

Linzagolix improves Haemoglobin and Iron-deficiency anaemia biomarkers in women with symptomatic Leiomyoma

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Background

- Linzagolix (LGX) is an oral, selective, non-peptide molecule gonadotropin-releasing hormone receptor antagonist that acts by suppressing the luteinizing and follicle stimulating hormones and estradiol in a dose-dependent fashion.
- LGX was developed for the treatment of uterine fibroids and endometriosis in women of reproductive age and is characterized by a half-life of 15 hours, no food effect.
- PRIMROSE 1 and 2, two double-blind similar placebo-controlled phase 3 trials of LGX that took place in the US and Europe, showed that LGX (100 mg or 200 mg) with or without add-back therapy (ABT) significantly reduced menstrual blood loss (MBL) in women with uterine fibroids (Donnez *et al.*, 2022).
- Given many women with uterine fibroids have anaemia due to MBL, we hypothesized that LGX benefit extends to improvements in haemoglobin (Hb) and other iron deficiency anaemia biomarkers for these women.

Objective

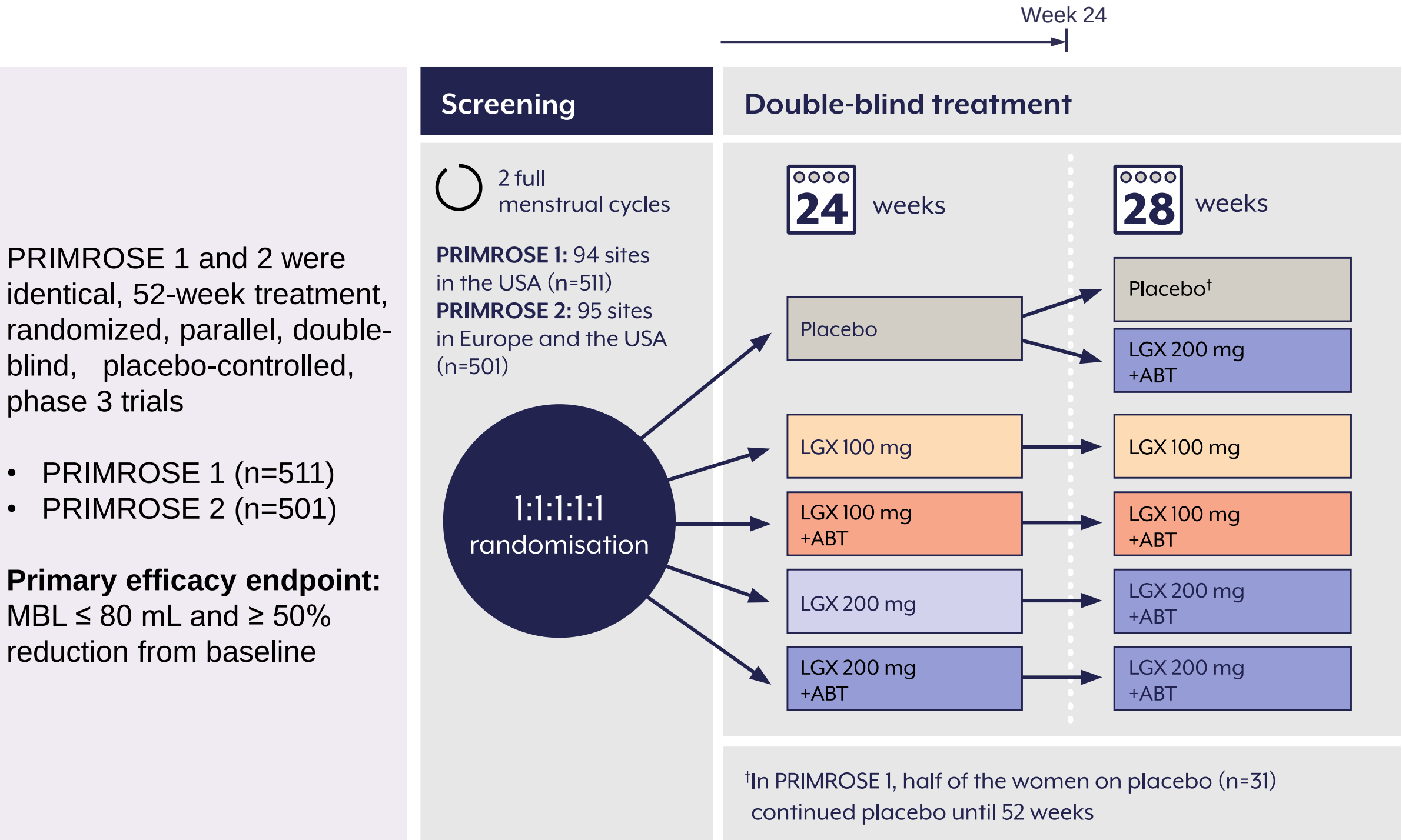
- To evaluate the effect of LGX in improving Hb and other biomarkers of iron deficiency anaemia in patients with ultra-sound confirmed uterine fibroids with heavy MBL and anaemia.

Methods

PRIMROSE trials, outcomes, and analysis

- The study used pooled data from PRIMROSE 1 and 2, two double-blind similar placebo-controlled phase 3 trials of LGX which took place in the US and Europe.
- The current post-hoc analysis focuses on women who had anaemia (Hb ≤12g/dL at baseline).
- Main outcome of this analysis was to evaluate the proportion of patients with anaemia who had improvement in their anaemia by week 4 (improvement in Hb by ≥2g/dL from baseline or increase in Hb to ≥12g/dL) and maintained it up to the last follow-up (scheduled at week 24).
- Change over time from baseline up to week 24 in Hb and other iron deficiency anaemia biomarkers (ie, ferritin and mean corpuscular volume (MCV)) were reported.
- Time to anaemia improvement with maintenance to week 24 was analyzed using Kaplan-Meier time to event methodology.

Fig 1. PRIMROSE clinical trial study design (Donnez *et al.*, 2022)



Results

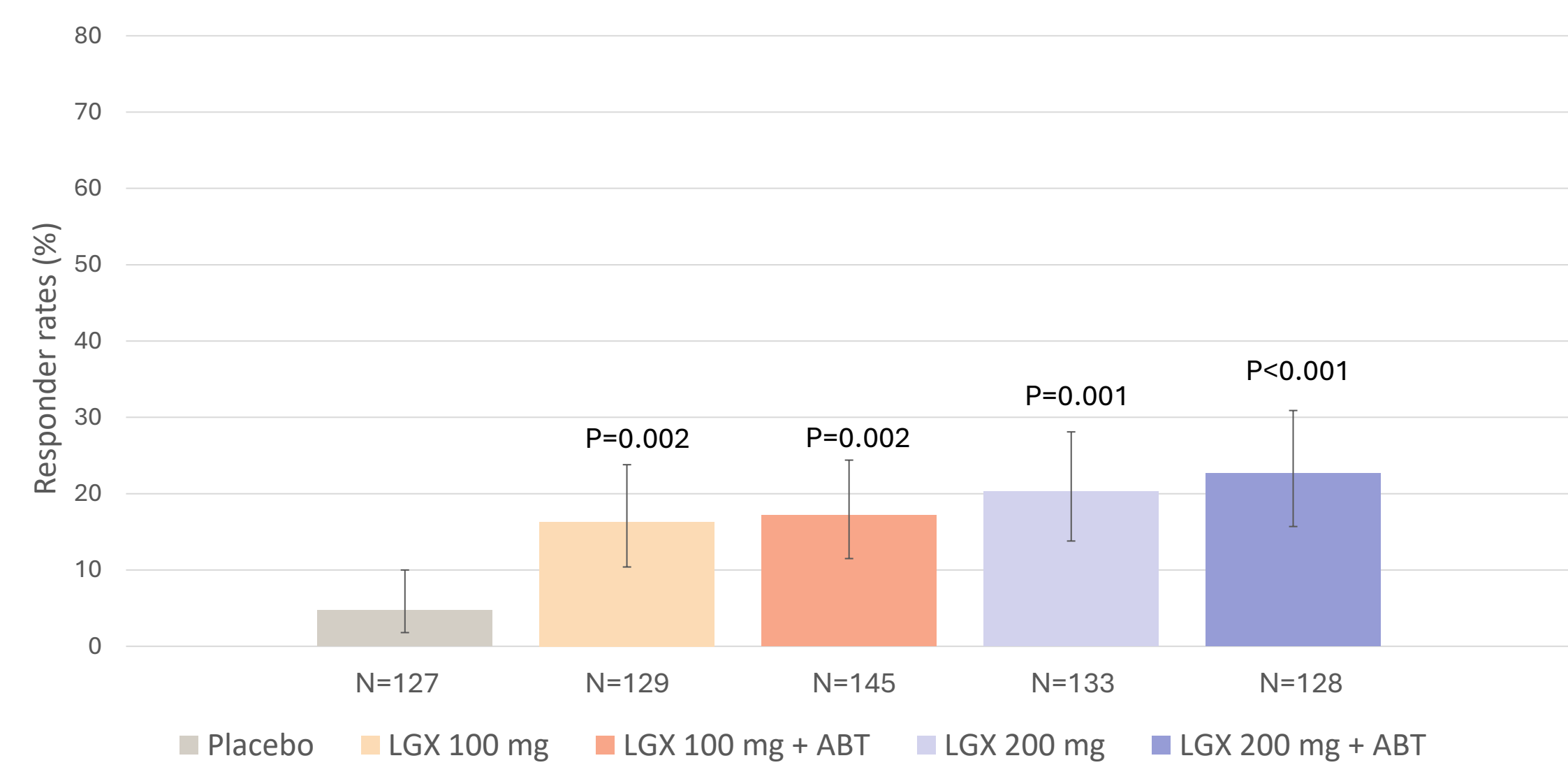
Tab 1. Demographic / Baseline Characteristics (Pooled data, n=662): Women with baseline anaemia (≤12g/dL)

	Placebo (N=127)	LGX 100mg without ABT (N=129)	LGX 100mg with ABT (N=145)	LGX 200mg without ABT (N=133)	LGX 200mg with ABT (N=128)	Total (N=662)
Study, n (%)						
PRIMROSE1	76 (60%)	68 (53%)	86 (59%)	76 (57%)	72 (56%)	378 (57%)
PRIMROSE2	51 (40%)	61 (47%)	59 (41%)	57 (43%)	56 (44%)	284 (43%)
Age (yrs), mean (SD)	42.28 (5.47)	42.87 (5.10)	42.14 (5.52)	42.11 (5.72)	42.31 (5.42)	42.34 (5.44)
Race, ¹ n (%)						
Black	56 (44%)	53 (41%)	61 (42%)	59 (44%)	56 (44%)	285 (43%)
White	70 (55%)	71 (55%)	79 (54%)	73 (55%)	70 (55%)	363 (55%)
MBL (mL) ² , med (Q1 – Q3)	179 (137 - 244)	191 (143 - 281)	175 (126 - 298)	177 (131 - 274)	184 (128 - 258)	182 (133 - 268)
Total fibroid volume (mL) ³ , med (Q1 – Q3)	53 (25 - 140)	63 (24 - 142)	57 (21 - 159)	48 (21 - 127)	59 (25 - 111)	57 (23 - 135)
BMI (kg/m²), mean (SD)	29.93 (7.06)	31.14 (7.58)	30.43 (7.01)	30.17 (6.79)	30.22 (7.18)	30.38 (7.11)
Hb (g/dL), mean (SD)	10.37 (1.23)	9.99 (1.35)	10.04 (1.42)	10.08 (1.33)	10.08 (1.32)	10.11 (1.34)
MCV(fL), mean (SD)	85.23 (9.24)	82.09 (9.36)	82.93 (8.53)	83.14 (9.15)	83.81 (8.94)	83.42 (9.07)
Ferritin (ug/L), mean (SD)	14.62 (20.98)	12.09 (12.94)	14.12 (15.89)	14.16 (18.30)	14.27 (15.38)	13.86 (16.86)
Use of oral iron therapy before week 24, n (%)	80 (63.0%)	79 (61.2%)	92 (63.4%)	81 (60.9%)	80 (62.5%)	412 (62.2%)

[1] Other races not shown (account for 1% in placebo and 1-4% in the treated).
[2] Baseline period defined as the first menstruation cycle post-screening (the third if the screening lasted for two cycles or the fourth if screening lasted for three cycles). Participants were to contact the site to schedule the Day 1 visit, which was to occur between the first and seventh days (inclusive) of the menstrual cycle.
[3] Fibroid dimensions were estimated using ultrasonography performed during screening visit. Volumes were calculated by the prolate ellipsoid formula: length×height×width×0.523. Up to the three largest fibroids were included in the total fibroid volume calculation. 1 ml = 1 cm³.

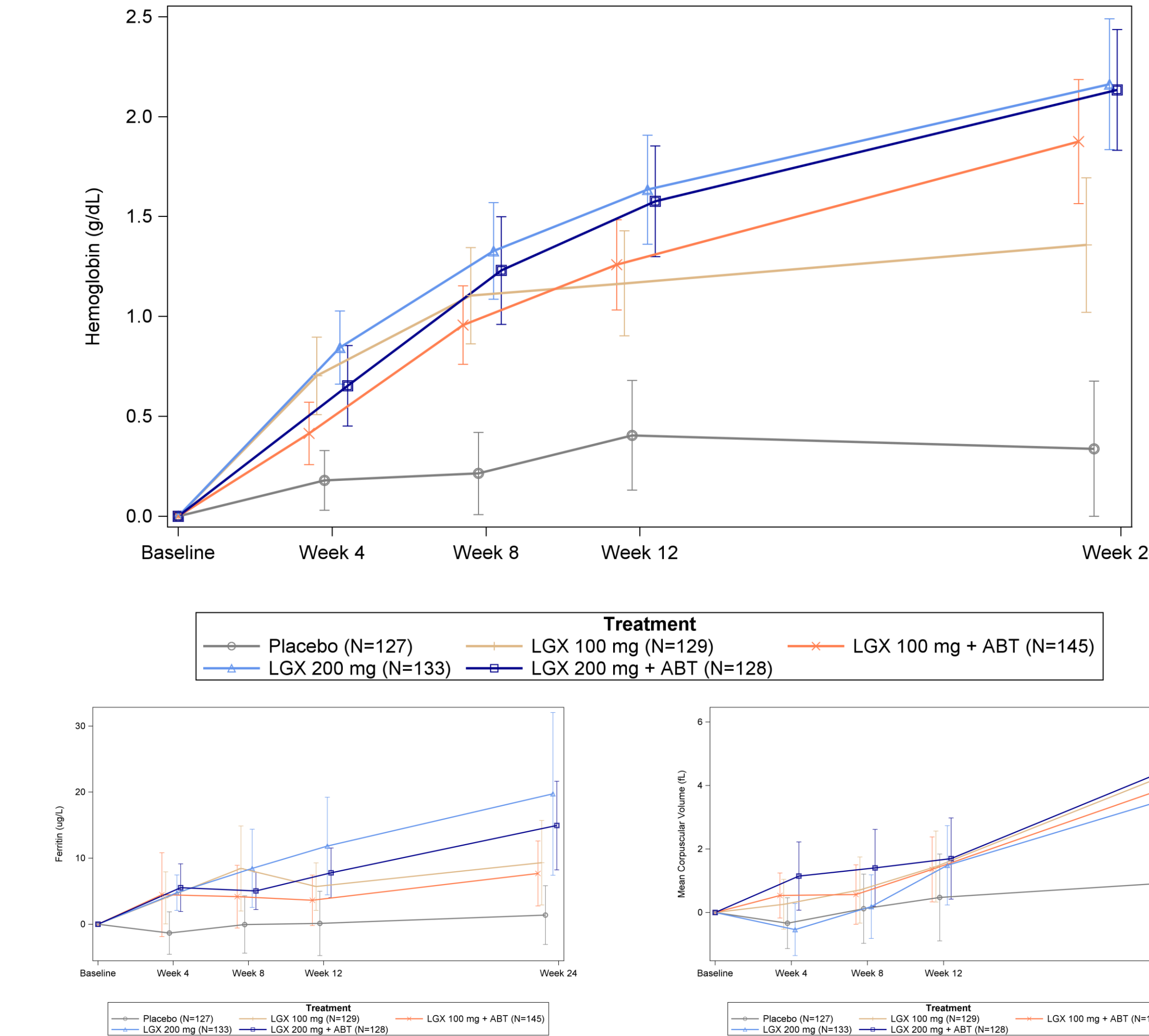
- In the pooled PRIMROSE samples, similar proportions of LGX and placebo-treated patients had baseline anaemia (64–70% vs 62%; all p>0.05) and received iron supplements anytime from randomization to week 24 (48–53% vs 48%; all p>0.05) (Tab 1).

Fig 2. Proportion with clinically significant anaemia improvement from baseline to week 4 that was maintained up to week 24¹



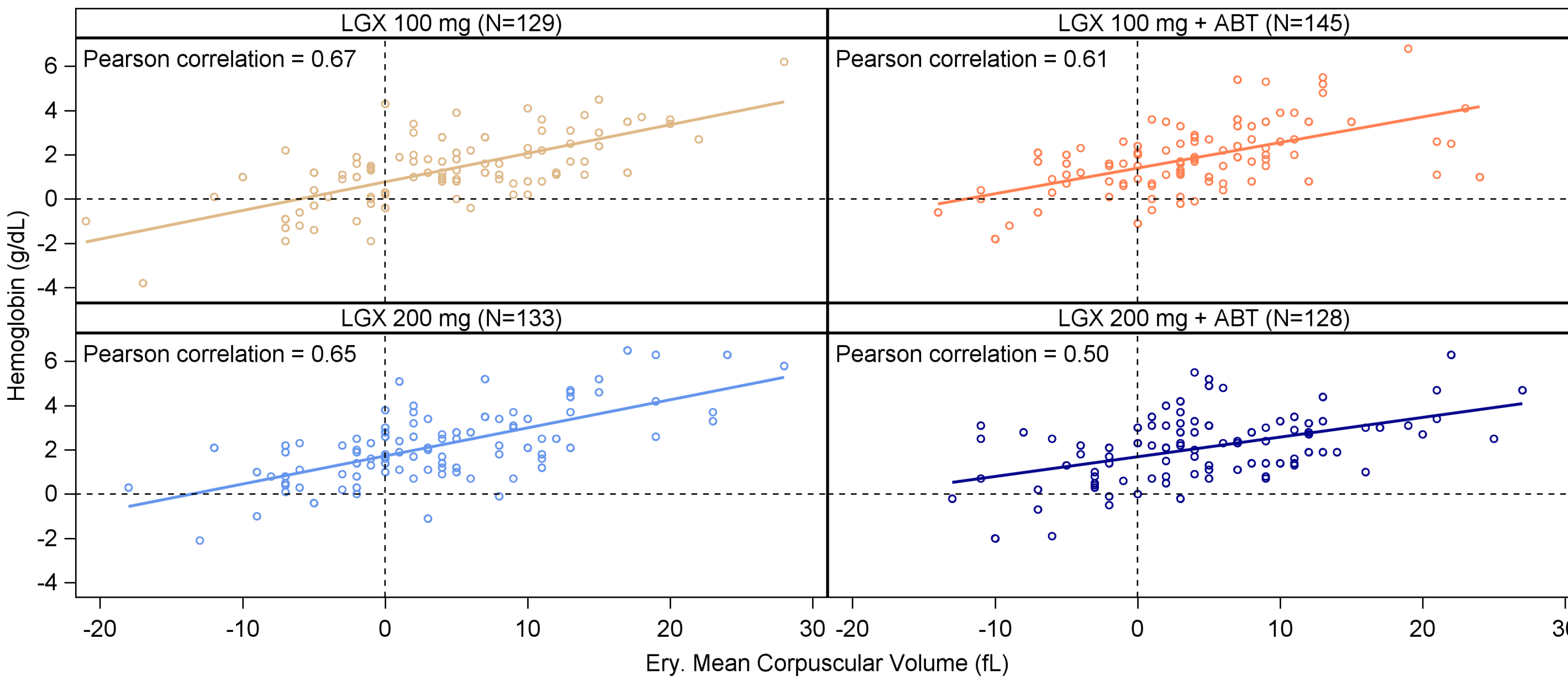
¹ In women with anaemia at baseline (Hb <12g/dL), improvement in anaemia was defined as Hb increase of ≥2g/dL from baseline or increase in Hb levels to ≥12g/dL, with maintenance of this improvement through to week 24. P-value obtained using a Fisher's exact test comparing the proportions of subjects with improvement for each treatment arm versus placebo.

Fig 3. Mean changes from baseline to week 24 in Hb (g/dL), MCV (fL) & Ferritin (µg/L) with 95% CIs



- Among women with anaemia, those threated with LGX were more likely to achieve improvements in anaemia by week 4 and maintain this improvement to week 24 (16-21% vs 5%; all p<0.05; Fig 2), and to have biomarker levels improved from baseline to week 24 (p<0.05 for 9 [75%] of the 12 treated vs placebo comparisons; Fig 3).

Fig 4. Correlation between Hb (g/dL) and MCV (fL) among LGX-treated subjects



- At week 24, patients treated with LGX 100mg with and without ABT and those treated with LGX 200mg without ABT exhibited a strong correlation between Hb and MCV (r = 0.61-0.67), while those treated with LGX 200mg with ABT exhibited a moderate correlation between Hb and MCV (r = 0.5) (Fig 4).

Conclusions

- This post-hoc analysis of the PRIMROSE trials demonstrated that women with uterine fibroids and anaemia treated with linzagolix had more improvements in Hb and other iron deficiency anaemia biomarkers than women treated with placebo.
- The positive and long-lasting effect on improvement in anaemia was rapidly observed after only 4 weeks of treatment (all doses).
- Haemoglobin and mean corpuscular volume were strongly correlated at week 24 among linzagolix-treated women.
- Linzagolix may be a suitable option for symptomatic uterine fibroids, where a rapid and sustained improvement in anaemia is required.

Disclosure

This study was funded by Theramex, which contributed to the design and interpretation of the data.

References

Donnez J, Taylor HS, Stewart EA, Bradley L, Marsh E, Archer D, 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.

Abbreviations

ABT, add-back therapy;
BMI, body mass index;
CI, confidence interval;
Hb, haemoglobin;
LGX, linzagolix;
MBL, menstrual blood loss;
MCV, mean corpuscular volume;
SD, standard deviation.