PART 1
AIC redacted

NICE National Institute for Health and Care Excellence

Relugolix with oestradiol and norethisterone acetate for treating uterine fibroids [ID3842]

Lead team presentation

Chair: Stephen O'Brien

Lead Team: Mike Chambers, Derek Ward, Ugochinyere Nwulu

ERG: Aberdeen HTA group

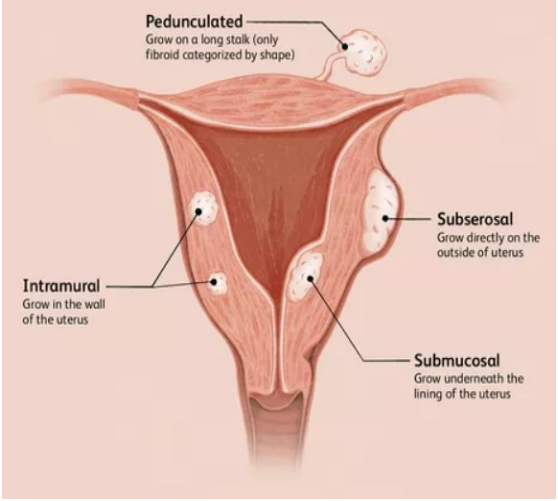
Technical team: Zain Hussain, Louise Crathorne, Ross Dent

Company: Gedeon Richter UK

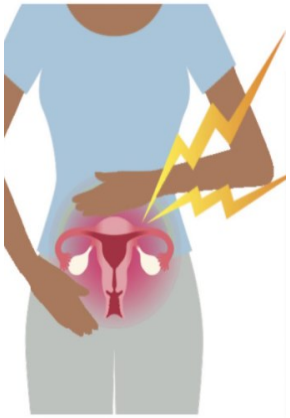
ACM1: 6th April 2022

Disease background

- Uterine fibroids (UF) are non-cancerous growths (myomas or leiomyomas) that develop in or around the uterus
- Although the aetiology of UF is not currently known, their development has been linked to oestrogen
- Fibroids can grow anywhere in the uterus and vary in size from a pea to a melon
- Risk factors for UF include race, age, obesity, having never been pregnant, hypertension, and vitamin D deficiency and diet



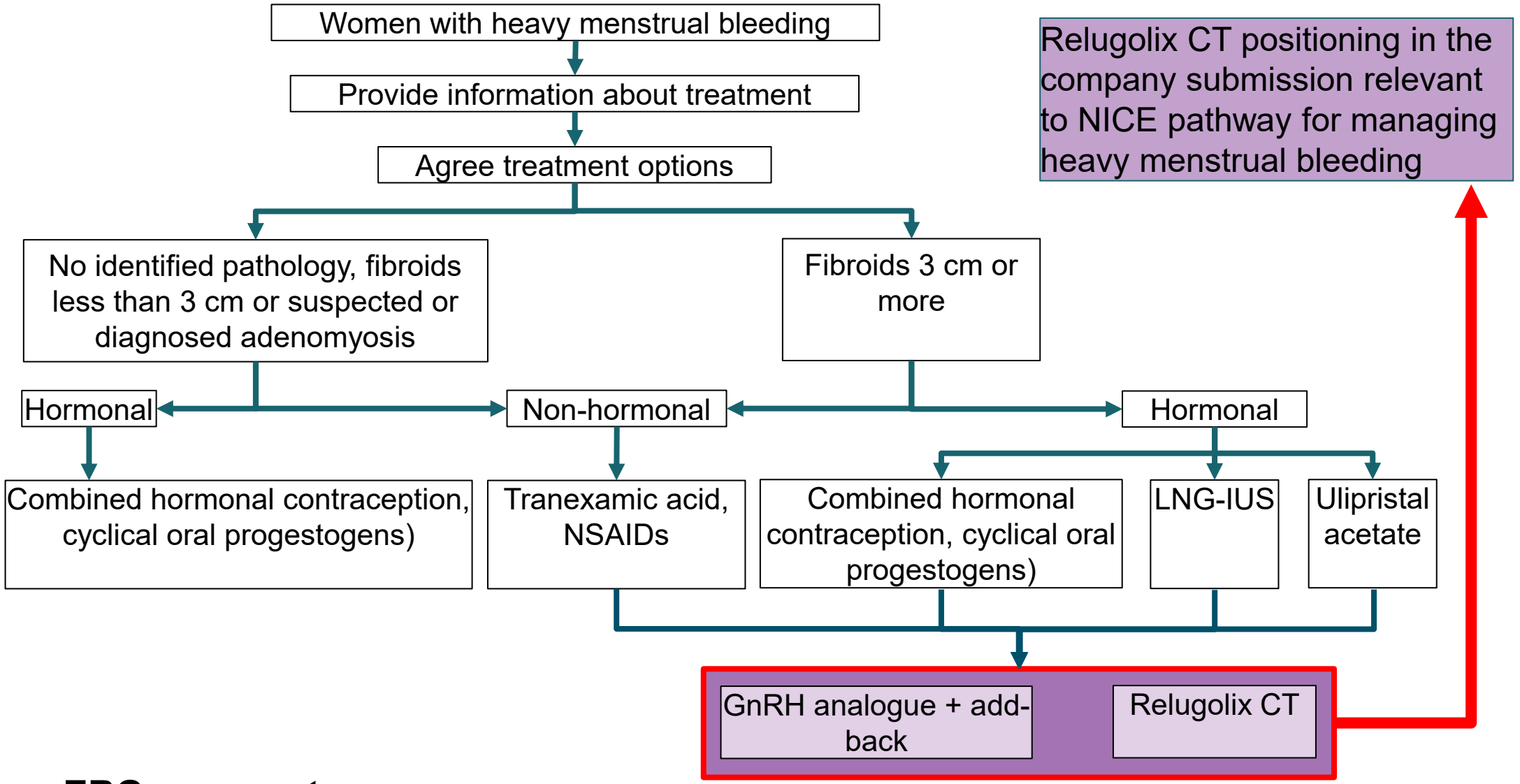
- Three distinct classes of symptoms:
  1. Prolonged or heavy menstrual bleeding
  2. Pelvic pressure and pain
  3. Reproductive dysfunction
- Other symptoms can include:
  - Abdominal pain
  - Frequent need to urinate
  - Constipation
  - Pain or discomfort during sex



- Approximately 1 in 3 women develop UF
- Peak incidence is in women in their 40s
  - 22.5 per 1,000 women-years in 2018
- 15,646 finished consultant episodes for leiomyomas of the uterus in England in 2020/21

UF can pose a significant economic burden to health care providers, patients, and society, due to treatments and also the loss of productivity and working days

Treatment pathway



ERG comment:

- Agree that the company's proposed pathway is representative of current clinical practice and the anticipated positioning of relugolix CT is within its licensed indication

CT: combination therapy; GnRH: gonadotropin-releasing hormone; LNG-IUS: levonorgestrel intrauterine system; NSAIDs: non-steroidal anti-inflammatory drugs

Patient organisation perspective

Submission from Fibroid Embolisation: Information, Support, Advice (FEmISA)

- Women with fibroids manage the significant impact of symptoms without any support
- Current treatment limitations:
  - Treatment of symptomatic fibroids used for short-term before hospital treatment
  - GnRH antagonists cause unacceptable menopausal side effects
    - Also associated with liver failure, thus withdrawn from the market
  - Hysterectomy and endometrial ablation are not options for women wishing to preserve their fertility
- **Unmet need:** A non-invasive, safe and effective treatment associated with low morbidity and mortality and that preserves fertility, sexual function, with minimal side effects and ability to return to work and normal life as quickly as possible
- Uncertain benefits of treatment with relugolix compared with other gonadotropin-releasing hormone (GnRH) antagonists
  - Need for evidence to demonstrate long-term safety, symptom control, impact on liver function and impact on hormone replacement therapy use at menopause
  - Potential use as pre-treatment before myomectomy and in older women near menopause assuming the impact of the use of hormone replacement therapy to treat menopausal symptoms is clear

'The social costs are not considered and should be. Many women have careers that are important to them, as well as juggling family life. They simply cannot afford to take months off work to recover from a very invasive operation, such as hysterectomy, especially if they run their own business'

Relugolix CT (Ryeqo, Gedeon Richter UK)

Mechanism of action	• **Relugolix** is a non-peptide GnRH antagonist that binds to, and inhibits, GnRH receptors in the anterior pituitary gland • **Oestradiol** is a potent agonist of the nuclear oestrogen receptor subtypes • **Norethisterone** is a synthetic progestogen that reduces the oestrogen-induced risk of endometrial hyperplasia in women without hysterectomy
Marketing authorisation (MA)	Indicated for 'the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age' (MA granted 9th August 2021)
Administration	One tablet of relugolix CT (relugolix 40 mg, oestradiol 1 mg and norethisterone acetate 0.5 mg) once daily
List price	£2.57 per 1 tablet of 40 mg/1mg/0.5mg or £72 per pack of 28 tablets or £939.21 per annum) There is no commercial arrangement for relugolix CT

CT: combination therapy; GnRH: gonadotropin-releasing hormone

Decision problem

	NICE scope	Company submission	ERG comment
P	People with moderate to severe symptoms associated with UF	As scope	Populations in LIBERTY trials appropriate, but do not match the comparative PEARL trials
I	Relugolix CT	As scope	Appropriate
C	Hormonal treatments including LNG-IUS, combined hormonal contraception, cyclical oral progestogens and GnRH analogues	Submission focuses on GnRH agonists	Clinical advice: GnRH antagonists more relevant than GnRH agonists. But agreed with company's justification to exclude GnRH antagonists
O	Change in menstrual blood loss (MBL) volume, time to MBL response, pain, uterine fibroid volume / uterine volume, haemoglobin levels, change in bone mineral density, rates and route of surgery, impact on fertility and pregnancy and teratogenic effects, mortality, adverse effects and health-related quality of life (HRQoL)	Outcomes in model include MBL volume, change in MBL volume, adverse effects and HRQoL	• Outcomes in the company submission appropriate. • The indirect treatment comparisons (ITCs) only use results for the mean percentage change in MBL and no results for other relevant outcomes

C: comparator; CT: combination therapy; GnRH: gonadotropin-releasing hormone; I: intervention; LNG-IUS: levonorgestrel intrauterine system; O: outcomes; P: population; UF: uterine fibroids

Key relugolix CT trials

Trial	LIBERTY 1	LIBERTY 2	LIBERTY 3
Design	Phase 3, double-blind, randomised		Open-label, single-arm
Interventions	• Relugolix CT (n=128) • Placebo (n=128) • Relugolix delayed CT (n=132)	• Relugolix CT (n=126) • Placebo (n=129) • Relugolix delayed CT (n=127)	• Relugolix CT (n=477)
Key inclusion criteria	• Premenopausal women aged 18 to 50 years • Regularly occurring menstrual periods of less than 14 days' duration with cycle of 21 to 38 days • Diagnosis of fibroids as confirmed on ultrasonography • Heavy menstrual bleeding, as assessed by the alkaline haematin method		• Completed 24 weeks in LIBERTY 1 or LIBERTY 2 • Negative urine pregnancy test at baseline visit • No expected gynaecological surgery or ablation procedures
Primary outcome	Proportion on relugolix CT vs placebo achieving MBL volume <80ml and ≥50% reduction from baseline MBL volume over last 35 days of treatment		Proportion of women who achieved or maintained primary outcome in LIBERTY 1 and 2
Outcomes used in the model	• MBL volume and change in MBL volume • Adverse events • Quality of life (QoL)		• MBL volume and change in MBL volume • QoL

CT: combination therapy; MBL: menstrual blood loss

Used to inform indirect treatment comparison versus GnRH agonist leuprorelin

LIBERTY 1 and LIBERTY 2 trial results

Endpoint	LIBERTY 1		LIBERTY 2	
	Placebo (n=127)	Relugolix CT (n=128)	Placebo (n=129)	Relugolix CT (n=125)
Primary efficacy endpoint				
Menstrual blood loss (MBL) volume <80 mL & ≥50% reduction*	19%	73%	15%	71%
Secondary efficacy endpoint				
Achieved amenorrhea over the last 35 days of treatment	6%	52%	3%	50%
Percentage change in MBL volume (week 24*): LS mean (SD)	-23.2 (±4.6)	-84.3 (±4.7)	-15.1 (±5.5)	-84.3 (±5.5)
Change in UFS-QoL BPD score (week 24*º): LS mean (SD)	-16.1 (±2.8)	-45.0 (±2.9)	-18.3 (±2.9)	-51.7 (±2.9)
Proportion of women with anaemia at baseline who achieved a haemoglobin increase of > 2 g/dL (week 24*): n/N (%)	5/23 (22%)	15/30 (50%)	2/37 (5%)	19/31 (61%)
Proportion of women who achieved a maximum numerical rating scale score ≤ 1 for UF-associated pain over the last 35 days of treatment in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomisation: n/N (%)	7/69 (10%)	25/58 (43%)	14/82 (17%)	32/68 (47%)
Percentage change in primary uterine fibroid volume (week 24*): LS mean (SD)	-0.3 (±5.40)	-12.4 (±5.62)	-7.4 (±5.9)	-17.4 (±5.9)
Percentage change in uterine volume (week 24*): LS mean (SD)	2.2 (±3.01)	-12.9 (±3.1)	-1.5 (±3.4)	-13.8 (±3.4)

Note: * from baseline, º score as measured by the UFS-QoL (Q1, Q2, Q5).
CT: combination therapy; LS: least-squares; SD: standard deviation; UFS-QoL BPD: uterine fibroid health and symptom-related quality of life bleeding and pelvic discomfort; UF: uterine fibroids

Comparator trial evidence

Trial	PEARL I	PEARL II
Design	Phase 3, double-blind, randomised	
Interventions	• Ulipristal acetate 5mg (n=96) • Ulipristal acetate 10mg (n=98) • Placebo (n=48)	• Ulipristal acetate 5mg (n=97) • Ulipristal acetate 10mg (n=104) • Leuprorelin (n=101)
Key inclusion criteria	• Women aged 18 to 50 years with symptomatic fibroids **with planned surgery** • At least 1 uterine fibroid >3 cm but <10 cm in diameter • Pictorial blood loss assessment chart (PBAC) score >100 during the first 8 days of menstruation • Fibroid uterus of a size equivalent to ≤ 16 weeks' gestation • Body mass index of 18 to 40 kg/m^2 • Haemoglobin <10.2 g/dL – (not a prerequisite for inclusion in PEARL II)	
Key exclusion	• History of uterine surgery, endometrial ablation or uterine artery embolization • Previous or current treatment of fibroids with GnRH agonists or other agents	
Primary outcome	Co-primary endpoints of reduction in uterine bleeding defined as PBAC score less than 75 and change in fibroid volume from baseline to week 13	Proportion of patients with control of uterine bleeding (PBAC score less than 75) at the end of week 13
Secondary outcomes	Fibroid volume, pain, QoL, and haemoglobin levels	Amenorrhoea, pain, and QoL

GnRH: gonadotropin-releasing hormone; QoL: quality of life

PEARL I and PEARL II trial results

PEARL I primary efficacy outcome

	Ulipristal 5mg (N = 95)	Placebo (N = 48)	**Difference, (95% CI), p value**
PBAC score <75 — n/N (%)	86/94 (91)	9/48 (19)	**73 (55 to 83), <0.001**
Percentage change from screening in total fibroid volume, Median (interquartile range)	−21.2 (−41.2 to −1.1)	3 (−19.7 to 23.0)	**−22.6 (−36.1 to −8.2), 0.002**

PEARL II primary efficacy outcome – per protocol population

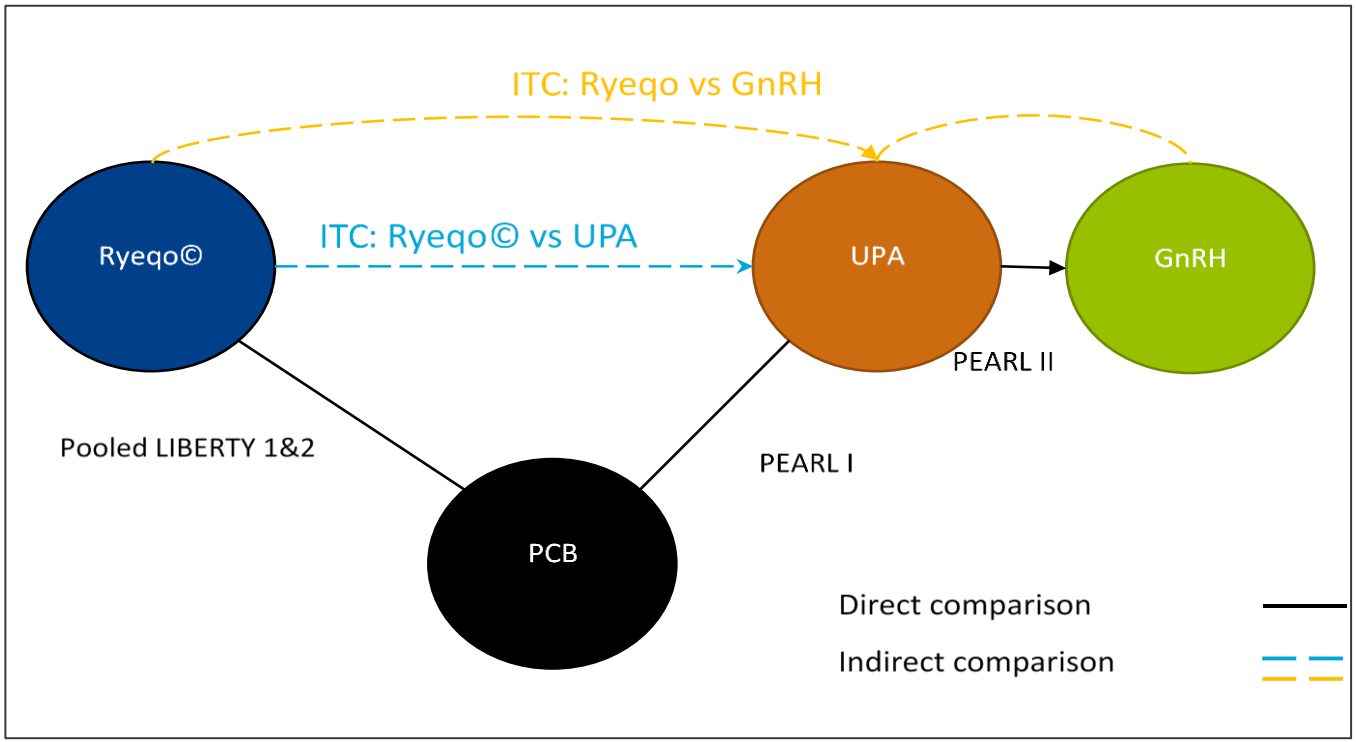
	Ulipristal 5mg (N = 93)	Leuprorelin (N = 93)	**Difference (95% CI)**
PBAC score less than 75 — n/N (%)	84/93 (90)	82/92 (89)	**1.2 (−9.3 to 11.8)**

NICE

CI: confidence interval; PBAC: pictorial blood loss assessment chart

Indirect treatment comparison (ITC) summary

- Company conducted separate indirect treatment comparisons (ITCs) based on evidence from LIBERTY 1, LIBERTY 2, PEARL I and PEARL II trials to inform the comparative effectiveness of relugolix CT versus GnRH agonists
  - PEARL I and PEARL II assessed the efficacy and safety of ulipristal acetate versus placebo and leuprorelin acetate (GnRH agonist) respectively, in the pre-operative treatment of symptomatic UF
- MBL volume used as the only outcome for the ITCs



Company submission document B, Figure 24.

NICE

CT: combination therapy; GnRH: gonadotropin-releasing hormone; MBL: menstrual blood loss; PCB: placebo; Ryeqo: relugolix CT; UF: uterine fibroids; UPA: ullipristal acetate

Outcomes evaluated: Menstrual blood loss

Definition of heavy menstrual bleeding:

- Heavy menstrual bleeding defined as:
  - ≥80 mL or more menstrual blood loss (MBL) or
  - Pictorial blood loss assessment chart (PBAC) score (range from 0 to >500 with higher numbers indicating more bleeding). Greater than 100 points correlated with ≥80 mL MBL. PBAC of >150 points is most often used as an inclusion criterion in studies

Assessment of menstrual blood loss:

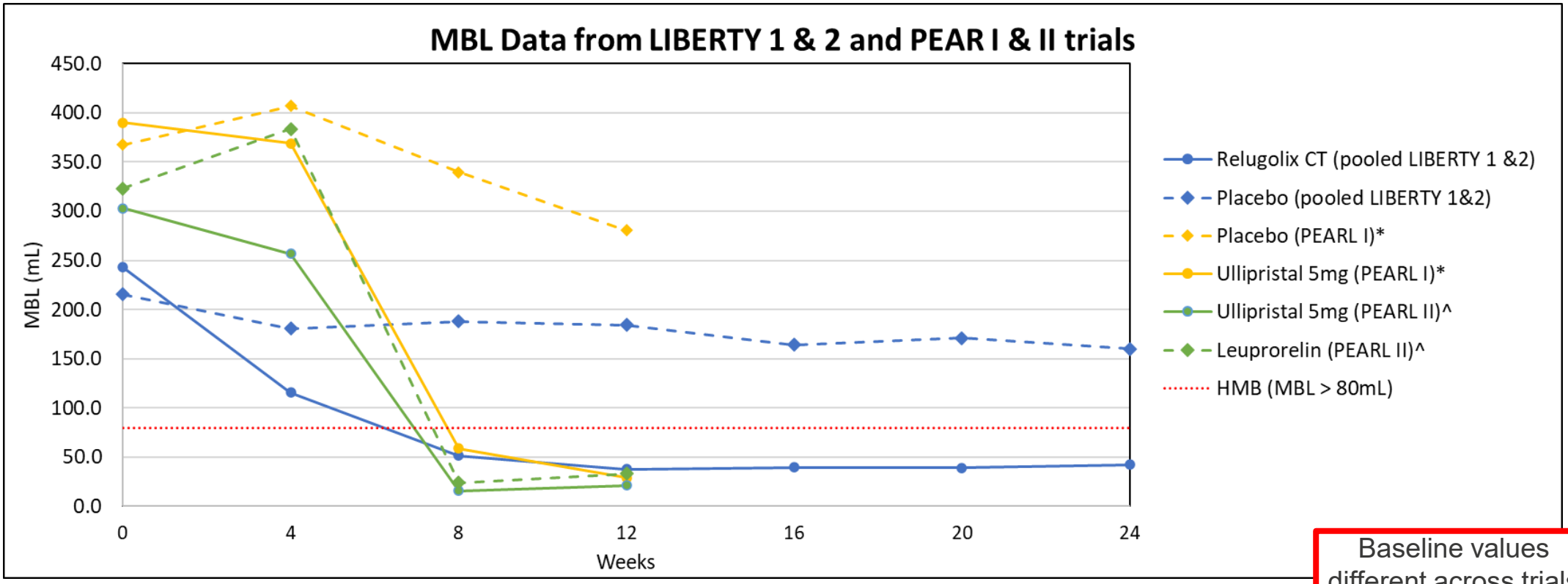
- Alkaline haematin (AH) technique: chemically measuring blood content of used sanitary products is considered the "gold standard" for MBL determination
- Pictorial blood loss assessment chart (PBAC): semiquantitative method for MBL assessment, good correlation to AH (Zakherah 2011)

References: Magnay et al. A systematic review of methods to measure menstrual blood loss. BMC Womens Health 2018; 18:142; Zakherah et al. Pictorial blood loss assessment chart in the evaluation of heavy menstrual bleeding: diagnostic accuracy compared to alkaline hematin. Gynecol Obstet Invest 2011; 71(4):281-284

	LIBERTY 1	LIBERTY 2	LIBERTY 3	PEARL 1	PEARL 2
Assessment of MBL	AH technique			PBAC*	
Outcome assessed	• Proportion of women "responding" → MBL volume of <80 mL + <50% reduction from baseline MBL volume over last 35 days of treatment • LIBERTY 3 extension proportion of women achieving and maintaining MBL volume of <80 mL + <50% reduction from parent study baseline MBL volume over last 35 days of treatment			• Control of uterine bleeding, PBAC score of <75	

* PBAC scores from PEARL I & II were transformed to MBL (alkaline hematin method) using 0.8*PBAC=MBL

LIBERTY 1 & 2 and PEARL I & II MBL data



Baseline values different across trials

Weeks	Relugolix CT (pooled LIBERTY 1 &2)		Placebo (pooled LIBERTY 1&2)		Placebo (PEARL I)		Ulipristal 5mg (PEARL I)		Ulipristal 5mg (PEARL II)		Leuprorelin (PEARL II)	
	n	MBL (mL)	n	MBL (mL)	n	MBL (mL)†	n	MBL (mL)†	n	MBL (mL)†	n	MBL (mL)†
0	253	243.0	256	215.3	48	367.8	95	390.0	93	303.1	93	323.4
4/5**	143	115.8	211	180.8	48	407.0	94	369.1	93	256.9	92	383.7
8/9**	193	51.3	218	187.8	48	339.5	93	58.7	93	15.8	92	24.1
12/13**	195	37.8	203	184.2	36	280.5	82	29.0	90	21.3	90	33.3
16	192	39.8	193	164.1	-	-	-	-	-	-	-	-
20	193	39.2	185	171.0	-	-	-	-	-	-	-	-
24	179	42.2	186	159.9	-	-	-	-	-	-	-	-

* Intention to treat population

^ Per protocol population

† PBAC scores from PEARL I & II were transformed to MBL (alkaline hematin method) using 0.8*PBAC=MBL

** Weeks 4, 8, 12 … LIBERTY 1 & 2 and Weeks 5, 9, and 13 PEARL I & II

CT: combination therapy; MBL: menstrual blood loss; HMB: heavy menstrual bleeding

ITC results

MBL data for relugolix CT, ulipristal and leuprorelin used to derive the ITC results

Week	Relugolix CT			Ulipristal			Leuprorelin		
	MBL (mL)	MBL CFB	% MBL CFB	MBL (mL)	MBL CFB	% MBL CFB	MBL (mL)	MBL CFB	% MBL CFB
0 (baseline)	229.1	-	-	229.1	-	-	229.1	-	-
4	115.8	-113.3	-49%	160.3	-68.8	-30%	231.6	2.5	1%
8	51.3	-177.8	-78%	40.9	-188.2	-82%	32.2	-196.9	-86%
12	37.8	-191.3	-84%	62.3	-166.8	-73%	58.9	-170.2	-74%

CFB: change from baseline; CT: combination therapy; MBL: menstrual blood loss

Baseline values → weighted average of pooled relugolix CT and placebo MBL volume from LIBERTY 1 and 2 = uniform baseline value

ITC results

Mean difference in percentage change from baseline MBL at:	Relugolix CT versus ulipristal	Leuprorelin versus ulipristal	Relugolix CT versus GnRH agonist*
Week 4 – % (95% CI), p-value	-19.4 (-55.3, 16.5), 0.29	31.1 (-52.5, 114.8)	**-50.6 (-141.6, 40.4)**
Week 8 – % (95% CI), p-value	4.5 (-22.6, 31.7), 0.74	-3.8 (-105.0, 97.5)	**8.3 (-96.5, 113.1)**
Week 12 – % (95% CI), p-value	-10.7 (-39.4, 17.9), 0.46	-1.5 (-71.1, 68.1)	**-9.2 (-84.5, 66.0)**

CI: confidence interval; CT: combination therapy; GnRH: gonadotropin-releasing hormone; ITC: indirect treatment comparison; MBL: menstrual blood loss

* Using the ITC results provided by the company, the ERG carried out ITCs comparing relugolix CT versus GnRH agonist (leuprorelin)

Note: Treatment in the PEARL I and II trials was discontinued after week 13.

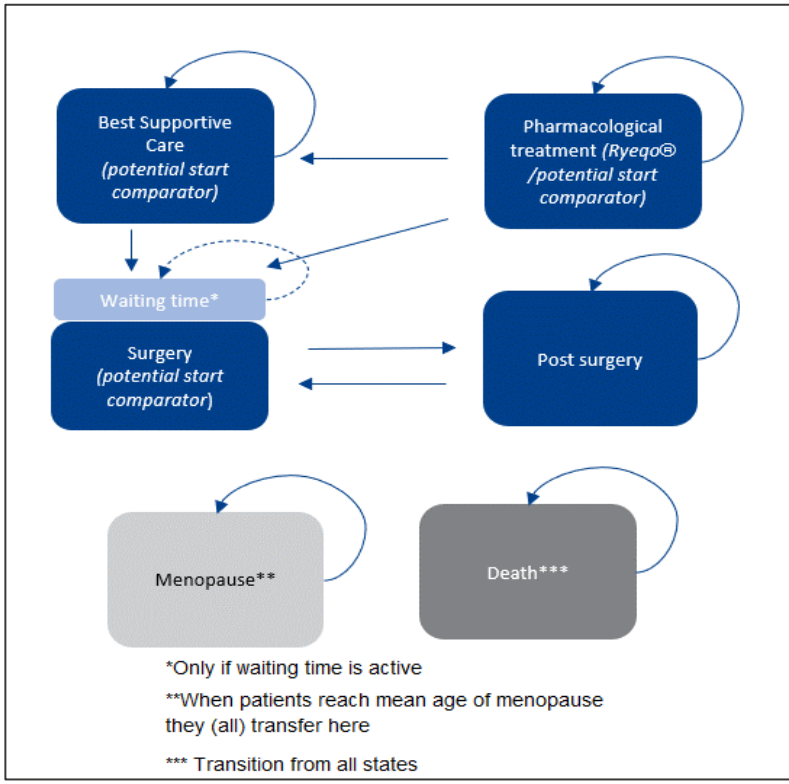
ERG: Agree that relugolix CT and GnRH agonists are equally effective in reducing MBL. However, the wide confidence intervals should be used in the probabilistic analysis

Cost-effectiveness model: summary

- Markov model with mutually exclusive “treatment” states informed by treatment discontinuation assumptions to capture cost and quality-adjusted life year (QALY) implications
- Monthly cycles over a life-time horizon
- It is assumed that all GnRH agonists are equally effective and the company’s fully incremental analysis shows the lowest cost GnRH agonist (monthly goserelin) dominates all other GnRH agonists. Therefore, ICERs for relugolix CT versus goserelin monthly are presented in the company submission

ERG comments:

- Modelling “treatment” states rather than states defined by “health” outcomes not fully justified
- "Health" states e.g. mild, moderate and severe bleeding symptoms or symptom control (controlled, uncontrolled) more appropriate (Nagy et al., 2014)
    - Allows menstrual blood loss data from the LIBERTY and PEARL II trials to be linked directly to treatment received
    - In clinical practice patient management is likely to be based on clinical need, determined by symptom control not necessarily treatment status (on or off)



ERG report, Figure 29.

NICE

CT: combination therapy; GnRH: gonadotropin-releasing hormone; ICER: incremental cost-effectiveness ratio

Key issues post technical engagement

Key issues unresolved post technical engagement	Status	Impact	Slide
Issue 1: Differences between the LIBERTY and PEARL trials in terms of the patient population and the use of relugolix CT and GnRH agonists in UK clinical practice	To discuss		17-21
Issue 2: Lack of formal comparison between relugolix CT and GnRH agonists	To discuss		22-24
Issue 4: Assumptions about treatment discontinuation in UK clinical practice for both relugolix CT and GnRH agonists	To discuss		25-27
Issue 3: The appropriateness of using "treatment" rather than "health" states in the economic model structure	Back up		36-37
Issue 5a: The appropriateness of a 'waiting time' health state post-treatment discontinuation	Back up		38-39
Issue 5b: What constitutes best supportive care in UK clinical practice for patients who discontinue treatment and do not wish to have surgery	Back up		40-41
Issue 6: The role of surgery in the treatment pathway and the lack of data to inform transitions to the surgery health state	Back up		42-43
Issue 7: Uncertainty surrounding the utility function	Back up		44-45
Issue 8: Monitoring and follow up resource use in UK clinical practice	Back up		46-47

Key: Large impact/Model driver  Unknown impact  Small/moderate impact 

CT: combination therapy; GnRH: gonadotropin-releasing hormone

Issue 1: Population: LIBERTY and PEARL Trials

Background

- The population for this appraisal in the NICE scope is 'people with moderate to severe symptoms associated with UF'
- Company's model assumes transition to surgery every month is based on data from PEARL II trial for GnRH agonists, and is applied to both relugolix CT and GnRH agonist arm
- **ERG comments:**
  - Population in the LIBERTY trials does not match that of the PEARL trials, which were used in the ITCs
    - Planned surgery after 13 weeks (PEARL trials) was an exclusion criterion for the LIBERTY trials
  - Surgery rates with relugolix CT highly uncertain
    - Surgery rates not collected in the LIBERTY trials → informed by PEARL II trial where all patients were considered for surgery. Therefore, these rates may be generalisable to women who are unable or do not wish to have surgery
  - Relevant to consider analysis within two different settings:
    1. Women who wish to improve symptoms but do not intend to undergo surgery
    2. Women who have already been listed for surgery

CT: combination therapy; GnRH: gonadotropin-releasing hormone; ITC: indirect treatment comparison; UF: uterine fibroids

Issue 1: Population: LIBERTY and PEARL Trials

Comparison of LIBERTY (relugolix CT) and PEARL II (GnRH agonist) trial data used in the economic model

	LIBERTY trials (relugolix CT)	PEARL II trial (GnRH agonist)
Population size	Pooled Relugolix CT arm: n = 731	Leuprorelin arm: n = 101
Intended use of treatment	Long-term use for women who wish to avoid surgery	Short-term use, in the pre-surgical setting
Duration of treatment discontinuation data available for	24 months	13 weeks
Percentage of women discontinuing treatment	• Month 1-6: 22% (LIBERTY 1 with 24 weeks follow-up) • Month 7-12: [redacted] (LIBERTY 3 with 28 weeks follow-up) • Month 13-24: [redacted] (LIBERTY extension study with 52 weeks follow-up)	6% (6 out of 101 patients withdrew from treatment before end of follow-up)
Measurement of menstrual blood loss	Pictorial blood loss assessment chart (PBAC)	Alkaline haematin (AH) technique
Percentage of women having surgery	Not included as an outcome	45.1% after 13 weeks (54.9% had their surgery cancelled due to symptom resolution)

CT: combination therapy; GnRH: gonadotropin-releasing hormone

Issue 1: Population: LIBERTY and PEARL Trials

Company's technical engagement response:

- The LIBERTY trials and PEARL II comprised similar populations
  - Relugolix CT is not restricted to pre-surgical use but rather as a longer-term treatment option for women who wish to delay or avoid surgery
- GnRH agonists are not used solely as a pre-operative treatment
  - 45.1% of patients in PEARL II had surgery after the 13-week treatment period, with the rest transferring to BSC → PEARL II and LIBERTY treatment arms comparable
- Modelled surgery rate lies within the bounds of available evidence sources:
  - HMB audit: **79%** of target population referred to secondary care and gynaecologist survey: **25% to 100%** of those who discontinue treatment
  - Lowest estimate of surgery rate (25%) produces a cost effective ICER ➔ relugolix CT cost-effective vs GnRH agonist even if surgery removed altogether

BSC: best supportive care; CT: combination therapy; GnRH: gonadotropin-releasing hormone; HMB: heavy menstrual bleeding; ICER: incremental cost-effectiveness ratio; UF: uterine fibroids; vs: versus

Issue 1: Population: LIBERTY and PEARL Trials

ERG's critique of company's technical engagement response:

- Company's positioning for relugolix CT → Women unwilling to have or cannot have surgery
- Marketing authorisation does not prevent relugolix CT use in the pre-surgical setting i.e. similar to GnRH agonist licensed use and their use in PEARL II trial
  - Relugolix CT is cost-effective in a scenario assuming 12 weeks treatment duration before transitioning to surgery (list prices)
    - A cost-minimisation analysis may be appropriate → company's ITC shows equal efficacy between relugolix CT and GnRH agonists
    - ITC for uterine fibroid volume may reduce uncertainty → outcome more indicative of surgical complexity success
- Differing goals of treatment in the LIBERTY and PEARL II trials adds substantial uncertainty to the use of data from PEARL II to inform transition to surgery
- Audit data indicate rate of progression to surgery remains highly uncertain. HMB audit data not comparable to modelled cohort or intended use of relugolix CT
  - Scenario analyses varying the transition to surgery from 0% to 100% illustrates the impact of uncertainty around the base case value on the ICER

CT: combination therapy; GnRH: gonadotropin-releasing hormone; ITC: indirect treatment comparison

Issue 1: Population: LIBERTY and PEARL Trials

Clinical expert comments:

- No direct RCT evidence comparing relugolix CT and leuprorelin acetate
- Relugolix CT could be used long term and also as a pre-surgical treatment to reduce MBL and improve haemoglobin levels, similarly to GnRH agonists for women with anaemia
- Surgery is still an important and dominant choice for women with completed families and failed treatment but some women do not want surgery (e.g. women with BAME backgrounds) and others feel it is the only option due to poor response rates or side effects of available treatments

Patient organisation comments:

- Relugolix CT should not be used for more than 1 year in absence of long-term clinical evidence

- **Does the evidence support the company's positioning of relugolix CT for the treatment of women who do not wish to have or cannot have surgery?**
- **Which transition to surgery rates are most appropriate for decision making – 45.1% (from PEARL) or audit data (79% and range 25% to 100%)?**

BAME: black, asian minority ethnic; CT: combination therapy; GnRH: gonadotropin-releasing hormone; MBL: menstrual blood loss; RCT: randomised controlled trial

Issue 2: Comparison: Relugolix CT vs GnRH agonists

ERG comments:

- Company's justification for not performing a network meta-analysis (NMA) was not considered satisfactory
  - An NMA would have been the most appropriate method
- Participants in the PEARL trials were expected to receive surgery after 13 weeks while those in the LIBERTY trials appear unlikely to be receiving surgery ➔ Suggests two different populations
- Model substantially under-estimates the uncertainty surrounding the company's preferred base case incremental cost-effectiveness ratio (ICER)
  - Point estimates of MBL treatment effect for relugolix CT versus GnRH agonists and best supportive care (BSC): so uncertainty of effect not incorporated into the probabilistic analysis

CT: combination therapy; GnRH: gonadotropin-releasing hormone; ICER: incremental cost-effectiveness ratio; MBL: menstrual blood loss; NMA: network meta-analysis

Issue 2: Comparison: Relugolix CT vs GnRH agonists

Company's technical engagement response:

- Relative efficacy is not a key determinant of cost-effectiveness
  - Assuming that efficacy of relugolix CT is equal to that of GnRH agonists produces a highly cost-effective ICER
- Full NMA would not have been more informative
- Analysis which assumed transitivity between changes in MBL from baseline between trials, was more transparent
  - An NMA including 14 timepoints, at which MBL measurements are used to derive utility values, would be required to provide inputs for the economic model
- ITCs of other outcomes were not feasible

Clinical expert comments:

- The LIBERTY trials show a significant reduction in MBL and improvement in haemoglobin levels for relugolix CT versus placebo, both of which are clinically relevant
- Lack of a formal comparison between relugolix CT and GnRH agonist make it difficult to compare outcomes between these therapy options

Patient organisation comments:

- No direct evidence that relugolix CT is superior with fewer side effects to another GnRH agonist or that it is more acceptable to women

BSC: best supportive care; CT: combination therapy; GnRH: gonadotropin-releasing hormone; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; MBL: menstrual blood loss; NMA: network meta-analysis

Issue 2: Comparison: Relugolix CT vs GnRH agonists

ERG's critique of company's technical engagement response:

- To provide a comprehensive assessment of the efficacy and safety of relugolix CT an ITC of other outcomes included in both the NICE final scope and the company decision problem should be considered the minimum requirement
- Outcomes should have been compared separately and not only as part of a composite outcome
  - i.e UFS-QoL capturing UF symptoms such as pain and pelvic discomfort
  - ITCs of UFS-QoL, or UFS-QoL mapped to EQ-5D utilities were not reported
- The company, by having access to all data collected in LIBERTY and PEARL trials, could have overcome some of these problems ➔ If it was not possible to use these data to inform relevant ITCs then appropriate data should have been obtained
- In the absence of direct ITC versus GnRH agonist, the ERG needed to re-produce the company's ITC to obtain standard errors for probabilistic analysis

In the absence of direct comparative evidence, are the company's ITCs appropriate?

CT: combination therapy; EQ-5D: euroqol-five dimension; GnRH: gonadotropin-releasing hormone; ITC: indirect treatment comparison; UF: uterine fibroids; UFS-QoL: uterine fibroid health and symptom-related quality of life

Issue 4: Treatment discontinuation

Background

- Company uses relugolix CT discontinuation data from the LIBERTY trials with modification based on clinical expert opinion and GnRH agonist discontinuation data from PEARL II
- **ERG comments:**
  - Adjustment based on subjective judgment
  - LIBERTY trials provide 24 months follow up versus 3 months from PEARL II
  - Important impact on ICER, due to impact on:
    - Treatment acquisition costs
    - Costs of follow-on treatment (best supportive care / surgery)
    - Duration of treatment benefits of relugolix CT
  - Prefer treatment discontinuation from the trials to ensure consistency between modelled costs and treatment benefit with relugolix CT

CT: combination therapy; GnRH: gonadotropin-releasing hormone; ICER: incremental cost-effectiveness ratio

Issue 4: Treatment discontinuation

Company's technical engagement response:

- Relugolix CT discontinuation rates in the model demonstrate good face validity
- 45% of discontinuations in LIBERTY 1 and 2 were indicated as being due to patient choice
  - Likely that a good proportion of discontinuations in LIBERTY 1 and 2 were due to the inconvenience of the alkaline haematin collection method for measuring MBL
  - After the initial 6 months, the model predicts discontinuation rates largely in line with the long-term discontinuation rates of relugolix CT rollover patients recruited to LIBERTY 3

Treatment discontinuation in ERG's base case model (ERG report, Figure 4)

- No published data are available on treatment discontinuation rates for GnRH agonists
  - Long-term treatment for UF is off-licence
  - Expert opinion: 7 UK gynaecologists provided evidence for treatment discontinuation

CT: combination therapy; GnRH: gonadotropin-releasing hormone; MBL: menstrual blood loss; UF: uterine fibroids

Issue 4: Treatment discontinuation

Clinical expert comments:

- Comparative trial most appropriate to ascertain treatment discontinuation rates

ERG's critique of company's technical engagement response:

- Treatment discontinuation should be modelled using the trial data
  - Relugolix CT discontinuation data from LIBERTY withdrawal study extrapolated for the remainder of the model time horizon to the age of menopause
  - Company has not provided Kaplan-Meier data to explore the impact of alternative time to treatment discontinuation approaches on the company's base case
- Company's technical engagement response implies discontinuation due to patient choice was excluded
  - Implies that discontinuation of relugolix CT may be substantially higher than that included in the company's economic model. But limited information provided by the company to explain this.
- Acceptable to extrapolate GnRH agonist discontinuation data beyond 6 months using KOL opinion
  - no published evidence on the long-term off license use of GnRH agonists

Which discontinuation rates should be used in the economic model?

CT: combination therapy; GnRH: gonadotropin-releasing hormone; KOL: key opinion leader

Other considerations – Innovation

Company position:

- Relugolix CT meets the unmet need for an effective, non-surgical treatment that can be administered orally and on a long-term basis which offers improved and sustained symptom relief with good tolerability while preserving the uterus and the fertility of patients
- LIBERTY 1 and LIBERTY 2 trials demonstrate substantial reduction in symptoms and incidence of adverse events ➔ LIBERTY 3 and LIBERTY withdrawal study support the long-term use of relugolix CT to 1 and 2 years, respectively

Clinical expert:

- Relugolix CT is a step change treatment of heavy menstrual bleeding due to UF
- Addresses many unmet needs and benefits in the care of patients with heavy menstrual bleeding due to UF
- Fewer contacts with healthcare provides for menstrual problems saving quality time for patients and medical staff, which is very important in women from lower socio-economic class and BAME group

- **Is relugolix CT an innovative treatment of moderate to severe symptoms of UF?**
- **Are there any additional benefits with relugolix CT that have not been captured?**

BAME: black, asian and minority ethnic; CT: combination therapy; UF: uterine fibroids

Other considerations – Equality

Company position:

- Women of Black African and African-Caribbean origin are 2-3 times more likely to develop UF than white women
    - Due to cultural and religious beliefs, they may be more opposed to surgery than white women, and thus, non-surgical interventions such as relugolix CT may provide a more suitable treatment option for this group
- Non-surgical interventions provide a more suitable treatment option for women who decline the option of surgery to avoid impacting work and family commitments

Clinical expert:

- Relugolix CT will reduce time and expenditure for BAME women in attending hospitals as compared to use of leuprorelin acetate that requires a visit to GP or gynaecologist. These visits are of significant cost (time and financial) to patients in lower socio-economic level which may increase the 'did not attend' rate to clinics.

Patient organisation:

- There should be equality of esteem with men's conditions. Men do not normally have prostatectomies unless they have progressive cancer, but women have their uterus and other reproductive organs removed often against their wishes

Are there any equality issues relevant to this appraisal?

BAME: black, asian and minority ethnic; CT: combination therapy; GP: general practitioner; UF: uterine fibroids

Cost-effectiveness results – list prices

Results with confidential discounts shown in Part 2

Total	Total costs (£)	Total QALYs	Incr. costs	Incr. QALYs	ICER (£/QALY)
Company's deterministic base case					
Goserelin monthly[1]	7,742	16.53	-	-	-
Relugolix CT	9,854	16.90	2,112	0.36	**5,796**
Company's probabilistic base case					
Goserelin monthly[1]	7,729	16.53	-	-	-
Relugolix CT	9,850	16.89	2,120	0.37	**5,808**
ERG's deterministic base case					
Goserelin monthly[1]	6,379	16.97	-	-	-
Relugolix CT	6,573	17.04	194	0.07	**2,795**
ERG's probabilistic base case					
Goserelin monthly[1]	6,376	16.96	-	-	-
Relugolix CT	6,573	17.03	197	0.07	**2,833**

[1] Company assumes that all GnRH agonists are equally effective and incremental analysis shows the lowest cost GnRH agonist (goserelin monthly) dominates all other GnRH agonists. Hence, ICERs for relugolix CT versus goserelin monthly are presented

CT: combination therapy; ICER: incremental cost-effectiveness ratio; Incr.: incremental; QALY: quality-adjusted life year

ERG's analysis: cost minimisation assumptions^

ERG scenarios	Treatment	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£)
ERG preferred base case	Goserelin monthly[1]	£6,379	16.97			-
	Relugolix CT	£6,573	17.04	+£194	+0.07	**£2,795**
1. Equal effectiveness on treatment (equalise utilities)*	Goserelin monthly[1]	£6,379	16.99			-
	Relugolix CT	£6,573	16.97	+£194	+0.02	10,014
2. Equal discontinuation rates	Goserelin monthly[1]	£6,631	16.97			-
	Relugolix CT	£6,573	17.04	-£58	+0.06	Dominant
3. 2 + transition to surgery in both arms equalised	Goserelin monthly[1]	£6,613	17.00			-
	Relugolix CT	£6,573	17.04	-£39	+0.06	Dominant
4. 1 + 2 + 3	Goserelin monthly[1]	£6,613	16.97			-
	Relugolix CT	£6,573	16.99	-£39	+0.01	Dominant
5. Equal adverse events	Goserelin monthly[1]	£6,376	16.98			-
	Relugolix CT	£6,573	17.04	+£198	+0.06	£3,370
6. Cost minimisation analysis (combined 1+2+3+4)	Goserelin monthly[1]	£6,608	16.99			-
	Relugolix CT	£6,573	16.99	-£34	+0.00	**N/A**

^ Applied to ERG's base case analysis, # Results include list prices for all treatments

* Incremental QALYs are different because treatment discontinuation in the short-term differs between the arms

[1] Company assumes that all GnRH agonists are equally effective and incremental analysis shows the lowest cost GnRH agonist (monthly goserelin) dominates all other GnRH agonists. Hence, ICERs for relugolix CT versus monthly goserelin are presented

CT: combination therapy; ICER: incremental cost-effectiveness ratio; Incr.: incremental; QALY: quality-adjusted life year

Key issues post technical engagement

Key issues unresolved post technical engagement	Status	Impact	Slide
Issue 1: Differences between the LIBERTY and PEARL trials in terms of the patient population and the use of relugolix CT and GnRH agonists in UK clinical practice	To discuss		17-21
Issue 2: Lack of formal comparison between relugolix CT and GnRH agonists	To discuss		22-24
Issue 4: Assumptions about treatment discontinuation in UK clinical practice for both relugolix CT and GnRH agonists	To discuss		25-27
Issue 3: The appropriateness of using "treatment" rather than "health" states in the economic model structure	Back up		36-37
Issue 5a: The appropriateness of a 'waiting time' health state post-treatment discontinuation	Back up		38-39
Issue 5b: What constitutes best supportive care in UK clinical practice for patients who discontinue treatment and do not wish to have surgery	Back up		40-41
Issue 6: The role of surgery in the treatment pathway and the lack of data to inform transitions to the surgery health state	Back up		42-43
Issue 7: Uncertainty surrounding the utility function	Back up		44-45
Issue 8: Monitoring and follow up resource use in UK clinical practice	Back up		46-47

Key: Large impact/Model driver  Unknown impact  Small/moderate impact 

CT: combination therapy; GnRH: gonadotropin-releasing hormone