either 100 mg or 200 mg) administered once a day, both with and without concomitant hormonal ABT. The drug was compared against a placebo for treatment of symptoms associated with uterine fibroids (15). The primary endpoint was a reduction in heavy menstrual bleeding by week 24. The results confirmed the efficacy of all 4 regimens, yielding a significant decrease in both uterine and uterine fibroid volume in women treated with 200 mg linzagolix daily (15).

The aim of the present extension study was to evaluate the long-term efficacy and safety of linzagolix therapy for uterine fibroids over a 52-week period (extension study), as well as 12 and 24 weeks after cessation of therapy (withdrawal study). Specifically, this study sought to determine whether the reduction in menstrual blood loss and other secondary outcomes, such as uterine volume and pain observed in short-term studies (24 weeks) (15), could be maintained over an extended treatment period.

Methods

Study design

PRIMROSE 1 and PRIMROSE 2 were two similar, randomized, parallel, double-blind, placebo-controlled phase 3 trials (described in detail in a prior publication (15), along with results from the primary analysis). In brief, for PRIMROSE 1, participants were recruited through 94 sites

in the United States, and for PRIMROSE 2, through 95 sites across Europe (Bulgaria, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania and Ukraine) and the United States from June 2017 to May 2020.

Eligible participants were randomized equally to four treatment arms (linzagolix 100 mg and 200 mg, with or without concomitant hormonal ABT containing 1-mg estradiol (E2) and 0.5 mg norethisterone acetate) and one placebo arm (Figure 1). The primary efficacy endpoint of the PRIMROSE 1 and 2 trials was menstrual blood loss (MBL) of less than 80 ml and at least a 50% reduction in MBL from baseline in the 28 days before week 24. Key secondary endpoints at week 24 were the time to reduced MBL, incidence of amenorrhoea, time to amenorrhoea, the number of days of uterine bleeding in the 28 days leading up to week 24, and haemoglobin concentrations in participants who were anaemic at baseline (15). Original protocols were approved by a central review board (Quorum Review, Seattle, WA) and an ethics committee or institutional review board at each participating center. The trials were conducted in accordance with guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki, and all participants provided written informed consent. The sponsor, ObsEva, performed the studies jointly with the investigators, while an independent data monitoring committee reviewed safety data throughout.

Participants

Participants eligible for inclusion in the PRIMROSE 1 and PRIMROSE 2 trials (see Table S1 with inclusion and exclusion criteria) were aged >18 years, had ultrasound-confirmed uterine fibroids (1 fibroid >2 cm in diameter or multiple small fibroids with a calculated uterine

volume of >200 cm^3), had no fibroids exceeding 12 cm, and had experienced heavy menstrual bleeding (HMB) every cycle for >2 cycles (with HMB defined as MBL of more than 80 ml).

PRIMROSE 1 and PRIMROSE 2 randomized 1,109 women, recruiting 1,012 of them for the full analysis set (Figure S1). Of those, 750 (74%) subjects were included in the week 52 full analysis set, and 567 (56%) entered the treatment-free follow-up period. Reasons for drop-outs are described in figure S2. Demographic characteristics of women included in PRIMROSE 1 and 2 (pooled data) are shown in Table S2.

Randomization and masking

As previously reported (15), a computer-generated list was acquired by random allocation of treatment according to permuted block randomization (block size 10) stratified by race using FlexRandomizer software, version 2.1.0.2 (Cytel, Boston, MA, USA). Masked treatment kits were delivered to each site and maintained in controlled conditions.

Using an interactive web response system at a 1:1:1:1:1 ratio, eligible individuals were randomly assigned to one of the following daily regimens: (1) placebo; (2) 100 mg linzagolix only; (3) 100 mg linzagolix with hormonal ABT (1 mg E2 and 0.5 mg norethisterone acetate); (4) 200 mg linzagolix only; or (5) 200 mg linzagolix with hormonal ABT (1 mg E2 and 0.5 mg norethisterone acetate). In the extension study, all subjects given the placebo or 200 mg linzagolix alone were switched to 200 mg linzagolix with ABT after 24 weeks, except 31 women taking the placebo who were randomly assigned to continue with it (Figure 1). Masking was achieved using inert pills that looked exactly the same as linzagolix treatments

and fake capsules that matched hormonal ABT. Participants, investigation teams at each site, and operational teams were blinded to group allocation.

Procedures and outcomes

The primary efficacy endpoint at 24 weeks (15) was the proportion of women experiencing menstrual bleeding amounting to 80 ml or less and a reduction of at least 50% in MBL by week 24. In the present extension and withdrawal study, the responder rate was evaluated at weeks 52 and 64. MBL was calculated by the alkaline haematin method for menstrual blood volume determination by chemically measuring the blood content of used menstrual products (16) in a central laboratory blinded to study treatments (Laboratorium für Klinische Forschung (LKF), Schwentinental, Germany).

Key secondary endpoints were assessed at weeks 52 and 64. They included rates of amenorrhoea and haemoglobin (Hb) concentrations in a prespecified subgroup of anaemic participants (Hb <12 g/dl at baseline). Further secondary endpoints included pain associated with uterine fibroids, uterine and fibroid volume, serum oestradiol (E2) levels and quality of life (QoL). Pain was self-assessed by patients in an electronic diary as previously reported (15) on day 1 using a numeric rating scale from 0 (no pain) to 10 (worst possible pain) covering the previous 28-day period and then at weeks 52 and 64. It was categorised as (i) none: 0; (ii) mild: 1–3; (iii) moderate: 4–6; and (iv) severe: 7–10. Uterine and fibroid dimensions were evaluated by ultrasound and volumes were calculated using the prolate ellipsoid formula: length × height × width × 0.523. Up to three of the largest fibroids were included in volume calculation. Serum E2 levels were assessed in a central laboratory using highly sensitive and

fully validated high-performance liquid chromatography tandem mass spectrometry assays (Esoterix Endocrinology, Calabasas Hills, CA, USA).

Safety evaluations included bone mineral density (BMD) analyses at screening and at weeks 52 and 76 using dual-energy X-ray absorptiometry (DEXA) that were compared to BMD assessments at week 24. Each site was required to use the same dual-energy X-ray absorptiometry equipment for the entire study. All DEXA scans were thoroughly checked by a central imaging laboratory (Canfield Scientific, Parsippany, NJ, USA) for scan quality. This involved prequalification and cross-calibration phantom scans, as well as monthly phantom scans and reviews of data quality at each site.

Clinical laboratory tests and adverse events were reported at each site. Endometrial biopsies were taken at screening, then at weeks 24 and 52 using a Pipelle de Cornier or its equivalent and were examined by pathologists in a central laboratory (Klimopath, Hamburg, Germany).

Statistical analysis

The full analysis set (FAS) included all randomly assigned women from PRIMROSE 1 and PRIMROSE 2 who had been given at least one dose of the study drug, but did not meet the exclusion criteria for liver function or bone mineral density based on pretreatment baseline tests reported after day 1 (women with these exclusion criteria were immediately withdrawn from the study). The safety analysis set (SAS) involved all randomly designated women who had received at least one dose of the study drug; subjects were analysed according to treatment received. The week 52 FAS and week 52 SAS included all subjects from the FAS or SAS who received at least one dose of double-blind study drug after week 24. The follow-up

FAS and follow-up SAS included all subjects from the FAS and SAS who entered the follow-up period (Figure S1).

As previously reported (15), active drug versus placebo efficacy comparisons were individually conducted using a Bonferroni type 1 error of 0·0125 to account for multiplicity in the four active treatment arms. Cochran-Mantel-Haenszel tests were applied with adjustment for race stratification to test the null hypothesis of no treatment effect for each linzagolix group versus the placebo in terms of proportions of women with reduced heavy menstrual bleeding. Odds ratios were estimated from the Cochran-Mantel-Haenszel tests, along with associated 95% CIs and corresponding p values. Proportions per treatment arm are shown with exact Clopper-Pearson 95% CIs.

The main secondary endpoints were analyzed sequentially in ranking order within each linzagolix treatment arm. Bone mineral density loss was compared between linzagolix treatment groups and the placebo, looking at the percentage change from baseline and z-scores.

Results

Demographics and clinical baseline characteristics for the randomized patients are shown in Table S2. Out of 1,012 participants, 511 and 501 were enrolled in PRIMROSE 1 and PRIMROSE 2 respectively, 349 (34%) of whom were black, 643 (64%) white, and 20 (2%) other. These subjects had a mean age ± SD of 42 ± 6 years, weight of 81 ± 19 kg and BMI of 29·9 ± 6·9 kg/m^2. Median total fibroid volume at baseline was 53 cm^3. MBL at baseline was comparable between all treatment groups, with a median volume at baseline of 164 ml. Among the 1,012

participants, 770 completed treatment up to week 24 across all trial arms. Of those included in the FAS, 750 (74%) subjects reached the week 52 FAS, and 567 (56%) entered the treatment-free follow-up period (Figure S1).

1) Reduction in heavy menstrual bleeding

After 52 weeks of treatment, improvements in heavy menstrual bleeding reported at week 24 (15) were maintained or increased in the week 52 FAS (Figure 2A). Proportions of women with reduced menstrual blood loss at weeks 24 (FAS) and 52 (week 52 FAS) were respectively 56.5% and 55.0% in the 100 mg group, 71.6% and 86.1% in the 100 mg with ABT group, 74.5% and 76.7% in the 200 mg group/200 mg with ABT, and 84.5% and 89.9% in the 200 mg with ABT group, respectively, compared to 32.2% and 41.9% in the placebo group.

Of the 367 subjects who had completed treatment with linzagolix and experienced amenorrhoea at week 52, 326 reported their first bleed or heavy bleeding in the eDiary between week 52 and week 64: 44.8% within 28 days of the week 52 visit, 50.0% between 29 and 56 days, and 52% between 57 and 84 days. The median (95% confidence interval [CI]) time to the first bleed or heavy bleeding was 31.0 (29; 31) days and similar across treatment groups, with the shortest interval in the 100 mg and 100 mg with ABT groups (Figure S3).

The percentage decrease in menstrual blood loss for each 28-day period up to 52 weeks (week 52 FAS) was around 80% (Figure S4) in women treated with 100 mg linzagolix with ABT and 200 mg linzagolix with or without ABT.

2) Amenorrhoea rate

By week 24 in the FAS, percentages of women in amenorrhoea were significantly higher in all linzagolix groups compared to the placebo ($p<0.001$) and remained high until week 52 (week 52 FAS, Figure 2B). Percentages of amenorrhoeic women at weeks 24 (FAS) and 52 (week 52 FAS) were respectively 16.6% and 29.0% in the placebo group, 36.1% and 41.4% in the 100 mg group, 52.4% and 70.8% in the 100 mg with ABT group, 65.4% and 65.0% in the 200 mg/200 mg with ABT and 69.0% and 77.9% in the 200 mg with ABT group. The percentage of amenorrhoeic women at week 52 in women on the placebo until week 24 who were switched to 200 mg with ABT was 69.1%.

3) Uterine and fibroid volume

By week 24 in the FAS, there were significant reductions of 38.8% in mean uterine volume and 48.1% in mean fibroid volume in the 200 mg linzagolix group. Decreases of 15–25% were observed in the 100 mg alone group and 200 mg with ABT group. At 52 weeks in the week 52 FAS, mean reductions in uterine and fibroid volumes were maintained. In the 200 mg alone group, which was switched to 200 mg with ABT at week 24, uterine volume increased after addition of ABT, but did not reach baseline values by 52 weeks. By week 64 in the follow-up FAS, 12 weeks after discontinuation of treatment, uterine and fibroid volumes had returned to baseline levels in most treated groups (Figure 3).

4) Changes in pain scores and quality of life

Pain was measured using a numerical rating scale (NRS), with a score of 0 representing no pain at all and a score of 10 representing the worst possible pain (Figure 4A and Table S3).

Changes from baseline in mean pain scores (SD) observed at 24, 52 and 64 weeks in the follow-up FAS were respectively as follows: -2.6 (3.2), -2.9 (3.1), and -2.0 (3.5) in the 100 mg group; -2.6 (3.0), -2.7 (3.0), and -1.0 (2.9) in the 100 mg with ABT therapy group; -3.5 (3.1), -2.8 (2.7), and -1.6 (3.0) in the 200 mg/200 mg with ABT group; and -2.8 (3.5), -3.2 (3.1), and -1.8 (3.2) in the 200 mg with ABT group. In the placebo/200 mg with ABT group, a reduction in pain was noted between week 24 and week 52 following the switch from placebo to active treatment. The mean (SD) change from baseline in the placebo/placebo group at week 52 was negligible (-0.4 [2.5]). After the end of treatment at week 64, the effect of pain reduction was maintained in the linzagolix groups, although an increase in pain levels towards baseline was noted in all treatment groups (Figure 4A). Pain reduction ranged from a mean (SD) of -1.0 (2.9) in the 100 mg with ABT treatment group to -2.0 (3.5) in the 100 mg treatment group. In the placebo/placebo group, the mean (SD) change from baseline remained similar between week 52 (-0.4 [2.5]) and week 64 (-0.6 [2.0]) (Table S3).

Quality of life (QoL) was assessed using the uterine fibroid symptom (UFS) scale and health-related quality of life (HRQL) score, with higher HRQL scores indicating improvement (Table S3). Improvements from baseline in HRQL total scores were evident in all linzagolix groups at week 24. By week 52, a mean (SD) difference from baseline (indicating improved status compared to baseline) was witnessed in all treatment groups, ranging from a mean (SD) of -34.1 (22.9) in the 200 mg with ABT treatment group to -19.1 (23.1) in the 100 mg treatment group. After the end of treatment at week 64, positive differences were still apparent in all treatment groups. They were, however, smaller than those observed at week 52.

5) Haemoglobin levels in anaemic subjects

Among anaemic subjects (those with Hb levels <12 g/dl at baseline), clinically significant improvements in Hb values were observed in all linzagolix groups. Overall, mean Hb levels rose steadily from baseline in the linzagolix groups until week 52, with the earliest and largest increases seen in the 200 mg treated groups. Following cessation of treatment, all linzagolix groups showed higher mean Hb levels at week 64 compared to baseline, albeit lower than those observed at week 52 (Figure 4B).

6) Estradiol levels

Median serum E2 levels were suppressed to less than 10 pg/mL in the 200 mg linzagolix group at week 4 and maintained for up to 24 weeks in the SAS. Median serum E2 levels in the other linzagolix groups were maintained in the 20–60 pg/mL range. From week 24 to week 52 in the week 52 SAS, median serum E2 levels remained between 20-60 pg/mL, including in the group of women who were switched from the placebo to 200 mg linzagolix with ABT as well as in the 200 mg/200 mg with ABT group. By week 64, median E2 levels were higher than those observed at week 52, and also higher than baseline in all groups previously treated with linzagolix (follow-up SAS, Figure S5). Values observed at week 64 demonstrated recovery of ovarian steroid secretion in all treated groups.

7) Bone mineral density

Changes in bone mineral density (BMD) for the follow-up SAS (Figure 4C) were observed in three specific anatomic sites; lumbar spine, femoral neck and total hip. From week 24 to week 52, rates of BMD loss were within 2% in the femoral neck and total hip sites, suggesting plateauing of BMD loss.

In the 200 mg/200 mg linzagolix with ABT group from the week 52 SAS, a 3.69% BMD reduction at lumbar spine was observed at week 24. Following addition of ABT, a 2.53% reduction from baseline was observed at week 52, indicating a positive effect of ABT on BMD.

After completion of treatment between week 52 and week 76, improvements were noted across all treatment groups (follow-up SAS, Figure 4C).

In line with the small magnitude of observed loss of BMD, median BMD z-scores at weeks 52 and 76 were >0 in all treatment groups from the follow-up SAS.

8) Hot flushes

At week 24 in the SAS, the most commonly encountered adverse event was hot flushes, reported in 33.3% of participants in the 200 mg linzagolix alone group, compared to 5–10% patients in the other linzagolix groups, similar to that observed in placebo patients (5%). From 24 to 52 weeks in the week 52 SAS, the incidence of hot flushes was low across all groups, including the 200 mg linzagolix group who had switched to 200 mg with ABT (0.6%). The rate returned to baseline values by week 64 in the follow-up SAS.

9) Laboratory assessment in relation to safety

During both treatment periods, occasional increases 3 times above the upper limit of normal values were seen for liver enzymes ALT and AST, mainly in the 200 mg linzagolix and 200 mg with ABT groups (data not shown). Values for these parameters generally returned to baseline during the second evaluation period, despite continued therapy. At week 64, there were no clinically relevant changes in liver enzymes following the end of treatment.

High-density lipoprotein (HDL) cholesterol showed relatively little change. From week 24 to week 52, lipid values returned to baseline in the 200 mg/200 mg with ABT group after initiation of therapy. Categorical data analysis of low-density lipoprotein (LDL) cholesterol and triglyceride levels revealed no change from baseline for most subjects in the treatment groups. Changes observed during treatment were less pronounced after the end of therapy, exhibiting a trend towards baseline values by week 64.

At week 52, transvaginal ultrasound showed small reductions in endometrial thickness compared to baseline in all treatment groups. By week 64, however, upon completion of treatment, the endometriums was thicker than seen under treatment at week 52, which is consistent with the end of E2 suppression during the follow-up period. There were no abnormal, clinically significant endometrial biopsy findings reported at weeks 52 or 64.

Discussion

In women with uterine fibroid-related HMB, linzagolix, an oral GnRH antagonist, was found to be effective at doses of 100 mg and 200 mg once a day, with or without ABT and irrespective of body mass index or race (15). The primary endpoint was achieving MBL of 80 ml or less, and a 50% or more reduction from baseline by 24 weeks. All ranked secondary

endpoints were shown to be improved, including high rates of amenorrhoea, diminished menstrual bleeding, less severe fibroid-associated pain and enhanced QoL (15). Significant decreases of 43 - 49% in fibroid volume were only observed with the 200 mg dose, which resulted in the greatest drop in E2 concentrations (15). The short time needed to significantly reduce HMB and achieve amenorrhoea was also recently reported (17).

The goal of the current paper is to share data on efficacy and safety at week 52 (long-term study) and 12 weeks after cessation of therapy (withdrawal study 64 weeks). BMD was also evaluated 24 weeks after stopping therapy (76 weeks).

At 52 weeks, responder rates (pooled data) for the primary endpoint of bleeding reduction are shown in Figure 2A. The highest rate was observed in the 200 mg linzagolix with ABT groups, where the response rate was 89.9%. Responder percentages were higher in all treated groups at week 52 than week 24 (15). The potential for varied responses in different BMI subpopulations was explored in pooled PRIMROSE 1 and PRIMROSE 2 populations, but no clear differences were noted. Similar observations were previously made in the relugolix and elagolix trials (16, 18-22). At week 52, the percentage decrease in MBL from each period at week 24 was maintained for up to 52 weeks. As determined in a subanalysis (15), while black and African American women experience a higher burden of symptomatic uterine fibroids and greater extent of disease than do other ethnic groups, efficacy in this subgroup was consistent with the overall study population, showing no difference between races. The same conclusion was reached in a recent study by Stewart et al (18), who analysed the efficacy of relugolix therapy in 241 Black or African American subjects recruited for the relugolix extension study.

Amenorrhoea rates observed at week 24 (15) were improved or maintained by week 52 (Figure 2B), the highest being in women treated with 200 mg linzagolix with ABT, similar to rates observed with relugolix combination therapy (CT) at week 52 (16, 20-22). In our study, more than 85% of women who were amenorrhoeic at week 52 reported their first bleed or HMB between weeks 52 and 64 (Figure S3). The same swift recurrence of bleeding was encountered in the randomized withdrawal study conducted by Al-Hendy (20), where patients treated with relugolix CT for up to 52 weeks showed evidence of relapse within the first 6-8 weeks of stopping therapy. Patients who relapsed were treated successfully by restarting relugolix CT.

At 52 weeks, mean reductions in uterine and fibroid volumes seen in the first 24 weeks of treatment were maintained. In the 200 mg linzagolix alone group, which was switched to 200 mg with ABT at 24 weeks, uterine and fibroid volume increased, but did not reach baseline values by 52 weeks. In all other groups, the 10-15 % decrease observed at week 24 was maintained. At 64 weeks, however, 12 weeks after cessation of therapy, uterine and fibroid volumes returned to baseline in most treated groups (Figure 3), demonstrating relatively quick regrowth of fibroids associated with swift recovery of ovarian steroid secretion. This is the first study to report such fast recurrence of myoma volume after cessation of therapy, similar to that of uterine adenomyosis, which is known to recur 12 weeks after stopping treatment (23). It appears to suggest that antagonist therapy should be continued if the patient experiences bulk symptoms, or systematically resumed after a period of interruption when and if symptoms recur.

In both studies, results on pain scores and QoL at 24 weeks (15) were maintained to 52 weeks, like in the Liberty studies performed with relugolix CT (16). Nevertheless, at week 64, there was an uptick in pain scores, but not as high as baseline values (Figure 4A).

As expected, given the drug's mechanism of action, reductions in BMD were observed with linzagolix treatment. At 24 weeks, dose-dependent decreases in BMD reached 4% in the lumbar spine with 200 mg linzagolix, and 2% with 100 mg linzagolix, both of which were mitigated by ABT (15). A similar decline was also seen in the Liberty studies, where patients were treated with relugolix alone for 12 weeks before they were switched to relugolix CT (14,20). In the PRIMROSE studies, minimal BMD decreases were observed at 52 weeks in the lumbar spine in groups treated with ABT. Indeed, this is known to be the most sensitive region to BMD change in the context of E2 suppression, suggesting plateauing of BMD loss between week 24 and week 52. The 200 mg linzagolix alone group showed the greatest decline at week 24. However, following addition of ABT, the percentage change from baseline at week 52 was lower than at week 24, pointing to a positive effect of ABT on BMD. The same positive impact of ABT was seen in women switched to relugolix CT after 12 weeks of relugolix alone (14,20).

After the end of treatment, between week 52 and week 76, improvements in BMD were noted across all treatment groups (Figure 4C). Indeed, results at 52 weeks are reassuring and provide useful information on long-term strategies for uterine fibroid-related HMB, offering patients the choice of uterus-preserving treatment. The ability to maintain BMD while effectively managing fibroid symptoms also gives both clinicians and patients reassurance about the safety of prolonged linzagolix treatment. Consistent with the small magnitude of BMD loss, median BMD z-scores at weeks 52 and 76 were >0 in all treatment groups,

indicating that the observed changes did not have any clinically relevant repercussions on overall bone health of study subjects.

Among anaemic subjects (those with Hb levels <12 g/dl at baseline), clinically significant improvements in Hb values were observed in all linzagolix groups (Figure 4B). As recently reported (24), oral GnRH antagonist therapy allows restoration of Hb levels before surgery in anaemic patients. Laboratory assessments confirmed the absence of any significant changes in hepatic enzymes, HDL or LDL cholesterol, or endometrial histology.

Strengths:

The extension study involved a very large number of patients and evaluated various doses of linzagolix with and without ABT. The withdrawal study allows us to evaluate symptom recurrence after cessation of therapy, as well as BMD recovery.

Limitations, reasons for caution:

This extension study has limitations. First, in previous key studies (15), many women with self-reported HMB did not pass initial screening due to strict assessment criteria. Indeed, while there was randomization of study populations and inclusion of women with symptomatic uterine fibroids, generalizing the findings was limited by the high proportion of ineligible patients. It is important to state that women were excluded if they did not meet the strict criteria for HMB (≥80 ml of MBL per cycle for ≥2 cycles), had a uterine volume exceeding 200 cm^3, or exhibited fibroids of ≥12 cm. The duration of the trial regimen was only 12 months and efficacy was compared between linzagolix and placebo groups. It will be important to

ascertain whether GnRH antagonists have significant benefits over first-line medications (25-27). Finally, pooling of data from PRIMROSE 1 and PRIMROSE 2 may result in bias if there are differences between participants in the two PRIMROSE trials that are not accounted for in the analysis. To mitigate this risk, current analyses were adjusted for key potential confounders, including race, age, body mass index, baseline FV levels, baseline MBL, analgesic use at baseline or in the 28 days leading up to the 24 week visit, and comparisons between the two studies.

Conclusion

Oral GnRH antagonists (elagolix [13], relugolix [14] and linzagolix [15]) provide a new approach to medical management of HMB and other symptoms linked to the presence of uterine fibroids (28). The positive effect of linzagolix in achieving a reduction in clinically significant HMB was fast, with a median interval of <4 weeks (17). The present study demonstrates the safety and efficacy of linzagolix over the course of 52 weeks of therapy, providing useful information on long-term strategies for uterine fibroid-related symptoms and offering patients the choice of uterus-preserving treatment (26-27).

The 100 mg dose of linzagolix was developed to exert a partial suppression effect that has the potential for longer-term use (>6 months) without hormonal ABT. Such an option might be important for women who prefer to avoid use of estrogens and progestogens, those in whom exogenous estrogen is contraindicated, or those at increased risk of estrogen- and progestogen-related adverse events. The 100 mg dose significantly reduced HMB in approximately two-thirds of women and decreased associated BMD loss observed with full

suppression using 200 mg linzagolix, which was the only dose that yielded substantial reductions in uterine and fibroid volume. Other studies have indeed demonstrated significant diminution in uterine and fibroid volume in women treated with high doses of GnRH antagonist alone (13,14,29). This effect was nevertheless attenuated when ABT was initiated.

In conclusion, linzagolix provides a promising long-term option for management of uterine fibroid symptoms, with sustained efficacy and a favorable safety profile, particularly in combination with ABT. Ultimately, linzagolix offers clinicians an effective non-surgical alternative that addresses a significant unmet need in the management of fibroid-related symptoms. Future studies should focus on optimizing treatment duration and exploring patient populations that may benefit most from this therapy.

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CRediT Authorship contribution Statement:

JD, HST and EB contributed to the protocol and design of the trials and interpretation of the results. JD and MMD contributed to the drafting of the manuscript. All authors (JD, FP, HT, CB, SV, FC, SH, EB, MMD) accessed and verified the data and critically reviewed and approved the final version.

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Declaration of interests:

JD was a member of the scientific advisory board of ObsEva and Preglem until 2023 and reports consulting fees from ObsEva, Gedeon Richter and Theramex. FP has received consulting fees and honoraria for lectures from Theramex. HT has received grants from Abbvie, reports consulting fees from ObsEva and Gedeon Richter, has a patent on endometriosis biomarkers owned by Yale University, and was a past president of American Society of reproductive Medicine (ASRM). CB was a member of the independent data monitoring board for the PRIMROSE trials and member of the advisory board for Spirit 1 and 2 trials. He was also the Chair for the ESHRE endometriosis guideline committee. Consulting fees from Myovant and Theramex went to the University of Oxford. SB has received consulting fees and honoraria for lectures from Theramex. FCH reports consulting fees or honoraria for lectures, presentations or educational events from Theramex and Gedeon Richter and was a member of a data safety monitoring board for Organon. EB and SH are employees of Theramex. MMD has received fees for lectures from Gedeon Richter and Theramex. Grant 5/4/150/5 was awarded to MMD by the FNRS.

Data availability: Appropriately de-identified patient-level datasets and supporting documents may be shared according to criteria established by Theramex and/or industry best practices to maintain the privacy of study participants.

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Figures and tables legends

FIGURE 1. Schematic of the study design

ABT = Add-back therapy (1mg estradiol / 0.5mg norethisterone acetate); LGX = Linzagolix

*Women allocated to placebo or 200 mg Linzagolix alone were switched to 200 mg Linzagolix with ABT after 24 weeks, except in PRIMROSE 1, in which 50% of the women on placebo continued placebo (selected at random assignment) until week 52.

FIGURE 2. Proportion of women with A) reduced heavy menstrual bleeding and B) amenorrhoea after 52 weeks (Week 52 Full Analysis Set)

ABT = Add-back therapy (1mg estradiol / 0.5mg norethisterone acetate); LGX = Linzagolix

FIGURE 3. Changes in uterine and fibroid volumes up to 64 weeks (Follow-up Full Analysis Set)

The error bars show the 95% C.I.

ABT = Add-back therapy (1mg estradiol / 0.5mg norethisterone acetate); LGX = Linzagolix

FIGURE 4. Changes in A) pain score (NRS), haemoglobin levels (g/dL) in anaemic patients at baseline (<12 g/dL) and C) mean percentage change in bone mineral density up to 64 weeks (Follow-up Full Analysis Set and Follow-up Safety Analysis Set)

The error bars show the 95% C.I.

ABT = Add-back therapy (1mg estradiol / 0.5mg norethisterone acetate); LGX = Linzagolix, NRS=Numerical Rating Scale

Pain was measured using NRS (0=no pain, 10=severe pain)

Supplemental figures and tables

FIGURE S1. Subject disposition up to Week 76 (pooled data)

FIGURE S2. Subject disposition up to Week 76 in A) PRIMROSE 1 and B) PRIMROSE 2

ABT: add-back therapy.

[a] Full Analysis Set

[b] Week 52 Full Analysis Set

[c] Follow-up Full Analysis Set

*For discontinued subjects between Week 24 and Week 52, follow-up data were collected up to Week 76 if the subject was willing to perform the follow-up visits.

FIGURE S3. Percentage decrease in menstrual blood loss for each 28-period up to 52 weeks (Week 52 Full Analysis Set)

The error bars show the 95% C.I.

ABT = Add-back therapy (1mg estradiol / 0.5mg norethisterone acetate); LGX = Linzagolix

FIGURE S4. KM-estimated time to first menstrual bleed following cessation of treatment in patients with amenorrhoea at week 52 in days (Follow-up Full Analysis Set)

ABT = Add-back therapy (1mg estradiol / 0.5mg norethisterone acetate); KM = Kaplan Meier; LGX = Linzagolix

FIGURE S5. Median serum Levels of E2 up to Week 64 (Follow-up Safety Analysis Set)

ABT: Add-back therapy (1mg estradiol / 0.5mg norethisterone acetate); E2 = Estradiol; LGX = Linzagolix

TABLE S1. Demographic and clinical characteristics of the participants at baseline (Full Analysis Set)

ABT: Add-back therapy (1mg estradiol / 0.5mg norethisterone acetate); UFS-QoL= Uterine Fibroid Symptom-Quality of Life questionnaire; UFS-QoL HRQL= Uterine Fibroid Symptom-

Quality of Life and Health-Related Quality of Life questionnaire.; LGX = Linzagolix; NRS=Numerical Rating Scale; SD: standard deviation

Data are presented as mean (SD), n (%), or median (Q1–Q3). *The z-scores are based on the safety analysis set, whereas all other variables are based on the full analysis set.

TABLE S2. Inclusion and exclusion criteria

The inclusion/exclusion criteria for PRIMROSE1 and PRIMROSE2 were identical.

ABT = Add-back therapy (1mg estradiol / 0.5mg norethisterone acetate); LGX = Linzagolix

TABLE S3. Summary of changes from baseline in Pain, Health-Related Quality of Life score (UFS-QoL), Quality of Life (EQ-5D) and Patient Global Impression of Improvement Scale (PGI-I) evaluated during the follow-up period (Follow-up Full Analysis Set)

ABT: Add-back therapy (1mg estradiol / 0.5mg norethisterone acetate); HRQL = Health-related quality of life; LGX = Linzagolix; NRS=Numerical Rating Scale; SD: standard deviation

Pain was measured using NRS (0=no pain, 10=severe pain). The range for the HRQL total score was 0 to 100 (with higher scores indicating better quality of life). EQ-5D VAS scores range from 0-100 (with higher scores indicating better health).