Medical Treatment Options against Uterine Fibroids

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Disclosures

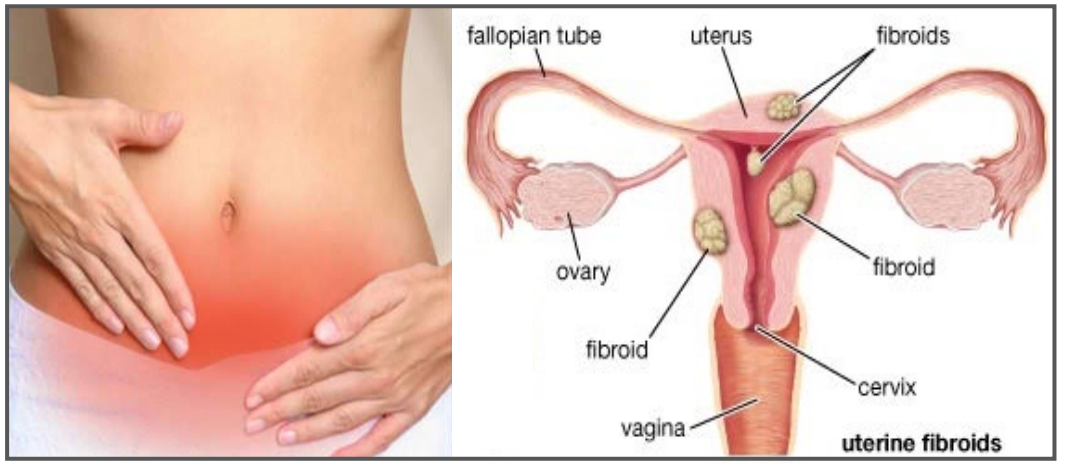
- Consultant: AbbVie, Bayer, Myovant, Novartis, Crila, Vittilabs, OBS-EVA
- Research Support: National Institutes of Health (R01 ES 028615-01, R01HD 087417, R01 HD 094378, R01 HD 094380, R01 HD 10036701, U54 MD 007602)
- Patent for methods for novel diagnostics and therapeutics for uterine sarcoma (US Pat No. 9,790,562 B2)

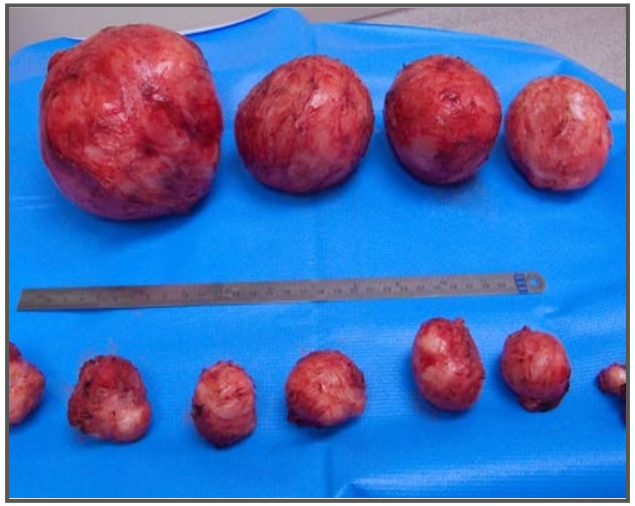
Uterine Fibroids

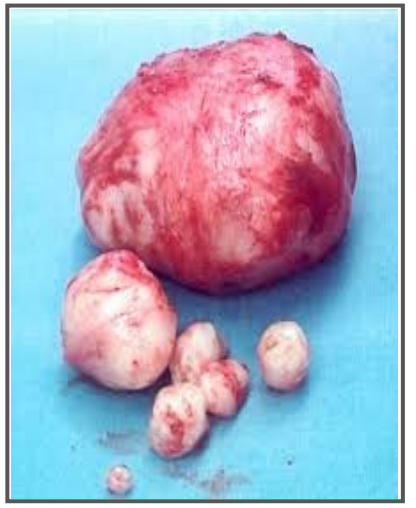
- Uterine leiomyomas (UL; fibroids) are ***benign*** smooth muscle tumors originating from the myometrium

- Most common human tumor:
  - tumors occur in 77% women
  - clinically apparent in 50% by age 45

- Significant source of morbidity:
  - leading indicator of hysterectomy
  - major cause of gynecologic dysfunction:
    - menometrorrhagia and anemia
    - pelvic pressure/bulk symptoms
    - infertility, recurrent miscarriage
    - preterm labor
- In US we do more hysterectomies/capita than any other developed country (double Germany, X5 times than Canada)





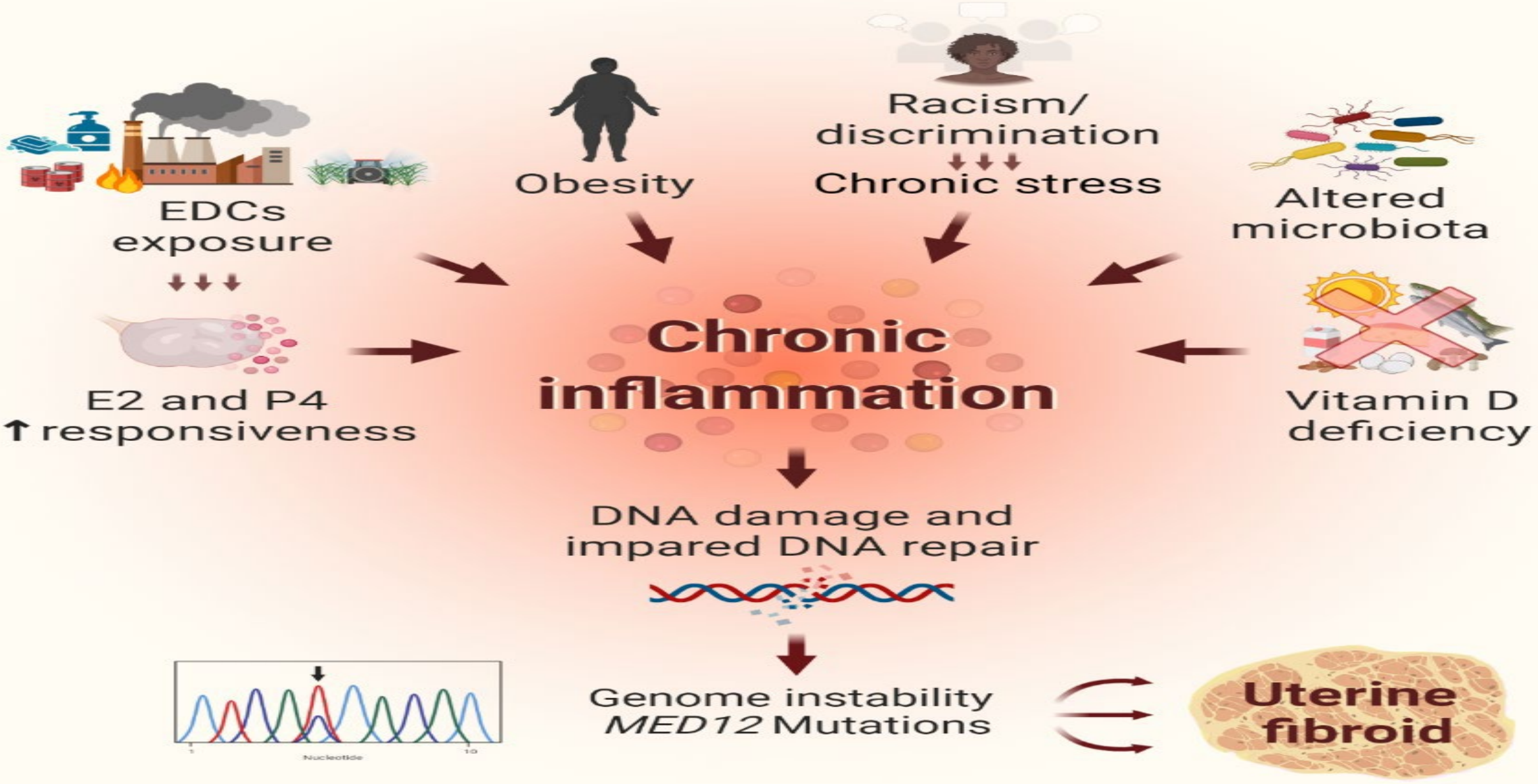


Patel et al. (2014) *Fertil Steril*, 2014
Moravek et al. *Hum Reprod Update*, 2015

Where do Uterine Fibroid Come from?

Why are they more common in Women of Color?,

Bariani et. al., *Endocrine Reviews*, 2021

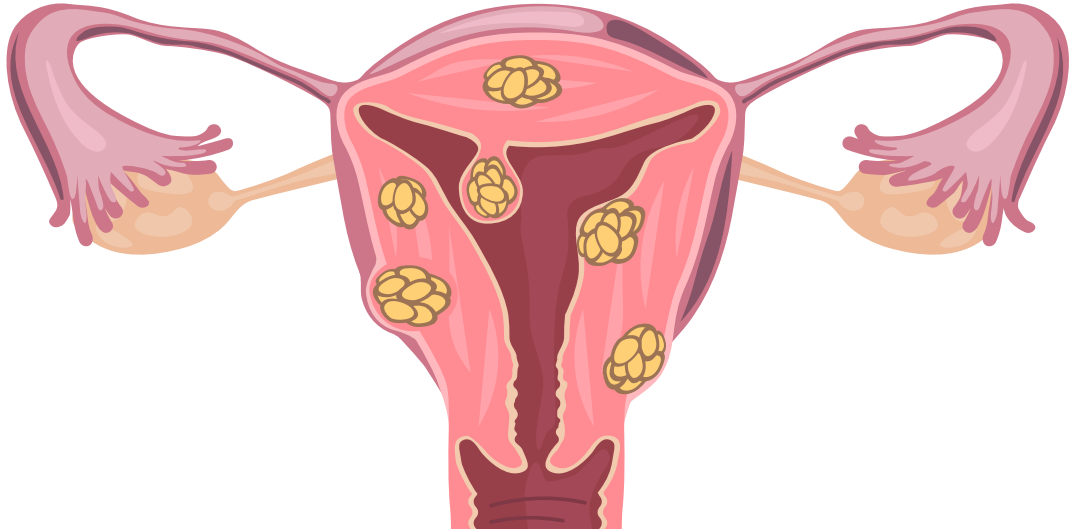


Majority of Women With Uterine Fibroids Experience Heavy Menstrual Bleeding[1]

Of the women affected by UF, up to **50% are symptomatic**[2]

73%

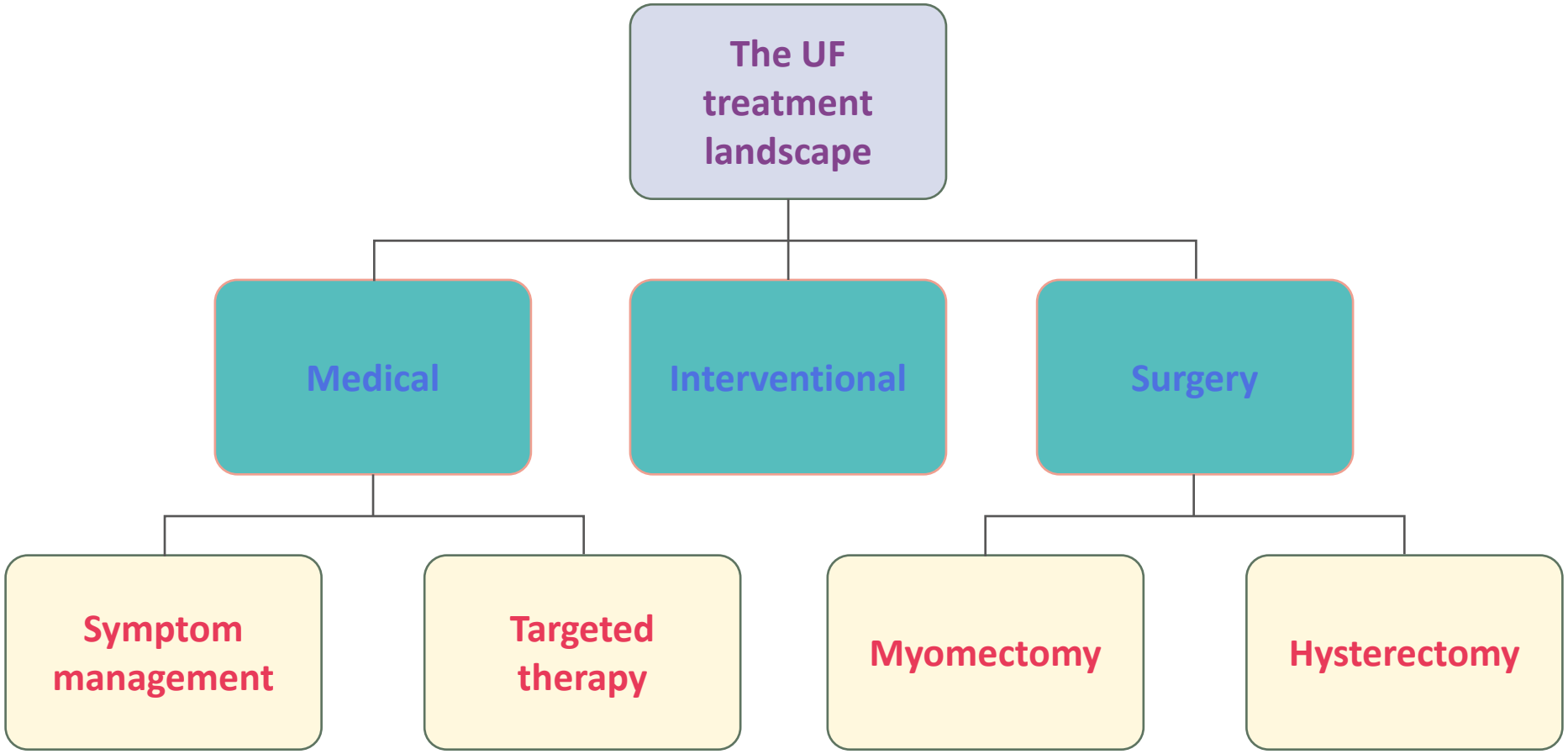
of women with symptomatic UF report HMB as a primary symptom[1]



HMB=heavy menstrual bleeding; UF=uterine fibroids.

1. Fuldeore MJ, Soliman AM. Int J Womens Health. 2017;9:403–411. 2. De La Cruz MS, Buchanan EM. Am Fam Physician. 2017;95(2):100–107.

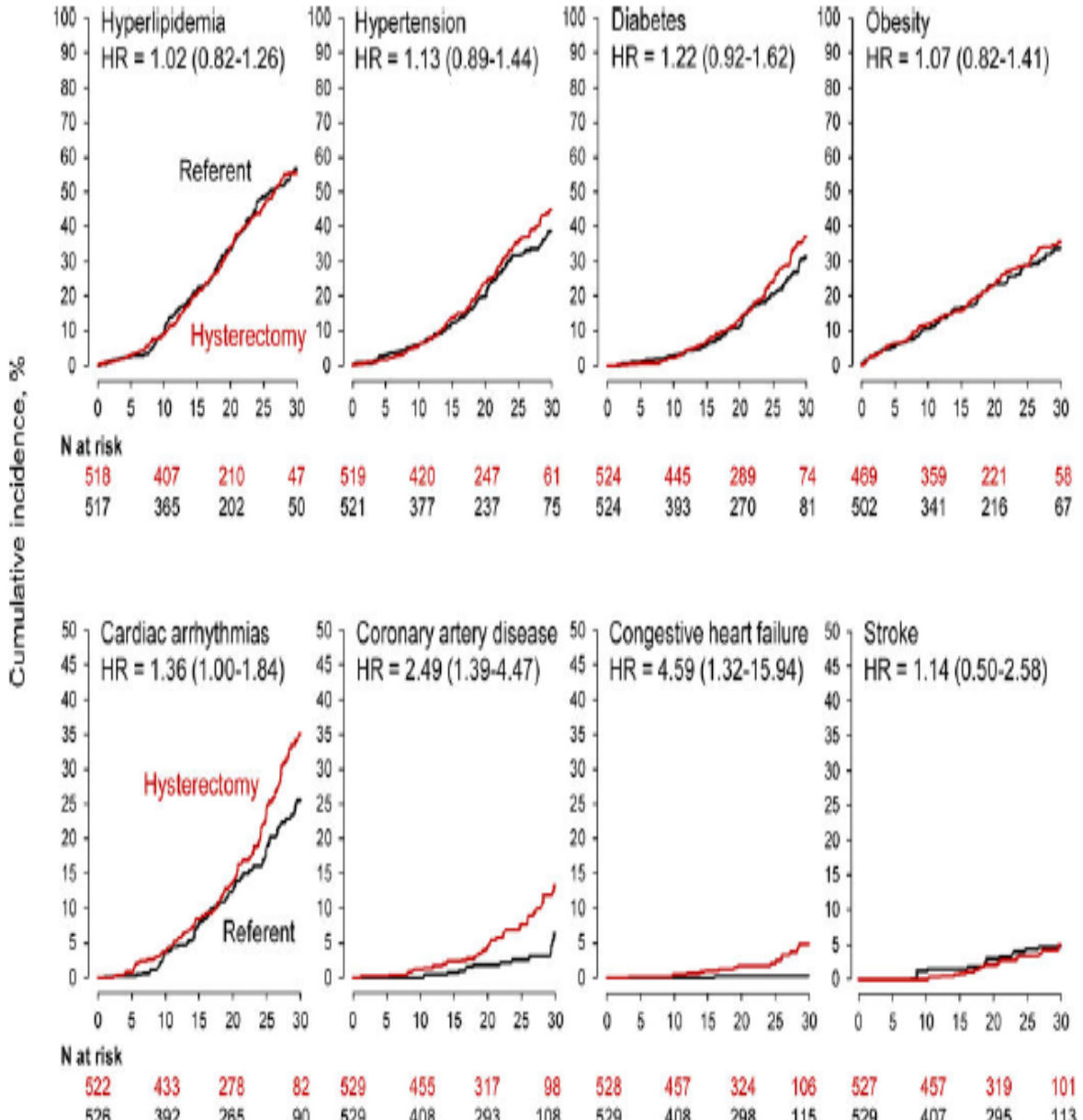
There Are Several Treatment Options



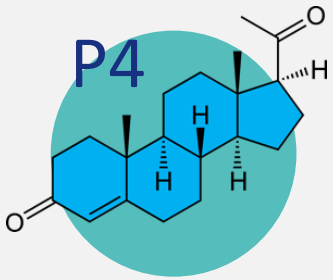
De La Cruz MS, Buchanan EM. Am Fam Physician. 2017;95(2):100–107.

Long Term Negative Impact of Hysterectomy (without BSO)

What We Know about the Long-Term Risks of Hysterectomy for Benign Indication-A Systematic Review. Madueke-Laveaux OS, Elsharoud A, Al-Hendy A. J Clin Med. 2021 Nov 16;10(22):5335. doi: 10.3390/jcm10225335



Hormonal Treatment of Uterine Fibroids



PROGESTINS

Mixed agonist/antagonists SPRM

Asoprisnil

ANTIPROGESTINS

Telapristone

MPA
NEA

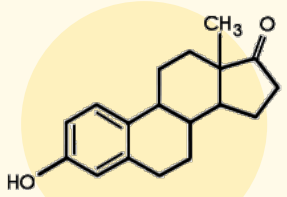
Ulipristal
Vilaprisan

R5020
PROGESTERONE
P-IUD

RU486

AGONIST — P4 activity — **ANTAGONIST**

GnRH analogues
Leuprolide
Elagolix
Relugolix
Linzagolix



Estrogen

Aromatase inhibitors

MPA=medroxyprogesterone acetate; NEA=norethindrone acetate; P-IUD=progestin intrauterine device; SPRM=selective progesterone receptor modulator.

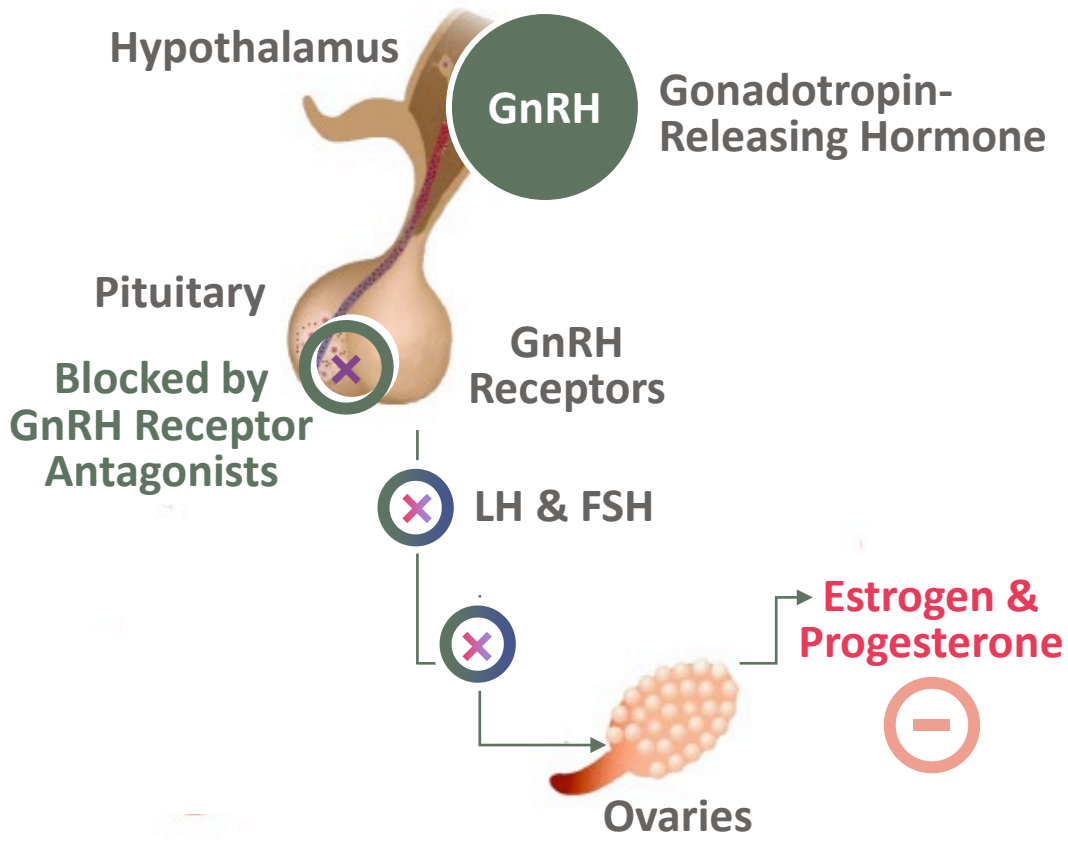
Sabry M, Al-Hendy A. Obstet Gynecol Int. 2012;2012:943635.

Oral GnRH Antagonists

GnRH Receptor Antagonists: Mechanism of Action

UNLIKE THE AGONISTS:

- Oral
- GnRH receptor antagonists do not induce an initial stimulation of gonadotropin release:
  - They cause an immediate and reversible suppression of gonadotropin secretion[1]
  - Results in subsequent rapid reduction of estradiol

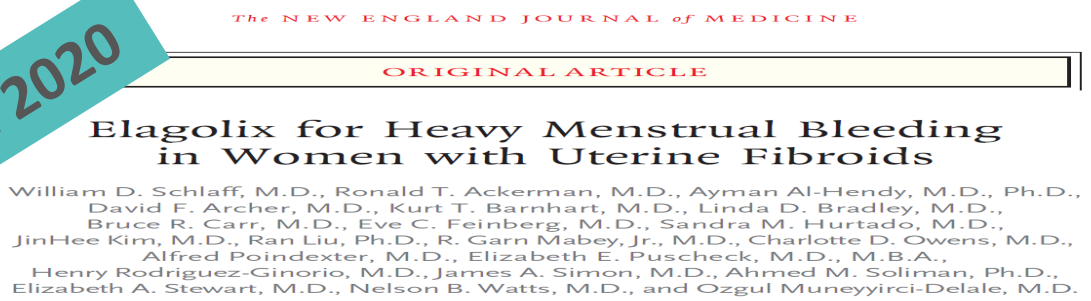


1.Huirne JA, Lambalk CB. Lancet. 2001;358(9295):1793–803.

GnRH Receptor Antagonists

ELAGOLIX[1]

Jan 2020


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Elagolix for Heavy Menstrual Bleeding in Women with Uterine Fibroids

William D. Schlaff, M.D., Ronald T. Ackerman, M.D., Ayman Al-Hendy, M.D., Ph.D., David F. Archer, M.D., Kurt T. Barnhart, M.D., Linda D. Bradley, M.D., Bruce R. Carr, M.D., Eve C. Feinberg, M.D., Sandra M. Hurtado, M.D., JinHee Kim, M.D., Ran Liu, Ph.D., R. Garn Mabey, Jr., M.D., Charlotte D. Owens, M.D., Alfred Poindexter, M.D., Elizabeth E. Puscheck, M.D., M.B.A., Henry Rodriguez-Ginorio, M.D., James A. Simon, M.D., Ahmed M. Soliman, Ph.D., Elizabeth A. Stewart, M.D., Nelson B. Watts, M.D., and Ozgul Muneyyirci-Delale, M.D.

with
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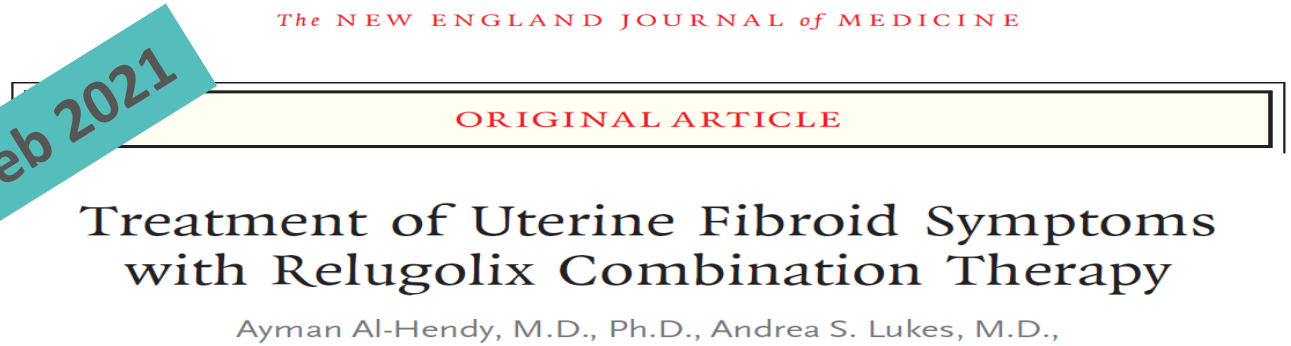
FDA Approval May 2020

RELUGOLIX[2]

Feb 2021


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy

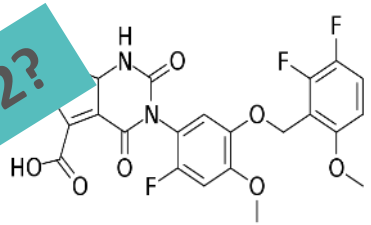
Ayman Al-Hendy, M.D., Ph.D., Andrea S. Lukes, M.D.,

riosis

FDA Approval June 2021

LINZAGOLIX[3]

2022?



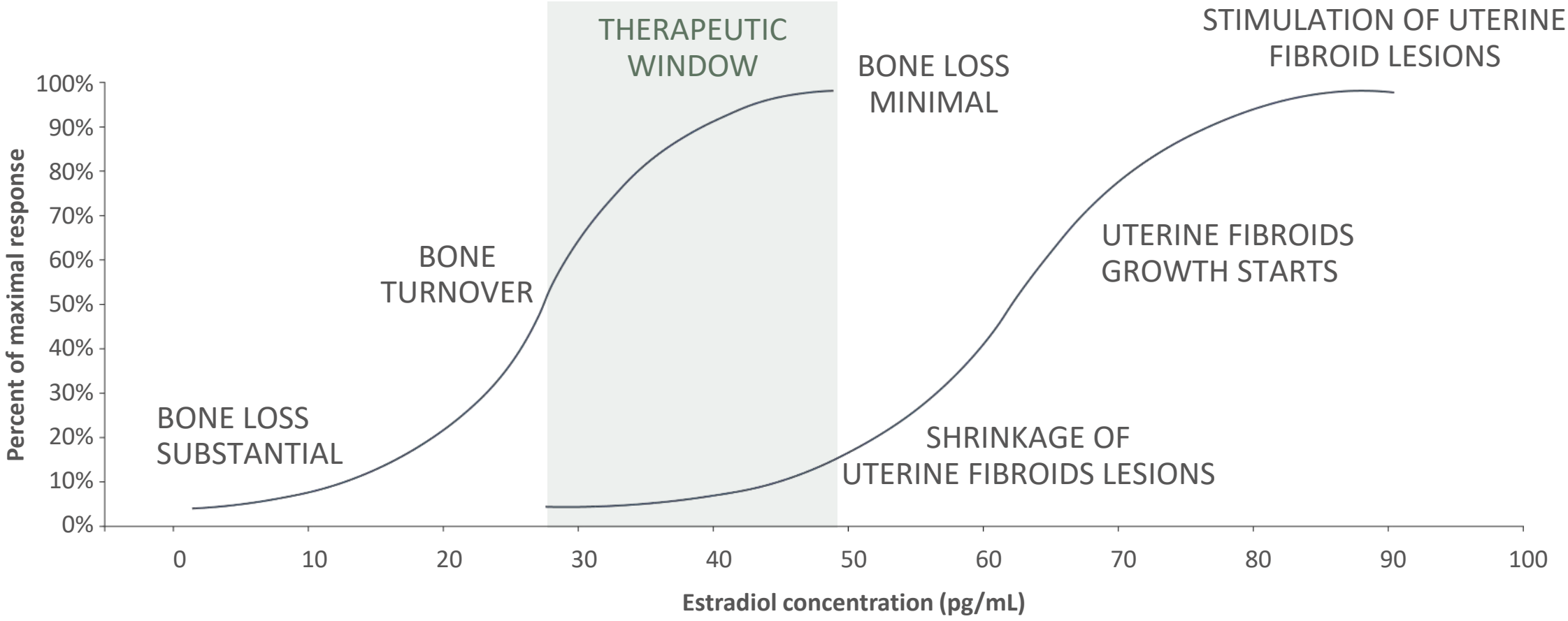
- Phase 3 development in uterine fib
  - 100 mg once-daily monotherapy
  - 200 mg once daily with E2/NETA

FDA Approval 2022?

*estradiol 1 mg / norethindrone acetate 0.5 mg

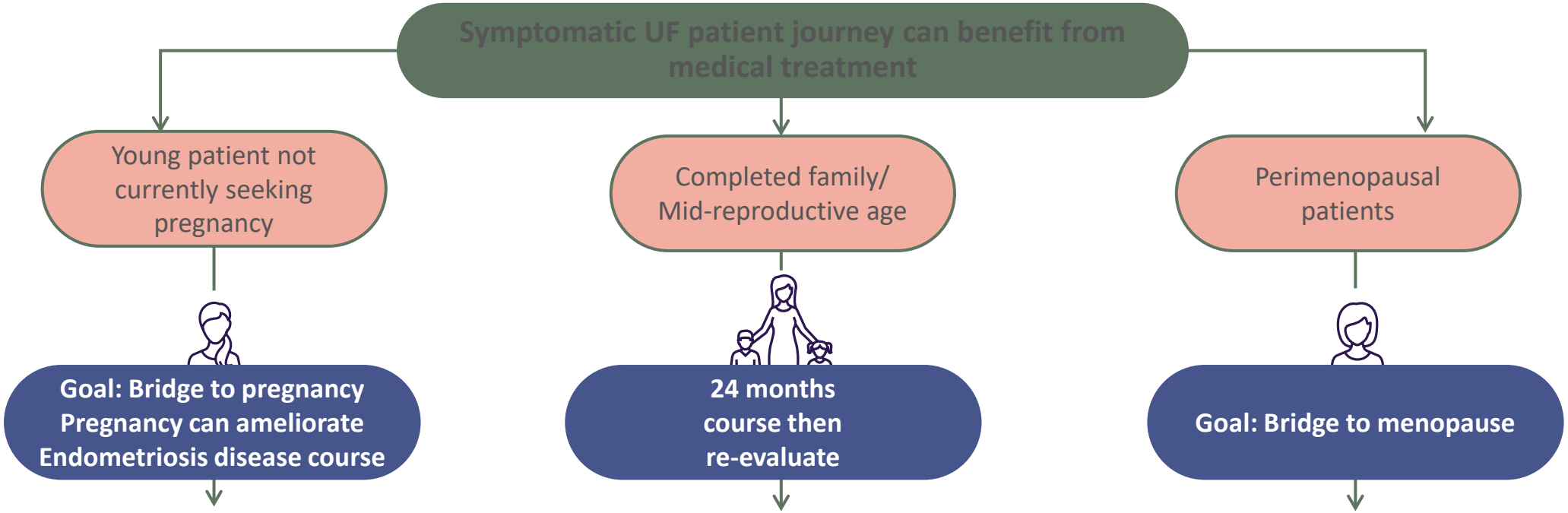
1. Farris M et al. Therapeutics and Clinical Risk Management 2019:15:157-178
2. Elsharoud A et al. Drugs of the Future 2019, 44(2):131-143
3. http://www.jefferies.com/CMSFiles/Jefferies.com/files/ObsEva.pdf

Estradiol Levels Within the Therapeutic Window May Improve Symptoms and Maintain Bone Health



Adapted from Barbieri RL. Am J Obstet Gynecol1992; 166(2):740-745.

Let’s Make Uterine Fibroids a Medical Disease Again!



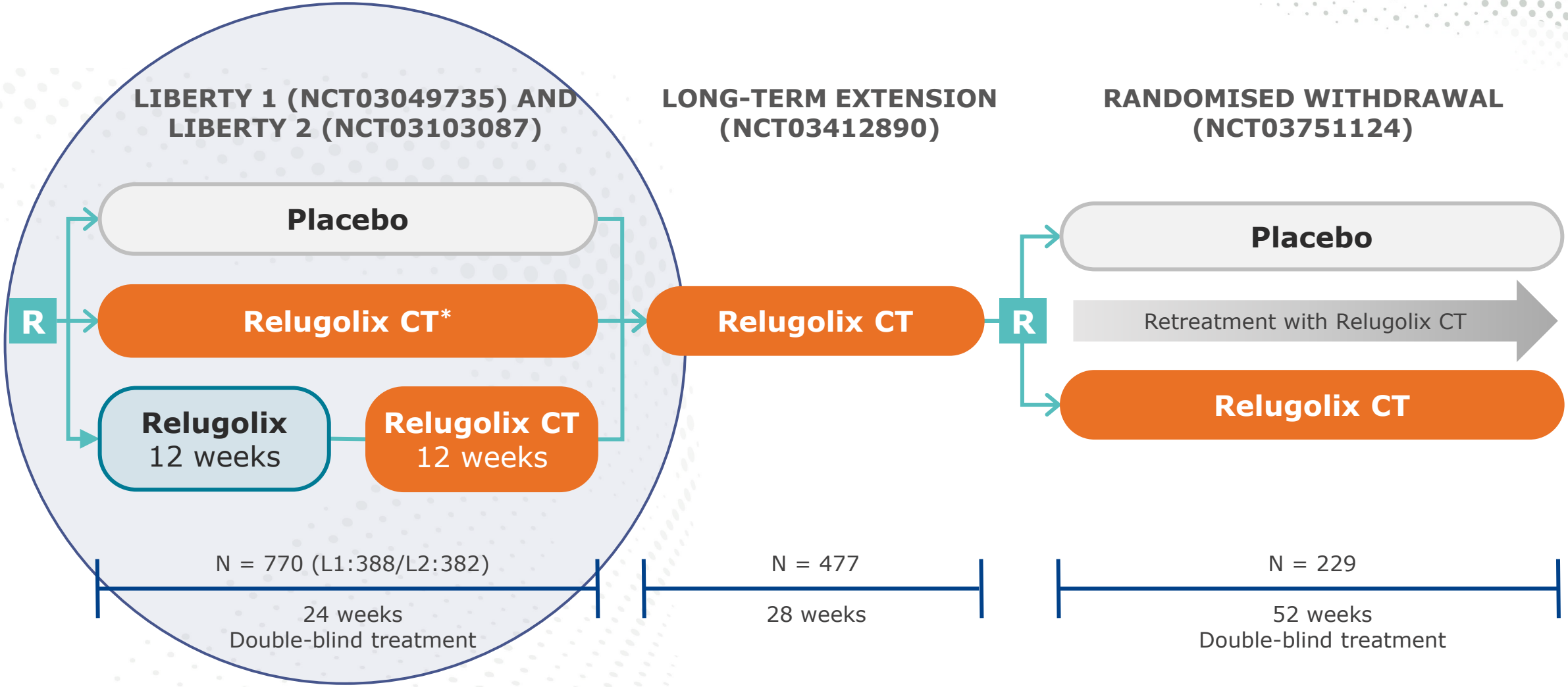
UF, uterine fibroids; US, ultrasound.

1. Laughlin SK, *et al*. *Fertil Steril*. 2010;94(6):2421–2423; 2. Schlaff WD, *et al*. *N Engl J Med*. 2020;382(4):328–340; 3. Al-Hendy A, *et al*. Presented at: American Society for Reproductive Medicine Annual Meeting; October 12–16, 2019; Philadelphia, PA; 4. Taylor H, *et al*. Presented at: ESHRE 36th Virtual Annual Meeting; July 5–8, 2020; 5. Hartmann KE, *et al*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2017 Dec. (Comparative Effectiveness Review, No. 195.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK537742/.

GEDEON RICHTER

Relugolix Combination Therapy in women with symptomatic uterine fibroids

LIBERTY clinical development program



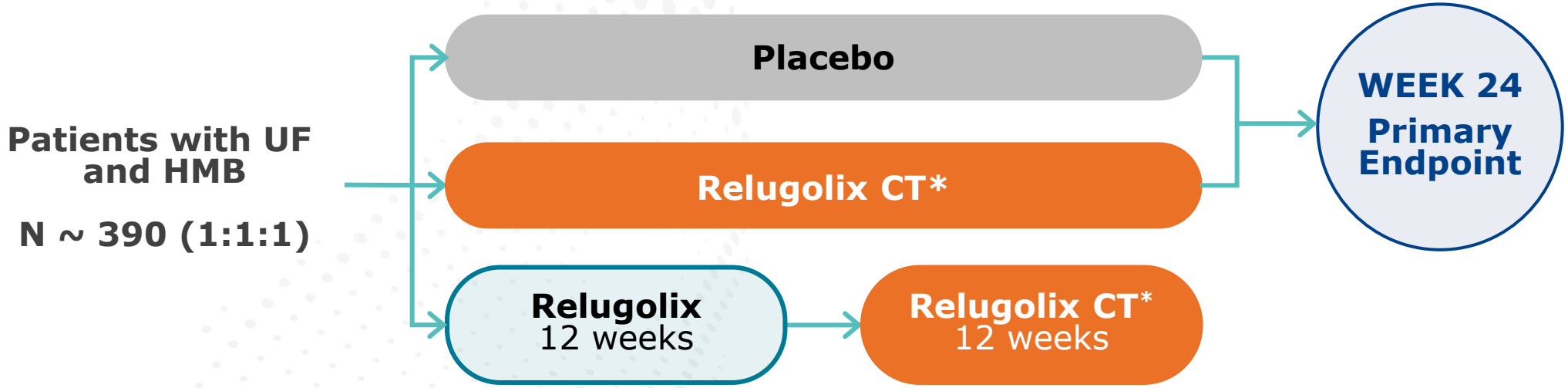
*Relugolix CT, Relugolix Combination Therapy (relugolix 40 mg + estradiol 1.0 mg and norethindrone acetate 0.5 mg)

Al-Hendy A, et al. N Engl J Med 2021;384:630–42

LIBERTY 1 & LIBERTY 2: Phase 3 study design

INCLUSION CRITERIA	**Patients with UF and heavy menstrual bleeding (HMB):** ≥160 mL during one cycle or ≥80 mL during each of two consecutive cycles
PRIMARY ENDPOINT	Proportion of responders with <80 mL menstrual blood loss/cycle and at least a 50% reduction in menstrual blood loss by alkaline haematin method

Objective: To evaluate the efficacy and safety of relugolix 40 mg once daily, administered alone or in combination



Double-blind treatment: **24 weeks**

*Relugolix CT, Relugolix Combination Therapy (relugolix 40 mg + estradiol 1.0 mg and norethindrone acetate 0.5 mg)

L1, LIBERTY Trial 1 (NCT03049735); L2, LIBERTY Trial 2 (NCT03103087)
Al-Hendy A, et al. N Engl J Med 2021;384:630–42

Baseline characteristics (mITT)

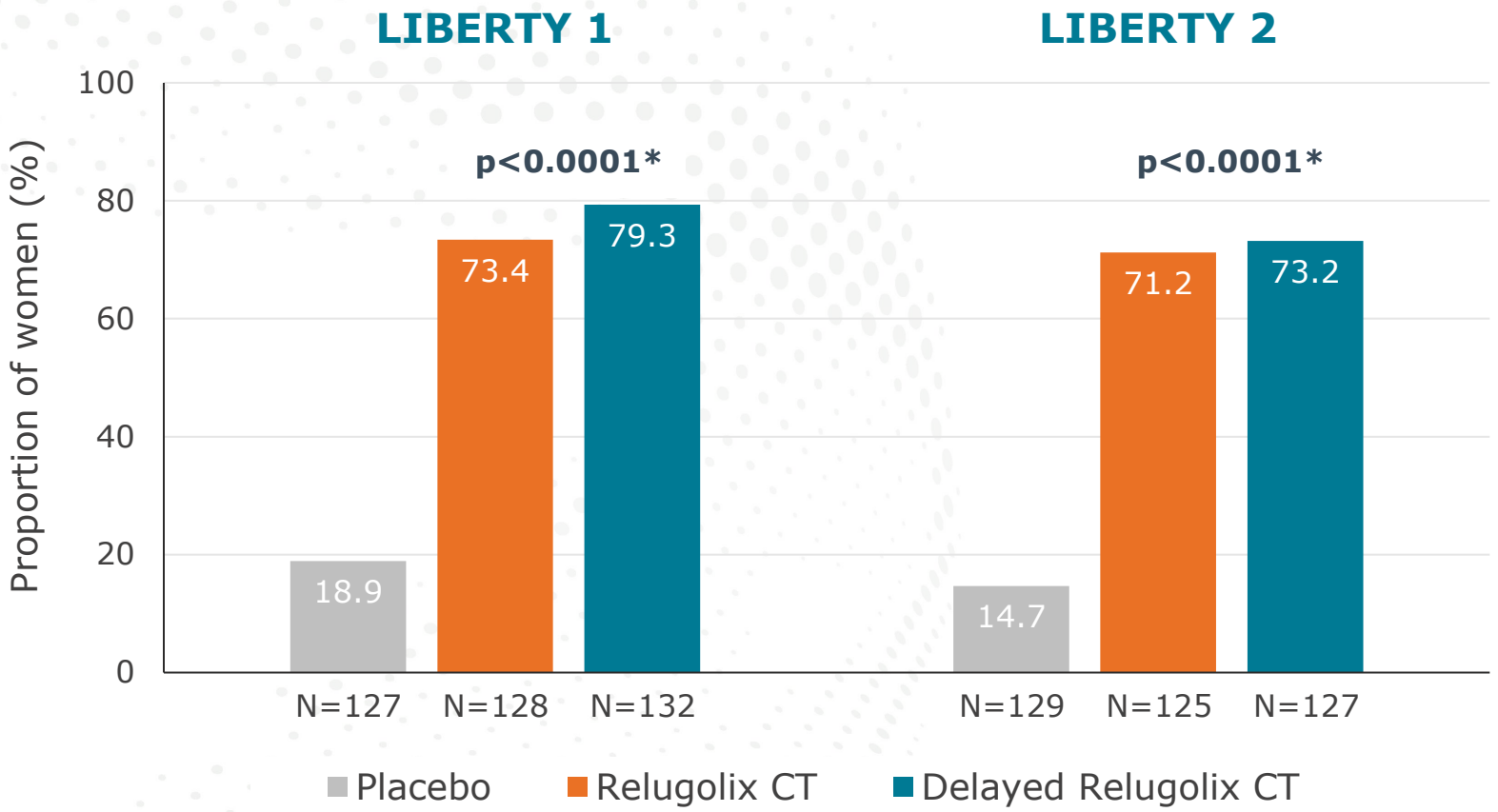
Characteristic	LIBERTY 1 (N=387)			LIBERTY 2 (N=381)		
	Placebo (n=127)	Relugolix CT (n=128)	Delayed Relugolix CT (n=132)	Placebo (n=129)	Relugolix CT (n=125)	Delayed Relugolix CT (n=127)
Mean **age,** years (SD)	42.2 (5.7)	42.5 (5.0)	41.3 (5.4)	41.8 (5.3)	42.4 (5.4)	42.1 (5.3)
Race, n (%)						
Black/African American	65 (51%)	59 (46%)	67 (51%)	74 (57%)	62 (50%)	66 (52%)
White	56 (44%)	64 (50%)	53 (40%)	49 (38%)	58 (46%)	50 (39%)
Other	6 (5%)	5 (4%)	12 (9%)	6 (5%)	5 (4%)	11 (9%)
Mean **BMI,** kg/m^2 (SD)	32.3 (7.5)	31.4 (7.6)	31.4 (7.3)	32.1 (7.6)	31.0 (6.6)	30.8 (5.7)
Mean **MBL,** mL (SD)	219 (125)	239 (180)	229 (160)	212 (130)	247 (186)	227 (134)
Mean **TUV,** cc^3 (SD)	398 (325)	379 (317)	470 (428)	408 (402)	388 (344)	403 (371)

BMI, body mass index; MBL, menstrual blood loss; mITT, modified intention-to-treat; Relugolix CT, Relugolix Combination Therapy; SD, standard deviation; TUV, total uterine volume

Al-Hendy A, et al. N Engl J Med 2021;384:630–42

Relugolix CT improved heavy menstrual bleeding

LIBERTY 1 & 2



Proportion of women responding with:

MBL volume <80 mL

AND

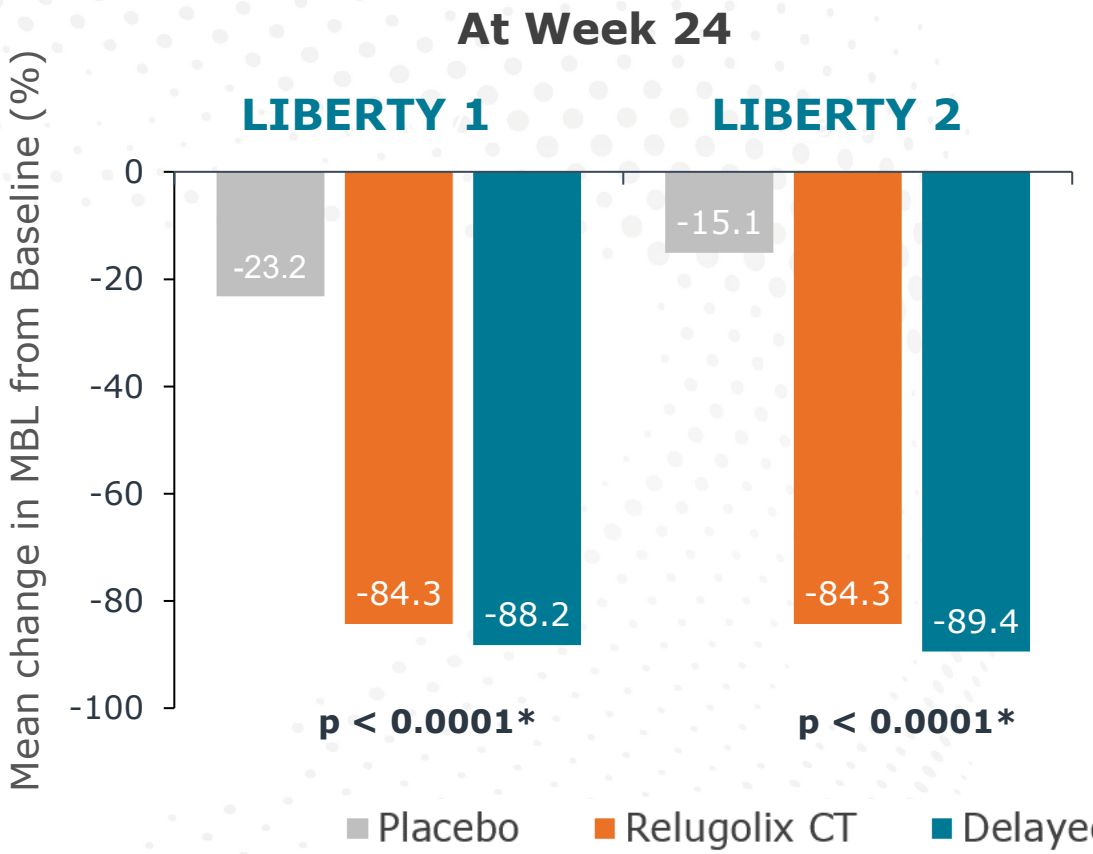
≥ 50% reduction from Baseline to Week 24 (last 35 days of treatment)

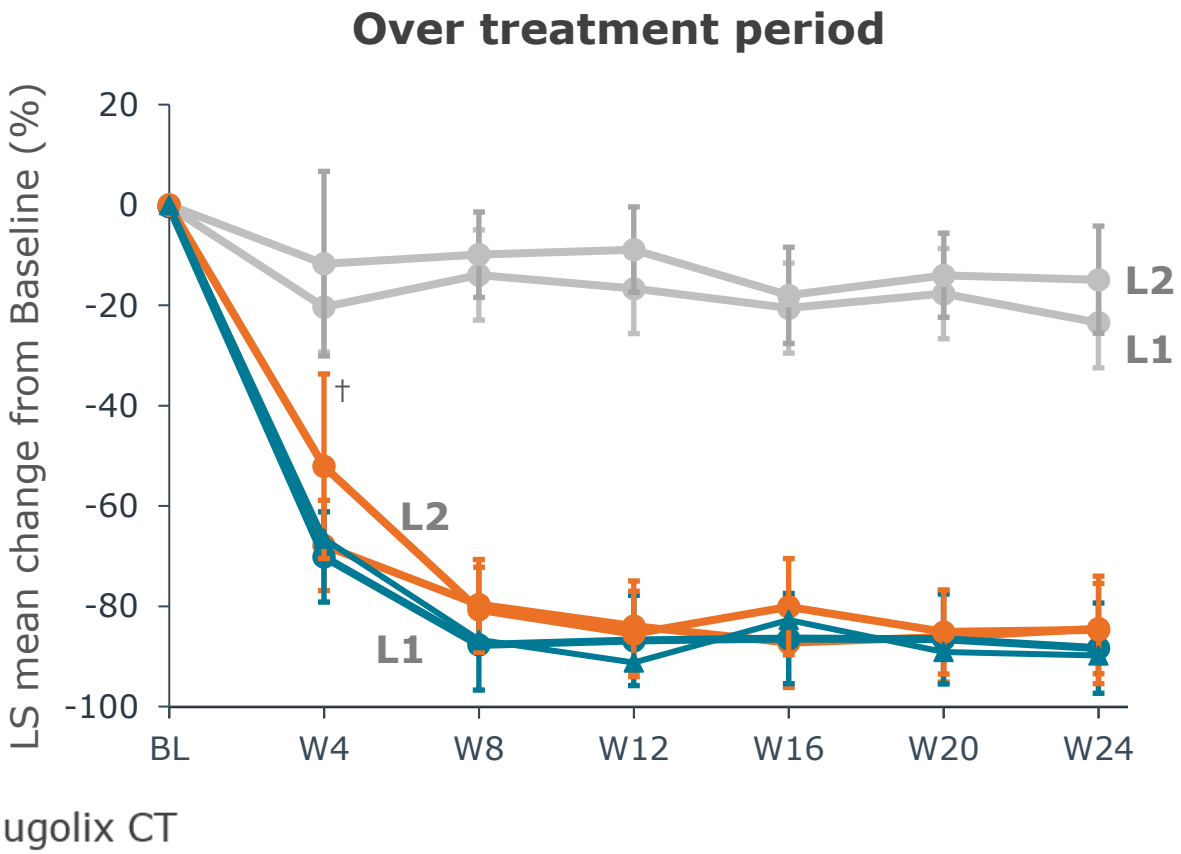
*p-value for comparison between Relugolix CT group and placebo group.
MBL, menstrual blood loss; Relugolix CT, Relugolix Combination Therapy

Al-Hendy A, et al. N Engl J Med 2021;384:630–42

Rapid and significant decrease in menstrual blood loss volume with Relugolix Combination Therapy

LIBERTY 1 & 2





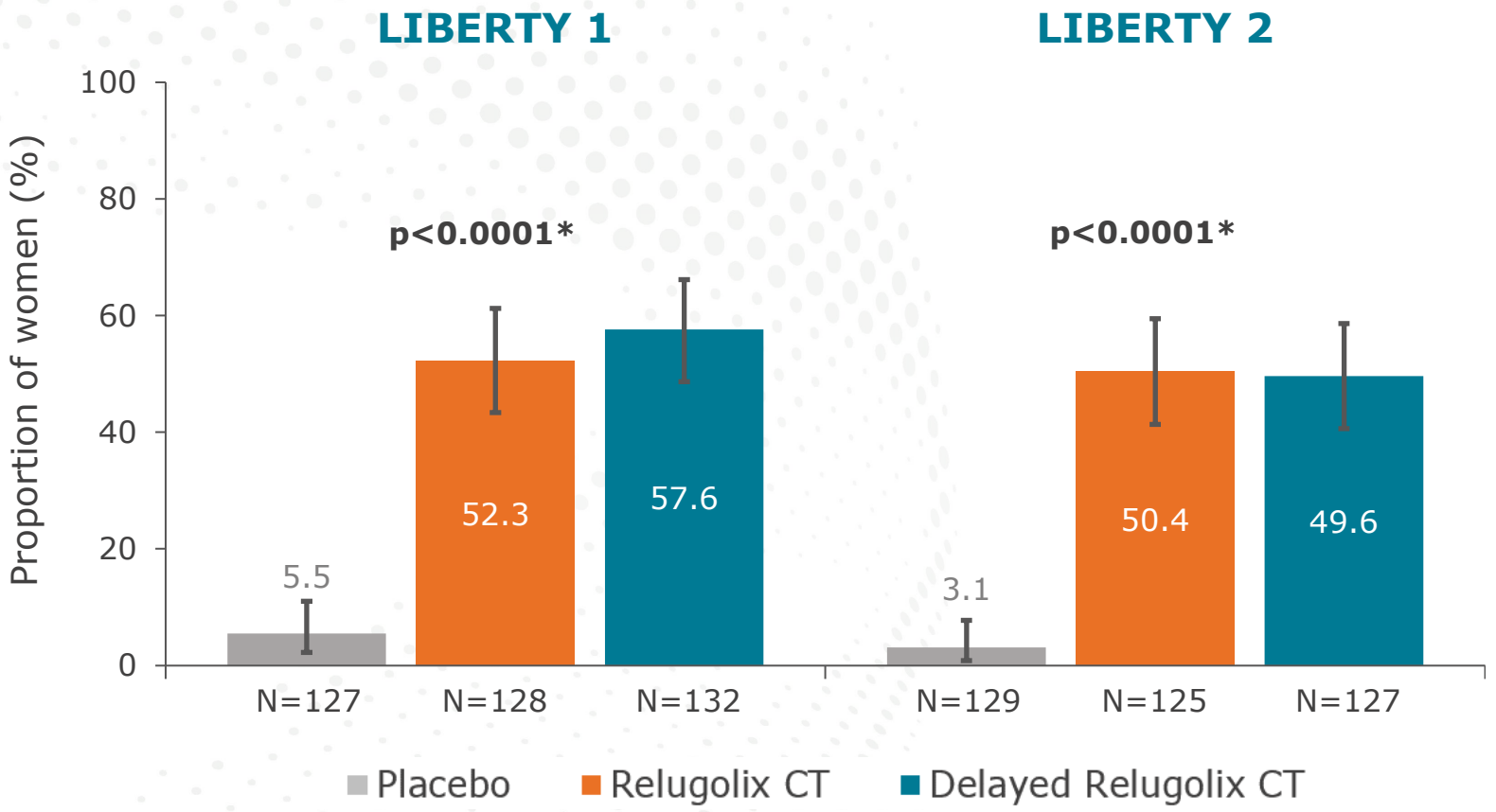
Placebo ■ Relugolix CT ■ Delayed Relugolix CT

†A patient with MBL volume of 2710.3 mL at Week 4 was excluded from the analysis.
*The difference between Relugolix CT and placebo was statistically significant.
BL, Baseline; L1, LIBERTY 1; L2, LIBERTY 2; MBL, menstrual blood loss; W, week

Al-Hendy A, et al. N Engl J Med 2021;384:630–42

Significantly more women achieved amenorrhoea with Relugolix CT

LIBERTY 1 & 2



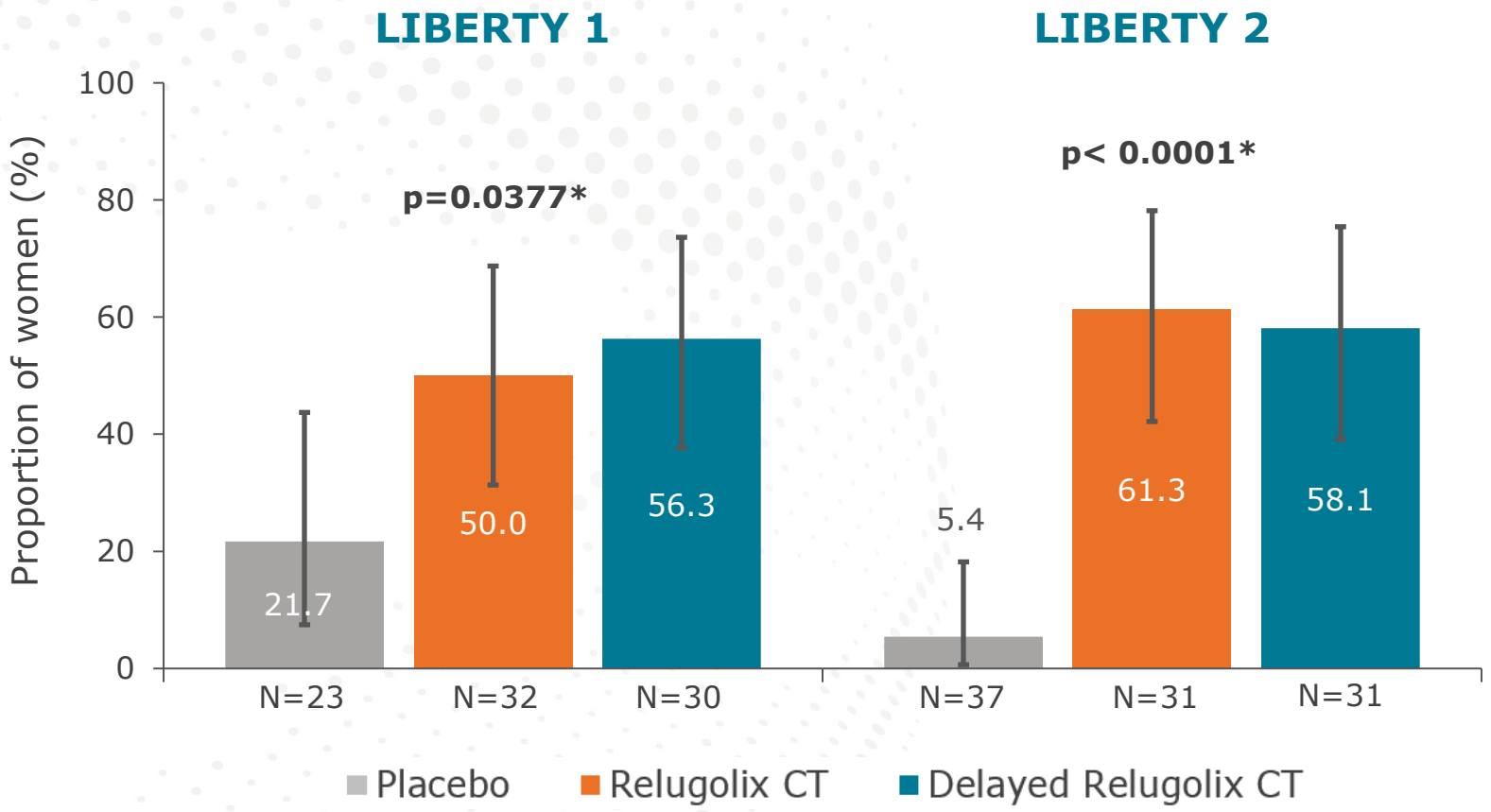
Proportion of women with **amenorrhoea** during the last 35 days of the study

Error bars represent 95% CI.
*The difference between Relugolix CT and placebo was statistically significant (p<0.0001).
CI, confidence interval; Relugolix CT, Relugolix Combination Therapy.

Al-Hendy A, et al. N Engl J Med 2021;384:630–42

Relugolix CT improved haemoglobin levels in women with anaemia at Baseline

LIBERTY 1 & 2



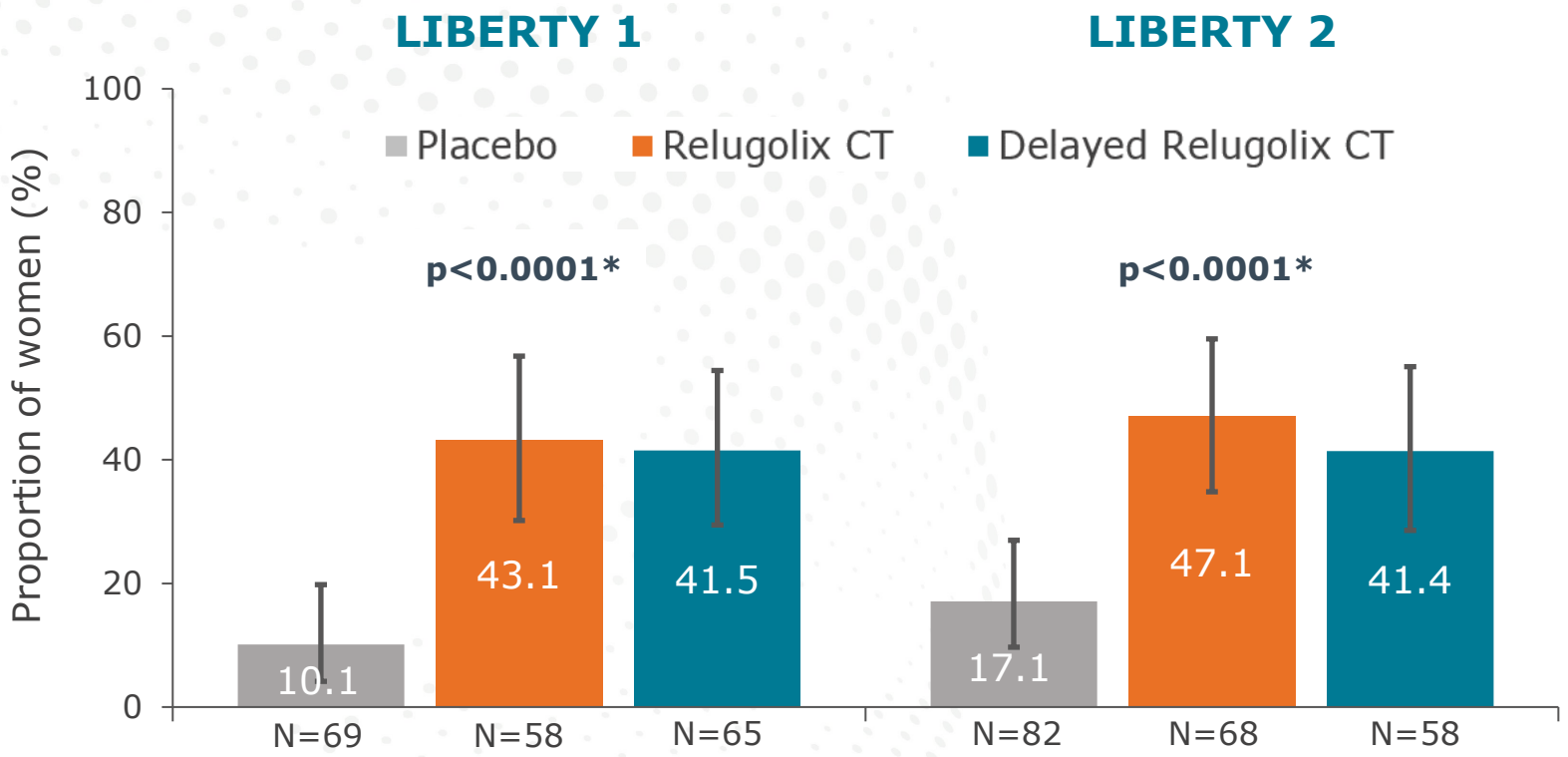
Proportion of women with **haemoglobin** ≤10.5 g/dL at Baseline who achieve an **increase of >2 g/dL** from Baseline to Week 24

Error bars represent 95% CI.
*The difference between Relugolix CT and placebo was statistically significant.
CI, confidence interval; Relugolix CT, Relugolix Combination Therapy

Al-Hendy A, et al. N Engl J Med 2021;384:630–42

Relugolix CT significantly reduced pain associated with UF

LIBERTY 1 & 2



Proportion of women with a maximum **NRS score ≤1** during the 35 days before the last dose of study drug in the pain-evaluable population†

Error bars represent 95% CI.
*The difference between Relugolix CT and placebo was statistically significant (p<0.0001)
†Pain-evaluable population, defined as moderate/ severe pain (NRS ≥4) associated with UF during the 35 days prior to randomisation, at least 28 days of e-diary entries during the last 35 days of treatment.
CI, confidence interval; NRS, numerical rating score; Relugolix CT, Relugolix Combination Therapy; UF, uterine fibroids

Al-Hendy A, et al. N Engl J Med 2021;384:630–42

Summary of adverse events

Adverse event, n (%)	LIBERTY 1 (N=387) Placebo (n=127)	LIBERTY 1 (N=387) Relugolix CT (n=128)	LIBERTY 1 (N=387) Delayed Relugolix CT (n=132)	LIBERTY 2 (N=381) Placebo (n=129)	LIBERTY 2 (N=381) Relugolix CT (n=126)	LIBERTY 2 (N=381) Delayed Relugolix CT (n=126)
Any	84 (66%)	79 (62%)	96 (73%)	76 (59%)	76 (60%)	90 (71%)
Leading to discontinuation	5 (4%)	7 (5%)	16 (12%)	6 (5%)	3 (2%)	14 (11%)
Leading to drug interruption	2 (2%)	2 (2%)	3 (2%)	2 (2%)	1 (1%)	0
Related to study drug	35 (28%)	54 (42%)	70 (53%)	31 (24%)	38 (30%)	74 (59%)
Grade ≥3	11 (9%)	7 (5%)	9 (7%)	8 (6%)	5 (4%)	6 (5%)
Grade ≥3, related*	3 (2%)	3 (2%)	5 (4%)	1 (1%)	2 (2%)	5 (4%)
Serious	2 (2%)	7 (5%)	3 (2%)	4 (3%)	1 (1%)	2 (2%)
Serious, related*	0	2 (2%)	0	0	0	0
Serious leading to discontinuation	0	0	0	1 (1%)	0	0

*Related to study drug. Relugolix CT, Relugolix Combination Therapy

Al-Hendy A, et al. N Engl J Med 2021;384:630–42

Adverse events reported for >5% in any group

LIBERTY 1 & 2

	LIBERTY 1 (N=387)			LIBERTY 2 (N=381)		
Adverse event, n (%)	**Placebo** (n=127)	**Relugolix CT** (n=128)	**Delayed Relugolix CT** (n=132)	**Placebo** (n=129)	**Relugolix CT** (n=126)	**Delayed Relugolix CT** (n=126)
Hot flush	10 (8%)	14 (11%)	47 (36%)	5 (4%)	7 (6%)	44 (35%)
Headache	19 (15%)	14 (11%)	14 (11%)	15 (12%)	11 (9%)	28 (22%)
Hypertension*	0				(4%)	7 (6%)
Arthralgia	4 (3%)				(1%)	8 (6%)
Cough	7 (6%)					1 (1%)
Nausea	6 (5%)				(5%)	4 (3%)
URTI	3 (2%)	1 (1%)	7 (5%)	7 (5%)	6 (5%)	3 (2%)
Anaemia	6 (5%)	4 (3%)	0	8 (6%)	2 (2%)	2 (2%)
Fatigue	5 (4%)	4 (3%)	6 (5%)	2 (2%)	1 (1%)	7 (6%)

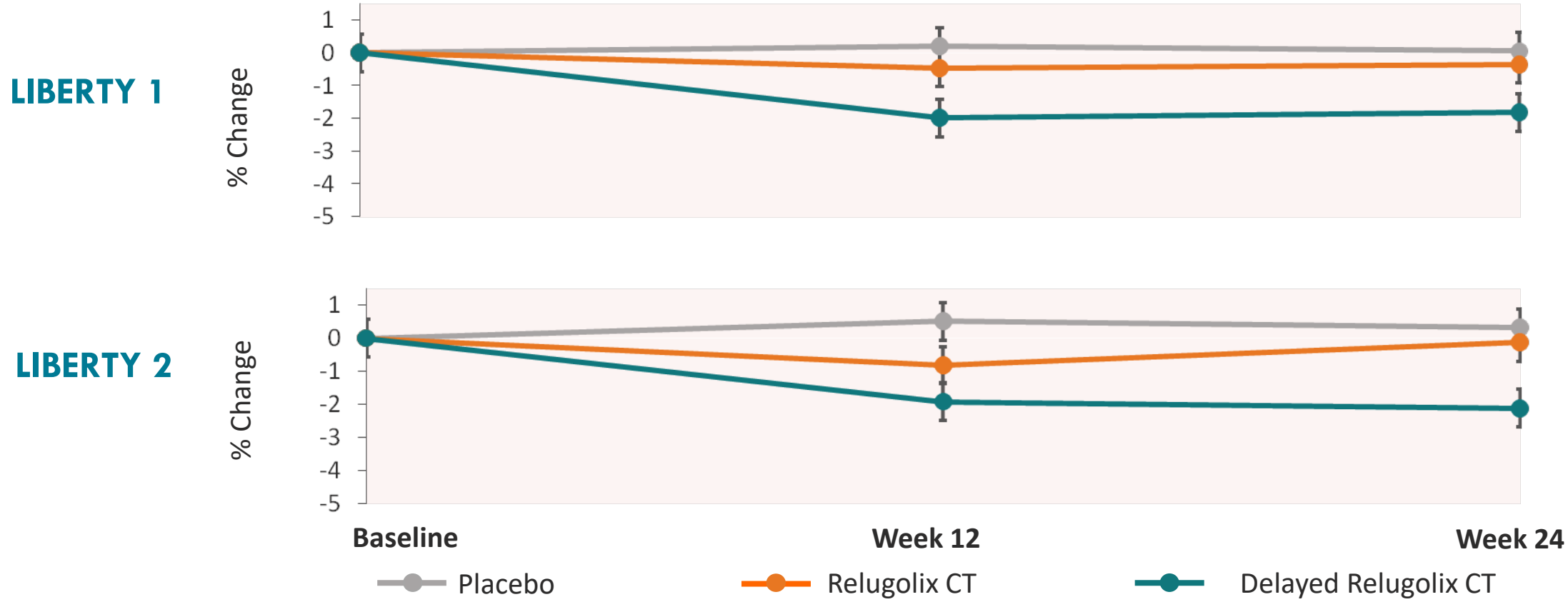
The incidence of adverse events with Relugolix CT was similar to that observed with placebo

*No increase in mean systolic or diastolic blood pressures was observed in study population

Relugolix CT, Relugolix Combination Therapy; URTI, upper respiratory tract infection

Al-Hendy A, et al. N Engl J Med 2021;384:630–42

Bone Mineral Density (BMD) (lumbar spine) at Week 24

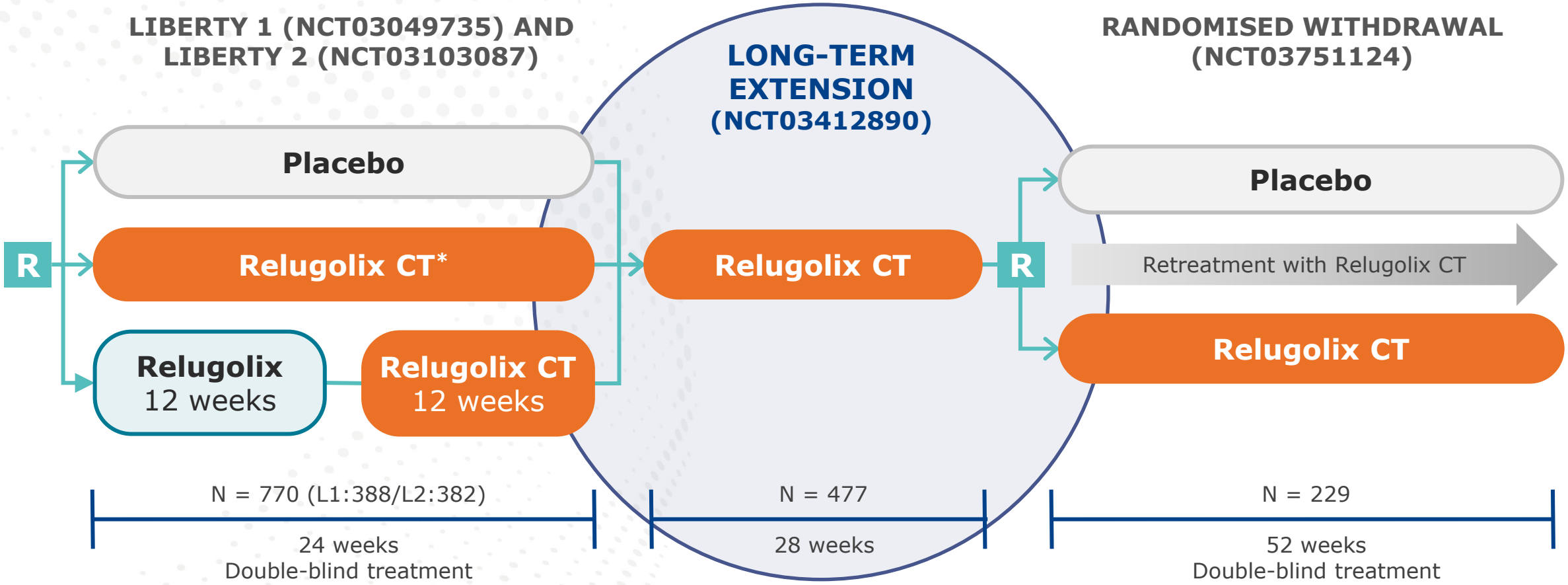


Error bars represent 95% CI.
Least squares means and p value for test of difference of Relugolix CT minus placebo based on mixed-effect model with baseline menstrual blood loss volume, region, age at baseline, body mass index at baseline, bone mineral density at baseline, race, visit, and treatment by visit interaction as fixed effects.
CI, confidence interval; Relugolix CT, Relugolix Combination Therapy.

Al-Hendy A, et al. N Engl J Med 2021;384:630–42

1-year data

LIBERTY clinical development program



Relugolix CT, Relugolix Combination Therapy (relugolix 40 mg + estradiol 1.0 mg and norethindrone acetate 0.5 mg)

Baseline characteristics in the Extension Safety Population were balanced between treatment groups

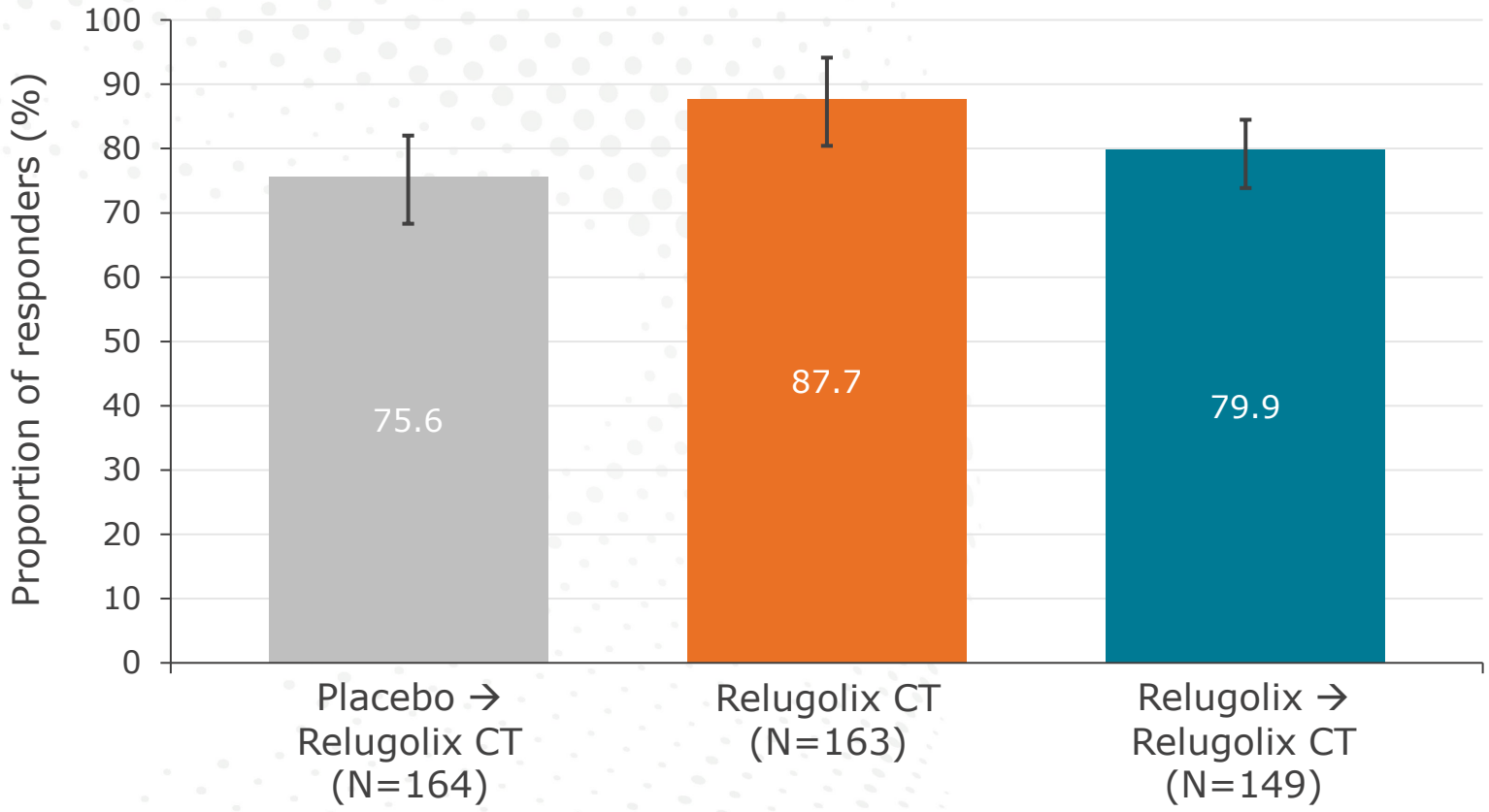
Extension Safety Population

Characteristic	Placebo → Relugolix CT (n=164)	Relugolix CT (n=163)	Relugolix → Relugolix CT (n=149)
Mean **age,** years (SD)	41.9 (5.4)	42.6 (5.1)	42.1 (5.6)
Race, n (%)			
Black/African American	88 (54%)	69 (42%)	81 (54%)
White	71 (43%)	85 (52%)	51 (34%)
Other	5 (3%)	9 (6%)	17 (11%)
Mean **BMI,** kg/m^2 (SD)	32.6 (7.5)	31.4 (7.0)	31.0 (6.4)
Mean **MBL,** mL (SD)	216 (124)	249 (197)	239 (155)
Mean **TUV,** cc^3 (SD)	401 (351)	387 (320)	442 (371)

BMI, body mass index; MBL, menstrual blood loss; Relugolix CT, Relugolix Combination Therapy; SD, standard deviation; TUV, total uterine volume

Al-Hendy A, et al. Fertil Steril 2020;114(3Suppl1):e1 (ASRM 2020, Abstract O-1)

Extension study at Week 52: Responders over the last 35 days of treatment



Proportion of women responding with:

MBL volume <80 mL

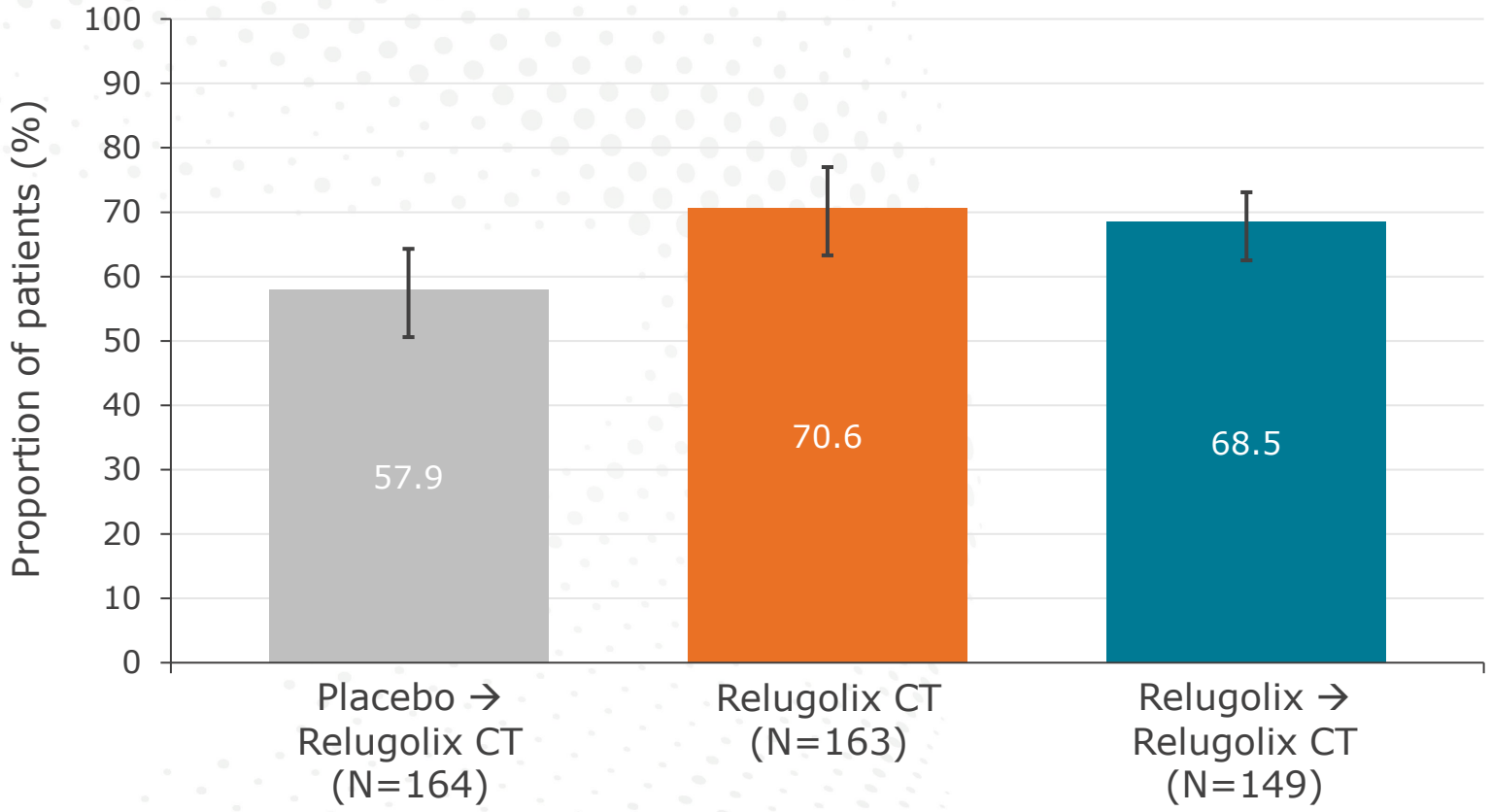
AND

≥ 50% reduction from Baseline to Week 52 (last 35 days of treatment)

Error bars represent 95% confidence intervals
MBL, menstrual blood loss; Relugolix CT, Relugolix Combination Therapy

Al-Hendy A, et al. Fertil Steril 2020;114(3Suppl1):e1 (ASRM 2020, Abstract O-1)

Most patients achieved amenorrhoea at Week 52 in all treatment groups

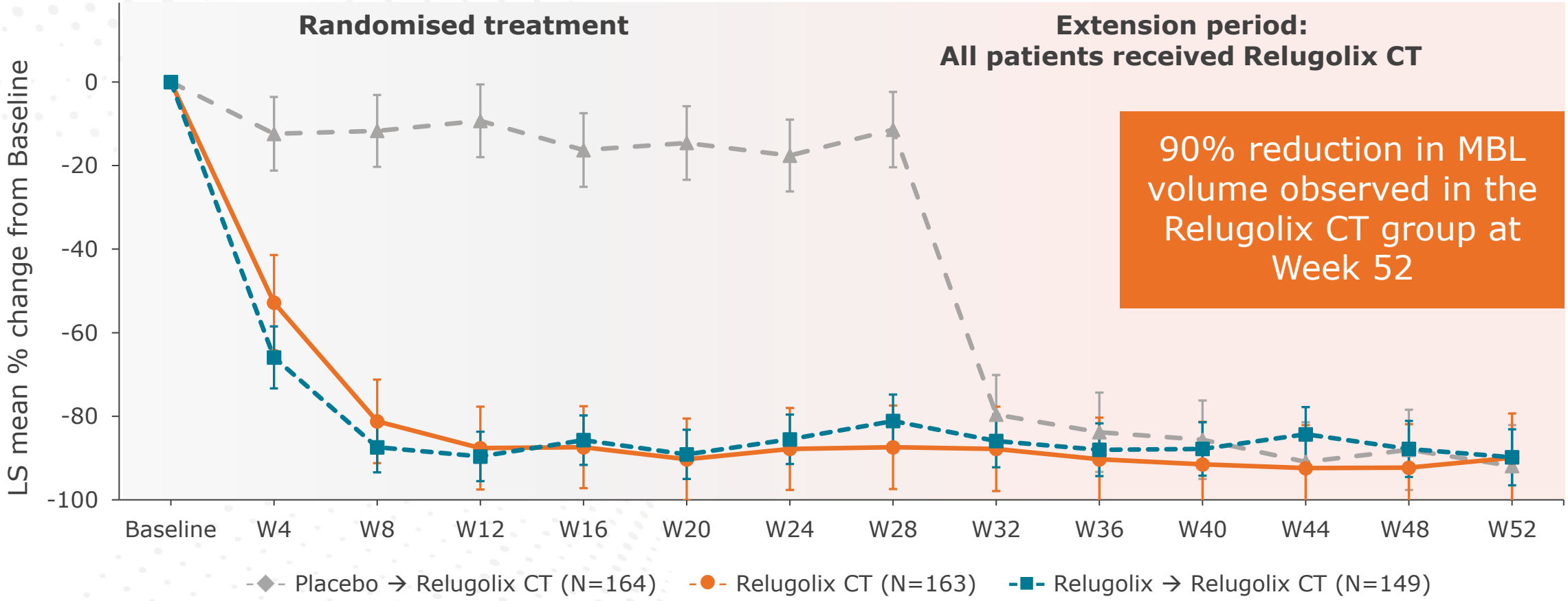


Proportion of women at Week 52 with **amenorrhoea** during the last 35 days of the study

Error bars represent 95% confidence intervals
MBL, menstrual blood loss; Relugolix CT, Relugolix Combination Therapy

Al-Hendy A, et al. Fertil Steril 2020;114(3Suppl1):e1 (ASRM 2020, Abstract O-1)

Menstrual blood loss reduced by 90% at Week 52 (% change from Baseline)



90% reduction in MBL volume observed in the Relugolix CT group at Week 52

Error bars represent standard error of the mean
LS, least squares; N, number of patients in the parent study treatment group; Relugolix CT, Relugolix Combination Therapy; W, week

Al-Hendy A, et al. Fertil Steril 2020;114(3Suppl1):e1 (ASRM 2020, Abstract O-1)

Summary of adverse events reported over 52 weeks of treatment

LIBERTY 3

Extension Safety Population

Adverse events, n (%)	Placebo → Relugolix CT (n=164)	Relugolix CT (n=163)	Relugolix → Relugolix CT (n=149)
Any	138 (84%)	127 (78%)	125 (84%)
Leading to discontinuation	9 (5%)	5 (3%)	5 (3%)
Grade 3 or higher	27 (16%)		
Serious	15 (9%)		
Fatal outcome	0		
Most common AEs (>10%)			
Headache	29 (18%)	21 (13%)	36 (24%)
Hot flush	24 (15%)	18 (11%)	58 (39%)

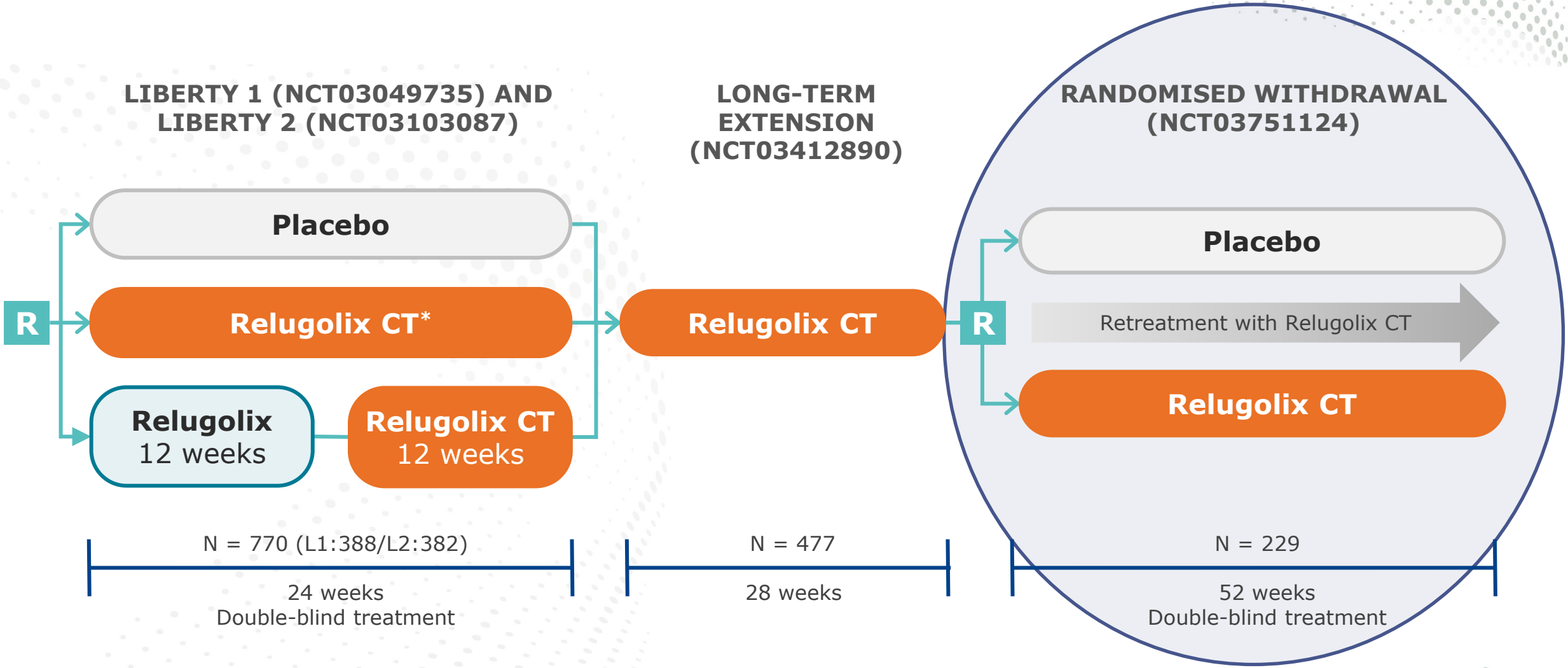
There were no safety signals reported for Relugolix Combination Therapy over 52 weeks of treatment

AE, adverse event; Relugolix CT, Relugolix Combination Therapy

Al-Hendy A, et al. Fertil Steril 2020;114(3Suppl1):e1 (ASRM 2020, Abstract O-1)

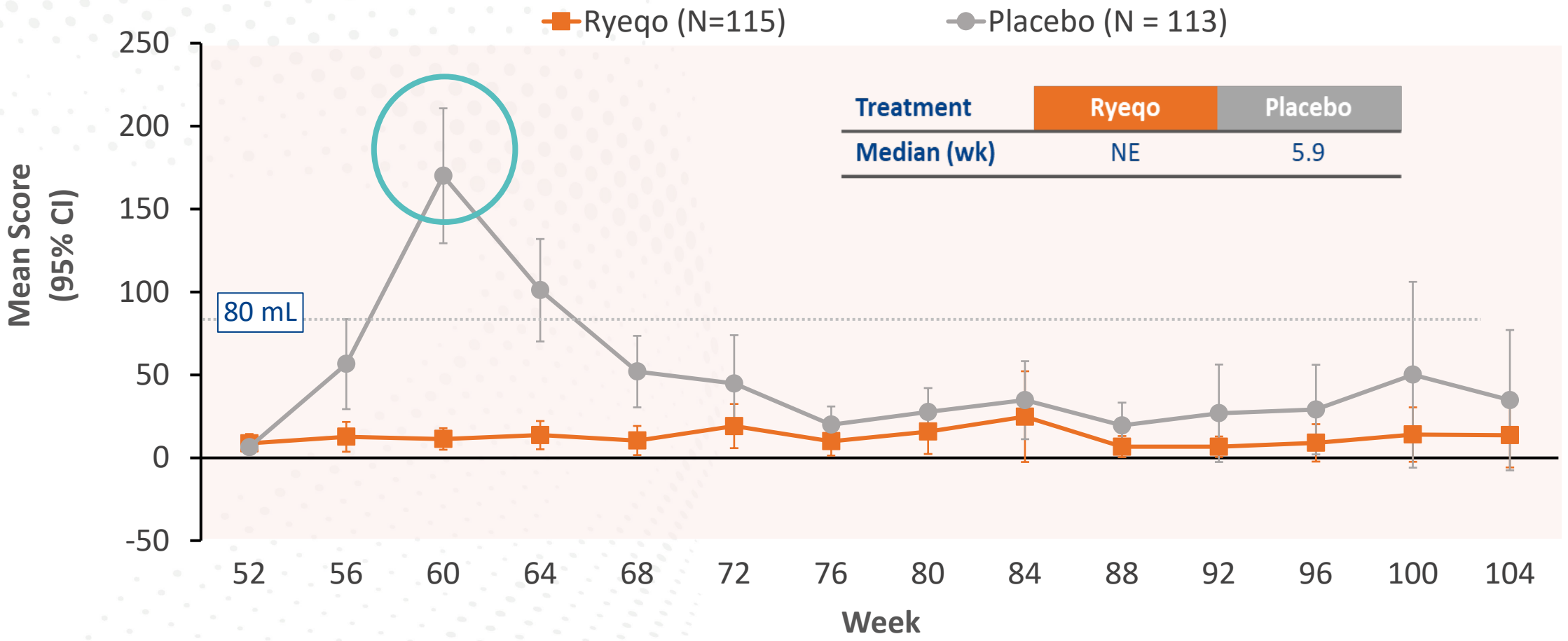
But what about longer term data… ?

LIBERTY clinical development program



*Relugolix CT, Relugolix Combination Therapy (relugolix 40 mg + estradiol 1.0 mg and norethindrone acetate 0.5 mg)

Summary of change in menstrual blood loss volume (mL) over 104 weeks



RWS: randomised withdrawal study

Data on file

Incidence of AEs >5%

Preferred Term, n (%)	Ryeqo (N = 116)	Placebo (N = 112)
No. of patients with at least one AE	68 (58.6%)	72 (64.3%)
Nasopharyngitis	13 (11.2%)	12 (10.7%)
Headache	8 (6.9%)	5 (4.5%)
Dysmenorrhoea		
Hot flush		
Hypertension		
Upper respiratory tract infection		
Pregnancy	0	1 (0.9%)

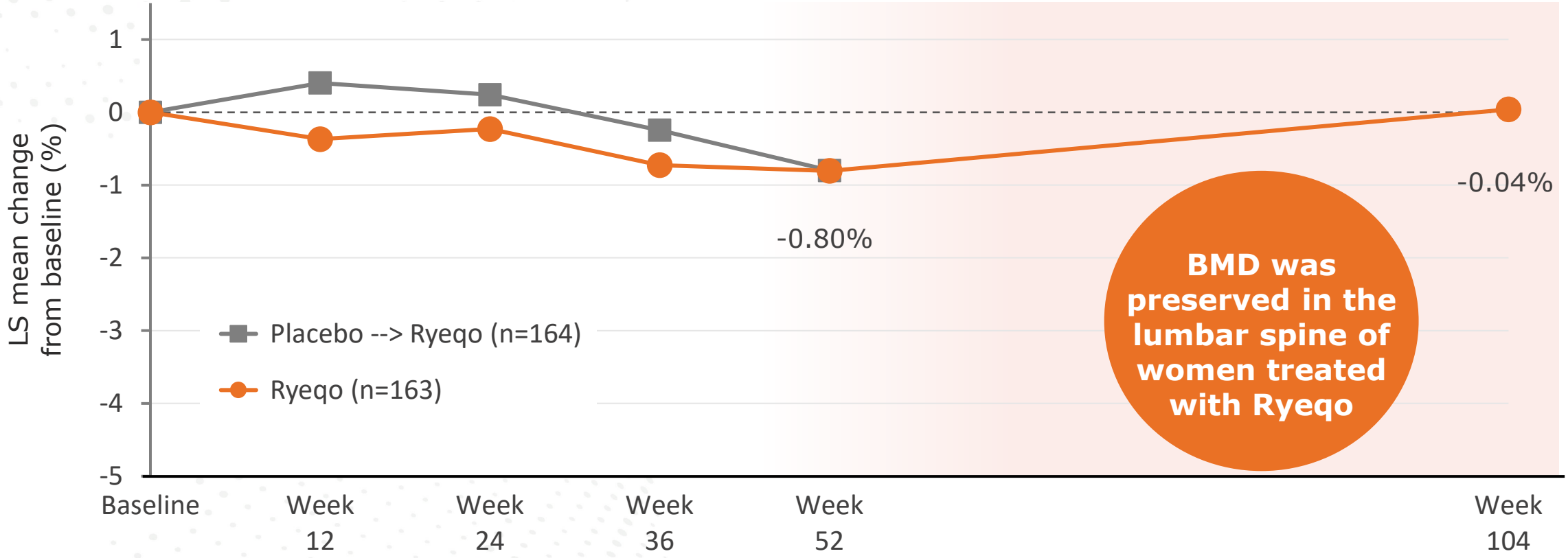
There were no safety signals reported for Relugolix Combination Therapy over 104 weeks of treatment

AE, adverse event; RWS: randomised withdrawal study

Data on file

Influence of 104 weeks of Relugolix CT treatment on lumbar spine **BMD**

RWS



BMD, bone mineral density

[1] Ryeqo SmPC

Conclusions on LIBERTY program

In women with UF, Relugolix CT:

Demonstrated a **statistically significant** ($p<0.0001$) and **clinically meaningful improvement in HMB**, compared with placebo, which were **maintained over 104 weeks of treatment**

- Greater reduction from Baseline in mean **MBL** volume through Week 104, and higher rates of **amenorrhoea**
- **Improvement of pain** in patients with moderate to severe pain at Baseline
- **Improvements in haemoglobin** concentration in patients with anaemia at Baseline
- Improvement in measures of **patient-reported outcomes**
- Reduction in **uterine volume**

Was **generally well tolerated** with an overall incidence of adverse events similar to placebo

- Comparable rate of **hot flush**
- No safety concerns identified with long-term treatment
- **Bone mass** preserved

Relugolix Combination Therapy represents a potential long-term treatment for women with heavy menstrual bleeding associated with uterine fibroids

BMD, bone mineral density; HMB, heavy menstrual bleeding; MBL, menstrual blood loss; Relugolix CT, Relugolix Combination Therapy; UF, uterine fibroids

Al-Hendy A, et al. N Engl J Med 2021;384:630–42; Al-Hendy A, et al. Fertil Steril 2020;114(3Suppl1):e1 (ASRM 2020, Abstract O-1); Data on file (Randomised Withdrawal Study); Al-Hendy A, et al. Fertil Steril 2020;114(3Suppl1):e85 (ASRM 2020, Abstract O-205)

Thank you

Q&A