NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Relugolix–estradiol–norethisterone acetate for treating moderate to severe symptoms of uterine fibroids [ID3842]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Relugolix–estradiol–norethisterone acetate for treating moderate to severe symptoms of uterine fibroids [ID3842]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Gedeon Richter

2. **Clarification questions and company responses**
   a. Clarification response
   b. Further response to Clarification question B9
   c. Updated cost-effectiveness results
   d. PEARL I and PEARL II menstrual blood loss results by visits

3. **Patient group, professional group and NHS organisation submissions** from:
   a. FEmISA – Fibroid Embolisation, Information, Support & Advice

4. **Evidence Review Group report** prepared by Aberdeen HTA Group

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Mr Alexander Oboh – clinical expert, nominated by Gedeon Richter

8. **Technical engagement responses from consultees and commentators:**
   a. FEmISA – Fibroid Embolisation, Information, Support & Advice
   b. Bayer

9. **Evidence Review Group critique of company response to technical engagement** prepared by Aberdeen HTA Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Relugolix with oestradiol and norethisterone acetate for treating uterine fibroids [ID3842; GID-TA10734]

Document B

Company evidence submission

October 2021

File name	Version	Contains confidential information	Date
ID3842_relugolixCT_GR_submission document B_REVISED_26.10.21	**1**	**Yes**	**26.10.21**

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Tables and Figures

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Abbreviations

Term	Definition
AE	Adverse event
AH	Alkaline haematin
ASRM	American Society for Reproductive Medicine
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
BPD	Bleeding and pelvic discomfort
BSC	Best supportive care
CFB	Change from baseline
CHASM	Cross-sectional survey of HRQoL And Symptoms of Myoma study
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cm	Centimetre
COC	Combined oral contraceptives
CRD	University of York Centre for Reviews and Dissemination
CSR	Clinical study report
DEXA	Dual-energy X-ray absorptiometry
dL	Decilitre
E2	Oestradiol
ECG	Electrocardiogram
EMA	European Medicines Agency
EOT	End of treatment
EQ-5D	European Quality of Life Five Dimension
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level
EU	European Union
FSH	Follicle-stimulating hormone
GnRH	Gonadotrophin-releasing hormone

GP	General practitioner
Hb	Haemoglobin
HCP	Healthcare professional
HES	Hospital Episode Statistics
HMB	Heavy menstrual Bleeding
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
HRU	Healthcare resource use
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
ITC	Indirect treatment comparison
ITT	Intention to treat
IUD	Intrauterine device
kg	kilogram
KOL	Key opinion leader
LH	Luteinising hormone
LNG-IUS	Levonorgestrel-releasing intrauterine system
LOCF	Last observation carried forwards
LS	Least squares
LUAO	Laparoscopic uterine artery occlusion
LYG	Life years gained
MAA	Marketing authorisation application
MBL	Menstrual blood loss
MD	Mean difference
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MIQ	Menorrhagia Impact Questionnaire
mITT	Modified Intent-to-Treat
mm	Millimetre

MRgFUS	Magnetic resonance-guided focused ultrasound
MRI	Magnetic resonance imaging
MT	Monotherapy
N ('n' or 'No.')	Number of patients
NE	Not estimable
NETA	Norethisterone acetate
NG88	NICE guideline 88
NHS	National Health Service
NRS	Numerical rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OLE	Open-label extension
OLS	Ordinary least squares
OWSA	One-way sensitivity analyses
P (or 'p')	Probability
PBLAC	Pictorial blood assessment chart
PCA	Prescription cost analysis
PCS	Physical component summary
pg	Picogram
PGA	Patient global assessment
PICO	Population, Intervention, Comparator, Outcome
pmol	Picomoles
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
Q1	Lower quartile
Q3	Upper quartile
QALY	Quality adjusted life year
QD	Once daily
QoL	Quality of life
R	Randomisation

RCT	Randomised control trial
Relugolix CT	Relugolix combination therapy (relugolix in combination with oestradiol and norethisterone)
RWS	Randomised withdrawal study
SAE	Serious adverse event
SD	Standard deviation
SF-12v2	Short Form 12 item (version 2) health survey
SF-36	Short Form 36-item survey
SLR	Systematic literature review
SmPC	Summary of product characteristics
TEAE	Treatment emergent adverse event
TTO	Time trade off
UAE	Uterine artery embolisation
UBP-WRS	Uterine Bleeding and Pain Women's Research Study
UF	Uterine fibroid
UFS-QoL	Uterine Fibroid Symptom and Quality of Life
UFV	Uterine fibroid volume
UPA	Ulipristal acetate
URTI	Upper respiratory tract infection
UTI	Urinary tract infection
UV	Uterine volume
VAS	Visual analogue scale
WHO	World Health Organization
Wk (or 'W')	Week of treatment
WPAI-SHP	Work Productivity and Activity Impairment: Specific Health Problem
WTP	Willingness to pay

• Decision problem, description of the technology and clinical care pathway

• *Decision problem*

The submission covers the technology's full marketing authorisation for this indication.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with moderate to severe symptoms associated with uterine fibroid(s) (UF)	Same as scope	
Intervention	Relugolix with oestradiol and norethisterone acetate (also known as norethindrone acetate), alone, or as an add on to non-hormonal pharmacological treatments *[Please note that relugolix in combination with oestradiol and norethisterone acetate is referred to as 'relugolix CT' throughout this submission; 'CT' is the abbreviation for 'combination therapy']*	Same as scope	
Comparator(s)	Hormonal treatments, including: • levonorgestrel-releasing intrauterine system (LNG-IUS; off-label for some LNG-IUS) • combined hormonal contraception (off-label for some combined hormonal contraceptives)	The submission will focus on gonadotrophin-releasing hormone (GnRH) agonists as the relevant comparator for relugolix CT.	Comparisons with a number of treatments in the final scope will not be considered formally in the submission. First line options such as levonorgestrel-releasing intrauterine system or combined hormonal contraception are not

	• cyclical oral progestogens • gonadotrophin-releasing hormone analogues (off-label for some gonadotrophin-releasing hormone analogues)		considered relevant at the anticipated positioning of relugolix CT for moderate to severe symptoms of UF. Furthermore, surgical procedures (e.g. myomectomy or hysterectomy) and uterine artery embolisation (UAE) may not provide resolution of UF symptoms or may be declined as options due to their invasive nature and recovery time. Clinical expert opinion received by Gedeon Richter indicates that GnRH agonists are the most relevant comparator for relugolix CT since these are the existing treatment options that are expected to be displaced by relugolix CT within the current NHS treatment pathway for moderate to severe symptoms of UF.
Outcomes	The outcome measures to be considered include: • change in menstrual blood loss (MBL) volume • time to MBL response • pain • uterine fibroid volume (UFV) / uterine volume (UV)	The outcome measures in the clinical effectiveness section include: • change in MBL volume • time to MBL response • pain • UFV/UV • haemoglobin levels	The following measures are not included in the clinical effectiveness section as they were not collected in the relugolix CT clinical trials: • rates and route of surgery

	• haemoglobin levels • change in bone mineral density (BMD) • rates and route of surgery • impact on fertility and pregnancy and teratogenic effects • mortality • adverse effects of treatment, including but not limited to vasomotor symptoms, incontinence and pelvic organ prolapse • health-related quality of life.	• adverse effects of treatment, including but not limited to vasomotor symptoms, incontinence and pelvic organ prolapse • health-related quality of life. The outcome measures in the cost-effectiveness model include: • MBL volume and change in MBL volume (used to derive utility) • Adverse effects • Quality of life	• impact on fertility and pregnancy and teratogenic effects Rates and route of surgery are, however, included in the economic model. Mortality is not included as no deaths were reported during the relugolix CT clinical trials. Whilst 'change in BMD' was explored in the relugolix CT clinical trials, it is not a relevant outcome in the economic model.*
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	Same as scope	

Special considerations including issues related to equity or equality		Black African and African-Caribbean origin, who are 2-3 times more likely to develop UF than white women, may be more opposed to surgery due to cultural and religious beliefs. Additionally, some women will choose to decline surgery in order to avoid impacting their personal circumstances with respect to work and family commitments such as childcare, etc.	

BMD: bone mineral density; CT: combination therapy; LNG-IUS: levonorgestrel-releasing intrauterine system; MBL: menstrual blood loss; UAE: uterine artery embolisation; UF: uterine fibroid

* **Bone mineral density**: in this submission, BMD is not an outcome in the economic model as it is assumed that BMD may resolve once treatment with GnRH agonist therapy (the comparator for relugolix CT) ceases and thus there may be no additional benefit to favour relugolix on this outcome. Despite this assumption, and as stated in section B.2.13, there is evidence to suggest that BMD may not be fully recoverable from GnRH agonist use which may underestimate the potential benefit that relugolix CT would provide to women with UF.

• *Description of the technology being appraised*

Table 2 provides an overview of relugolix CT (relugolix in combination with oestradiol and norethisterone acetate). The SmPC is included in Appendix C.

Table 2 Technology being appraised

UK approved name and brand name	Relugolix in combination with oestradiol and norethisterone acetate [Brand name: Ryeqo®]
Mechanism of action	Relugolix is a non-peptide GnRH receptor antagonist that binds to and inhibits GnRH receptors in the anterior pituitary gland. In humans, inhibition of GnRH receptor results in a dose dependent decrease in the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are reduced. The reduction in FSH concentrations prevents follicular growth and development, thereby reducing the production of oestrogen. Prevention of an LH surge inhibits ovulation and development of the corpus luteum, which precludes the production of progesterone.
Marketing authorisation/CE mark status	Ryeqo® received marketing authorisation from the European Medicines Agency on 16 July 2021 and UK Medicines and Healthcare products Regulatory Agency (MHRA) on 9th August 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication for Ryeqo® is as a treatment for moderate to severe symptoms of UF in adult women of reproductive age.
Method of administration and dosage	One tablet of Ryeqo® must be taken once daily, at about the same time with or without food. Ryeqo® should be taken with some liquid as needed. Each tablet of Ryeqo® contains relugolix (40mg), oestradiol (1mg) and norethisterone acetate (0.5mg).
Additional tests or investigations	A dual-energy x-ray absorptiometry (DEXA) scan is recommended after 52 weeks of treatment to verify that there is no unwanted degree of BMD loss that exceeds the benefit of treatment with Ryeqo®.

List price and average cost of a course of treatment	The drug acquisition cost for Ryeqo® is the accepted list price of £72 for a 28-pack of 40 mg/1 mg/0.5 mg tablets. There is no set time duration (specified course) for this treatment.
Patient access scheme (if applicable)	N/A

- ***Health condition and position of the technology in the treatment pathway***

Uterine fibroids (UF) are noncancerous growths that develop in or around the uterus

- they are also known as uterine myomas or leiomyomas. The true incidence of UFis unknown, since the condition is mainly asymptomatic and therefore not identified.(1) However, UF are known to be common, with around 1 in 3 women developing them at some point in their life.(2) It is thought that incidence increases with reproductive age with cases occurring in 20–50% in women older than 30 years(1) and increasing to as much as 70% of women by the onset of menopause.(3)

The exact cause of fibroids is not known, but they have been linked to the hormone oestrogen. As such, they usually develop during a woman's reproductive years (typically age 16–50) when oestrogen levels are highest.(2) Fibroids tend to shrink when oestrogen levels are low, such as after menopause.(4)

Furthermore, fibroids are more common in the following groups of women:(4)

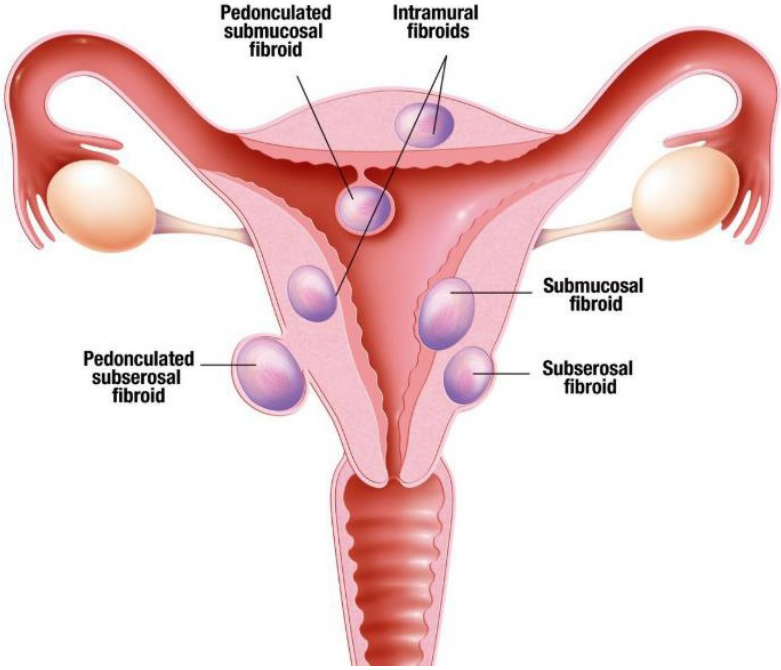
- Black women: fibroids are two to three times more common in black women although the exact reason is not known
- Women who have never been pregnant
- Women whose mother or sister have had fibroids (suggesting that genetic factors may play a role)
- Women who are very overweight.

Fibroids are less common in women who have had multiple children and also women who have used birth control pills for several years.(4)

In women presenting with UF symptoms, these may include: heavy or painful periods, abdominal pain, lower back pain, a frequent need to urinate, constipation or pain/discomfort during sex. In addition to symptoms, fibroids can affect pregnancy and a woman's fertility.(2)

Fibroids are generally classified by their location. Intramural fibroids grow within the muscular uterine wall. Submucosal fibroids grow in the muscle layer beneath the uterus' inner lining and grow into the uterine cavity. Subserosal fibroids develop outside of the uterus and grow into the pelvis.

Figure 1 Types of fibroids (2)



Diagnosis of UF is usually confirmed in the hospital setting by tests that rule out other possible causes of symptoms. These tests may include ultrasound scan, hysteroscopy, laparoscopy and/or biopsy.(5) In asymptomatic women, fibroids may only be discovered during routine gynaecological (vaginal) examinations or tests for other problems.(5)

Burden associated with uterine fibroids

UF can pose a significant economic burden to health care providers, patients, and society, due to treatment interventions (e.g. high costs associated with surgery) and also the loss of productivity (presenteeism) and working days (absenteeism).

Surgery is a mainstay option for the treatment of UF in symptomatic women and is associated with follow-up treatments, hospital stays and potential complications.

Direct costs for fibroid-related surgeries include hospital admissions, outpatient visits and prescription costs.(6)

A study by Fernandez *et al.* (2009) reviewed data from national hospital activity databases, for women admitted for a surgical or radiologic intervention for UF, in Germany, France and England. In 2005, the number (rate) of hospital admissions involving interventions for uterine myomas was 18,274 (0.71/1000 women) in England. The annual cost of these interventions to payers was €52,674,672 in England. Furthermore, the percentage of interventions that included a hysterectomy was 64.1% in England.(7)

UF are also associated with a considerable societal burden and affect the productivity of women at work as well as lost work time. The CHASM (Cross-Sectional Survey of HRQoL And Symptoms of Myoma) study, a study across 5 European countries exploring the burden associated with UF, included 113 women from the UK. Measures in the study included absenteeism and presenteeism. The study found that absenteeism was reported in more than 32.7% of employed women with fibroids (based on pooled analyses). This accounted to missed work time in the UK of 6.4% (2.3-10.5%), as measured by WPAI-SHP (Work Productivity and Activity Impairment: Specific Health Problem questionnaire) absenteeism scores. Presenteeism (lost productivity time while working) was also high in women with UF, ranging from 26.6% (France) to 37.9% (UK).(8)

Impact on quality of life

The symptoms associated with UF significantly impact quality of life by causing social, emotional and physical distress.(4) Women with symptomatic UF experience significantly worse health-related quality of life (HRQoL) compared to women without fibroids, which improves with appropriate treatment.(9–11)

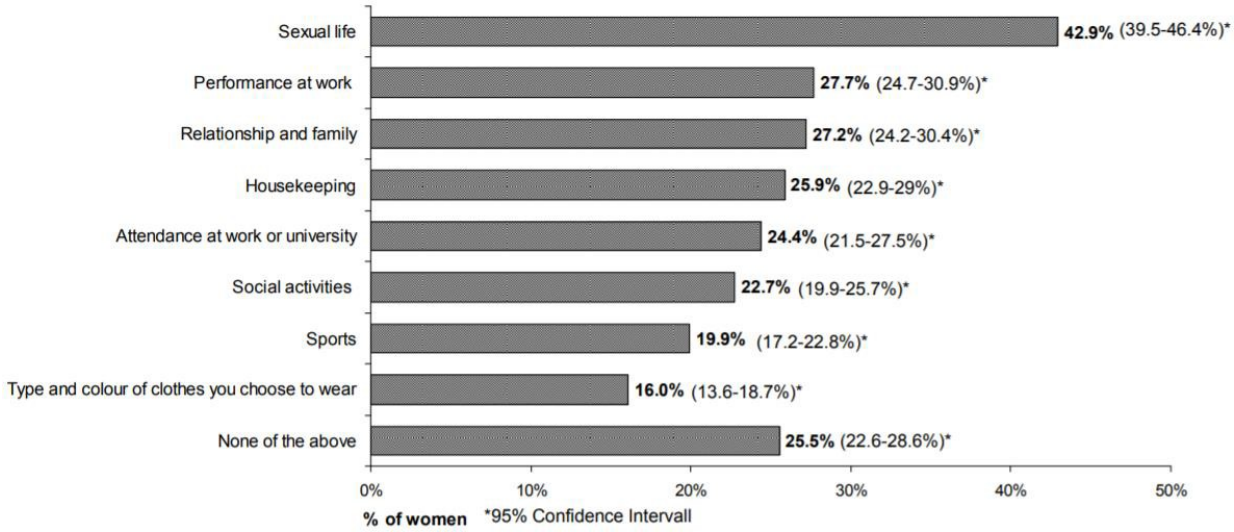
The Uterine Fibroid Symptom and Quality of Life (UFS-QoL) symptom severity scale uses eight items to assess the level of distress experienced by women due to different UF-related symptoms, with higher symptom severity scores indicating more severe symptoms (normalised score, range 0-100). The UFS-QoL HRQoL scale

consists of the following six subscales: Concern, Activities, Energy/Mood, Control, Self-consciousness, and Sexual function. Higher scores on the HRQoL scale indicate better QoL (normalised score, range 0-100).(12) To calculate the UFS-QoL total score, the scores of each individual scale (concern, activities, revised activities, energy/mood, control, self-conscious, and sexual function) are summed and transformed into normalised scores.

The CHASM study found a mean UFS-QoL HRQoL symptom score of 59.2 (95% CI, 54.2–64.2) among women in the UK, suggesting moderate HRQoL impairment. In the same study, HRQoL was also measured using SF-12v2. Mean SF-12v2 Physical Component Summary (PCS) scores ranged from 43.8 in the UK (95% CI, 41.6 – 46.0) to 49.6 in France (95% CI, 48.0 – 51.1), while SF-12v2 Mental Component Summary (MCS) scores ranged from 38.5 (95% CI, 36.4–40.5) for women in the UK to 42.0 (95% CI, 40.6–43.4) for women in Italy, indicating a considerable QoL impairment in each country (this impairment was consistent across all five countries).(8)

The UBP-WRS (Uterine Bleeding and Pain Women's Research Study) is a cross-sectional large-scale online study with survey directly recorded the experiences relating to uterine bleeding and pain of more than 21,000 women from diverse regional and demographic groups worldwide, including 2,500 women from the UK. Asking the women with diagnosed UF (n=1,533) about the impact of their symptoms in the last 12 months on their daily life, 14.8% (95% CI: 13.1-16.7%) of women reported a severe negative impact, 18.3% (95% CI: 16.4-20.4%) a moderate negative impact and 20.6% (95% CI: 18.6-22.7%) a mild negative impact. Almost 37.2% (95% CI: 34.8-39.7%) of diagnosed women answered that the symptoms do not have any impact on their daily life, whereas 9.0% (95% CI: 7.6-10.5%) did not know. Those women who reported a mild to severe impact of symptoms, were additionally asked which activities were negatively affected by their symptoms. About 42.9% (95% CI: 39.5-46.4%) of women stated that their sexual life was negatively affected, followed by performance at work (27.7%; 95% CI: 24.7-30.9%), relationship & family (27.2%; 95% CI:24.2-30.4%) and housekeeping (25.9%; 95% CI: 22.9-29.0%).(13)

Figure 2 Activities negatively affected by uterine fibroid symptoms (13)



Limited studies have explored the impact of UF on QoL using the EuroQol 5 dimensions (EQ-5D) instrument. A study by Hux et al. (2015), involving 909 Canadian women, showed that utility for uncontrolled bleeding was 0.55 (95% CI: 0.54, 0.57). However, higher utility was reported for women who were able to gain control over the excessive menstrual bleeding that was due to their fibroids with a utility improvement (associated with bleeding control) of 0.18 (95% CI: 0.17, 0.19).(14) A cost-effectiveness analysis study by Sculpher et al. (2004)(15) based on results from the eVALuate randomised controlled trial (RCT) comparing laparoscopic hysterectomy with conventional hysterectomy (vaginal or abdominal), found that utility (measured using EQ-5D) improved as a result of all the procedures, indicating a higher utility as a result of relief or improvement of UF symptoms. For example, in the abdominal hysterectomy trial, a mean baseline utility of 0.690 increased to 0.892 one year post procedure.(15)

A limited number of studies have examined the emotional and psychological aspect of UF on women. These suggest that UF are associated with:

- Psychological distress(16)
- Anxiety: including fear from the unpredictability of fibroid symptoms having a negative effect on women their daily activities(17), and fear of risk of UF developing into cancer(9)
- Feelings of helplessness(16,18)

- Negative body image and sexuality(16)
- Negative impact upon family life: including feelings of isolation due to lack of understanding from families(16) and significant morbidity negatively impacting upon relationships with friends and family.(18)

Moreover, heavy menstrual bleeding (HMB) is common in women with symptomatic fibroids, and is in itself associated with a considerable QoL burden with high impact on a woman's life(19,20), including psychological and social factors,(21) and disruption to a normal routine such as interference with work, family life, or the practical burden of sanitary care.(22)

Treating uterine fibroids

Current therapies aim to reduce or eliminate the symptoms of UF by reducing bleeding and pain, decreasing fibroid size, or removing the fibroids or uterus. Oestrogen and progesterone control the proliferation and maintenance of UF. Most pharmacological treatments act by interfering with hormone production or function.(13)

For people with UF less than 3 cm in diameter and not causing distortion of the uterine cavity, NICE guideline 88 (NG88) recommends considering a levonorgestrel-releasing intrauterine system (LNG-IUS) for the treatment of HMB. If HMB worsens or an LNG-IUS is not suitable, pharmacological treatments (such as tranexamic acid and non-steroidal anti-inflammatory drugs) and hormonal treatments (such as combined hormonal contraception, cyclical oral progestogens and gonadotrophin-releasing hormone [GnRH] analogues) are recommended. Surgery (second-generation endometrial ablation or hysterectomy) is recommended as an option if treatment is unsuccessful or declined, or symptoms are severe. For people with submucosal UF less than 3 cm in diameter hysteroscopic removal should be considered. For people with UF of 3 cm or more in diameter, the same pharmacological and surgical treatments are recommended as options as well as uterine artery embolisation and myomectomy. Pre-treatment with a gonadotrophin-releasing hormone analogue before hysterectomy and myomectomy should be

considered if UF are causing an enlarged or distorted uterus.(21) Table 3 provides an overview of the treatment options for UF.

Table 3 Overview of treatment options for uterine fibroids (21,23-29)

Approach	Appropriate population	Advantages	Disadvantages	Potential issues for fertility / future pregnancy
Pharmacological therapies				
LNG-IUS	• Young or premenopausal women. Fibroids less than 3 cm in diameter, not causing distortion of the uterine cavity.	• Reduces menstrual blood loss	• May cause irregular bleeding pattern • Risk of expulsion increased with UF • Not approved for UF • Distortion of endometrial cavity by UF may preclude insertion or increase risk of uterine perforation	• Is a contraceptive
Combined oral contraceptives (COC)	• Young or premenopausal women. When LNG-IUS is not suitable or declined.	• Cost-effective • May be used long-term	• Efficacy is limited • Not approved for UF • Not appropriate for those at increased risk of thrombotic events	• Is a contraceptive
Oral progestogen	• Young or premenopausal women. When LNG-IUS is not suitable or declined.	• Reduces menstrual blood loss	• Irreversible loss of BMD may occur with prolonged use • May cause irregular bleeding pattern • Not approved for UF • Risks and benefits of treatment beyond 2 years must be evaluated in the individual patient	• Is a contraceptive

Approach	Appropriate population	Advantages	Disadvantages	Potential issues for fertility / future pregnancy
Non-Steroidal Anti-inflammatory Drugs (NSAIDs)	• Young or premenopausal women. When LNG-IUS is not suitable or declined.	• Cost-effective • May reduce pain	• Do not address the multifactorial symptoms associated with fibroids (including pain due to fibroid growth, pelvic pressure, urinary frequency etc.) • Not approved for UF	• None
Tranexamic acid	• Young or premenopausal women. When LNG-IUS is not suitable or declined. Fibroids 3cm or more in diameter.	• Reduces menstrual blood loss • Only taken during bleeding periods	• Cannot be used concurrently with hormonal contraceptives • Not approved for UF in EU • Contraindicated in women at increased risk of thromboembolic events	• None
Esmya® (ulipristal acetate, UPA)	• Adult women who have not reached menopause when UF embolisation and/or surgical treatment options are not suitable or have failed. Fibroids 3 cm or more in diameter.	• Nonsurgical • Treats multifactorial symptoms of UF beyond just bleeding • Rapid and sustained reduction in heavy bleeding • Continuous reduction of fibroid size	• Safety concern: reported cases of liver injury and hepatic failure • Limited indication: Treatment courses are limited to 3 months each but can be repeated intermittently	• Inhibits ovulation in most women while on treatment

Approach	Appropriate population	Advantages	Disadvantages	Potential issues for fertility / future pregnancy
GnRH agonists	• Preoperative therapy in young or premenopausal women. Should be considered if UF are causing an enlarged or distorted uterus.	• Nonsurgical • Associated with treating symptoms of UF, beyond just bleeding (including pain, anaemia, urinary frequency)	• Temporary treatment (3 to 6* months), fibroid re-growth on cessation • Adverse effects including loss of BMD and menopausal symptoms • Route of administration: Injections (pain, administrative cost and drug cannot be interrupted at any time) • Flare effect during the first month	• It can take up to 3 months for menstruation to return after treatment
Surgical and non-surgical procedures				
Hysterectomy	• Women who require removal of uterus, who are close to menopause, or who do not desire fertility. • If fibroids are severe, prior treatment unsuccessful, pharmacological treatments declined, or fibroids 3cm or more in diameter.	• Definitive therapy • Removes entire uterus and therefore prevents fibroid regrowth	• Loss of fertility • Surgical morbidity including post-operative pain, infection and urinary complications, and/or mortality • Requires hospitalisation and is a costly procedure • Severe complications in about 1% of patients • Increased mortality rate • Early menopause • Prolapse • Mood (depression)	• Complete loss of fertility

Approach	Appropriate population	Advantages	Disadvantages	Potential issues for fertility / future pregnancy
Endometrial ablation (second generation)	• Can be used to treat small fibroids in the endometrium. • If fibroids are severe, prior treatment unsuccessful, pharmacological treatments declined	• Quick to perform	• Mainly used to reduce heavy bleeding • Severe or prolonged pain	• Risk of miscarriage and problems can be high
Myomectomy	• Women with visible and/or palpable fibroids. • If fibroids are severe, prior treatment unsuccessful, or fibroids 3cm or more in diameter.	• A surgical alternative to treat fibroids in women who wish to preserve their fertility	• Recurrence of fibroids may occur; a re-intervention rate of 10% to 25% has been reported • Surgical morbidity including post-operative pain, infection, urinary complications, injury to bladder, bowel, and blood vessels, post-operative adhesions (can cause bladder obstruction and pain), and/or mortality	• Potential uterine rupture during pregnancy • Uterine adhesions may make it difficult to conceive
Uterine artery embolisation (UAE)	• Women who have small UF (<8cm) that are not subserous, submucosal, or pedunculated. • If fibroids are severe, prior treatment unsuccessful, or fibroids 3cm or more in diameter.	• Treats uterus globally • No blood loss • Minimally invasive surgical procedure	• Morbidity including pain, possible post-embolisation syndrome, possibility of severe complications • Fertility requires further investigation • Costly; must be performed by an interventional radiologist	• Potential ovarian failure • Abnormal placenta development • Contradictory outcomes in pregnancy after UAE

Approach	Appropriate population	Advantages	Disadvantages	Potential issues for fertility / future pregnancy
			• Re-intervention rate of 15% to 35%	
Magnetic Resonance-guided Focused Ultrasound (MRgFUS)		• Incisionless and bloodless (therefore allows fast return to normal activities)	• Insufficient data is available regarding the effect of MRgFUS on fertility, likeliness of recurrence of fibroids, and long-term effects • Experimental procedure only available at very few centres • Costly; must be performed by an interventional radiologist	• Unknown
Laparoscopic uterine artery occlusion (LUAO)	• Women with small or large fibroids, subserosal fibroids	• Treats uterus globally	• Requires technical skill • Dependent on fibroid location • Recurrence of fibroids may occur • Effect on fertility is unclear • Data on LUAO is limited, and there is insufficient long-term data available	• Unknown

* GnRH agonist treatment duration is longer than 3–6 months in some instances, especially with delays in planned surgical procedures due to COVID-19

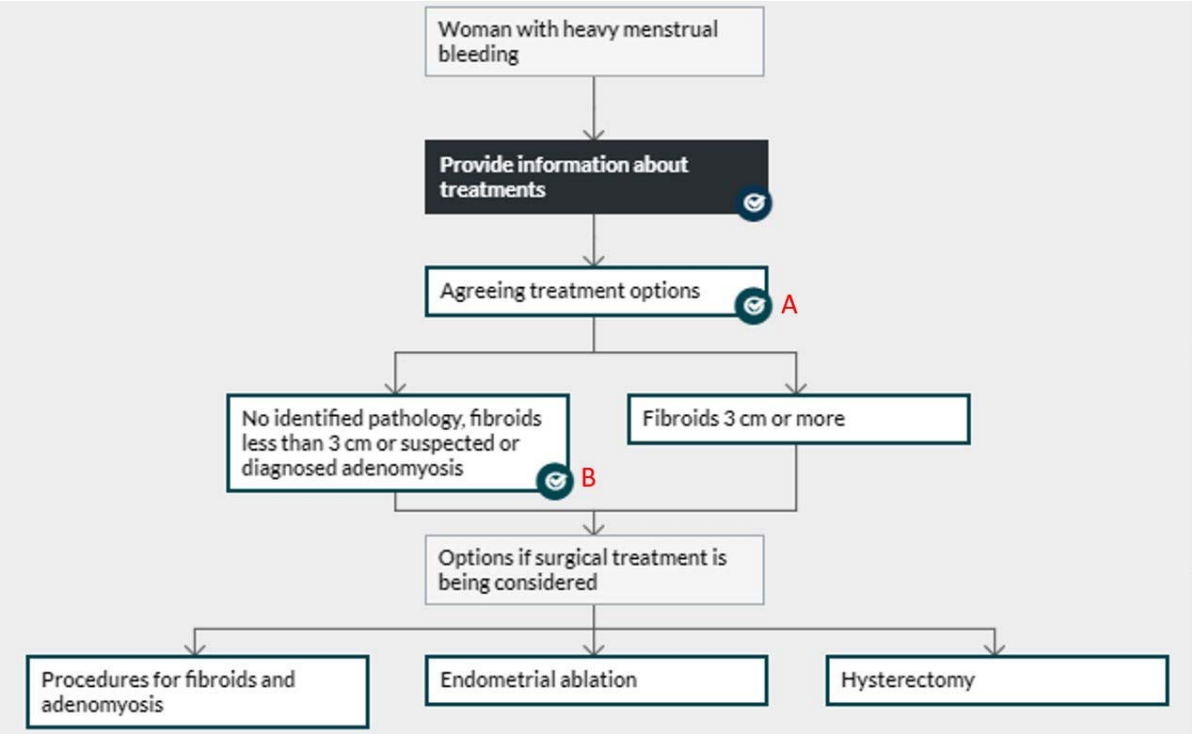
COC: Combined Oral Contraceptive; GnRH: gonadotrophin-releasing hormone; HMB: heavy menstrual bleeding; LNG-IUS: Levonorgestrel Intrauterine System; MRgFUS: magnetic resonance imaging-guided focused ultrasound surgery; NSAID: non-steroidal anti-inflammatory drug; Q1: Quarter 1; UAE: uterine artery embolisat

Surgery is one of the main treatment strategies for women with UF when treatment with LNG-IUS or pharmacological treatments are unsuitable or unsuccessful. The type of surgery is dependent on a number of factors including the patient's desire to preserve fertility, and the number and size of fibroids. Surgical management has disadvantages, including risks and complications associated with surgery, and reluctance on behalf of some patients to undergo surgery. There are many reasons why women may wish to decline surgery, including the desire to preserve fertility, to avoid complications or surgical recovery time, for religious or cultural beliefs, or preference to wait for menopause (when UF symptoms resolve). GnRH agonists and Esmya® [ulipristal acetate (UPA)] are second line pharmacological options that have an approved indication for UF. However, Esmya® has a limited indication for moderate to severe UF(30,31) and its usage has been commonly replaced with GnRH agonists in the absence of other pharmacological options. Furthermore, GnRH agonists are limited to 6-month treatment courses and are administered by injection by a healthcare professional. Pharmacological options are therefore limited at this present time.

Clinical pathway

The most relevant clinical pathway in managing UF is the NICE Pathway for managing HMB (2021).(29)

Figure 3 NICE pathway for managing HMB (29)



A: Agreeing treatment options (29)

When agreeing treatment options for HMB with women, take into account:

- the woman's preferences
- any comorbidities
- the presence or absence of fibroids (including size, number and location), polyps, endometrial pathology or adenomyosis
- other symptoms such as pressure and pain.

B: No identified pathology, fibroids less than 3 cm or suspected or diagnosed adenomyosis (29)

Consider an LNG-IUS as the first treatment for HMB in women with:

- no identified pathology or
- fibroids less than 3 cm in diameter, which are not causing distortion of the uterine cavity or
- suspected or diagnosed adenomyosis.

Note that this is an off-label use for some LNG-IUSs.

If a woman with HMB declines an LNG-IUS or it is not suitable, consider the following pharmacological treatments:

- non-hormonal:
    - tranexamic acid
    - NSAIDs
- hormonal:
    - combined hormonal contraception
    - cyclical oral progestogens.

Note that this is an off-label use for NSAIDs and some combined hormonal contraceptives. See prescribing medicines for more information.

Be aware that progestogen-only contraception may suppress menstruation, which could be beneficial to women with HMB.

If treatment is unsuccessful, the woman declines pharmacological treatment, or symptoms are severe, consider referral to specialist care for:

- investigations to diagnose the cause of HMB, if needed, taking into account any investigations the woman has already had and
- alternative treatment choices, including:
    - pharmacological options not already tried (see above)
    - surgical options:
        - second-generation endometrial ablation
        - hysterectomy.

For women with submucosal fibroids, consider hysteroscopic removal.

For women with fibroids of 3cm or more in diameter (29)

- Offer non-hormonal (tranexamic acid, NSAIDs) whilst investigations and definitive treatment are being organised; women should continue to use NSAIDs and/or tranexamic acid for as long as they are found to be beneficial
- Hormonal treatment (LNG-IUS, combined hormonal contraception, cyclical oral progestogens, UPA)
- UAE
- Surgical: myomectomy or hysterectomy
- Only consider UPA for the intermittent treatment of moderate to severe symptoms of UF in premenopausal women if surgery and UAE are not suitable, declined or have failed surgery or UAE
- Consider second-generation endometrial ablation for those who meet the criteria
- Consider pre-treatment with GnRH analogues before hysterectomy and myomectomy if UF are causing an enlarged or distorted uterus.

Issues with current treatments (unmet need)

Currently, surgery is a common method of treating and managing issues with UF that are not controllable through first-line pharmacological treatments such as NSAIDs and hormonal contraceptives. Surgery, being an invasive intervention option, may not be a suitable choice for women who have busy lifestyles, are worried about fertility, have certain religious or cultural beliefs that do not allow surgery, or through their own choice would prefer not to undergo a surgical procedure. Consequently, there is a significant unmet need for pharmacological treatments for moderate to severe UF due to the absence of satisfactory medical treatments.

Ideally, treatments for UF should satisfy the following characteristics:

- Non-invasive
- Easy to administer
- Cost-effective
- Preserve fertility

- Preserve BMD
- Efficacious
- Offer quick relief from symptoms
- Lead to fibroid size reduction
- Acceptable tolerability and safety (with few adverse events [AEs] or complications)
- Result in low incidence of fibroid recurrence
- Long-term (not time restricted) indication in premenopausal women
- Suitable for long term use.

There is currently no other treatment option available that meets the unmet need and has a long-term (not time restricted) indication in premenopausal women with moderate to severe UF.

Proposed place of relugolix CT

As described above, there is an 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. Relugolix CT (Ryeqo®) is a novel GnRH antagonist indicated for the treatment of moderate to severe symptoms of UF in adult women of reproductive age that provides a new option for patients in this area of high unmet need. There are currently no oral pharmacological treatment options available that can be used on a long-term basis (not time restricted) in premenopausal women with moderate to severe UF.

- ***Equality considerations***

Gedeon Richter wishes to highlight potential equity or equality issues relating to relugolix CT that may affect women of Black African and African-Caribbean origin, who are 2-3 times more likely to develop UF than white women. It is understood that due to cultural and religious beliefs, women of Black African and African-Caribbean origin may be more opposed to receiving surgery than white women, and thus, non-

surgical interventions such as relugolix CT may provide a more suitable treatment option for this group.

Additionally, through clinical expert opinion, we understand that a significant proportion of women exercise their choice in declining the option of surgery to avoid impacting their personal circumstances with respect to work and family commitments such as childcare, etc. Non-surgical interventions such as relugolix CT may provide a more suitable treatment option for these women.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D1.1 for full details of the process and methods used to identify and select the clinical evidence relevant to relugolix CT [relugolix 40 mg (with oestradiol 1 mg and norethisterone acetate 0.5 mg)] for the treatment of HMB associated with UF.

A total of three Phase 3 trials relating to relugolix CT met the inclusion criteria: LIBERTY 1, LIBERTY 2 and LIBERTY 3 (also known as LIBERTY EXTENSION). Nine records were retrieved, all of which were published conference abstracts:

- One reporting on LIBERTY 1: Al-Hendy et al. (2019)(32)
- 7 reporting on results from both LIBERTY 1 and LIBERTY 2
  - Mean blood loss results: Venturella et al (2020) (33)
  - Anaemia/haemoglobin results (2 abstracts) by Venturella et al (2020) (34)(35)
  - Pain due to fibroids results: Al-Hendy et al. (2020)(36) and Stewart etal. (2020) (37)
  - Quality of life (UFS-QoL) results: Al-Hendy et al. (2020) (38)
  - Patient distress due to fibroids results: Stewart et al. (2020) (39)
- One reporting on LIBERTY 3: Al-Hendy et al. (2020) (40)

Additionally, the findings from LIBERTY 1 and LIBERTY 2 pivotal trials have been recently published by Al-Hendy et al. (2021) in the New England Journal of Medicine.(41)

Appendix D1.1 and Section B2.9 details how studies were identified for inclusion in the indirect treatment comparison (ITC). As a result of the SLR, plus additional PICO and criteria that were applied, the search identified four RCTs for inclusion in the ITC: LIBERTY 1, LIBERTY 2, PEARL I and PEARL II.

B.2.2 List of relevant clinical effectiveness evidence

The efficacy, safety, and tolerability of relugolix CT has been demonstrated through a series of two (replicate) multicentre Phase 3 trials (LIBERTY 1, LIBERTY 2) and one Phase 3 open-label extension study of LIBERTY 1 and LIBERTY 2 called LIBERTY 3 (also known as LIBERTY EXTENSION).

The trial identifiers are as follows:

- LIBERTY 1 (MVT-601-3001): NCT03049735
- LIBERTY 2 (MVT-601-3002): NCT03103087
- LIBERTY 3 (MVT-601-3003): NCT03412890

Results from LIBERTY 1 and LIBERTY 2 are published in the New England Journal of Medicine(41) and LIBERTY 3 findings were presented at the American Society for Reproductive Medicine (ASRM) 2020 scientific meeting as an oral presentation(40). Where unavailable in the publications, data in this submission are also taken from the LIBERTY 1 and LIBERTY 2 clinical study reports, both dated January 2020,(42)(43) and the LIBERTY 3 clinical study report, dated May 2020.(44)

In the LIBERTY 1 and LIBERTY 2 trials, participants were randomised by 1:1:1 ratio to receive either:

- 24 weeks of relugolix CT
- 12 weeks of relugolix monotherapy (MT) (i.e. without oestradiol and norethisterone acetate) followed by 12 weeks of delayed relugolix CT [this arm is known hence force as ‘relugolix-delayed CT’]
- 24 weeks placebo therapy.

Eligible participants were enrolled into the LIBERTY 3 extension study on completion of either of the two parent studies (LIBERTY 1 or LIBERTY 2).

Table 4 Clinical effectiveness evidence: LIBERTY 1 and LIBERTY 2

Study	LIBERTY 1 (MVT-601-3001; NCT03049735) & LIBERTY 2 (MVT-601-3002; NCT03103087)				
Study design	Phase 3, randomised, double-blind, placebo-controlled efficacy and safety trials				
Population	Pre-menopausal women, aged 18–50, with HMB associated with uterine fibroids				
Intervention(s)	Relugolix 40 mg in combination with oestradiol 1 mg and norethisterone acetate 0.5 mg [relugolix CT]				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	LIBERTY 1 & 2 are the pivotal trials of relugolix CT in the treatment of uterine fibroids. The studies provided data for the MAA and represent the primary evidence base in the submission.				
Reported outcomes specified in the decision problem **Mark in bold the outcomes used in the model**	• **MBL volume and change in MBL volume** (used to derive utility) • Achievement of amenorrhoea • Uterine volume • Uterine fibroids volume • Pain (associated with uterine fibroids) • **Adverse effects of treatment**				
All other reported outcomes **Mark in bold the outcomes used in the model**	• **Quality of life** • Change in haemoglobin				

CT: combination therapy; E2: oestradiol; HMB: heavy menstrual bleeding; MAA: marketing authorisation application; MBL: menstrual blood loss; NETA: norethisterone acetate

Table 5 Clinical effectiveness evidence: LIBERTY 3

Study	LIBERTY 3 (also known as LIBERTY EXTENSION) (MVT-601-3003; NCT03412890)				
Study design	Multinational phase 3, open-label, single-arm, long-term efficacy and safety extension study				
Population	Eligible patients who completed LIBERTY 1 or LIBERTY 2				
Intervention(s)	Relugolix 40 mg in combination with oestradiol (E2) 1 mg and norethisterone acetate (NETA) 0.5 mg [relugolix CT]				
Comparator(s)	N/A				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	LIBERTY 3 is the open-label extension study, providing efficacy and safety data for relugolix from 24 weeks in the parent trials (LIBERTY 1 & LIBERTY 2) up to a total of 52 weeks.				
Reported outcomes specified in the decision problem **Mark in bold the outcomes used in the model**	• **MBL volume and change in MBL volume** (used to derive utility) • Achievement/maintenance of amenorrhoea • Uterine volume • Uterine fibroids volume • Pain (associated with uterine fibroids) • Adverse effects of treatment				
All other reported outcomes **Mark in bold the outcomes used in the model**	• **Quality of life** • Change in haemoglobin				

E2: oestradiol; MAA: marketing authorisation application; MBL: menstrual blood loss; NETA: norethisterone acetate

An overview of the clinical effectiveness evidence for PEARL I and PEARL II, is available in Appendix M1.5 (see Table 124 and Table 125).

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B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

A comparative summary of the relugolix CT trials is as follows:

Table 6 Comparative summary of trial methodology (relugolix studies)

Trial number (acronym)	**MVT-601-3001 (LIBERTY 1)**	**MVT-601-3002 (LIBERTY 2)**	**MVT-601-3003 (LIBERTY 3)**
Location	80 centres globally, including centres in the USA, Brazil, Italy, Poland, South Africa and the UK. Approximately 25% of patients were enrolled at sites outside of North America.	99 centres globally, including centres in the USA, Belgium, Brazil, Chile, Czech Republic, Hungary, Poland and South Africa. Approximately 25% of patients were enrolled at sites outside of North America.	149 centres in the USA, Belgium, Brazil, Chile, Czech Republic, Hungary, Italy, Poland and South Africa.
Trial design	Phase 3 randomised, double-blind, placebo-controlled trial		Phase 3, open-label, single-arm, long-term efficacy and safety extension study
Eligibility criteria for participants	Premenopausal women 18 to 50 years of age with regularly occurring menstrual periods of <14 days' duration with cycle of 21 to 38 days; who had a diagnosis of fibroids as confirmed on ultrasonography and who had HMB, as assessed by the AH method, were eligible		Completed 24 weeks of study drug treatment and study participation in either LIBERTY 1 or LIBERTY 2. Was not expected to undergo gynaecological surgery or ablation procedures for UF within the study period, including during the Safety Follow-up period. Negative urine pregnancy test at Week 24/Baseline visit.
Trial drugs	Participants were randomly assigned, in a 1:1:1 ratio, by means of an interactive website to receive blinded placebo for 24 weeks, relugolix CT (40 mg relugolix in combination with 1 mg oestradiol and 0.5 mg norethisterone acetate) for 24 weeks, or relugolix-delayed CT (relugolix monotherapy followed by relugolix CT, each for 12 weeks).*		477 patients enrolled to receive open-label relugolix CT (40 mg relugolix in combination with 1 mg oestradiol and 0.5 mg norethisterone acetate) for 28 weeks. This comprised >75% of patients who completed one of the parent studies (LIBERTY 1 or LIBERTY 2).

	• LIBERTY 1: 388 randomised: relugolix CT (128), placebo (128), relugolix-delayed CT (132) • LIBERTY 2: 382 randomised: relugolix CT (126), placebo (129), relugolix-delayed CT (127) Trial visits occurred at baseline and every 4 weeks for 24 weeks.		
Primary outcomes	Proportion of women 'responding' in the relugolix CT versus the placebo group where a 'responder' was classified as a women who achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the AH method.		Proportion of women who achieved or maintained an MBL volume of < 80 mL and at least a 50% reduction from parent study baseline MBL volume to the last 35 days of treatment, as measured by the AH method
Other outcomes used in the economic model/specified in the scope	Outcomes in the model: • MBL volume and change in MBL volume (used to derive utility) • Adverse events • Quality of life Other outcomes in the scope: • Achievement of amenorrhoea • Uterine volume • Uterine fibroids volume • Pain (associated with uterine fibroids) • Change in haemoglobin		Outcomes in the model: • MBL volume and change in MBL volume (used to derive utility) • Quality of life Other outcomes in the scope: • Adverse events • Achievement of amenorrhoea • Uterine volume • Uterine fibroids volume • Pain (associated with uterine fibroids)
Pre-planned subgroups	N/A	N/A	N/A

* The relugolix-delayed CT group was included to allow for the comparison of BMD and vasomotor symptoms in the combination and monotherapy groups during the first 12 weeks of the trial. This arm does not relate to the licenced indication for relugolix CT.

A comparative summary of trial methodology for PEARL I and PEARL II is available in Appendix M1.5 (see Table 123).

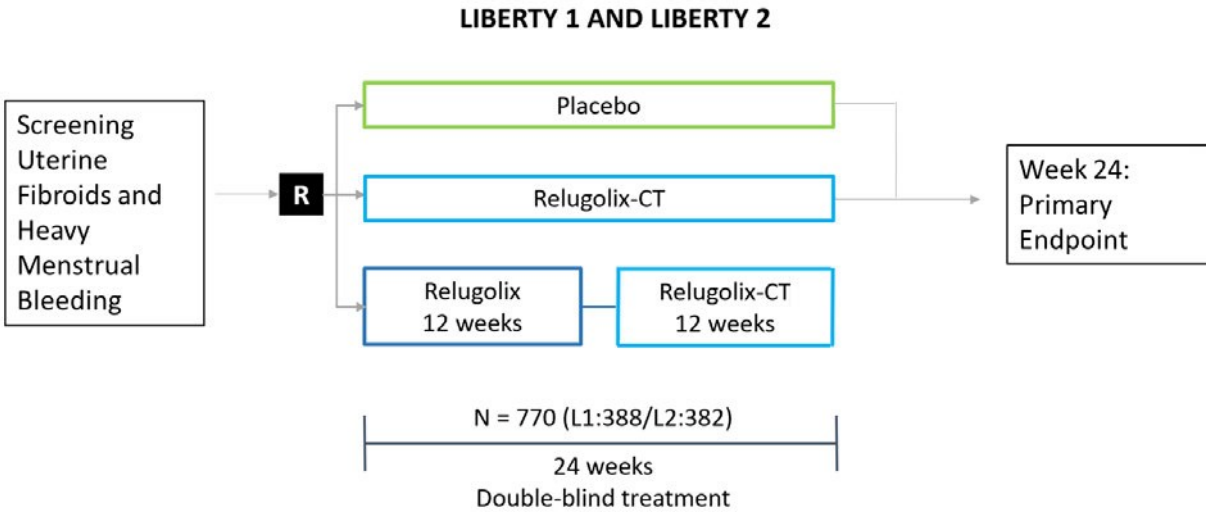
LIBERTY 1 and LIBERTY 2

Trial design

LIBERTY 1 and LIBERTY 2 were two multicentre Phase 3, randomised, double-blind, placebo-controlled efficacy and safety trials conducted between March 2017 and July 2019. The objective of LIBERTY 1 and LIBERTY 2 was to determine the benefit of relugolix CT compared with placebo for 24 weeks. The primary endpoint was the assessment of the effect on HMB associated with UF.

The study design for LIBERTY 1 and LIBERTY 2 is shown in Figure 4.

Figure 4 LIBERTY 1 and LIBERTY 2 study design schematic (45)



L1: LIBERTY 1; L2: LIBERTY 2; N: number of subjects; R: randomisation

Participants were randomly assigned, in a 1:1:1 ratio, by means of an interactive website to receive blinded placebo for 24 weeks, relugolix CT for 24 weeks, or relugolix-delayed CT. A 40 mg relugolix tablet and a capsule containing oestradiol and norethisterone acetate, or a placebo tablet and capsule, were packaged together in blister cards for once-daily coadministration. The relugolix-delayed CT group received the 40 mg relugolix tablet and a placebo capsule for 12 weeks, followed by the active agent tablet and capsule for 12 weeks. The relugolix-delayed CT group was included to allow for the comparison of bone mineral density and vasomotor symptoms in the combination and monotherapy groups during the first 12

weeks of the trial. Trial visits occurred at baseline and every 4 weeks for 24 weeks.(41)

Patient population and baseline characteristics in LIBERTY 1 and LIBERTY 2

The planned study population focused on premenopausal women 18 to 50 years of age with HMB associated with UF (≥ 80 mL per cycle for two consecutive cycles or ≥160 mL for one cycle as measured by the alkaline haematin (AH) method during the screening period). Since the primary endpoint assessed the effect on HMB, a population of premenopausal women was selected.(41)

The key inclusion and exclusion criteria for LIBERTY 1 and LIBERTY 2 are described in Table 7.

Table 7 Key eligibility criteria for LIBERTY 1 and LIBERTY 2 (45)

Inclusion	Exclusion
Premenopausal women, age 18 to ≤50 years, with regularly occurring menstrual periods of <14 days' duration with cycle of 21 to 38 days	Expected to undergo gynaecological surgery or ablation procedures for UF within the 6 months following enrollment
Diagnosis of UF confirmed by a transvaginal ultrasound examination performed during screening: • Subserosal, intramural, or <50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or • Multiple small fibroids with a total UV ≥130 cm^3	Pathology on endometrial biopsy, history of osteoporosis or other metabolic bone disease, contraindications to treatment with low-dose E2/NETA.
Menstrual blood loss of ≥160 mL during 1 cycle or ≥80 mL per cycle for 2 menstrual cycles during screening (assessed by the AH method)	Unexplained vaginal bleeding outside the patient's regular menstrual cycle
Agreed to use non-hormonal contraception during the study and for 30 days following the last dose of study drug	Weight that exceeds the weight limit of the dual-energy X-ray absorptiometry (DEXA) scanner
	History of the use of bisphosphonates, calcitonin/calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat BMD loss
	Had a baseline bone mineral density z-score <-2.0 at the spine, total hip, or femoral neck

BMD: bone mineral density; DEXA: dual-energy X-ray absorptiometry; E2: oestradiol; NETA: norethisterone acetate; UF: uterine fibroids

A more detailed overview over the key inclusion and exclusion criteria for LIBERTY 1 and LIBERTY 2 is provided in the Appendix M1.1 as Table 116.

In total for LIBERTY 1 and LIBERTY 2, 770 subjects were randomised into a treatment group.

Efficacy analyses were performed using the modified Intent-to-Treat (mITT) population, unless otherwise specified. The mITT population comprised randomised patients who received any amount of study drug (relugolix, oestradiol, norethisterone acetate or placebo). Efficacy analyses were performed by treatment group as randomised. The safety population was the same as the mITT population and is defined as all randomised patients who have received any amount of study drug.(42,43) Safety data were analysed by treatment group according to the actual treatment received (not the randomised treatment).

It is worth noting that in LIBERTY 1, one patient in the placebo group was randomised but not treated because a serious adverse event was observed prior to initiation of blinded study drug.(42) In LIBERTY 2, in the relugolix CT group, one patient was excluded from the mITT population because the patient was randomised in error before eligibility was confirmed and was never dosed with study drug.(43) Additionally, one patient in LIBERTY 2 was randomised to the relugolix -delayed CT group but received relugolix CT. This patient is included in the relugolix CT group for safety analyses. In the LIBERTY 2 placebo group, all randomised patients were included in the mITT and safety populations.(43)

A summary of the randomised, mITT and safety population numbers are provided in Table 8.

Table 8 Number of study participants in LIBERTY 1 and LIBERTY 2 (41)

	LIBERTY 1	**LIBERTY 2**	**Total**
Randomised	**N=388** Placebo (N=128); Relugolix CT (N=128); Relugolix-delayed CT (N=132)	**N=382** Placebo (N=129); Relugolix CT (N=126); Relugolix-delayed CT (N=127)	**N=770** Placebo (N=257); Relugolix CT (N=254); Relugolix-delayed CT (N=259)

mITT population	**N=387** Placebo (N=127); Relugolix CT (N=128); Relugolix-delayed CT (N=132)	**N=381** Placebo (N=129); Relugolix CT (N=125); Relugolix-delayed CT (N=127)	**N=768** Placebo (N=256); Relugolix CT (N=253); Relugolix-delayed CT (N=259)
Safety population	**N=387** Placebo (N=127); Relugolix CT (N=128); Relugolix-delayed CT (N=132)	**N=381** Placebo (N=129); Relugolix CT (N=126); Relugolix-delayed CT (N=126)	**N=768** Placebo (N=257); Relugolix CT (N=254); Relugolix-delayed CT (N=258)

CT: combination therapy; E2: oestradiol; miTT: modified intent-to-treat; NETA: norethisterone acetate

The baseline characteristics of patients in LIBERTY 1 and LIBERTY 2 are shown in Table 9.

Table 9 Patient characteristics for LIBERTY 1 and LIBERTY 2 (mITT population) (41)

	LIBERTY 1			LIBERTY 2		
Characteristic	**Placebo (N=127)**	**Relugolix CT (N=128)**	**Relugolix-delayed CT (N=132)**	**Placebo (N=129)**	**Relugolix CT (N=125)**	**Relugolix-delayed CT (N=127)**
Age Mean (SD)	42.2 (5.70)	42.5 (4.99)	41.3 (5.39)	41.8 (5.26)	42.4 (5.38)	42.1 (5.25)
Race n (%) White Black or African American Other	56 (44.1%) 65 (51.2%) 6 (5%)	64 (50.0%) 59 (46.1%) 5 (4%)	53 (40.2%) 67 (50.8%) 12 (9%)	49 (38.0%) 74 (57.4%) 5 (4%)	58 (46.4%) 62 (49.6%) 2 (2%)	50 (39.4%) 66 (52.0%) 8 (6%)
Hispanic ethnic group n (%) Hispanic or Latino	23 (18.1%)	34 (26.6%)	33 (25.0%)	32 (24.8%)	18 (14.4%)	34 (26.8%)
BMI (kg/m^2) Mean (SD)	32.287 (7.5276)	31.434 (7.6276)	31.355 (7.2874)	32.055 (7.5937)	30.972 (6.6093)	30.777 (5.7280)

CT: combination therapy; miTT: modified intent-to-treat; SD: standard deviation; BMI: Body Mass Index

The disease-specific baseline characteristics of patients in the mITT population for LIBERTY 1 and LIBERTY 2 are presented in Table 10 and Table 11, respectively. Overall, the disease-specific baseline characteristics observed were consistent with a population of women with symptomatic UF, including HMB (mean of 229.05 mL per cycle in LIBERTY 1 and 228.45 mL per cycle in LIBERTY 2), low mean haemoglobin concentrations (LIBERTY 1: 11.25 g/dL and LIBERTY 2: 11.16 g/dL), UFS-QoL BPD scale scores indicative of moderate distress due to bleeding and pelvic discomfort (LIBERTY 1: 68.90 and LIBERTY 2: 70.89). In general, disease-specific baseline characteristics were comparable among treatment groups.

Please refer to Appendix section “M1.6 LIBERTY vs PEARL studies” for a comparison of the baseline characteristics in the LIBERTY vs PEARL studies.

Table 10 Disease-specific baseline characteristics of patients in the mITT population (LIBERTY 1) (42)

	Relugolix CT (N = 128)	Relugolix-delayed CT (N = 132)	Placebo (N = 127)	Total (N = 387)
MBL volume (mL)				
Mean (SD)	239.44 (180.292)	228.89 (159.623)	218.76 (125.039)	229.05 (156.576)
MBL volume[a] n (%)				
< 225	84 (65.6%)	86 (65.2%)	85 (66.9%)	255 (65.9%)
≥ 225	44 (34.4%)	46 (34.8%)	42 (33.1%)	132 (34.1%)
MBL volume n (%)				
< 160	40 (31.3%)	40 (30.3%)	46 (36.2%)	126 (32.6%)
≥ 160	88 (68.8%)	92 (69.7%)	81 (63.8%)	261 (67.4%)
Haemoglobin (g/dL)				
Mean (SD)	11.24 (1.563)	11.13 (1.653)	11.40 (1.357)	11.25 (1.531)
Haemoglobin n (%)				
< 8	2 (1.6%)	4 (3.0%)	0	6 (1.6%)
≥ 8 - < 10.5	39 (30.5%)	39 (29.5%)	28 (22.0%)	106 (27.4%)
≥ 10.5 - < 12	39 (30.5%)	50 (37.9%)	56 (44.1%)	145 (37.5%)
≥ 12	48 (37.5%)	39 (29.5%)	43 (33.9%)	130 (33.6%)
Index uterine fibroid volume (cm^3)				
Mean (SD)	71.88 (128.070)	93.83 (143.781)	71.78 (123.986)	79.32 (132.414)
Index uterine fibroid volume n (%)				
< 25 cm^3	64 (50.0%)	53 (40.2%)	61 (48.0%)	178 (46.0%)
≥ 25 cm^3	63 (49.2%)	78 (59.1%)	66 (52.0%)	207 (53.5%)
Missing	1 (0.8%)	1 (0.8%)	0	2 (0.5%)
Uterine volume (cm^3)				
Mean (SD)	379.08 (316.843)	469.86 (427.943)	397.79 (324.860)	416.28 (362.299)
Uterine volume n (%)				
< 300 cm^3	74 (57.8%)	57 (43.2%)	64 (50.4%)	195 (50.4%)
≥ 300 cm^3	53 (41.4%)	75 (56.8%)	63 (49.6%)	191 (49.4%)
Missing	1 (0.8%)	0	0	1 (0.3%)
Any surgery for uterine fibroids				
Yes	20 (15.6%)	15 (11.4%)	13 (10.2%)	48 (12.4%)
No	108 (84.4%)	117 (88.6%)	114 (89.8%)	339 (87.6%)
UFS-QoL (BPD subscale)				
Mean (SD)	66.80 (22.083)	68.51 (22.864)	71.40 (21.274)	68.90 (22.115)

BPD: bleeding and pelvic discomfort; CT: combination therapy; MBL: mean blood loss; miTT: modified intent-to-treat; ml: millilitres; n: number of subjects; SD: standard deviation; UFS-QoL: Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire

[a] Menstrual blood loss volume category at baseline was calculated based on observed MBL volume and used in the stratified analyses. While the SAP specified to use IWRS stratification variables for analyses, there were a small number of patients (n = 9) stratified incorrectly by the site.
Note: Percentages are based on the total number of patients in each treatment group or total.

Table 11 Disease-specific baseline characteristics of patients in the mITT population (LIBERTY 2) (43)

	Relugolix CT (N = 125)	Relugolix-delayed CT (N = 127)	Placebo (N = 129)	Total (N = 381)
MBL volume (mL)				
Mean (SD)	246.72 (186.027)	227.41 (134.350)	211.75 (129.903)	228.45 (152.205)
MBL volume n (%)				
< 225	80 (64.0%)	80 (63.0%)	86 (66.7%)	246 (64.6%)
≥ 225	45 (36.0%)	47 (37.0%)	43 (33.3%)	135 (35.4%)
MBL volume n (%)				
< 160	46 (36.8%)	45 (35.4%)	55 (42.6%)	146 (38.3%)
≥ 160	79 (63.2%)	82 (64.6%)	74 (57.4%)	235 (61.7%)
Haemoglobin (g/dL)				
Mean (SD)	11.34 (1.459)	11.10 (1.626)	11.05 (1.574)	11.16 (1.556)
Haemoglobin n (%)				
< 8	1 (0.8%)	4 (3.1%)	5 (3.9%)	10 (2.6%)
≥ 8 - < 10.5	38 (30.4%)	39 (30.7%)	41 (31.8%)	118 (31.0%)
≥ 10.5 - < 12	40 (32.0%)	44 (34.6%)	48 (37.2%)	132 (34.6%)
≥ 12	46 (36.8%)	40 (31.5%)	35 (27.1%)	121 (31.8%)
Index uterine fibroid volume (cm^3)				
Mean (SD)	73.67 (126.679)	78.90 (157.481)	74.11 (123.011)	75.56 (136.244)
Index uterine fibroid volume n (%)				
< 25 cm^3	59 (47.2%)	52 (40.9%)	58 (45.0%)	169 (44.4%)
≥ 25 cm^3	66 (52.8%)	75 (59.1%)	71 (55.0%)	212 (55.6%)
Uterine volume (cm^3)				
Mean (SD)	387.73 (344.021)	402.65 (371.109)	407.85 (402.017)	399.52 (372.555)
Uterine volume n (%)				
< 300 cm^3	74 (59.2%)	72 (56.7%)	65 (50.4%)	211 (55.4%)
≥ 300 cm^3	51 (40.8%)	55 (43.3%)	64 (49.6%)	170 (44.6%)
Any surgery for uterine fibroids				
Yes	11 (8.8%)	15 (11.8%)	11 (8.5%)	37 (9.7%)
No	114 (91.2%)	112 (88.2%)	118 (91.5%)	344 (90.3%)
UFS-QoL (BPD subscale)				
Mean (SD)	66.80 (22.083)	68.51 (22.864)	71.40 (21.274)	68.90 (22.115)

BPD: bleeding and pelvic discomfort; CT: combination therapy; MBL: mean blood loss; miTT: modified intent-to-treat; ml: millilitres; n: number of subjects; SD: standard deviation; UFS-QoL: Uterine Fibroid Symptom and Health Related Quality of Life Questionnaire
Note: Percentages are based on the total number of patients in each treatment group or total.

An overview of the patient disposition for LIBERTY 1 and LIBERTY 2 is included in Appendix D1.2 (see Figure 37 and Figure 38).

Study sites in LIBERTY 1 and LIBERTY 2 (42)(43)

LIBERTY 1 involved 80 centres globally, including centres in the USA, Brazil, Italy, Poland, South Africa and the United Kingdom. Approximately 25% of patients were enrolled at sites outside of North America.

LIBERTY 2 involved 99 centres globally, including centres in the USA, Belgium, Brazil, Chile, Czech Republic, Hungary, Poland and South Africa. As with LIBERTY 1, approximately 25% of patients were enrolled at sites outside of North America.

Trial interventions in LIBERTY 1 and LIBERTY 2

In LIBERTY 1 and LIBERTY 2, patients were randomised in a 1:1:1 ratio to receive either:

- 24 weeks of relugolix CT [relugolix 40 mg tablet administered in combination with E2 (1.0 mg) / NETA (0.5 mg) co-formulated capsule]
- A relugolix-delayed CT regimen comprising 12 weeks of relugolix monotherapy (MT) followed by 12 weeks of relugolix CT [relugolix 40 mg tablet for 12 weeks, followed by relugolix 40 mg tablet administered with E2 (1.0 mg) / NETA (0.5 mg) co-formulated capsule for 12 weeks]
- 24 weeks placebo therapy [relugolix 0 mg placebo tablet administered in combination with E2/NETA 0 mg placebo capsule].

All regimens were administered orally, once daily.(41)

Placebo versions of relugolix and E2/NETA were designed to match their experimental counterpart in size, shape, colour and odour.(42,43)

Outcomes – primary endpoint in LIBERTY 1 and LIBERTY 2 (41)

The objective of the LIBERTY 1 and LIBERTY 2 trials was to determine the benefit of relugolix CT compared to placebo for 24 weeks on HMB associated with UF, and the studies primary endpoint were:

- Proportion of women 'responding' in the relugolix CT versus the placebo group where a 'responder' was classified as a women who achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the AH method.

Outcomes – secondary endpoints in LIBERTY 1 and LIBERTY 2

Secondary endpoints measured in LIBERTY 1 and LIBERTY 2 included achievement of amenorrhoea, change in MBL volume, UV and pain (as measured by the NRS score).(41) A summary of the key secondary endpoints is displayed in Table 12.

Table 12 Key secondary endpoints in LIBERTY 1 and LIBERTY 2 (45)

Objective	Endpoint
1. Achievement of amenorrhoea	Proportion of women who achieve amenorrhoea over the last 35 days of treatment
2. HMB associated with UF	% change from baseline to Week 24 in MBL volume
3. Impact of UF on symptoms, activities and HRQoL as measured by the UFS-QoL	Change from baseline to Week 24 in the UFS-QoL bleeding and pelvic discomfort (BPD) score
4. Change in haemoglobin	Proportion of women with haemoglobin ≤10.5 g/dL at baseline who achieve an increase of >2 g/dL from baseline at Week 24
5. Pain associated with uterine fibroids	Proportion of patients with a max. NRS score ≤ 1 during the 35 days before the last dose in the pain-evaluable population
6. UFV	% change from baseline to Week 24 in UFV
7. UV	% change from baseline to Week 24 in UV

BPD: bleeding and pelvic discomfort; HMB: heavy menstrual bleeding; HRQoL: health-related quality of life; MBL: menstrual blood loss; NRS: numerical rating scale; UFS-QoL: uterine fibroid health and symptom-related quality of life

Benefits of 24 weeks of relugolix CT compared with placebo were captured as exploratory analyses using the patient-reported European Quality of Life Five-

Dimension Five-Level [EQ-5D-5L] quality of life scale.(42,43) Whilst EQ-5D was captured as part of the studies, it should be highlighted that utility in the cost-effectiveness model was derived by mapping from the UFS-QoL and MBL to EQ-5D. During the LIBERTY 1 & LIBERTY 2 trials, it became clear to the investigators that the time point of administration of the EQ-5D instrument was not appropriate to measure the impact of UF on patients' quality-of-life. Since the EQ-5D-5L has a recall of "today," it only reflects what a patient experienced on the day of the administration (i.e. the study visit), which generally did not occur during menstruation. This is explained within the cost-effectiveness section.

Safety evaluations included the monitoring of vital signs, physical examination, adverse events, clinical laboratory variables, and 12-lead electrocardiography. Changes in bone mineral density were assessed by means of dual-energy x-ray absorptiometry at baseline and every 3 months during the trials. Endometrial biopsies were performed at baseline and at week 24 or the end of the treatment period (i.e. after the participant's last dose of relugolix CT or placebo). (41)

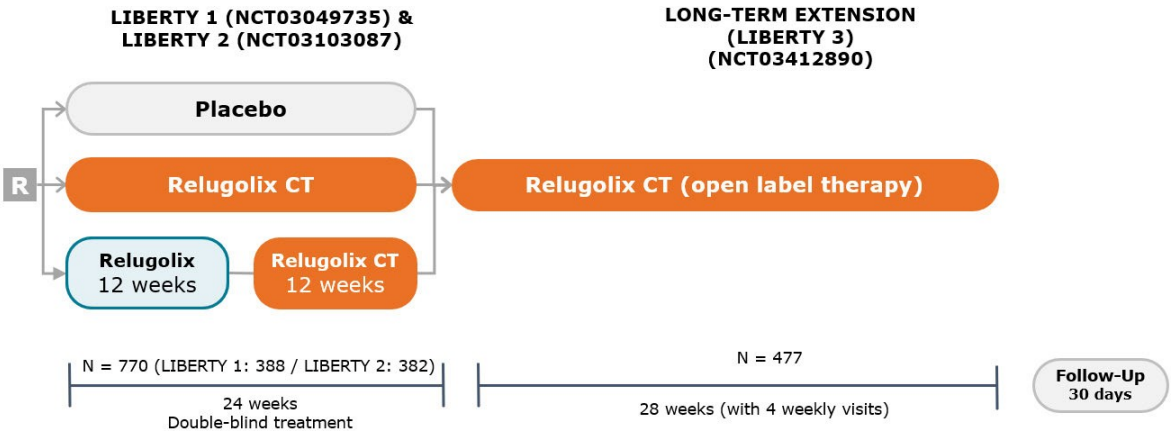
LIBERTY 3 (also known as LIBERTY EXTENSION)

Trial design

LIBERTY 3 is a phase 3, open-label, single-arm, long-term efficacy and safety extension study to evaluate relugolix CT in women with HMB associated with UF who have completed one of the parent studies LIBERTY 1 or LIBERTY 2. LIBERTY 3 is a 28-week extension study. (40)

The study design for LIBERTY 3 is shown in Figure 5.

Figure 5 LIBERTY 3 study design schematic (44)



Patient population and baseline characteristics in LIBERTY 3 (40)(44)

A total of 477 patients were enrolled to receive open-label relugolix CT, which represents > 75% of patients who completed the parent studies (LIBERTY 1 and LIBERTY 2). An overview of the patient disposition for LIBERTY 3 is included in Appendix D1.2 as Figure 39.

The key inclusion and exclusion criteria for LIBERTY 3 are described in Table 13.

Table 13 Key eligibility criteria for LIBERTY 3 (44)

Inclusion	Exclusion
Completed 24 weeks of study drug treatment and study participation in either LIBERTY 1 or LIBERTY 2	Had undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolisation, magnetic resonance-guided focused ultrasound for fibroids, or endometrial ablation for abnormal uterine bleeding at any time during the parent study
Voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures for LIBERTY 3	Had a weight that exceeded the weight limit of the dual-energy X-ray absorptiometry (DEXA) scanner or had a condition that precluded an adequate DEXA measurement at the lumbar spine and proximal femur (e.g. bilateral hip replacement, spinal hardware in the lumbar spine)
Was not expected to undergo gynaecological surgery or ablation procedures for UF within the study period, including during the Safety Follow-up period	Had a Z-score < -2.0 or had a ≥ 7% decrease in BMD from the parent study baseline at lumbar spine, total hip, or femoral neck, based on the parent study Week 24 DEXA assessment of BMD
Had a negative urine pregnancy test at the Week 24/Baseline visit	Had any contraindication to treatment with E2/NETA (CT)

Agreed to continue to use acceptable nonhormonal contraceptive methods consistently during the Open-Label Treatment period and for at least 30 days after the last dose of study drug	Was inappropriate for participation in this study because of conditions that may have interfered with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, subinvestigator or medical monitor
	Met a withdrawal criterion in the parent study (LIBERTY 1 or LIBERTY 2)

BMD: bone mineral density; CT: combination therapy; DEXA: dual-energy X-ray absorptiometry; E2: oestradiol; NETA: norethisterone acetate

The extension study population was defined as all patients who enrolled and received any amount of open-label study drug in the open-label extension study. All efficacy analyses were performed using the extension study population, unless otherwise specified. Efficacy analyses were performed by treatment group as randomised in the parent studies.

The extension safety population was defined as all enrolled patients who received any amount of open-label study drug in the open-label extension study. All safety analyses were performed using the extension safety population, unless otherwise specified. Safety data was analysed by parent study treatment group according to the actual treatment received (not the randomised treatment). Any patient who received at least one dose of relugolix was considered as a relugolix patient, consistent with analysis in the parent studies.

Except for one patient in the parent study (LIBERTY 2) who was originally randomised to the relugolix-delayed CT group who was enrolled in error and did not receive treatment, all enrolled patients were included in the extension study population and the extension safety population. Hence, 476 patients were included in the extension study population and the safety study population. The baseline characteristics of patients in LIBERTY 3 (Long Term Extension) are shown in Table 14, categorised by their parent study treatment group.

Table 14 Patient characteristics for LIBERTY 3 (safety population) (44)

Characteristics	LIBERTY 3 (Long Term Extension)			
	Placebo (N=164)	**Relugolix CT (N=163)**	**Relugolix-delayed CT (N=149)**	**Total (N=476)**
Age Mean (SD)	41.9 (5.43)	42.6 (5.08)	42.1 (5.58)	42.2 (5.36)

Race				
White	71 (43.3%)	85 (52.1%)	51 (34.2%)	207 (43.5%)
Black or African American	88 (53.7%)	69 (42.3%)	81 (54.4%)	238 (50.0%)
Asian	0	0	3 (2.0%)	3 (0.6%)
Other	5 (3.0%)	9 (5.5%)	14 (9.4%)	28 (5,9%)
Ethnicity				
Not Hispanic or Latino	126 (76.8%)	122 (74.8%)	113 (75.8%)	361 (75.8%)
Hispanic or Latino	36 (22.0%)	38 (23.3%)	34 (22.8%)	108 (22.7%)
Not reported	2 (1.2%)	3 (1.8%)	2 (1.3%)	7 (1.5%)
BMI (kg/m^2)				
Mean	32.577	31.384	30.997	31.675
SD	7.4556	7.0470	6.4000	7.0162

CT: combination therapy; E2: oestradiol; NETA: norethisterone acetate; SD: standard deviation; BMI: Body Mass Index

Study sites (44)

LIBERTY 3 was conducted at 149 centres in the USA, Belgium, Brazil, Chile, Czech Republic, Hungary, Italy, Poland and South Africa.

Trial interventions (40)

In the LIBERTY 3 extension study, all patients (regardless of parent study intervention) received 28 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of E2 1 mg and NETA 0.5 mg. Each patient was instructed to take one tablet and one capsule orally per day. The doses selected for this open-label extension study, relugolix 40 mg, E2 1 mg, and NETA 0.5 mg, were the same as those administered in the parent studies (LIBERTY 1 and LIBERTY 2).

Outcomes primary and secondary

The objective of LIBERTY 3 was to evaluate the long-term efficacy and safety of relugolix CT for up to 52 weeks of treatment (among patients who previously completed a 24-week treatment period in one of the parent studies, LIBERTY 1 or LIBERTY 2) on HMB associated with UF.

The study's primary endpoint was:

- Proportion of women who achieved or maintained an MBL volume of < 80 mL and at least a 50% reduction from parent study baseline MBL volume to the last 35 days of treatment, as measured by the AH method.(40)

The parent study baseline was, in general, used as the reference point for the extension study for all change from baseline-related endpoints, unless otherwise specified.

Secondary endpoints measured in LIBERTY 3 (Long Term Extension) included achievement/maintenance of amenorrhoea, change in UV and UFV. A summary of the key secondary endpoints is displayed in Table 15.(44)

Table 15 Key secondary endpoints in LIBERTY 3 (44)

Objectives	Endpoints
Achievement / maintenance of amenorrhoea	• Change from parent study baseline to Week 52 in MBL volume • Proportion of women who achieved or maintained amenorrhoea over the last 35 days of treatment
Haemoglobin	• Proportion of women with a haemoglobin concentration below the lower limit of normal at parent study baseline who achieved an increase of ≥ 1 g/dL from parent study baseline at Week 52 • Proportion of women with a haemoglobin concentration ≤ 10.5 g/dL at parent study baseline who achieve an increase of > 2 g/dL from parent study baseline at Week 52 • Change from parent study baseline to Week 52 in haemoglobin concentration
Changes in symptom severity and quality-of-life related to UF, as measured by the UFS-QoL	• Change from parent study baseline to Week 52 in UFS-QoL symptom severity scale • Change from parent study baseline to Week 52 in UFS-QoL subscales and total score
Impact of HMB on social, leisure, and physical activities, as measured by the MIQ (Menorrhagia Impact Questionnaire)	• Change from baseline to Week 52 in activities, concern, energy/mood, self-conscious, sexual function, and revised activities scales, and total scale score
UV	• Change from parent study baseline to Week 52 in UV
UFV	• Change from parent study baseline to Week 52 in UFV

MBL: menstrual blood loss; MIQ: Menorrhagia Impact Questionnaire; UFS-QoL: uterine fibroid health and symptom-related quality of life; UV: uterine volume; UFV: uterine f broid volume

As with the parent studies, LIBERTY 3 also conducted exploratory analyses to evaluate the benefit of relugolix CT on patient-reported quality-of-life outcomes (EQ-5D-5L) for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies.(44)

Safety was assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, BMD by dual-energy X-ray absorptiometry, and transvaginal ultrasound.(44)

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical analyses for LIBERTY 1, LIBERTY 2 and LIBERTY 3 is available in Table 16. An overview of the key aspects for each trial then follows with any further statistical analysis information of interest provided in section “Appendix M1.2 Further statistical analysis information (LIBERTY 1 & 2)” and ”M1.3 Further statistical analysis information (LIBERTY 3)”.

Table 16 Summary of statistical analyses (LIBERTY studies)

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
LIBERTY 1 & 2 (41)	The primary hypothesis tested in this study was whether relugolix CT was superior to placebo in the primary endpoint defined as the percentage of women who achieved both an MBL volume of < 80 mL and at least a 50% reduction in MBL volume over the last 35 days of treatment as compared with baseline	mITT population; two-sided 95% CI of the difference in proportions between relugolix CT and placebo Cochran-Mantel-Haenszel method	Planned sample size of 390 patients per trial (randomised 1:1:1) Actual sample: n=769 mITT population	For the primary analysis, patients with missing MBL volumes at Week 24/EOT (end of treatment) are identified per missing data handling rules. A mixed-effects model approach is used to impute missing data for the primary analysis.
LIBERTY 3 (40)(44)	As above for LIBERTY 1 & 2	Responder rate and two-sided 95% CI for each treatment group	Expected sample size of 600 based on (75% of 780 patients who were randomised into the parent studies) Actual sample: n=477, of which n=363 completed 53 weeks of treatment	For the evaluation of the primary endpoint, missing data handling rules are implemented to derive responder status at Week 52/EOT.

E2: oestradiol; EOT: end of treatment; CI: confidence interval; MBL: menstrual blood loss; NETA: norethisterone acetate

LIBERTY 1 and LIBERTY 2

The efficacy and safety analyses were conducted using a modified Intent-to-Treat (mITT) population, defined as all randomised patients who received at least one dose of study treatment.(41)

Randomisation was 1:1:1 with the stratification variables of geographic region and mean screening MBL volume (mL per AH method) as follows:

- Geographic region: North America versus Rest of World
- Mean screening MBL volume: < 225 mL versus ≥ 225 mL.

Primary efficacy analysis

The primary hypothesis tested in the LIBERTY 1 and LIBERTY 2 studies was whether relugolix CT was superior to placebo in the primary endpoint defined as the percentage of women who achieved both an MBL volume of < 80 mL and at least a 50% reduction in MBL volume over the last 35 days of treatment as compared with baseline.(42)(43)

The comparison of the primary endpoint between relugolix CT and placebo was analysed with the use of a Cochran-Mantel-Haenszel test for proportions, with stratification according to the baseline mean volume of menstrual blood loss (<225 ml vs. ≥225 ml) and geographic region (North America vs. rest of world).(41)

The primary endpoint was tested at a two-sided 0.05 significance level. The primary endpoint was met if the treatment effect observed in the relugolix CT group compared with that observed in the placebo group was statistically significant with a two-sided p-value of <0.05.

Key secondary efficacy analyses(41)

In each trial, the primary endpoint was tested first; if the p-value was less than 0.05, the key secondary efficacy endpoints were tested as prespecified in the statistical analysis plans. In LIBERTY 1, the first four key secondary endpoints were tested

sequentially, and the remaining three secondary endpoints were to be tested with the use of the Hochberg step-up procedure.

In LIBERTY 2, the first, second, third, and fifth secondary endpoints were tested sequentially, followed by testing of the other three key secondary endpoints (fourth, sixth, and seventh) with the use of the Hochberg procedure. This change in the order of hierarchical testing was made on the basis of the results of trial LIBERTY 1 before unblinding and the analysis of data in trial LIBERTY 2.

Statistical methods: safety

Safety analyses was carried out using the safety population. The safety population is the same as the mITT population and is defined as all randomised patients who have received any amount of study drug.(42,43) Safety data were analysed by treatment group according to the actual treatment received (not the randomised treatment).

Safety assessments included adverse events, vital signs, physical examinations (including visual acuity), clinical laboratory tests, 12-lead ECGs, endometrial biopsies, and assessments of BMD. Safety analyses were based on all randomised patients who received any amount of study treatment. Drug exposure was summarised by descriptive statistics. Severity of all adverse events was evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE version 5.0) and were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events was summarised by MedDRA system organ class and preferred term, relationship to study drug, and severity. (42,43)

Sample size

The enrolment of approximately 390 participants in each of the trials (LIBERTY 1 and LIBERTY 2) would provide each trial with more than 90% power to detect a difference of at least 30 percentage points in the primary endpoint, at a two-sided alpha level of 0.05, between the relugolix CT groups and placebo groups, assuming that 25% of the participants in the placebo group would have a response and that 20% of the participants would withdraw.(41)

Handling of dropouts or missing data (41)

Rules for the handling of missing data were implemented for deriving the response status at Week 24/EOT period (last 35 days of the treatment period), with consideration for the duration of exposure to treatment or placebo and for adherence to the collection of menstrual products against entries in the electronic diary (i.e., the number of days with returned menstrual products, divided by the number of days with reported bleeding and product use, according to the data recorded in the electronic diary). In participants with 100% adherence, response status was based on the observed volume of menstrual blood loss.

Participants who reported amenorrhoea or "spotting or negligible bleeding," as confirmed by data collected in the electronic diary, were considered to have had a response. Participants who received treatment or placebo for less than 4 weeks or who withdrew to undergo surgical intervention for UF were considered not to have had a response.

LIBERTY 3

Statistical methods: efficacy (44)

Descriptive assessments of efficacy and safety were made between the parent study (LIBERTY 1 or LIBERTY 2) baseline and the end of the open-label extension study (Week 52) on the extension study population, defined as patients who enrolled in LIBERTY 3 (i.e., who received at least one dose of study drug in the open-label extension study), separately for the treatment groups originally randomised in the parent studies.

The parent study baseline was, in general, used as the reference point for the extension study for all change from baseline-related endpoints, unless otherwise specified. No formal treatment comparisons were performed for this extension study.

Primary efficacy endpoint (40)(44)

The primary efficacy endpoint was the proportion of women who achieved an MBL volume of < 80 mL and at least a 50% reduction from parent study baseline in MBL volume over the last 35 days of treatment, as measured by the AH method. The

primary endpoint was referred to as a responder rate and derived on the basis of the total MBL volume measured at the Week 52/Early Termination visit window taking into consideration the patient's compliance with the return of feminine products and completion of the paper patient diary. The primary analysis of the primary endpoint was the responder rate and two-sided 95% CI for each treatment group.

Secondary efficacy endpoints

A table summarising the statistical analyses of each of the secondary efficacy endpoints in LIBERTY 3 can be found in Table 117 in Appendix M1.3.

Sample size (44)

As LIBERTY 3 was an extension study, the sample size was determined by the numbers of patients who completed either parent study and who were eligible and willing to participate in the extension study. It was estimated that approximately 600 patients (75% of 780 patients who were randomised into the parent studies) would participate in this extension study.

Participant flow

Details of participant flow through LIBERTY 1, LIBERTY 2 and LIBERTY 3 are provided in Appendix D1.2.

B.2.5 Quality assessment of the relugolix CT clinical effectiveness evidence

LIBERTY 1, LIBERTY 2 and LIBERTY 3 were assessed for quality using the York Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare. The summary of the findings are presented in Table 17 with more detailed results in Table 90 and Table 91 (which can be found in Appendix D1.3)

Table 17 Summary of the quality assessment results

Trial number (acronym)	MVT-601-3001 (LIBERTY 1)	MVT-601-3002 (LIBERTY 2)	MVT-601-3003 (LIBERTY 3)
Was randomisation carried out appropriately?	Yes	Yes	N/A
Was the concealment of treatment allocation adequate?	Yes	Yes	N/A
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	N/A
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	No
Was there good quality assurance for this study?	Yes	Yes	Yes
Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)			

The LIBERTY 1 and LIBERTY 2 trials were all good quality, robust RCTs that included randomisation, appropriate blinding of groups without any imbalances in the dropouts between groups nor evidence to suggest any measurement of more outcomes than reported. As an open-label extension trial, LIBERTY 3 also maintained good quality standards. Randomisation and blinding were not applicable to this open-label study, however, randomisation was performed in the parent study

trials from which participants were enrolled and all participants received 28 weeks of relugolix CT, thus minimising any bias due to treatment allocation. Differences in drop outs between groups were fully documented and reported.

As detailed in Section B.2.13, the eligibility criteria of the LIBERTY trials ensured that the study population was balanced and a good representation of women with symptomatic UF and significant disease burden who would likely be treated in clinical practice. The baseline age, BMI and menstrual blood loss volume of participants in the trials are representative of the average woman who would likely be treated in clinical practice and the trials included a good proportion of non-white patients (approximately only half were white) which provides further good representation of Black women who are more likely affected by UF.

Note: A quality assessment of the PEARL I and PEARL II studies is provided in Table 92 and Table 93, respectively, in Appendix D1.3.

B.2.6 Clinical effectiveness results of the relevant trials

Efficacy results of relugolix CT for the treatment of symptoms associated with UF were demonstrated in a series of Phase 2 and Phase 3 trials. The efficacy results relevant to this submission include LIBERTY 1, LIBERTY 2 and open-label extension study, LIBERTY 3.

As part of this submission, only efficacy and safety data from participants in the relugolix CT and placebo groups are presented and utilised in the model as only data from these two study arms relate to the submission population and drug indication.

LIBERTY 1 and LIBERTY 2

A summary of the results for the key efficacy endpoints in LIBERTY 1 and LIBERTY 2 are summarised in Table 18 further below.

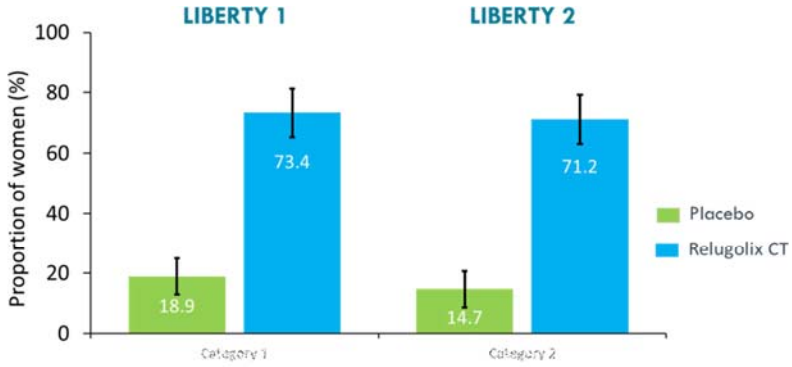
Primary efficacy endpoint

In the primary efficacy analysis in each trial, a response was defined as both a volume of MBL of less than 80 ml and a reduction of at least 50% from the baseline volume of MBL, as measured by the AH method, over the last 35 days of the treatment period. In the relugolix CT groups of the trials, 73% of the participants in LIBERTY 1 and 71% of those in LIBERTY 2 had a response, as compared with 19% and 15%, respectively, of the participants in the placebo groups (P<0.001 for both comparisons) (see Figure 6)(41).

The observed difference between the two groups was 54.54% (95% CI: 44.3% to 64.78%) in LIBERTY 1 and 56.47% (95% CI: 46.45% to 66.49%) in LIBERTY 2 in favour of the relugolix CT group and was statistically significant (p<0.0001).(42,43)

In each trial, the observed treatment effects appeared to be similar, regardless of race or other characteristics of the participants at baseline.(41)

Figure 6 Primary efficacy endpoint: Participants with reduction in HMB (LIBERTY 1 & LIBERTY 2) (41)



No. of Patients	127	128	129	125
Difference vs Placebo – percentage points		55		56
95% CI		(44-65)		(46-66)
P-value vs. Placebo		< 0.0001		< 0.0001

Error bars represent 95% CI. CI: confidence interval

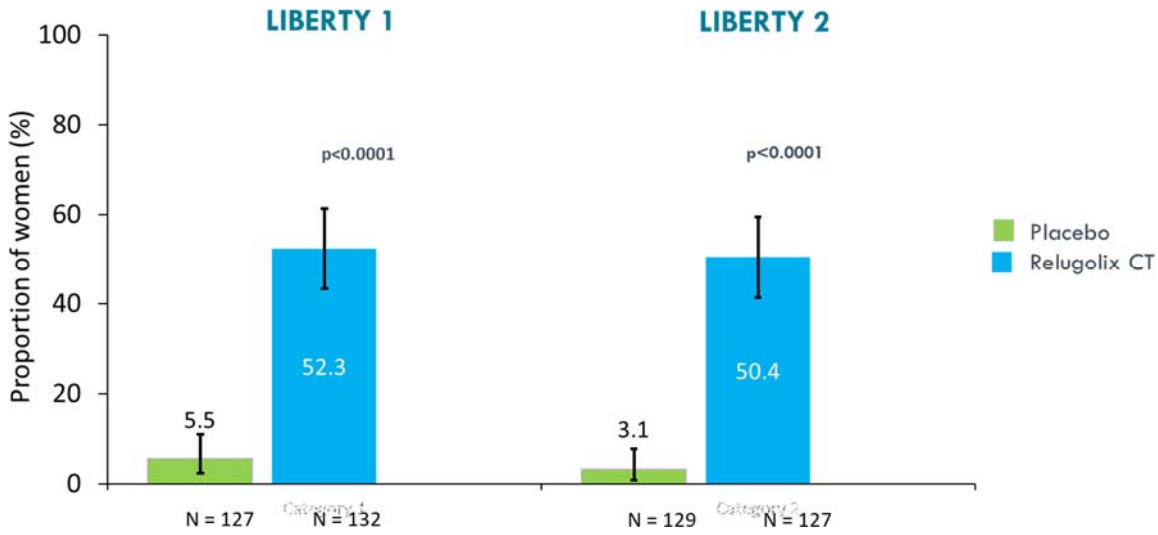
Secondary efficacy endpoints

Relugolix CT was superior to placebo with regard to six of seven key secondary endpoints that were tested hierarchically in LIBERTY 1 and LIBERTY 2.(41)

Amenorrhoea over the last 35 days of treatment period

Amenorrhoea over the last 35 days of the treatment period occurred in 52% and 50% of the participants receiving relugolix CT in LIBERTY 1 and LIBERTY 2, respectively, as compared with 6% and 3%, respectively, of those receiving placebo (P<0.001 for both comparisons).(41) (See Figure 7)

Figure 7 Secondary efficacy endpoint: Proportion of women with amenorrhoea during the last 35 days of the study (LIBERTY 1 & LIBERTY 2) (41–43)



Note: The difference between relugolix CT and placebo was statistically significant (p<0.0001). Least squares means and p-value for test of difference of relugolix CT minus placebo based on mixed-effects model with baseline MBL, region, treatment, visit and treatment by visit as fixed effects.
Error bars represent 95% CI
CI: confidence interval

The proportion of patients in the relugolix CT group who achieved sustained amenorrhoea, was significantly higher (nominal p < 0.0001) than in the placebo group at Weeks 8, 12, 16, 20, and 24. Additionally, beginning at Week 8, the proportion of patients who achieved sustained amenorrhoea in the relugolix CT group increased at each subsequent time point. Only few patients in the placebo group reached amenorrhoea at any time point and achieved sustained amenorrhoea by Week 24 (42,43)

These findings demonstrate that treatment with relugolix CT was associated with a significant reduction in MBL volume through Week 24 and that more patients treated with relugolix CT met the amenorrhoea criteria.(42,43)

MBL volume

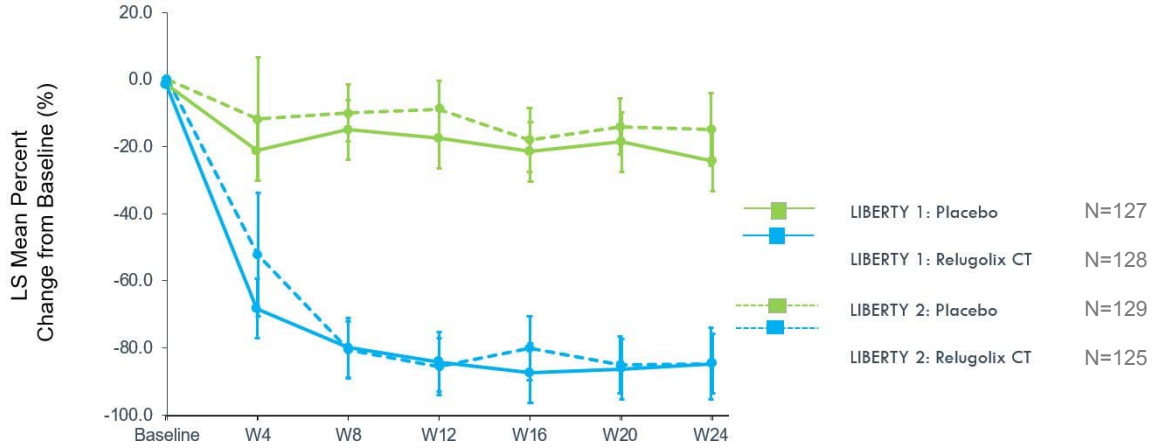
The mean reduction in MBL from baseline to week 24 in the relugolix CT groups was 84.3% in both LIBERTY 1 and LIBERTY 2, as compared with 23.2% and 15.1%, respectively, in the placebo groups (P<0.001 for both comparisons).(41)(See Figure 8)

Figure 8 Secondary efficacy endpoint: Mean change in MBL volume from baseline to Week 24 (LIBERTY 1 and LIBERTY 2) (42,43)

Patient numbers: N=127 N=128 N=129 N=125
Error bars represent 95% CI. CI: confidence interval
Note: The difference between Relugolix CT and placebo was statistically significant (p<0.0001). Least squares means and p-value for test of difference of Relugolix CT minus placebo based on mixed-effects model with baseline MBL, region, treatment, visit and treatment by visit as fixed effects.

Reduction in blood loss occurred by week 4 and was sustained through week 24 for patients in the relugolix CT groups(41)(see Figure 9).

Figure 9 Secondary efficacy endpoint: Summary of percent change in Menstrual Blood Loss volume by Visit (LIBERTY 1 & LIBERTY 2) (45)



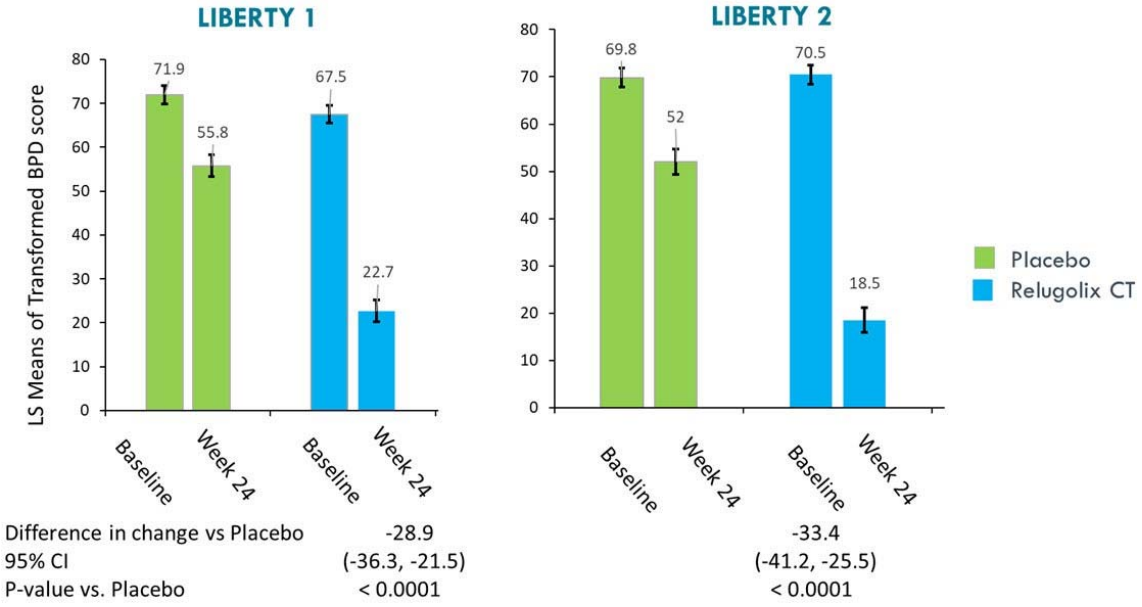
LS: least squares; W: Week
Error bars represent 95% confidence interval.
Note: least squares means and P value for test of difference of relugolix CT minus placebo was based on a mixed-effects model with baseline menstrual blood loss, region, treatment, visit, and treatment by visit as fixed effects; lines are staggered for visibility.

Bleeding and Pelvic Discomfort

In both the LIBERTY 1 and LIBERTY 2 trials, scores on the BPD scale, as measured by the UFS-QoL, improved significantly from baseline in the relugolix CT groups as compared with those in the placebo groups.(41)

The reductions from baseline to Week 24 in the UFS-QoL BPD scale score are presented in Figure 10.

Figure 10 Secondary efficacy endpoint: Reduction in bleeding and pelvic discomfort (LIBERTY 1 & LIBERTY 2) (45)



Patient numbers in LIBERTY 1: placebo N=127, relugolix CT N=128. LIBERTY 2: placebo N=129, relugolix CT N=125
Note: The BPD transformed score ranges from 0 to 100, with higher scores indicating greater symptom severity.
Error bars represent 95% CI. CI denotes confidence interval.

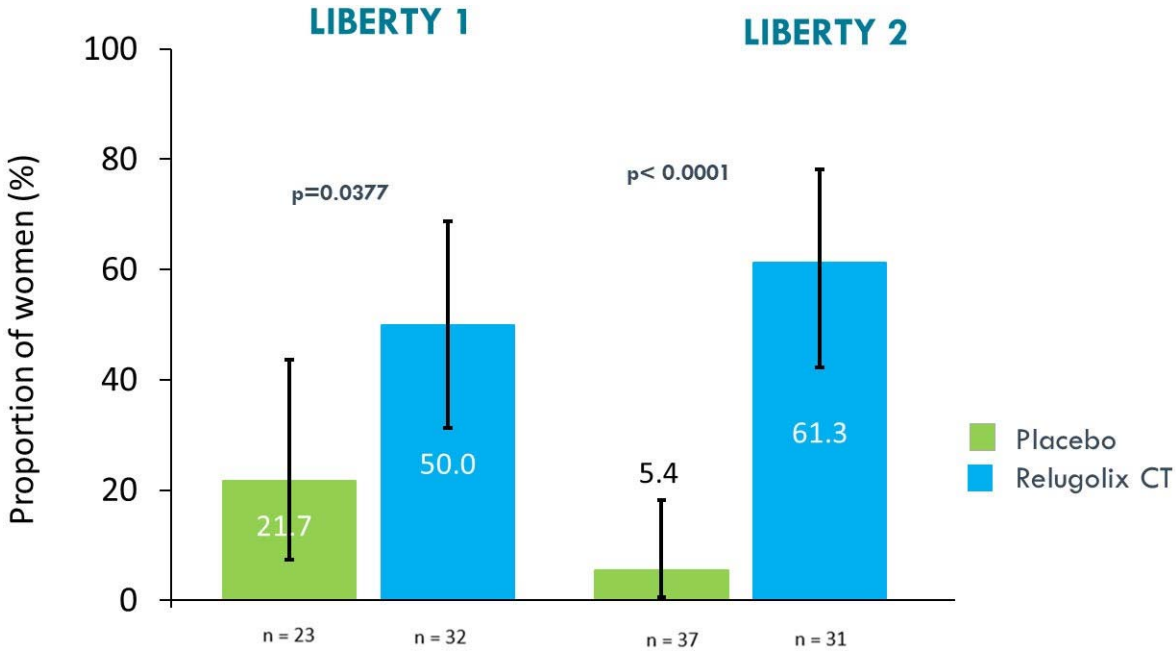
Haemoglobin levels

In LIBERTY 1, more than 50% of the participants who had anaemia at baseline (i.e. ≤10.5 g/dL) had an increase of more than 2 g/dL in haemoglobin levels with relugolix CT, as compared with 22% of placebo.(41) The difference between groups was statistically significant (p = 0.0377).(42)

In LIBERTY 2, 19 patients (61.3%) in the relugolix CT group and 2 patients (5.4%) in the placebo group met this endpoint. The difference between groups was statistically

significant (p < 0.0001).(43) The percent change for both studies is shown in Figure 11).

Figure 11 Secondary efficacy endpoint: Percent change from baseline in haemoglobin concentration for patients with ≤ 10.5 g/dL at baseline who achieve an increase of >2 g/dL from baseline to Week 24 (LIBERTY 1 & LIBERTY 2) (42,43)



Error bars represent 95% CI. The difference between relugolix CT and placebo was statistically significant.

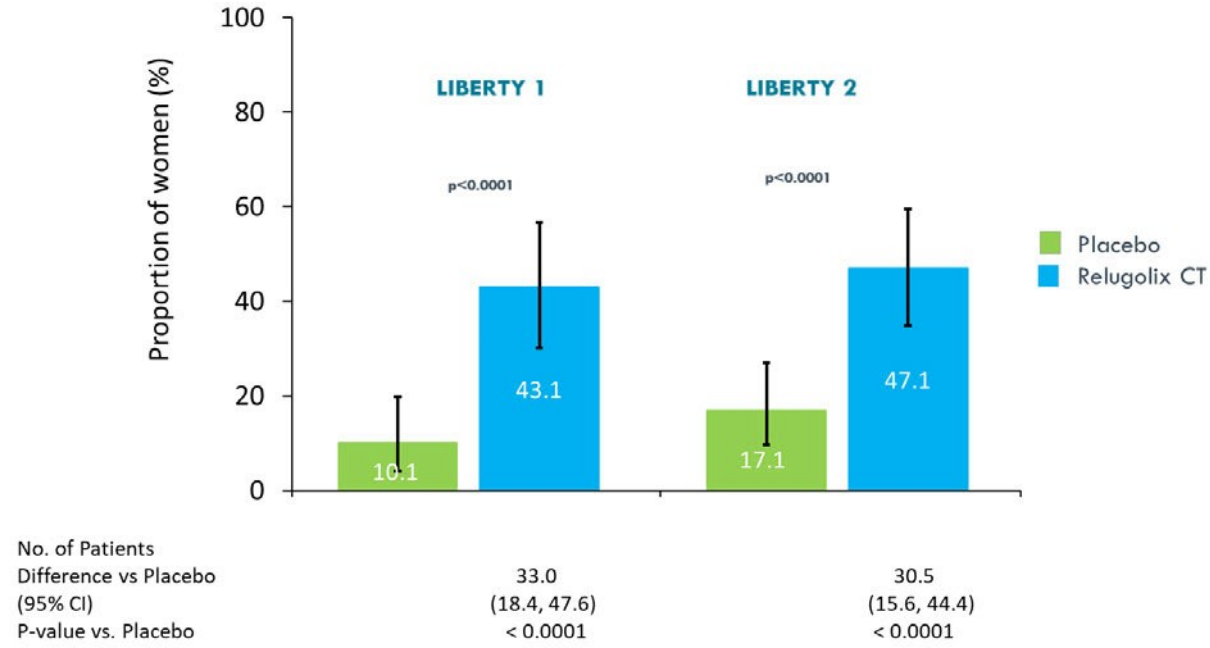
UF-associated pain

In LIBERTY 1, 45.3% of the relugolix CT group and 54.3% of the placebo group were included in the pain evaluable population.(42) Similarly, 54.4% of the relugolix CT group and 63.6% of the placebo group in LIBERTY 2 were included.(43)

Among the approximately 50% of the participants with moderate-to-severe pain at baseline who met the trial pain-evaluation requirements, the percentages of participants who had reductions to minimal or no pain (maximum numerical rating scale score, ≤1) over the last 35 days of the treatment period were significantly greater in the relugolix CT groups (LIBERTY 1: 43%; LIBERTY 2: 47%) than in the placebo groups (LIBERTY 1: 10%; LIBERTY 2: 17%) (P<0.001 for both comparisons)(41).

Figure 12 depicts the proportion of patients with minimal or no pain (maximum NRS score ≤ 1) during the last 35 days of treatment in a subset of pain evaluable patients.

Figure 12 Proportion of patients with a maximum NRS score ≤ 1 during the 35 days before the last dose of study drug (LIBERTY 1 & LIBERTY 2) (45)



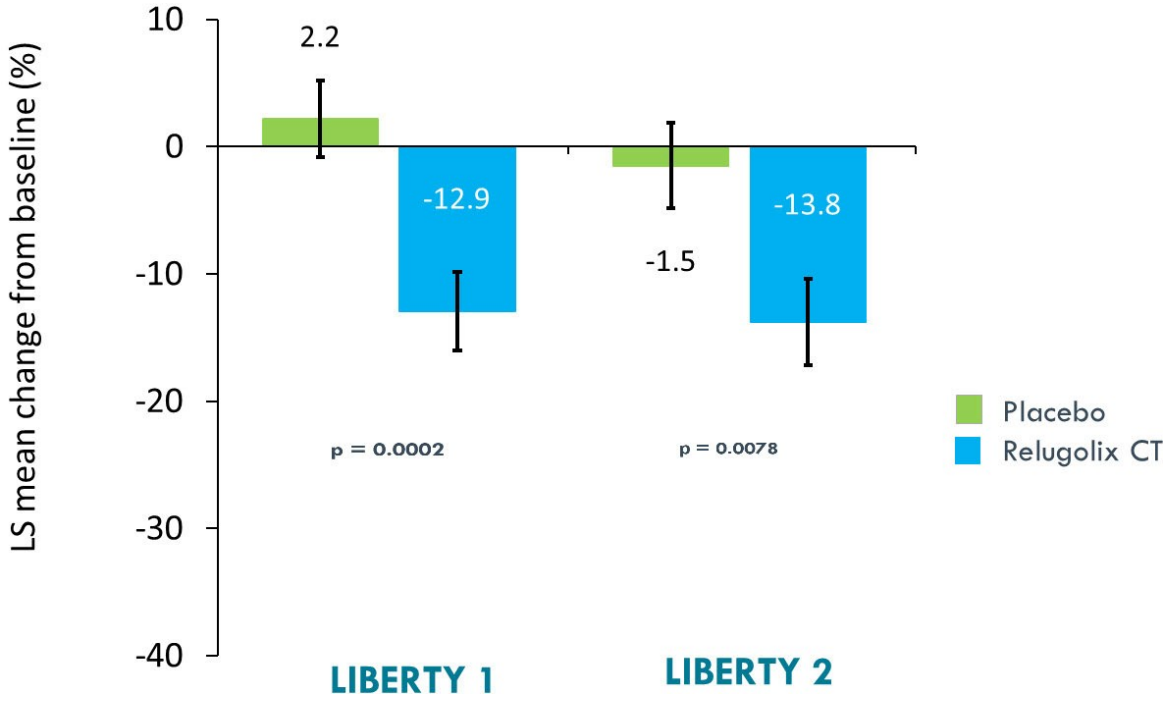
Error bars represent 95% CI.
CI: confidence interval; P or p: probability

Uterine volume

The overall UV was decreased to a greater extent with relugolix CT than with placebo, suggesting a reduced fibroid burden. In the relugolix CT group, the LS mean percent change from baseline to Week 24 in baseline-adjusted UV was greater than with placebo (-12.9% versus 2.2%; p<0.001 in LIBERTY 1 and -13.8% versus -1.5%; p=0.008 in LIBERTY 2).(41)

The percent change in UV is shown in Figure 13.

Figure 13 Secondary efficacy endpoint: Percent change in UV from baseline (LIBERTY 1 & LIBERTY 2) (42,43)

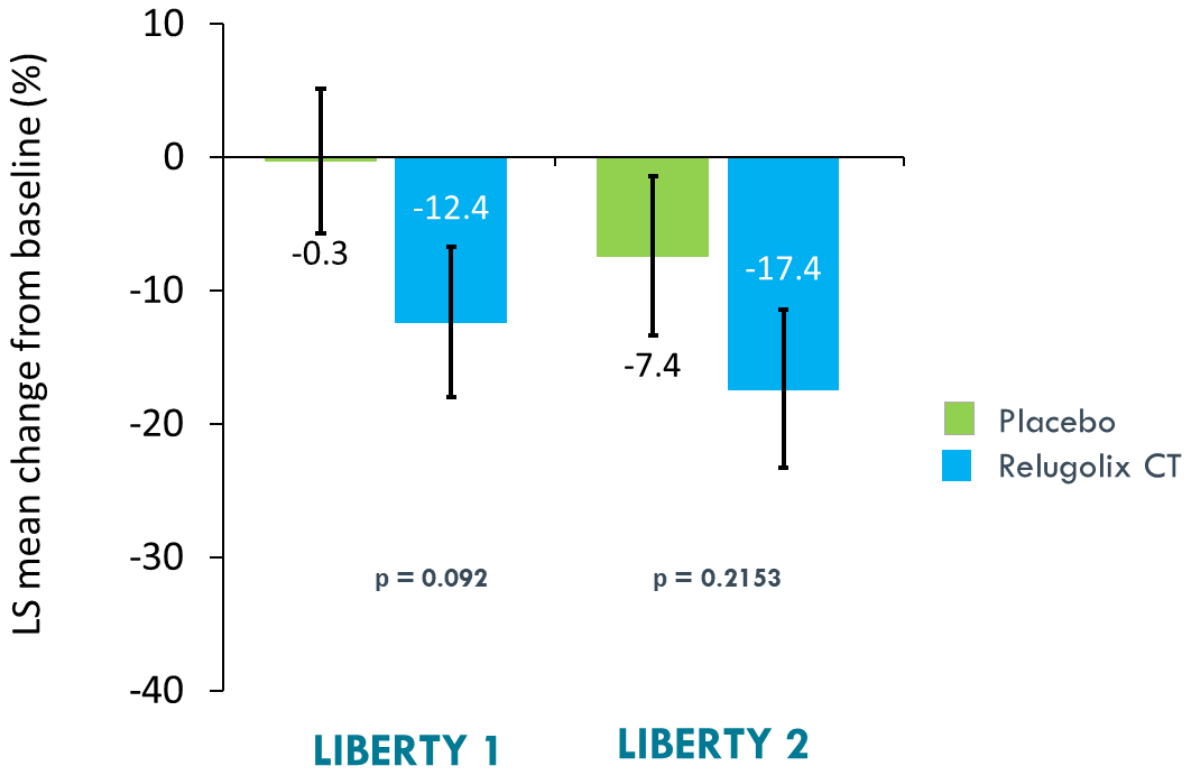


Patient numbers in LIBERTY 1: placebo N=127, relugolix CT N=128. LIBERTY 2: placebo N=129, relugolix CT N=125
Error bars represent standard error. LS: least squares

Primary UFV

Changes in the volume of the largest fibroid with relugolix CT did not differ significantly from those with placebo. In the relugolix CT groups, the least squares (LS) mean percent change from baseline to Week 24 in UFV trended towards greater reduction compared with placebo but the differences between groups did not reach statistical significance according to the Hochberg procedure (-12.4% versus -0.3%; p = 0.09 in LIBERTY 1 and -17.4% versus -7.4.0%; p = 0.22 in LIBERTY 2).(See Figure 14). (42,43)

Figure 14 Secondary efficacy endpoint: Percent change in UFV from baseline (LIBERTY 1 & LIBERTY 2) (42,43)



Patient numbers in LIBERTY 1: placebo N=127, relugolix CT N=128. LIBERTY 2: placebo N=129, relugolix CT N=125
Error bars represent standard error. LS: least squares

Summary of key efficacy endpoint results

Results for key efficacy endpoints in LIBERTY 1 and LIBERTY 2 are summarised in Table 18.

Table 18 Results for key efficacy endpoints in LIBERTY 1 and LIBERTY 2(41)

Endpoint	LIBERTY 1 Relugolix CT (n=128) Placebo (n=127)	LIBERTY 2 Relugolix CT (n=125) Placebo (n=129)
Primary Efficacy Endpoint		
MBL volume < 80 mL & ≥ 50% reduction*		
Relugolix CT vs Placebo n (%) Difference from placebo 95% CI (unadjusted) p-value	94 (73%) vs 24 (19%) 55% (44%, 65%) < 0.001	89 (71%) vs 19 (14.73%) 56% (46%, 66%) < 0.001
Secondary Efficacy Endpoint		
Proportion achieved amenorrhoea over the last 35 days of treatment		

Relugolix CT vs Placebo n(%) Difference 95% CI p-value	67 (52%) vs 7 (6%) 47% (37%, 56%) < 0.001	63 (50%) vs 4 (3%) 47% (38%, 57%) < 0.001
% change MBL volume (baseline to Week 24)		
Relugolix CT vs Placebo n(SD) Difference 95% CI p-value	-84.3 (±4.7) vs -23.2 (±4.6) -61.1 (-73.5, -48.6) < 0.001	-84.3 (±5.5) vs -15.1 (±5.5) -69.2 (-84.1, -54.3) < 0.001
Change in UFS-QoL BPD score (baseline to Week 24º)		
Relugolix CT vs Placebo [n (SD)] Difference 95% CI p-value	-45.0 (±2.9) vs -16.1 (±2.8) -28.9 (-36.3, -21.5) < 0.001	-51.7 (±2.9) vs -18.3 (±2.9) -33.4 (-41.2, -25.5) < 0.001
Proportion of women with a Hb increase of > 2 g/dL (baseline to Week 24) †		
Relugolix CT vs Placebo Difference 95% CI p-value	15/30 (50%) vs 5/23 (22%) 28% (4%, 53%) 0.04	19/31 (61%) vs 2/37 (5%) 56% (37%, 75%) < 0.001
Proportion of women who achieved a maximum NRS score ≤ 1 for UF-associated pain §		
Relugolix CT vs Placebo Difference 95% CI p-value	25/58 (43%) vs 7/69 (10%) 33% (18%, 48%) < 0.001	32/68 (47%) vs 14/82 (17%) 30% (16%, 44%) < 0.001
% change in primary UFV (baseline to Week 24)		
Relugolix CT vs Placebo Difference 95% CI p-value	-12.4 (±5.62) vs -0.3 (±5.40) -12.1 (-26.3, 2.0) 0.09	-17.4 (±5.9) vs -7.4 (±5.9) -10.0 (-25.8, 5.8) 0.2153
% change in UV (baseline to Week 24)		
Relugolix CT vs Placebo Difference 95% CI p-value	-12.9 (±3.1) vs2.2 (±3.01) -15.1 (-23.0, -7.3) <0.001	-13.8 (±3.4) vs -1.5 (±3.4) -12.2 (-21.3, -3.2) 0.008

* from baseline MBL volume. º score as measured by the UFS-QoL (Q1, Q2, Q5). † with a Hb level ≤10.5 g/dL at baseline.
§ achieved 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.
Hb: Haemoglobin; UFS-QoL BPD: uterine fibroid health and symptom-related quality of life bleeding and pelvic discomfort; CI: Confidence Interval; CT: Combination Therapy; MBL: menstrual blood loss; NRS: numerical rating scale; UF: uterine fibroid; UFS-QoL: uterine fibroid health and symptom-related quality of life
Note: Plus–minus values are least-squares means ±SD

Exploratory analysis: EQ-5D-5L

Overall, changes in the five domains of the EQ-5D-5L in LIBERTY 1 and LIBERTY 2 were similar across treatment groups. The majority of patients (over 75%) in the treatment groups had no change or improvement from baseline to Week 24 for mobility, self-care, usual activities, anxiety/depression, and pain/discomfort. The EQ-5D-5L summary of categorical change at Week 24 results are available in Table 118 (LIBERTY 1) and Table 119 (LIBERTY 2) in Appendix M1.4.

At baseline, mean EQ-5D-5L visual analogue scale scores were 75.9 (LIBERTY 1) and 77.6 (LIBERTY 2) in the relugolix CT group and 73.5 (LIBERTY 1) and 75.8 (LIBERTY 2) in the placebo group. At Week 24, the mean change from baseline was 4.6 and 4.2, respectively, in LIBERTY 1, and 8.3 and 4.2, respectively in LIBERTY 2.(42,43)

Table 19 LIBERTY 1: summary of categorical change from baseline in EQ-5D-5L at Week 24 (mITT population) (46)

	Relugolix CT (N = 128)	**Placebo (N = 127)**
VAS Baseline (n)	126	127
Mean (SD)	75.9 (17.41)	73.5 (18.48)
Median	79.5	80.0
(Q1,Q3)	(69.0, 90.0)	(60.0, 90.0)
Min, Max	20, 100	25, 100
Change from baseline at week 24 (n)	98	104
Mean (SD)	4.6 (19.07)	4.2 (19.82)
Median	7.0	1.0
(Q1,Q3)	(-4.0, 16.0)	(-5.0, 11.0)
Min, Max	-50, 80	-40, 70

N: number of patients; Q1: lower quartile; Q3: upper quartile; SD: standard deviation
Note: percentages are based on the total number of patients in each treatment group

Table 20 LIBERTY 2: summary of categorical change from baseline in EQ-5D-5L at Week 24 (mITT population) (47)

	Relugolix CT (N = 125)	**Placebo (N = 129)**
VAS Baseline (n)	123	126
Mean (SD)	73.9 (19.29)	5.8 (19.51)
Median	80.0	80.5
(Q1,Q3)	(60.0, 90.0)	(69.0, 90.0)
Min, Max	6, 100	8, 100
Change from baseline at week 24 (n)	98	95
Mean (SD)	8.3 (17.83)	4.2 (21.30)
Median	7.5	1.0
(Q1,Q3)	(-1.0, 19.0)	(-4.0, 10.0)
Min, Max	-40, 85	-85, 56

N: number of patients; Q1: lower quartile; Q3: upper quartile; SD: standard deviation
Note: percentages are based on the total number of patients in each treatment group

LIBERTY 3 (open-label extension study)

Primary efficacy endpoint: Proportion of Responders with Menstrual Blood Loss Volume < 80 mL and ≥ 50% Reduction from Parent Study Baseline Over the Last 35 Days of Treatment (extension safety population)

In LIBERTY 3, the relugolix CT group demonstrated sustained improvement in HMB through 52 weeks with 87.7% of patients meeting the definition of responder.(40)

As shown in Table 21, the proportion of patients meeting the criteria for the individual components of the composite primary endpoint was similar, indicating no single component (i.e., MBL volume < 80 mL or percent change from parent study baseline of at least 50%) influenced the results for the primary endpoint. In the placebo group (i.e. patients randomised to placebo in the parent study), [redacted] achieved an MBL volume of < 80 mL and at least a 50% reduction from parent study baseline in MBL volume over the last 35 days of treatment.(44)

Table 21 Primary efficacy analysis: Proportion of responders at Week 52/EOT (extension study population) LIBERTY 3 (44)

	Relugolix CT (n=163)		Placebo (n=164)	
	N (%)	**95% CI**	**N (%)**	**95% CI**
Number of responders	143 (87.73)	[redacted]	[redacted]	[redacted]
Number of patients with MBL <80mL over the last 35 days of treatment	142 (87.12%)	[redacted]	[redacted]	[redacted]
Number of patients with >= 50% reduction (parent study baseline - the last 35 days of treatment)	145 (88.96%)	[redacted]	[redacted]	[redacted]

CI: confidence interval; E2: oestradiol; NETA: norethisterone
Note: There were six patients (two patients who were lost to follow-up and four who withdrew consent due to social reasons) deemed non-responders based on Week 24 MBL volumes, for whom last observation carried forward methodology was applied as part of the intent-to-treat analysis used for all treatment groups. Inclusion of these patients as non-responders may help explain the lower responder rate observed in the placebo group.

Figure 15 shows the proportion of responders achieving the primary efficacy endpoint and the proportion of responders with MBL below 80 mL and those with at least 50% reduction from parent study baseline separately. Figure 16 presents a summary of percent change from parent study baseline in MBL volume by study visit.

Figure 15 Primary efficacy endpoint: Proportion of responders with MBL volume < 80 mL and ≥ 50% reduction from parent study baseline over the last 35 days of treatment LIBERTY 3 (44)

Figure 16 Summary of percent change from parent study baseline in MBL volume by visit (extension study population) LIBERTY 3 (44)

Secondary efficacy endpoint: Proportion of women who achieved or maintained amenorrhoea over the last 35 days of treatment

The secondary endpoint evaluating amenorrhoea, showed that 70.6% of women on relugolix CT achieved or maintained amenorrhoea over the last 35 days of treatment.(40).

A summary of the proportion of patients who achieved or maintained amenorrhoea over the last 35 days of treatment is presented in Figure 17.

Figure 17 Secondary efficacy endpoint: Proportion of patients who achieved amenorrhoea at Week 52 (last 35 days of treatment) (extension study population) LIBERTY 3 (44)

In relugolix CT group, 115 patients (70.6%) achieved amenorrhoea over the last 35 days of treatment.(40) In contrast, a lower response rate was observed in the placebo group with [redacted] having achieved amenorrhoea over the last 35 days of treatment, which may reflect a shorter time of therapy compared with the longer term relugolix CT group.(44)

Secondary efficacy endpoint: Improvement of anaemia assessed by changes in haemoglobin concentrations

The secondary endpoints evaluating haemoglobin concentrations included the proportion of women with anaemia (haemoglobin concentrations ≤ 10.5 g/dl) at parent study baseline who achieved an increase of ≥ 2 g/dl at Week 52. (40)(44)

LIBERTY 3 results show that the reductions in MBL led to substantial improvements (> 2 g/dl) in haemoglobin concentrations at Week 52 for most (59.0%) patients with anaemia(< 10.5 g/dl) at parent study baseline.(40) (See Figure 18) In the placebo group, of the patient [redacted] with a haemoglobin concentration ≤ 10.5 g/dl at parent study baseline, [redacted] achieved an increase of > 2 g/dl at Week 52.(44)

Figure 18 Secondary efficacy endpoint: Proportion of patients with a haemoglobin concentrations 10.5 g/dl at parent study baseline who achieved > 2 g/dl increase in haemoglobin at week 52 (extension safety population) LIBERTY 3 (44)

Similar results were demonstrated with regards to the proportion of women with a haemoglobin concentration below the lower limit of normal at parent study baseline who achieved ≥ 1 g/dl increase in haemoglobin concentration at Week 52. In the relugolix CT group, of the patients with a haemoglobin concentration below the lower

limit of normal at parent study baseline, [redacted] achieved an increase of ≥ 1 g/dL at Week 52. In the placebo group, of the patients with a haemoglobin concentration below the lower limit of normal at parent study baseline, [redacted] achieved an increase of 2 1 g/dL at Week 52.(44) (see Figure 19)

Figure 19 Secondary efficacy endpoint: Proportion of patients with a haemoglobin concentration below the lower limit of normal (11.6 g/dl) at parent study baseline who achieved an increase of 1 g/dl from parent study baseline to week 52 (extension study population) LIBERTY 3 (44)

In terms of change in haemoglobin concentration from parent study baseline to Week 52, patients in the relugolix CT group saw their mean haemoglobin concentrations [redacted] At Week 24, the LS mean percent change from parent study baseline haemoglobin concentration was [redacted] and with continued relugolix CT treatment, the LS mean percent change from parent study baseline was [redacted] at Week 52. (44)

In the placebo group for patients with a haemoglobin concentration ≤ 10.5 g/dL at parent study baseline, LS mean haemoglobin concentrations rose slightly during the parent study, ranging from [redacted] at Week 4 to [redacted] Week 24. Once treatment with relugolix CT was initiated in the open-label extension study, LS mean percent

change in haemoglobin concentrations [redacted], ranging from [redacted] at Week 28 to [redacted] at Week 52.(44)

Figure 20 Secondary efficacy endpoint: Percent change from parent study baseline to Week 52 in haemoglobin concentration for women with haemoglobin :::10.5 g/dl (extension study population) LIBERTY 3 (44)

Secondary efficacy endpoint: UFS-Qol scores

USF-QoL BPD (Bleeding Pain and Discomfort) scale score

The change from parent study baseline to Week 52 in UFS-Qol BPD scale score, with a range of possible scores from Oto 100, where higher score values are indicative of greater distress and lower scores are indicative of minimal distress was evaluated.(44) The secondary endpoints evaluating patient-reported outcomes on the UFS-Qol BPD scale included the mean change from parent study baseline to Week 52 in UFS-QoL BPD scale (Figure 21) and the proportion of responders, defined as patients who achieved a reduction of at least 20 points in UFS-Qol BPD scale score at Week 52 (Figure 22).(44)

Consistent with the change observed at Week 24, the BPD scale score was reduced by 51.3 points from parent study baseline to Week 52, indicating that reduction in measures of symptom-associated distress were substantial and sustained.(40)

In the placebo group, the LS mean change from parent study baseline to Week 52 UFS-Qol BPD scale score was -48.6 (indicating improvement) and was greater than the change observed at Week 24.(44)

The proportion of patients who met the responder threshold, at least a 20-point reduction at Week 52 on the transformed score for BPD scale is presented in Figure 22.(44)

Figure 21 Secondary efficacy endpoint: Summary of change from parent study baseline in UFS-Qol BPD scale score (extension study population) LIBERTY 3 (44)

The proportion of responders on the UFS-Qol BPD scale at Week 52 was [redacted] in the relugolix CT group and [redacted] in the placebo group. Numerically, the proportion of responders observed at Week 52 was [redacted] observed at Week 24 and Week 36.(44)

[redacted]

For those who remained on study, the [redacted]

The proportion achieving responder status in the placebo group after crossing over to relugolix CT [redacted]

Figure 22 Secondary efficacy endpoint: Proportion of patients who achieved 20-point reduction on BPD scale by visit (extension study population) LIBERTY 3 (44)

UFS-QoL symptom severity scale score

The other secondary endpoints evaluating patient-reported outcomes on the UFS-QoL included the mean change from parent study baseline to Week 52 in UFS-QoL symptom severity scale (Figure 23), and in Health Related UFS-QoL total and subscale scores. Additionally, the proportion of responders, defined as patients who achieved a reduction of at least 20 points in UFS-QoL BPD scale score at Week 52 were evaluated.(44)

Figure 23 Secondary efficacy endpoint: Least squares mean change from parent study baseline to week 52 in UFS-QoI symptom severity scale over time (extension study population) LIBERTY 3 (44)

LS = least squares; **Wk** = week
Note: Error bars represent 95% CIs.
Note: Shaded area represents time in parent studies.

At parent study baseline, the LS mean symptom severity scale scores across treatment groups were consistent with parent study baseline values observed in other study of women with symptoms associated with UF. In the relugolix CT group, the LS mean symptom severity scale score [redacted] at Week 24 and that [redacted] Mean scores at Week 52 were [redacted].

In the placebo group, the LS mean symptom severity scale scores [redacted] at Week 24. After initiation of

open-label relugolix CT, scores [redacted] at Week 52. This score was [redacted] at Week 52 and mean values observed in women without UF.(44)

Health Related UFS-QoL total scores

At Week 52 the LS mean change from parent study baseline scores for the relugolix CT group [redacted] in UFS-QoL total score, [redacted] in quality of life observed [redacted]

In the placebo group that transitioned to the relugolix CT group at Week 24, the LS mean UFS-QoL total score [redacted] at Week 52 relative to parent study baseline. [redacted] on -treatment (i.e., relugolix CT) time period with a [redacted] 24 weeks of the study during placebo treatment [redacted]

For the activities, concern, energy/mood, self-conscious, sexual function, and revised activities scales, and total scale score LS mean scores at Week 52 in [redacted]

Secondary efficacy endpoints: UV and UFV

LIBERTY 3 showed reductions in UV and UFV at Week 24 in the parent studies were sustained out to Week 52 in LIBERTY 3.(40) The secondary endpoint evaluating UV was the percent change from parent study baseline to Week 52 in UV. In the relugolix CT group, the LS mean percent change in UV from parent study baseline was [redacted]. In the placebo group, the LS mean percent change in UV from parent study baseline [redacted]

The secondary endpoint evaluating UFV was the percent change from parent study baseline to Week 52 in UFV. In the relugolix CT group, the LS mean percent change

in UFV from parent study baseline was [redacted] In the placebo group, the LS mean percent change in UFV from parent study baseline was [redacted]

Exploratory analysis: EQ-5D-5L

[redacted] both the relugolix CT and placebo groups) [redacted] from parent study baseline to Week 52 for mobility, self-care, usual activities, anxiety/depression and pain/discomfort. The LIBERTY 3 EQ-5D-5L summary of categorical change results are available in Table 120 in Appendix M1.4.

At parent study baseline, mean EQ-5D-5L visual analogue scale (VAS) scores were [redacted] (relugolix CT group) and [redacted] (placebo group). At Week 52, the mean change from baseline was [redacted]

Table 22 LIBERTY 3: summary of categorical change from baseline in EQ-5D-5L (extension study population) (48)

	Relugolix CT (N = 163)	Placebo (N = 164)
VAS Baseline (n)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
(Q1,Q3)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Change from baseline at week 24 (n)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
(Q1,Q3)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]
Change from baseline at week 52 (n)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
(Q1,Q3)	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]

N: number of patients; Q1: lower quartile; Q3: upper quartile; SD: standard deviation; VAS: visual analogue scale
Note: percentages are based on the total number of patients in each treatment group

B.2.7 Subgroup analysis

As stated in Section B.2.4, subgroup analyses of the primary efficacy endpoint were conducted in LIBERTY 1, 2 and 3 trials comparing the relugolix CT group versus the placebo group to assess whether treatment effects were consistent across clinically important subgroups of the study population (e.g. age, race, geographic region, etc). Across all subgroups, treatment differences were consistent with the primary analysis with a higher proportion of patients who received relugolix CT meeting the definition for responder than patients who received placebo, as indicated by the point estimate and lower bound of the 95% CI for the odds ratios being above 1 favouring relugolix CT over placebo. The magnitude of the responses across these subgroups was generally consistent with that observed in the analysis of the primary efficacy endpoint in the overall population, especially in the subgroups with larger sample sizes.(42,43)

Furthermore, treatment effect in LIBERTY 2 was slightly higher in the rest of world than in North America and in White patients compared with Black or African American patients. Small sample sizes in Asian and other racial groups made it difficult to make robust comparisons. Smaller treatment differences were observed in the subgroups of women with larger uterine volumes (≥ 300 cm^3) relative to the rest of the subgroups; however, the odds ratio (95% CI) in these subgroups was still in favour of relugolix CT group.(42,43)

B.2.8 Meta-analysis

Not applicable.

B.2.9 Indirect and mixed treatment comparisons

Since direct head-to-head randomised control trial (RCT) data is not available, an indirect treatment comparison (ITC) was conducted to compare the efficacy of relugolix CT with UPA 5mg (Esmya®) and GnRH agonist (leuprorelin 3.75mg).

The outcomes of the ITC are used in conjunction with a QoL algorithm that translates disease specific outcomes related to MBL (the primary outcome from the clinical

trials included in the ITC) into health utilities, which are ultimately used to calculate quality-adjusted life-years (QALYs) in the economic model. MBL volume (mean percentage decrease) is an outcome of high clinical relevance in the clinical studies and also in clinical practice for the assessment of UF treatment effect. This outcome was the most comparable outcome in the LIBERTY and PEARL studies, used in the ITC. Other than MBL, outcomes such as pain may be clinically relevant but were not captured for the full patient population in the LIBERTY studies. Safety outcomes were not assessed in the ITC. The trial data used in the ITC covered a period of 3 months and no relevant safety events were observed in the LIBERTY or PEARL studies during this time period.

To estimate QoL on the population level, the following outcomes were estimated through an ITC and used in the model:

- Mean MBL volume for relugolix CT, UPA 5mg (Esmya®), and leuprorelin 3.75mg, at weeks 4, 8, 12, and 24.

Included studies

From the 205 identified studies from the SLR results, studies had to fulfill the following selection criteria to be considered for inclusion in the ITC:

- Randomised control trial
- Trial arms include one or more of the following interventions: UPA 5 mg, relugolix 40 mg and leuprorelin 3.75 mg
- Patient population consist of women of reproductive age with symptomatic UF
- MBL is included as outcome.

Regarding the interventions, UPA and leuprorelin are understood to be the most applicable clinical and price comparators on a European level. Of note, UPA 10mg was not included in the criteria since it is not available in the European market and leuprorelin 3.75mg was selected as it is the most common dose of GnRH agonist. Furthermore, leuprorelin 3.75mg was the only GnRH agonist used in the criteria since it is acknowledged, from Cochrane reviews(49)(50), that all GnRH agonists are equivalent when it comes to treatment of UF, therefore it seemed appropriate to focus on one (the main) GnRH agonist, leuprorelin 3.75mg, as part of the search.

Thirteen trials were identified for possible inclusion in the ITC from the systematic literature review on efficacy and safety. From the identified eligible trials, the trials were then selected for comparison based on similarity of endpoints and population, trial quality and size.

Similarity of endpoints was the main reason for exclusion. To be fit for purpose, the outcomes of the ITC were aligned with the inputs of the QoL algorithm. The QoL algorithm in the model has been developed for MBL as a continuous variable, i.e. mean MBL volume. Therefore, mean MBL volume was the target outcome of the ITC. Moreover, different methods such as AH method or PBAC, can be used to estimate MBL volume. The calibration coefficients to the AH method differ between studies and have to be publicly available to translate PBAC into AH measurement and facilitate comparison. In addition, endpoints should be measured at similar time points during the trial.

A table of the excluded trials and exclusion rationale can be found in Table 88 (in Appendix D1.4 Indirect Treatment Comparison (ITC) methodology).

As a result of the exploration of available trials, the LIBERTY 1, LIBERTY 2, PEARL I and PEARL II trials were included in the ITC. Data on mean MBL volume at different time points were available from the trial Clinical Study Reports (CSRs).

PEARL I and PEARL II

In the SLR, the PEARL I and PEARL II trials were identified through 3 published papers. PEARL I was a 13-week randomised, parallel-group, double blind, placebo controlled, phase 3 trial in women with symptomatic fibroids and excessive MBL who were eligible for surgery for UF comparing daily-oral placebo (n=48), UPA 5 mg (n=96) or UPA 10 mg (n=98). The coprimary efficacy endpoints were control of uterine bleeding (PBAC score <75) and reduction in UFV at week 13, after which patients could undergo surgery.

The PEARL I safety and efficacy findings were published (and identified in the SLR) through the following 2 papers:

- Donnez et al. (2012)(51) reporting on the trial findings

- Barlow et al. (2014)(52) reporting on the secondary outcome measure of vaginal bleeding pattern.

PEARL I demonstrated that treatment with UPA for 13 weeks effectively controlled excessive menstrual bleeding due to UF and reduced the size of fibroids. At 13 weeks, uterine bleeding was controlled in 91% of the women receiving 5 mg UPA, 92% of those receiving 10 mg UPA, and 19% of those receiving placebo. The rates of amenorrhea were 73%, 82%, and 6%, respectively, with amenorrhea occurring within 10 days in the majority of patients receiving UPA. The median changes in total fibroid volume were −21%, −12%, and +3%. UPA induced benign histologic endometrial changes that had resolved by 6 months after the end of therapy. Serious adverse events occurred in one patient during treatment with 10 mg UPA (uterine haemorrhage) and in one patient during receipt of placebo (fibroid protruding through the cervix). Headache and breast tenderness were the most common adverse events associated with UPA but did not occur significantly more frequently than with placebo.(51)

PEARL II was randomised, parallel-group, double-blind, double-dummy, active-comparator-controlled, phase 3 noninferiority trial to assess the efficacy and safety of daily-oral UPA (either 5mg [n=98] or 10mg [n=104]) compared with leuprolide acetate (3.75mg once-monthly intramuscular injections, n=101), in the preoperative treatment of symptomatic UF. The safety and efficacy findings for PEARL II were published (and identified in the SLR) through a separate paper by Donnez et al. (2012).(53) The study found that uterine bleeding was controlled in 90% of patients receiving 5 mg UPA, in 98% of those receiving 10 mg UPA, and in 89% of those receiving leuprolide acetate, for differences (as compared with leuprolide acetate) of 1.2 percentage points (95% confidence interval [CI], −9.3 to 11.8) for 5 mg UPA and 8.8 percentage points (95% CI, 0.4 to 18.3) for 10 mg UPA. Moderate-to-severe hot flushes were reported for 11% of patients receiving 5 mg UPA, for 10% of those receiving 10 mg UPA, and for 40% of those receiving leuprolide acetate (P<0.001 for each dose of UPA vs. leuprolide acetate). PEARL II demonstrated that both the 5 mg and 10 mg daily doses of UPA were noninferior to once-monthly leuprolide acetate in controlling uterine bleeding and were significantly less likely to cause hot flushes.(53)

The 3 identified studies for PEARL I and PEARL II are listed in Table 87 (in Appendix D1.1). A quality assessment of the PEARL I and PEARL II studies is provided in Table 92 and Table 93, respectively, in Appendix D1.3.

The following items are also available in Appendix M:

- An overview of key trial findings and conclusions is provided in Appendix M1.5
- A comparative summary of trial methodology for PEARL I and PEARL II (Table 123)
- Patient characteristic details for PEARL I and PEARL II are provided in Table 121 and Table 122, respectively
- A summary of clinical effectiveness evidence for PEARL I and PEARL II is available in Table 124 and Table 125, respectively
- A summary of statistical analyses for PEARL I and PEARL II is available (Table 126)
- A critique of the LIBERTY vs. PEARL studies is provided in Appendix M, section “M1.6 LIBERTY vs PEARL studies”.

Exclusion of Osuga et al. 2019 study (54)

One study by Osuga et al. 2019 (reporting on TAK-385-CCT-002: leuprorelin 1.88/3.75mg, relugolix monotherapy and placebo) was identified via a review paper by Barra et al. 2019.(55) This phase 3, randomised, double-blind study investigated the noninferiority of relugolix 40 mg monotherapy once-daily for 12 weeks compared with monthly leuprorelin acetate injections in reducing HMB associated with UF (primary endpoint); and efficacy, pharmacodynamics, and safety for 24 weeks. The study involved 281 Japanese women. Mean PBAC score was 254.3 in the relugolix group and 263.7 in the leuprorelin group. The proportion of patients with total PBAC score of less than 10 for weeks 6–12 was 82.2% in the relugolix group and 83.1% in the leuprorelin group, demonstrating noninferiority of relugolix compared with leuprorelin (relugolix–leuprorelin difference 20.9%; 95% CI: –10.10 to 8.35; prespecified noninferiority margin –15%; P=0.001). Additionally, relugolix was associated with an earlier effect on menstrual bleeding than leuprorelin (PBAC score

of less than 10, 64.2% vs 31.7% [relugolix–leuprorelin difference 32.5%; 95% CI: 20.95–44.13%] for weeks 2–6 and PBAC score of 0, 52.6% vs 21.8% [30.7%; 95% CI: 19.45–42.00%] for weeks 2–6) and faster recovery of menses after treatment discontinuation (relugolix median [Q1, Q3], 37 days [32.0, 46.0]; leuprorelin median, 65 days [54.0, 77.0]).(55)

Whilst the Osuga study directly compared the effect of relugolix and leuprorelin for 24 weeks in Japanese women, the relugolix treatment was 40mg, once daily monotherapy and not relugolix CT. Critically, it was not possible to convert data from PBAC to AH from this trial using the same factor for conversion as for PEARL I. The specific factor is not the same between studies and depends on the type of collection method (e.g. sanitary product) used making it incorrect to use the same calculations and translations between PBAC and AH across studies. For PEARL I this factor can be derived from information provided in the publication, however, for the Osuga 2019 study this information was not found, not even with access to the study protocol and clinical study report (CSR).

A summary of missing information that could not be found for the TAK-385-CCT-002 study [despite access to the publication (Osuga et al. 2019), study protocol and CSR] include:

- Uses PBAC but does not report the conversion rate derived from AH calibration for this particular trial (e.g. dependent on sanitary products used)
- Does not report mean MBL volume, only share of patients reaching PBAC threshold < 10 (MBL volume is used in the model QoL algorithm and is as such preferred)
- PBAC threshold <10 likely is below threshold used in LIBERTY studies (cannot be validated as no conversion rate is specified).

Due to these reasons, it was not possible to include TAK-385-CCT-002 within the ITC.

Table 23 Summary of trials used to carry out the ITC

	Relugolix 40 mg	Ulipristal acetate 5 mg	Leuprorelin 3.75 mg	Placebo
LIBERTY 1	Yes			Yes
LIBERTY 2	Yes			Yes
PEARL I		Yes		Yes
PEARL II		Yes	Yes	

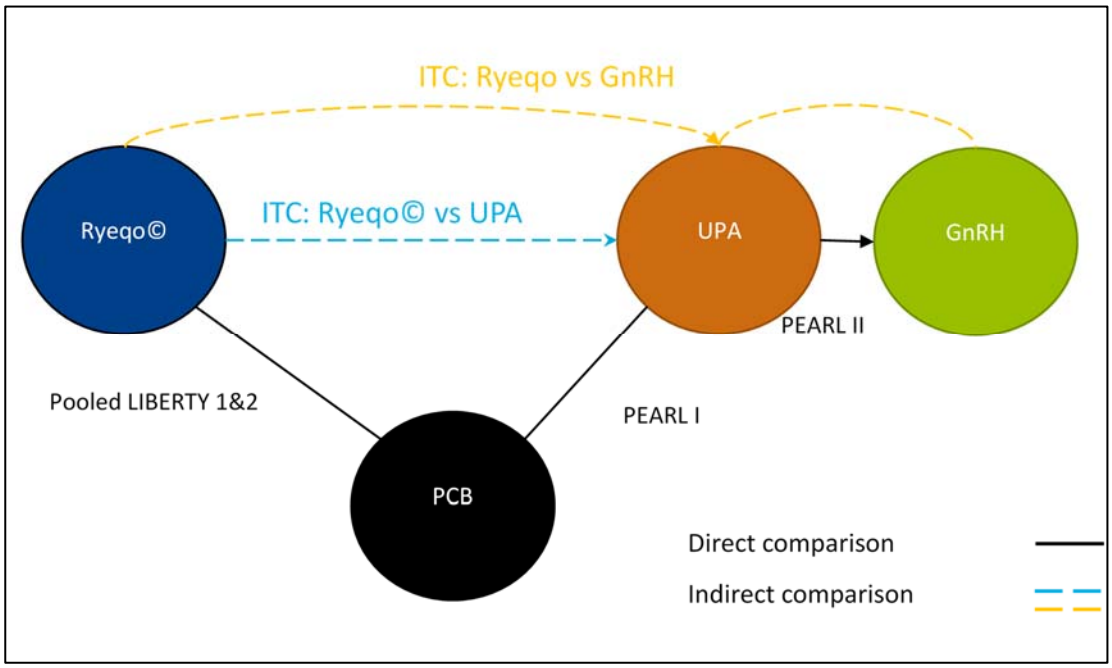
Comparisons using the included trials

Using data from the 4 included clinical trials (LIBERTY 1, LIBERTY 2, PEARL I and PEARL II), the following sets of comparisons were conducted:

- Relugolix CT vs. UPA 5mg (indirect comparison via placebo)
- UPA 5mg vs. leuprorelin 3.75mg (direct comparison)

Given that no study could be included with a common comparator arm between relugolix and leuprorelin (GnRH), the relative effect had to be estimated from an extended network. This method implicitly assumes that the UPA arms in PEARL I and PEARL II can be set equal. This assumption is reasonable given the similarity between the studies in terms of study design, inclusion criteria and patient characteristics. Figure 24 provides an overview of the comparisons.

Figure 24 Indirect comparison overview



The methodology for the ITC is included in Appendix D1.4. A summary of the trials excluded from the ITC is also available in Appendix D1.4 (see Table 88).

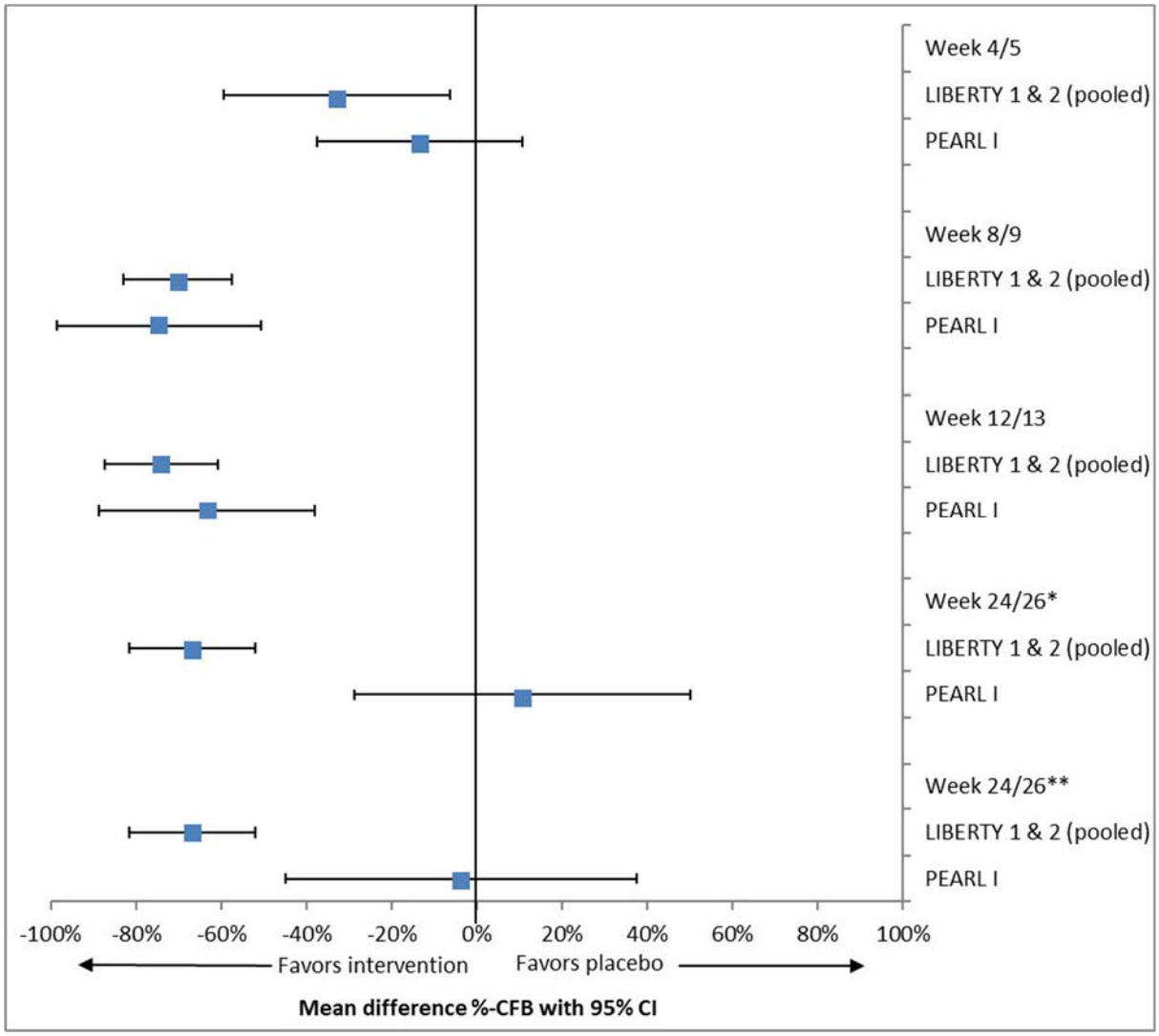
Pooled of MBL values from LIBERTY 1 and LIBERTY 2

Pooled values of MBL volume from LIBERTY 1 and LIBERTY 2 were used in the model for the relugolix CT and placebo arm (see Table 95 and Table 96 in Appendix D1.4 for the trial and pooled data values). For baseline values, the weighted average of the pooled relugolix CT and placebo MBL volume was used in order to create one uniform baseline value (see Table 97 in Appendix D1.4).

Results of the indirect treatment comparison

The forest plot (Figure 25 below) shows the results from the individual studies (pooled LIBERTY 1 and 2, and PEARL I) of intervention (relugolix CT/UPA) vs. placebo.

Figure 25 Forest plot of mean difference in percentage CFB in MBL for relugolix CT vs. placebo (LIBERTY 1 & 2 pooled) and UPA vs. placebo (PEARL I)



* Per-protocol population in PEARL I without hysterectomy or endometrium ablation ** Per-protocol population in PEARL I without surgery
Note: Treatment in the PEARL I and II trials was discontinued after week 13.
CFB: change from baseline; MBL: mean blood loss; CI: confidence interval

Table 24 and Table 25 show the results for mean difference in percentage change from baseline (CFB) from the ITC for relugolix CT vs. UPA, and the direct comparisons of GnRH vs. UPA, respectively. To be used in the cost-effectiveness model, mean MBL by treatment and time point, was calculated using the formulas shown in the ITC Methodology section (see Appendix D1.4). The transformed model input is described in Table 26.

Mean percentage decrease in MBL was larger (19.43% at week 4) for relugolix CT compared with UPA (Table 24). At week 8, however, UPA had a slightly larger percentage decrease compared with relugolix CT (4.53%). At week 12, relugolix CT had a larger decrease compared with UPA (10.73%). At week 24, relugolix CT had a substantially larger decrease in MBL compared with UPA (for both populations from PEARL I and II, i.e. without hysterectomy/endometrium ablation and without surgery, respectively). This finding was expected since UPA was discontinued in the PEARL trials after week 13. MBL results at week 24 were therefore not included in the model. The Chi^2 heterogeneity test indicates whether the observed differences in results are due to chance alone. The low p-value for week 24 results ($p<0.05$) indicate that there is heterogeneity of intervention effects. For week 4–13 results, no indications of heterogeneity were found. However, care must be taken when interpreting the Chi^2 test which has a low power when the number of studies included is low (n=2).

At week 4, leuprorelin had a smaller decrease in MBL compared with UPA, but a larger decrease at week 8 and 12. This entails that relugolix CT had a larger decrease in MBL, and consequently absolute MBL value (Table 26), at week 4 compared with UPA and leuprorelin. At week 8, relugolix CT had a smaller decrease in MBL compared with UPA and leuprorelin and therefore a higher absolute MBL value. At week 12, absolute MBL was lower in relugolix CT compared with UPA and leuprorelin.

Table 24 ITC results: relugolix CT vs. UPA

	Mean difference %-CFB Week 4	**Mean difference %-CFB Week 8**	**Mean difference %-CFB Week 12**	**Mean difference %-CFB Week 24-no hysterectomy* (UPA patients not on treatment)**	**Mean difference %-CFB Week 24-no surgery** (UPA patients not on treatment)**
Relugolix CT vs. UPA	-19.43%	+4.53%	-10.73%	-77.63%	-63.06%
Heterogeneity statistic Chi^2	1.125 (p=0.289)	0.107 (p=0.744)	0.538 (p=0.463)	13.021 (p<0.001)	7.936 (p=0.005)

CFB: Change from baseline

* No hysterectomy or endometrium ablation post treatment in the PEARL trials.

** No surgery post treatment in the PEARL trials.

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

Table 25 ITC results: leuprorelin vs. UPA

	Mean difference %-CFB Week 4	Mean difference %-CFB Week 8	Mean difference %-CFB Week 12	Mean difference %-CFB Week 24-no hysterectomy*	Mean difference %-CFB Week 24-no surgery**
Leuprorelin vs. UPA	+31.14%	-3.79%	-1.50%	+23.45%	+14.12%

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

Table 26 Model inputs (from the ITC)

	Baseline	Week 4	Week 8	Week 12
Relugolix CT	229.1	115.8	51.3	37.8
UPA	229.1	160.3	40.9	62.3
Leuprorelin	229.1	231.6	32.2	58.9

Note: Treatment in the PEARL I and II trials was discontinued after week 13. MBL results at week 24 were therefore not included in the model.

Conclusions / interpretation of the ITC findings

Based on the relative effect towards the common comparator arm (placebo), mean percentage decrease in MBL was larger (19.43%) at week 4 for relugolix CT compared with UPA. At week 8, however, UPA had a slightly larger percentage decrease compared with relugolix CT (4.53%). At week 12, relugolix CT had a larger decrease compared with UPA (10.73%). The direct comparison between UPA and GnRH agonist shows the flare effect of GnRH agonist at week 5 but almost equal effect at week 9 and 13.

The ITC results show that the effect of relugolix CT on reducing MBL volume is at least equal to, and potentially better, than UPA. Under the reasonable assumption that the UPA arms in both PEARL studies are very similar, and given the equal effect of UPA and GnRH agonist, it can be concluded that the effect of relugolix CT on reducing MBL volume is also at least equal to, and potentially better than, GnRH agonist.

Uncertainties in the indirect treatment comparisons

The indirect treatment comparison has some limitations. MBL outcomes were not measured at same time points in the LIBERTY and PEARL trials. In LIBERTY, MBL was measured at week 4, 8, 12, and 24 and at week 5, 9, 13, and 26 in PEARL. Although MBL was measured only one week apart for those follow-ups relevant for the cost-effectiveness model (4/5, 8/9, 12/13), the effect of relugolix CT might be slightly underestimated if it can be assumed that both treatments have a similar time-to-effect.

Another limitation is that the trial populations (LIBERTY 1 and 2, PEARL I and II) are assumed to be similar in all factors that may affect outcome. This assumption has to be made when conducting a Bucher indirect comparison. Patients in the PEARL trials had higher average bleeding scores at baseline compared with patients in the LIBERTY trial which may indicate that patients with more severe bleeding were included in the PEARL trials. For example, median MBL at baseline in the placebo group was 186 in LIBERTY 1, and median PBAC in PEARL I was 376 (corresponding to approximately 301 AH MBL). This issue was somewhat compensated through use of percentage change from baseline (CFB) figures and not absolute CFB.

Adverse reactions

LIBERTY 1 and LIBERTY 2

Safety evaluations included the monitoring of vital signs, physical examination, adverse events, clinical laboratory variables, and 12-lead electrocardiography. Changes in bone mineral density were assessed by means of dual-energy x-ray absorptiometry at baseline and every 3 months during the trials. Endometrial biopsies were performed at baseline and at week 24 or the end of the treatment period (i.e., after the participant's last dose of relugolix CT or placebo).(41)

An overview of the key safety endpoints is provided in Table 27.

Table 27 Key safety endpoints of LIBERTY 1 and LIBERTY 2(42,43)

Objective	Endpoint
Safety of 24 weeks of once-daily relugolix CT	Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms
Change in BMD (lumbar spine) at Week 12	% change from baseline to Week 12 in BMD at the lumbar spine (L1 - L4) in the relugolix CT arm, as assessed by DEXA
Change in BMD at Week 24	% change from baseline to Week 24 in BMD at the lumbar spine (L1 - L4), total hip, and femoral neck, as assessed by DEXA
Incidence of vasomotor symptoms	Incidence of vasomotor symptoms

BMD: bone mineral density; CT: combination therapy; DEXA: dual-energy x-ray absorptiometry

In LIBERTY 1, the overall incidence of adverse events was 66% in the placebo group and 62% in the relugolix CT group in LIBERTY 2, the incidence was 59% and 60%, respectively. Serious adverse events were reported infrequently; each serious adverse event that was reported occurred in one participant in a given trial group. No deaths were reported.(41)(see Table 28)

Table 28 Summary of adverse events in LIBERTY 1 and LIBERTY 2 (safety population)(41)

Characteristics N (%)	LIBERTY 1		LIBERTY 2	
	Placebo (N=127)	Relugolix CT (N=128)	Placebo (N=129)	Relugolix CT (N=126)
Any	84 (66%)	79 (62%)	76 (59%)	76 (60%)
Leading to discontinuation	5 (4%)	7 (5%)	6 (5%)	3 (2%)
Serious	2 (2%)	7 (5%)	4 (3%)	1(1%)
Fatal outcome	0	0	0	0

Abbreviations: E2 = oestradiol; n = number of patients in subset; N = number of patients; NETA = norethisterone acetate.
Note: Percentages are based on the total number of patients in each treatment group.

A summary of frequent adverse events by preferred term reported in at least 5% of patients in any treatment group is presented in Table 29.

Table 29 Adverse events reported for >5% in any group in LIBERTY 1 and LIBERTY 2 (41)

Characteristics N (%)	LIBERTY 1		LIBERTY 2	
	Placebo (N=127)	Relugolix CT (N=128)	Placebo (N=129)	Relugolix CT (N=126)
Hot flush	10 (8%)	14 (11%)	5 (4%)	7 (6%)
Headache	19 (15%)	14 (11%)	15 (12%)	11 (9%)
Hypertension	0	7 (5%)	4 (3%)	5 (4%)
Arthralgia	4 (3%)	4 (3%)	4 (3%)	1 (1%)
Cough	7 (6%)	1 (1%)	4 (3%)	0
Nausea	6 (5%)	4 (3%)	10 (8%)	6 (5%)
URTI	3 (2%)	1 (1%)	7 (5%)	6 (5%)

Anaemia	6 (5%)	4 (3%)	8 (6%)	2 (2%)
Fatigue	5 (4%)	4 (3%)	2 (2%)	1 (1%)

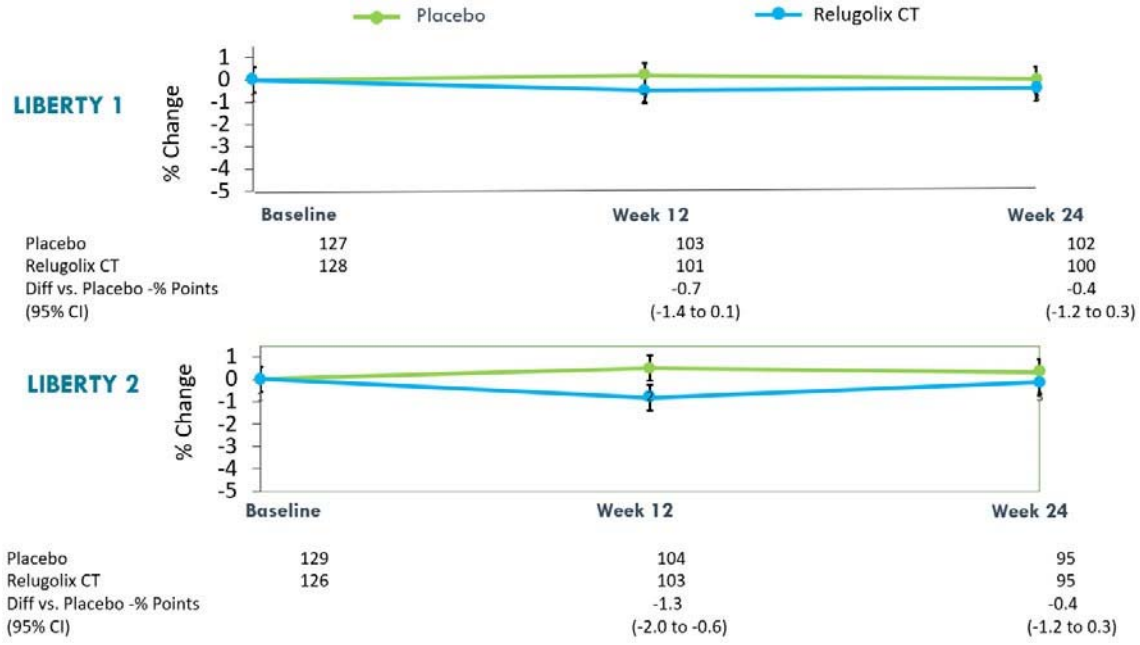
CT: combination therapy; URTI: upper respiratory tract infection

Hot flush was the most frequently reported adverse event in both trials. In LIBERTY 1, hot flush occurred in 8% of the participants in the placebo group and in 11% of those in the relugolix CT group; in LIBERTY 2, the incidence was 4% and 6%, respectively.(41)

In LIBERTY 1, hypertension as an adverse event was reported in no participants in the placebo group and in 5% of the participants in the relugolix CT group. In LIBERTY 2, the incidence was 3% and 4%, respectively.(41)

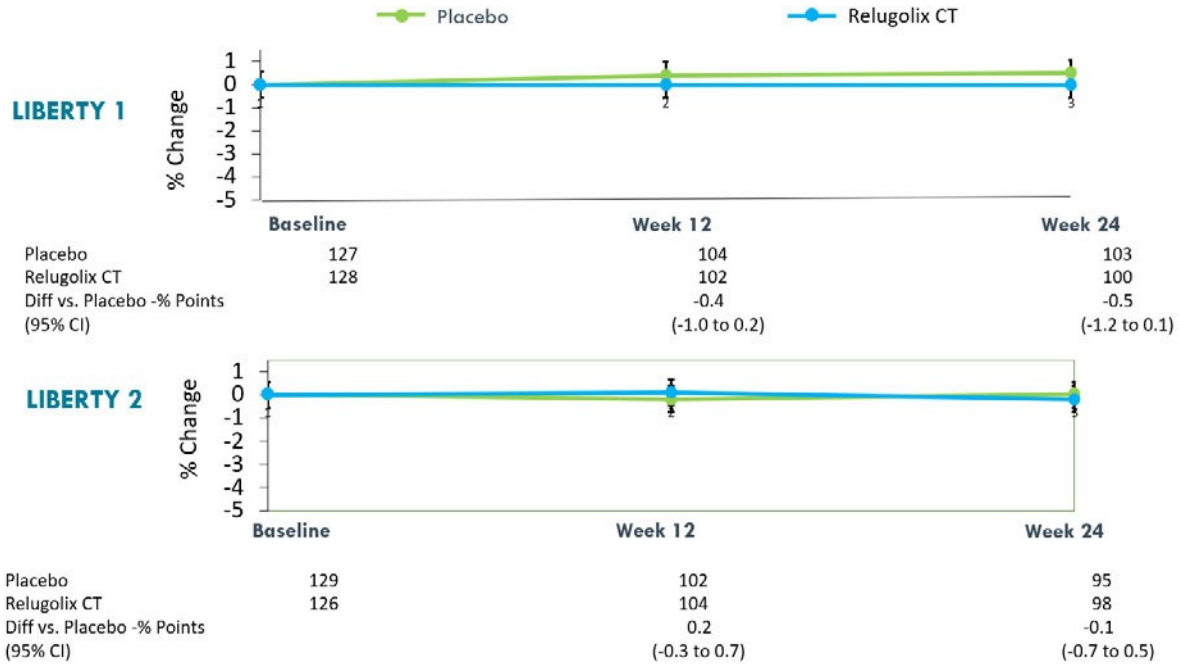
Data from LIBERTY 1 and LIBERTY 2 showed that bone mass was preserved in the relugolix CT group. The percent changes from baseline to weeks 12 and 24 in bone mineral density at the lumbar spine (L1 through L4) and the total hip were similar in the relugolix CT group and the placebo group in both trials (see Figure 26 and Figure 27).

Figure 26 Changes in BMD - Lumbar spine (LIBERTY 1 & LIBERTY 2) (41)



Error bars show 95% confidence interval

Figure 27 Changes in BMD - Total hip (LIBERTY 1 & LIBERTY 2) (41)



Error bars show 95% confidence interval

Laboratory tests and vital signs, including systolic and diastolic blood pressures, were similar among the groups. There were no meaningful differences in the mean changes from baseline or in the percentages of participants who met prespecified limits of change for any analysis, including liver-function tests and lipid levels.(41)

At week 24, no cases of endometrial hyperplasia or endometrial cancer had occurred in the relugolix CT group. Endometrial hyperplasia without atypia was observed in two participants in the placebo group in LIBERTY 1. No pregnancies were reported in the relugolix groups in either trial.(41)

Serious adverse events

In LIBERTY 1, serious adverse events were reported for 2 patients (1.6%) in the placebo group and 7 patients (5.5%) in the relugolix CT group. In general, serious adverse events were reported each for a single patient and in a single treatment group except for serious adverse events of ankle fracture, reported in one patient each in the relugolix CT groups. Both events of ankle fracture were associated with accidental trauma. In the relugolix CT group there were two serious adverse events related to expulsion/prolapse of UF, one of them being related to study drugs.(42)

In LIBERTY 2, serious adverse events were reported for 4 patients (3.1%) in the placebo group and 1 patient (0.8%) in the relugolix CT group. None of the events were assessed as related to study drug.(43)

Overall, the incidence of serious adverse events and nonserious adverse events was similar overall in the relugolix CT groups and the placebo groups.(41)

LIBERTY 3 (open-label extension study)

Safety for LIBERTY 3 was evaluated in the same way as in the parent trials LIBERTY 1 and LIBERTY 2. While all patients in this open-label extension study received relugolix CT, all data presented are based on the randomised treatment received in one of the parent studies (i.e., original treatment assignment). Due to differences in the duration of exposure to relugolix CT, no cross-comparisons across groups were performed.(44)

Overall, there was no disproportionate increase in the incidence of either serious or nonserious AEs in the relugolix CT group through the 52 weeks. The most frequently reported AEs were headache and hot flush. BMD was preserved with a mean percentage reduction of -0.80% (95% confidence interval: -1.36, -0.25) for lumbar spine BMD at Week 52.(40) The LS mean percent reduction to Week 36 from parent study baseline at the lumbar spine BMD was -0.726%. The LS mean percent changes from parent study baseline at the total hip BMD at Week 36 and Week 52 were [redacted] and [redacted], respectively. The number of patients [redacted]

Treatment emergent adverse events

A cumulative summary of adverse events reported for patients enrolled in this extension study is presented in Table 30. For each treatment group, adverse events are summarised in two columns:

- One for adverse events reported since randomisation in one of the parent studies (“cumulative”)

- One for adverse events reported since initiation of open-label study treatment in this open-label extension study ("extension").

The frequency of subjects who reported TEAEs in the placebo group [redacted]. Regarding cumulative adverse events in the LIBERTY parent study and LIBERTY 3, [redacted] subjects who were in the placebo group in the parent study experienced [redacted] subjects who were treated with relugolix CT throughout the LIBERTY parent study and LIBERTY 3.(44)

Table 30 Summary of cumulative adverse events and adverse events in LIBERTY 3 (extension safety population) (44)

Characteristics	LIBERTY 3			
	Placebo (N=164)		Relugolix CT (N=163)	
	Cumulative	Extension	Cumulative	Extension
Any	[redacted]	[redacted]	[redacted]	[redacted]
Leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Leading to drug interruption	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 or above	[redacted]	[redacted]	[redacted]	[redacted]
Serious	[redacted]	[redacted]	[redacted]	[redacted]
Serious, leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Fatal outcome	[redacted]	[redacted]	[redacted]	[redacted]
Related to Study Drug	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 or above related to study drug	[redacted]	[redacted]	[redacted]	[redacted]
Serious and related to study drug	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: E2 = oestradiol; N = number of patients; NETA = norethisterone acetate

Note: Percentages are based on the total number of patients in each treatment group.

Note: Adverse event grades were evaluated based on NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 5)

Note: Cumulative represents the entire treatment period since randomisation in LIBERTY 1 or LIBERTY 2. Data in the Extension columns relate to the treatment period since enrolment into LIBERTY 3 only.

Overall, there were [redacted] relugolix CT group versus placebo. In the relugolix CT group, cumulatively over the 52-week treatment period (parent plus extension study), [redacted] compared to [redacted] in the placebo group. [redacted] in the relugolix CT extension group [redacted] in the open-label extension study [redacted] placebo extension group. Additionally, [redacted]

[redacted] in the relugolix CT open-label extension group, as shown in Table 30.(44) In comparison, [redacted] were reported in the placebo group, [redacted] assessed by the investigator as possibly [redacted]. Over the 52-week treatment period, [redacted] in the placebo group with reports occurring in the open-label extension study [redacted]

Frequently reported adverse events

A cumulative summary of treatment-emergent adverse events reported since the time of first dose of study drug in one of the parent studies, by preferred term reported in at least 2 percent of patients in any parent treatment group, is presented in Table 31. The incidence of adverse events with previous enrolment in any of the relugolix groups in the parent study [redacted]

Table 31 Cumulative summary of adverse events reported for >2% in any group in LIBERTY 3 (extension safety population) (44)

Preferred Term	LIBERTY 3			
	Placebo (n=164)		Relugolix CT (N=163)	
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Pelvic pain	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]

In the relugolix CT group, over the 52-week treatment period in the parent studies and the open-label extension study, the most frequently reported adverse events included Headache [redacted]), Hot flush [redacted], Nasopharyngitis [redacted] Pelvic pain ([redacted] Hypertension [redacted] Back pain ([redacted] Alopecia ([redacted] and Abdominal pain [redacted] For most of these preferred terms, the adverse events were reported within [redacted]

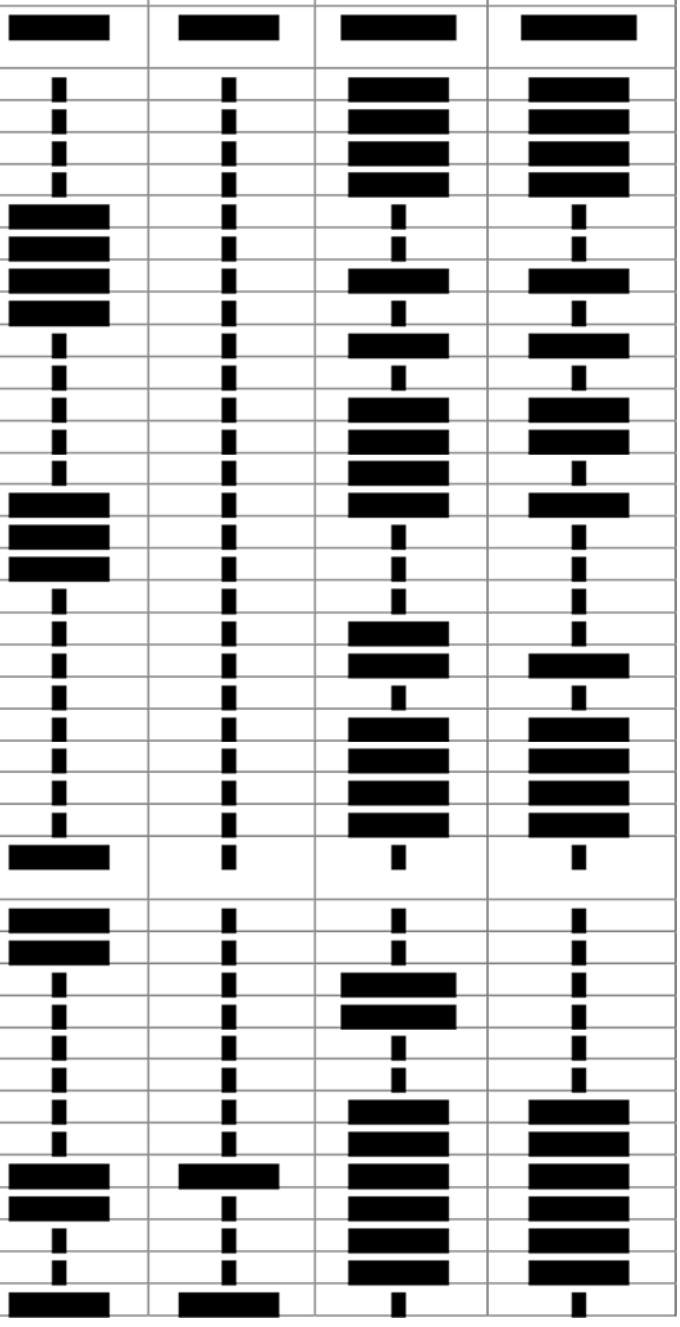
In the placebo group, over the 52-week treatment period in the parent studies and open-label extension study, the most frequently reported adverse events included Headache [redacted] Hot flush [redacted] Anaemia [redacted], Nasopharyngitis ([redacted] Hypertension [redacted], Nausea [redacted] Cough ([redacted] Back pain [redacted], Upper respiratory tract infection [redacted] and Fatigue [redacted], the distribution of events between the parent studies and open-label extension study was [redacted]

Deaths and Serious Adverse Events (SAE)

A summary of the SAEs reported during LIBERTY 3 is reported in Table 32. [redacted], over the course of the 52-week treatment period, serious adverse events were reported for [redacted] In the relugolix-delayed CT group, over the course of the 52-week treatment period, serious adverse events were reported [redacted]. In the placebo group, over the course of the 52-week treatment period, [redacted]

Table 32 Summary of Serious Adverse Events by System Organ Class and Preferred Term (extension safety population) LIBERTY 3 (44)

Preferred Term	Relugolix CT (N=163)		Placebo (N=164)	
	Cumulative	**Extension**	**Cumulative**	**Extension**
No. of patients with at least one serious AE n (%)				
Blood and lymphatic disorders				
Anaemia				
Cardiac disorders				
Atrial fibrillation				
Eye disorders				
Vitreous detachment				
Hepatobiliary disorders				
Cholecystitis				
Cholecystitis acute				
Cholelithiasis				
Infections and infestations				
Appendicitis				
Pneumonia				
Injury, poisoning and procedural complications				
Ankle fracture				
Avulsion fracture				
Forearm fracture				
Radius fracture				
Road traffic accident				
Wrist fracture				
Investigations				
Blood pressure increased				
Musculoskeletal and connective tissue disorders				
Intervertebral disc protrusion				
Neoplasms benign, malignant and unspecified (including cysts & polyps)				
Uterine leiomyoma				
Uterine myoma expulsion				
Nervous system disorders				
Syncope				
Psychiatric disorders				
Panic attack				
Renal and urinary disorders				
Nephrolithiasis				
Reproductive system and breast disorders				
Menorrhagia				
Metrorrhagia				
Ovarian cyst ruptured				
Uterine haemorrhage				



Abbreviations: AE = adverse event; n = number of patients in subset; N = number of patients.
Note: Percentages are based on the total number of patients in each treatment group.
Note: Patients with multiple events for a given preferred term or system organ class were counted only once for each preferred term and system organ class.
Note: Cumulative represents the entire treatment period since randomisation in study LIBERTY 1 or LIBERTY 2. Data in the Extension columns relate to the treatment period since enrolment into LIBERTY 3 only.

B.2.11 Ongoing study: LIBERTY withdrawal study

The LIBERTY withdrawal study (NCT03751124, MVT-601-035) is a phase 3, double-blind, placebo-controlled, randomised study. The study has completed and currently awaits final reporting.

Patients completing the LIBERTY 3 (long term extension) study, who met the definition of responder and all other eligibility criteria, were randomised 1:1 to blinded treatment to either continue with oral relugolix CT once daily or to be put onto placebo (placebo relugolix plus a capsule of placebo E2 and NETA) for up to 52 weeks. Week 52 of the LIBERTY 3 study defined the baseline for this randomised withdrawal study and was used as the reference point for all changes from baseline-related endpoints.(56)

Table 33 Summary of ongoing study NCT-03751124; LIBERTY withdrawal (56)

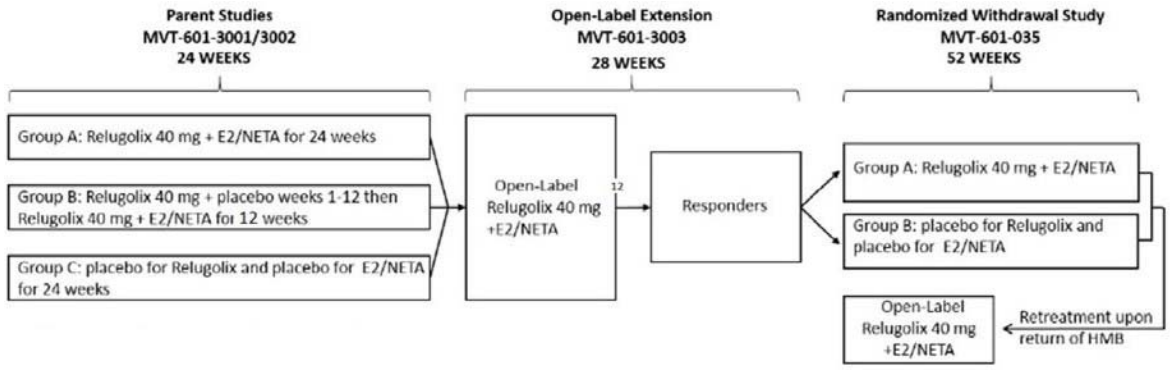
Objectives	The objectives of this randomised withdrawal study were to evaluate the long-term efficacy and safety of the combination of relugolix, E2 and NETA, once daily, for up to 104 weeks in patients with UF who had completed a total of 52 weeks of treatment, including a 24-week treatment period in a parent study (LIBERTY 1 or LIBERTY 2) and a 28-week treatment period in the open-label extension study (LIBERTY 3), and who met the definition of responder, defined as a patient who demonstrated a MBL of < 80 mL and at least a 50% reduction from parent study baseline MBL volume on the AH analysis of the feminine products returned at Week 48 in the extension study.
Trial population	A total of 228 patients were enrolled to the LIBERTY withdrawal study.
Primary endpoints	The study's primary endpoint was the proportion of women who maintain an MBL volume < 80 mL at week 24 (week 72 relative to the parent study baseline).
Secondary endpoints	• Proportion of women who maintained an MBL volume of < 80 mL at Week 52 (Week 104 relative to the parent study baseline) • Change in MBL volume from baseline up to Week 52 (Week 104 relative to the parent study baseline) • Proportion of women who responded (MBL volume > 80 mL) to treatment during retreatment period at Week 52 (Week 104 relative to the parent study baseline) • Proportion of women with HMB at Week 24 and 52 (Week 72 and Week 104 relative to the parent study baseline) • Time to resumption of HMB up to Week 52 (Week 104 relative to the parent study baseline) • Proportion of women with suppression of bleeding at Week 24 and 52 (Week 72 and Week 104 relative to the parent study baseline) • Time to resumption of menses who were amenorrhoeic up to Week 52 (Week 104 relative to the parent study baseline) • Change in haemoglobin concentration up to Week 52 (Week 104 relative to the parent study baseline) • Change in impact on quality of life (UFS-QoL) from baseline up to Week 52 (Week 104 relative to the parent study baseline) • Change in Patient Global Assessment (PGA) for symptoms from baseline up to Week 52 (Week 104 relative to the parent study baseline)

	• Change in PGA for function from baseline up to Week 52 (Week 104 relative to the parent study baseline) • BMD from parent study baseline up to Week 104 • Percentage of participants with AEs as a measure of safety and tolerability up to 52 weeks • Serum oestradiol concentrations up to 52 weeks
Inclusion criteria	• Completed the open-label extension study (LIBERTY 3) • Was a 'responder': Had a menstrual blood loss of < 80 mL AND at least a 50% reduction from the parent study baseline based on the results of the AH testing performed on the feminine products returned at the Week 48 visit of the extension study • Was not expected to undergo gynaecological surgery or ablation procedures for UF within the study period
Exclusion criteria	• Had undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolisation, magnetic resonance guided focused ultrasound for fibroids, or endometrial ablation for abnormal uterine bleeding at any time during the Parent study or extension study • Had a weight that exceeded the weight limit of the DEXA scanner • Had developed any contraindication to treatment with oestradiol or norethisterone acetate • Was currently pregnant or lactating, or intended to become pregnant during the study period • Met a withdrawal criterion in the OLE study

CT: combination therapy; DEXA: dual-energy x-ray absorptiometry; MBL: mean blood loss; OLE: open-label extension; PGA Patient Global Assessment; UFS-QoL: Uterine Fibroid Symptom and Health-Related Quality of Life

Study design

Figure 28 LIBERTY withdrawal study design



MVT-601-3001: LIBERTY 1; MVT-601-3002: LIBERTY 2; MVT-601-3003: LIBERTY 3; MVT-601-035: LIBERTY withdrawal
E2: oestradiol; HMB: heavy menstrual bleeding; NETA: norethisterone acetate

The patient flow is available in Appendix D1.2 (see Figure 40).

Efficacy results

Whilst the full reporting for LIBERTY withdrawal study is not yet available, a top-line data summary report is available and was provided to the European Medicines Agency (EMA) in May 2021.(57)

A total of 229 patients were randomised to the study, 115 patients to relugolix CT and 114 to placebo. A total of 175 patients (76.4%) completed, and the percentage who completed relugolix CT (77.4%) and placebo (75.4%) were similar. Of the 229 randomised patients, 228 patients were treated and defined as the modified intent-to-treat (mITT) population for efficacy analysis and safety population for safety data analysis.

Table 34 LIBERTY withdrawal: Primary and key secondary efficacy outcomes (mITT population) (57)

	Relugolix CT (N = 115)	**Placebo (N = 113)**
Primary endpoint		
Sustained responder rate at Week 76	[redacted]	[redacted]
(95% CI)	[redacted]	[redacted]
Difference from placebo	[redacted]	
95% CI	[redacted]	
P-value	[redacted]	
Key Secondary endpoints		
Time to MBL >= 80mL (weeks)		
25th percentile	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75th percentile	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
P-value	[redacted]	
Sustained responder rate at Week 104	[redacted]	[redacted]
(95% CI)	[redacted]	[redacted]
Difference from placebo	[redacted]	

95% CI	[redacted]	
P-value	[redacted]	
Number (%) of patients achieved or maintained amenorrhoea by Week 76	[redacted]	[redacted]
(95% CI)	[redacted]	[redacted]
Difference from placebo (95% CI)	[redacted]	
P-value	[redacted]	
Number (%) of patients were amenorrhoea at Week 52/Baseline	[redacted]	[redacted]
Number (%) of patients were not amenorrhoea at Week 52/Baseline	[redacted]	[redacted]

CI: confidence interval; MBL: mean blood loss; N: number of patients; NE: not estimable

For the primary endpoint, 78.4% of women who continued on relugolix CT remained responders (menstrual blood loss < 80 mL) through Week 76 compared with 15.1% of women who discontinued treatment and initiated placebo at Week 52 (p<0.0001).(58)

Through Week 104, 88.3% of women randomised to placebo at Week 52/baseline relapsed with HMB with a median time to relapse of 5.9 weeks.(58)

Among the [redacted] in the placebo group who [redacted] relugolix CT with an MBL < 80mL. [redacted], median time to relapse [redacted] in the relugolix CT group [redacted]

Compared with the placebo group, women in the relugolix CT group had [redacted]

Through 2 years, 69.8% of women who continued on relugolix CT remained responders compared with 11.8% of women who received placebo (p < 0.0001), supporting durability of treatment effect.(58)

[redacted]proportion of women were [redacted] with continued treatment with relugolix CT relative to those receiving placebo [redacted])

Safety results

Please note that in the relugolix CT group, women received relugolix CT as blinded treatment or open label as rescue, after their MBL volume reached ≥ 80 mL. In the placebo group, women received placebo initially, and most transitioned to open-label as rescue relugolix CT after their MBL volume reached ≥ 80 mL. Therefore, adverse event data in the placebo group are reflective of the sequence of placebo followed by relugolix CT in most patients, which limits safety comparisons between groups. The mITT population is for efficacy data analysis according to randomised treatment, and the safety population is for safety data analysis according to the actual treatment received. Both populations have the same total of patients (n = 228). Since one patient was randomised to placebo and was treated with relugolix CT, that patient was counted as part of the safety population. (57)

The incidence of adverse events over one additional year of treatment was consistent with those observed in prior studies, with no new safety signals observed.(58)

The frequency of adverse events over 52 weeks of treatment is summarised below by treatment group (Table 35).

Table 35 LIBERTY withdrawal: overall summary of adverse events (safety population)

No. of patients with at least one AE n (%)	Relugolix CT (N=116)		Placebo (N=12)	
Any	[redacted]	[redacted]	[redacted]	[redacted]
Leading to study treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Leading to study treatment interruption	[redacted]	[redacted]	[redacted]	
Related to study drug	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 or higher	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 or higher related to study drug	[redacted]		[redacted]	[redacted]
Serious	[redacted]	[redacted]	[redacted]	[redacted]
Serious and related to study drug	[redacted]		[redacted]	[redacted]

Serious and leading to treatment discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Fatal outcome	[redacted]		[redacted]	

AE: adverse event; N=number of patients
Note: Percentages are based on the total number of patients in each treatment group at time of randomisation.

Adverse events were [redacted] Adverse events leading to discontinuation, adverse events grade 3 or higher, and serious adverse events were [redacted] Adverse events in [redacted] adverse events with fatal outcome [redacted]

Adverse events most frequently reported (≥ 3%) in either group are presented in Table 36. (57) The most commonly reported adverse event in at least 10% of women treated with relugolix combination therapy was nasopharyngitis.(58)

Table 36 LIBERTY withdrawal: adverse events by decreasing frequency ≥ 3% in any group of preferred terms (safety population) (57)

Preferred Term	**Relugolix CT (N=116)**	**Placebo (N=112)**
No. of patients with at least one AE n (%)	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]
Breast pain	[redacted]	[redacted]
Cellulitis	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]
Pelvic pain	[redacted]	[redacted]
Abdominal pain lower	[redacted]	[redacted]
Breast tenderness	[redacted]	[redacted]
Dysmenorrhoea	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]
Menorrhagia	[redacted]	[redacted]

AE: adverse event; N=number of patients
Note: Percentages are based on the total number of patients in each treatment group.

The most frequently (≥ 5%) reported adverse events in patients taking relugolix CT during 52 additional weeks of treatment were nasopharyngitis and headache. [redacted]. The number of patients with at least one AE leading to treatment discontinuation was [redacted] in the placebo group. (57)

Bone mineral density was maintained through two years in the subset of women who were continuously treated with relugolix CT (n=31) from parent study baseline to Week 104,(58) [redacted] In women who received placebo for 24 weeks followed by relugolix CT for 80 weeks [redacted]

B.2.12 Innovation

As described previously, there is an 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. Relugolix CT is a novel GnRH antagonist indicated for the treatment of moderate to severe symptoms of UF in adult women of reproductive age that meets this unmet need. There are currently no oral pharmacological treatment options available that can be used on a long-term basis (not time restricted) in premenopausal women with moderate to severe UF.

In the LIBERTY 1 and LIBERTY 2 trials, once-daily relugolix CT resulted in a substantial reduction in HMB in women with UF, with resolution of anaemia, a reduction in pain, and reduced distress related to bleeding and pelvic discomfort, while preserving bone density and minimising the incidence of hot flushes associated with relugolix monotherapy.(41) LIBERTY 3 and LIBERTY withdrawal study support the long-term use of relugolix CT to 1 and 2 years, respectively.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Clinical effectiveness

The efficacy of relugolix CT has been demonstrated through a series of two multicentre Phase 3 trials (LIBERTY 1, LIBERTY 2) and one Phase 3 open-label extension study of LIBERTY 1 and LIBERTY 2 (LIBERTY 3).

In the LIBERTY 1 and LIBERTY 2 trials, relugolix CT demonstrated superiority compared with placebo. Bleeding control was achieved in a significantly higher proportion of patients receiving relugolix CT (LIBERTY 1: 73%, LIBERTY 2: 71%) compared with placebo (LIBERTY 1: 19%, LIBERTY 2: 15%) over the last 35 days of treatment, as measured by the AH method. The proportion of patients achieving amenorrhoea was 52% (LIBERTY 1) and 50% (LIBERTY 2) in the relugolix CT group compared with 6% (LIBERTY 1) and 3% (LIBERTY 2) of patients on placebo, with amenorrhoea occurring over the last 35 days of treatment. (41)

Regarding changes in haemoglobin, the proportion of women with a haemoglobin level ≤10.5 g/dL at baseline who achieved an increase of > 2 g/dL from baseline at Week 24 was significantly higher (LIBERTY 1: 50%, LIBERTY 2: 61%) in the relugolix CT group compared to patients treated receiving placebo (LIBERTY 1: 22%, LIBERTY 2: 5%) (p-value of 0.04 in LIBERTY 1 and $p<0.001$ in LIBERTY 2).(41) Furthermore, relugolix CT significantly reduced UF associated pain, with 43% (LIBERTY 1) and 47% (LIBERTY 2) of patients in the relugolix CT group achieving a maximum NRS score ≤ 1 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 compared to 10% (LIBERTY 1) and 17% (LIBERTY 2) of patients in the placebo group.(41)

The open-label extension study, LIBERTY 3, showed through an assessment of multiple measures, including responder rate, mean reduction in MBL volume, amenorrhoea rate, and improvement in haemoglobin concentrations, that 52 weeks of treatment with relugolix CT resulted in sustained improvement in HMB associated with UF. The majority of patients (87.7%) taking relugolix CT for 52 weeks met the primary endpoint, a responder rate that reflected the proportion of women who achieved an MBL volume of < 80 mL and at least a 50% reduction from parent study

baseline MBL volume over the last 35 days of treatment. On average, patients in the relugolix CT group had an 89.9% reduction in MBL volume from parent study baseline, which is a clinically meaningful improvement in HMB.(40) In fact, in a prior study, reductions in HMB of 22% or greater were considered meaningful by patients with HMB.(59)

Safety

LIBERTY 1 and 2 demonstrated that relugolix CT was generally well tolerated and no safety concerns were identified. The incidence of adverse events, both serious and nonserious, was overall balanced between relugolix CT and placebo treatment groups. The most frequently reported adverse events were headache and hot flush; only hot flush was reported more frequently in the relugolix CT group than in the placebo group (LIBERTY 1: 11% versus 8%; LIBERTY 2: 6% vs. 4%).(41)

Data from the open-label, single-arm, long-term efficacy and safety LIBERTY 3 study, shows that relugolix CT was generally well tolerated with no unexpected safety issues with extended administration for up to 52 weeks.(40)

Bone mineral density

Whilst there is data to show that BMD was maintained through two years (in the subset of women continuously treated with relugolix CT) in the LIBERTY withdrawal study(57,58), BMD is not an outcome in the economic model as it is assumed that BMD may resolve once treatment with GnRH agonist therapy (the comparator for relugolix) ceases and thus there may be no additional benefit to favour relugolix on this outcome. However, it is worth highlighting that longer-term treatment with GnRH agonist therapy, of 6 months duration or more, is associated with bone loss with controversy surrounding the issue of whether bone loss is recoverable after cessation of GnRH agonist therapy. Whereas some studies in women receiving GnRH agonist suggested that bone loss is recovered when treatment is discontinued,(60,61) others reported a sustained decrease without recovery.(60,62–64) A further study by Pierce et al (2000) (65) showed that in a population of women with an average age of approximately 40 years that even 6 years after completion of

a course of agonist treatment the bone had not fully recovered, and that overall prolonged use may increase the future risk of osteoporosis.

This lack of bone recovery particularly in this age group of the population can have considerable effects on their long-term risk of trauma fracture and osteoporosis. It is estimated that on average the rate of normal premenopausal bone loss is between 0.7-1.3% at the lumbar spine.(66,67) It is estimated that having a BMD that is 2.5 standard deviations below the mean of the adult reference population increases the risk of osteoporosis by approximately 20%.(68) Therefore, if the normal level of bone loss is further increased by the use of products such as GnRH agonists, which even up to 6 years post treatment is not fully recoverable, then this group of the population will have a substantial potential for increased risk.

In comparison, it has been shown from the clinical trial data that relugolix CT, even over a period of 104 weeks of continuous treatment, preserves BMD with no significant loss during treatment. Additionally, the average change from baseline in BMD was 0.04% in patients with continued use of relugolix CT over 104 weeks (n=32).(69) Hence it would appear that relugolix CT has the potential benefit to preserve BMD even when used without interruption for extended periods of time.

Strengths and limitations of the relugolix CT clinical evidence base

Strengths

The clinical evidence base described in this submission is derived principally from the LIBERTY studies: LIBERTY 1, LIBERTY 2, LIBERTY 3 (open-label) and LIBERTY withdrawal (awaiting final reporting). Data from these studies capture evidence on MBL volume, time to achieve MBL volume response, haemoglobin levels, pain, hormone levels, mortality, HR QoL and AEs, all of which feature in the scope and are relevant outcomes in clinical practice.

The studies met the primary efficacy endpoint of demonstrating superiority in improvement of HMB associated with UF when compared with placebo. In the RCTs, 73% (in LIBERTY 1) and 71% (in LIBERTY 2) patients in the relugolix CT group achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment compared with 19% (LIBERTY 1)

and 15% (LIBERTY 2) in the placebo group (p<0.001) at Week 24.(41) The robustness of the efficacy analyses were supported by sensitivity analyses and subgroup analyses.(42,43) For the open-label extension study, LIBERTY 3, data at Week 52 showed that 87.73% of patients met the primary endpoint,(40) and the robustness was supported by subgroup analyses.(40,44)

Limitations

The clinical evidence from the LIBERTY trials do not provide a direct comparison between relugolix CT and GnRH agonists or standard of care (e.g. first line oral contraceptives). Despite this, the LIBERTY 1 and LIBERTY 2 trials provide the pivotal RCT efficacy and safety data for relugolix CT and are the most appropriate evidence base. An ITC has been conducted to provide evidence that was not captured via RCTs. The LIBERTY 1 and LIBERTY 2 RCT evidence is also limited in its provision of EQ-5D-5L utility data – which was an exploratory analysis and captured at baseline and at the end of treatment, and as a result, the findings are not sensitive to capturing utility for women on relugolix CT through the trial. A mapping algorithm has been applied to derive utility based on MBL outcome.

Many subjects in the LIBERTY 1 and LIBERTY 2 trials with self-reported HMB and UF did not pass screening owing to strict assessment criteria, which is a situation that could limit generalisability, and the duration of the trial regimen.(41)

Validity of the study results (LIBERTY 1 and LIBERTY 2)

The eligibility criteria for this study were selected to ensure that the study population was representative of the population of women with symptomatic UF who are likely to be treated in clinical practice. All patients were confirmed to have HMB by objectively assessing MBL volume by the AH method. In meeting this criterion, other characteristics common to women with UF (i.e. anaemia, pain, reduced quality-of-life) were observed.(42,43)

In general, demographic and baseline characteristics were balanced among treatment groups and representative of patients with symptoms associated with UF who would seek treatment in the community setting and who have significant disease burden.(42,43)

The robustness of the primary efficacy analysis result was supported by sensitivity analyses and subgroup analyses. Results from these analyses confirmed the results of the primary endpoint analyses (i.e., 24 weeks of treatment with relugolix CT) demonstrated a comprehensive and significant improvement in MBL volume that was generally consistent across the subgroups analysed.(42,43)

Validity of the study results (LIBERTY 3)

The baseline characteristics and demographics of the study population (and each of the treatment groups) are consistent with the populations analysed in the parent studies and are representative of patients who suffer with symptoms associated with UF who would seek treatment in the community setting, and who have significant disease burden.(44)

Despite the consistency with the parent studies in baseline characteristics and demographics, it must be acknowledged that there could be some selection bias among the patients who enrolled in this open-label extension study; however, the risk of this potential bias to meaningfully affect the study conclusions is considered small. Reasons for early termination in the parent study, patients' perceptions regarding parent study treatment assignment and treatment response, and patient motivation to continue or initiate open-label treatment could all play a role in decision making to continue into the open-label extension study.(44)

The robustness of the primary efficacy analysis result was supported by subgroup analyses. Results from these analyses confirmed the results of the primary endpoint analysis (i.e. 52 weeks of treatment with relugolix CT) demonstrated a comprehensive and significant improvement in MBL volume that was generally consistent across the subgroups analysed.(44)

The increased incidence of adverse events observed in the placebo group may have been related to ascertainment bias associated with the open-label nature of the extension study. Investigators and patients were aware that all patients were receiving relugolix CT during this study and may have been more inclined to report adverse events, particularly when those potentially associated with hormonal changes were observed.(44)

Although there is an inherent selection bias driven by the need to complete one of the parent studies to be eligible to enter this extension study, the fact that most patients completed the studies and most of those who completed entered the extension, makes this potential bias less likely to affect significantly the interpretation of the results.(44)

LIBERTY trials representative of women in England

The mean age trial of relugolix CT patients in the LIBERTY 1 and 2 trials (42.5 and 42.4, respectively) is representative of women in England who would likely use relugolix CT. Likewise, mean BMI of relugolix CT patients was 31.4 (LIBERTY 1) and 31.0 (LIBERTY 2) which, based on clinical expert opinion, are representative of women with UF in England at the mean age. Patients from the relugolix CT groups entered the trials with MBL volume of 239.4 ml (LIBERTY 1) and 246.7 ml (LIBERTY 2) indicating heavy MBL volume which would be representative of patients in England with moderate to severe blood loss and eligible for relugolix CT in a clinical setting. LIBERTY 1 and LIBERTY 2 also included a good proportion of non-white patients (only approximately half were white), which provides good representation of women of Black African and African-Caribbean origin, who are 2-3 times more likely to develop UF than white women.(41)

Note: a critique of the LIBERTY vs. PEARL studies is provided in Appendix M, section “M1.6 LIBERTY vs PEARL studies”.

Relugolix CT in general clinical practice

According to feedback from gynaecologists, relugolix CT is positioned for women with UF who have failed or are unsuitable for conventional hormonal therapies such as contraceptives and the intrauterine device (IUD). The only other pharmacological intervention used in this position is GnRH agonist administered subcutaneously as either a monthly or 3-monthly injection.

The GnRH agonists that are licensed for the treatment of UF in the UK are leuprorelin acetate, goserelin acetate and triptorelin acetate. All three GnRH agonists are also available as long-acting (3-monthly) formulations, but only long-acting leuprorelin acetate and triptorelin are licensed for the treatment of UF. However,

based on clinical expert opinion, gynaecologists often use long-acting goserelin ‘off-license' and prescribe this to women with moderate to severe symptoms of UF.

GnRH agonists are licensed for presurgical use up to a maximum of 6 months and use for periods longer than this is considered off-license. However, many women with UF wish to avoid surgery, either due to fear of infertility, busy lifestyle or cultural/religious reasons, and surgery other than hysterectomy is often not curative.(70,71) For those open to surgery, due to the COVID-19 pandemic waiting lists for surgery for UF can be up to 18 months according to gynaecologists surveyed by Gedeon Richter. As a result, GnRH agonists may be given for extended periods in order to manage symptoms over the longer term, usually in combination with hormonal replacement therapy such as raloxifene or tibolone in order to preserve BMD and reduce side effects.(72,73)

It is unclear which GnRH agonists are more commonly used in England as they are also licensed for other conditions (e.g. prostate cancer) therefore the volumes prescribed in prescription cost analyses cannot be used to estimate shares in this indication. In general, the available GnRH agonist formulations are considered equivalent in terms of efficacy.(50)

Life expectancy

UF are benign tumours and are thus not associated with increased mortality. There is no data to suggest that fibroids alter life expectancy and fatalities due to fibroids are typically related to surgical procedure risks rather than the condition itself.

Patient numbers

The estimated number of incident cases of UF with HMB symptoms is reported as 9,685 in the United Kingdom (74). Relugolix CT is positioned for a subset of these patients who have failed or are unsuitable for hormonal treatments such as cyclical oral progestogens and contraceptives. These patients would thus be eligible for treatment with GnRH, however there are no reported patient numbers for those with symptomatic UF receiving GnRH treatment. It is not possible to calculate the number of women prescribed GnRH from prescription-cost analyses (PCA) because the quantities reported in PCA are not disaggregated by indication i.e. it is not known

what proportion of GnRH is prescribed for UF vs. other indications (e.g. prostate cancer and fertility treatment).

It is assumed that patients who meet the eligibility criteria for relugolix CT are similar to those who would have been prescribed Esmya® (ulipristal acetate) prior to the restriction of the label in May 2018. Prior to the label restriction Esmya® was indicated for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age, including prior to surgery. The number of patients who were prescribed Esmya® prior to this restriction was sourced from 2017-18 England PCA data (75) using the quantity of tablets sold and the number of days per year tablets are taken, as Esmya® requires treatment breaks. The original label states that treatment consists of one tablet to be taken once daily for treatment courses of up to 3 months each (76). Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion (76). There is thus a minimum of 2 months required for a treatment break. It was assumed that patients treated with Esmya® prior to the label restriction would have 3 months on treatment with 2 months off treatment. The annual number of patients treated with Esmya® prior to the label restriction was thus calculated by annualising the quantity of tablets of Esmya® sold between October 2017 and January 2018 and adjusting for the treatment duration and breaks (2823/3*5), resulting in a total of 4,705 patients. It is thus assumed that 4,705 patients would be eligible for treatment with relugolix CT.

End-of-life criteria

Gedeon Richter considers that this technology does not meet the end-of-life criteria.

B.3 *Cost effectiveness*

B.3.1 Published cost-effectiveness studies

A systematic literature review (SLR) of cost-effectiveness analyses returned 63 records. The search was designed to identify cost-effectiveness studies of pharmacological interventions used to treat women with fibroids who are unsuitable for or have failed conventional hormonal therapy.

Following full text screening, 14 studies were included. Ten of the included studies were cost-effectiveness analyses, the remaining four studies were solely focused on cost or resource data. None of the included studies included an intervention listed within the decision problem, however they were included to help inform the model structure. Nagy et al. (2014) is an updated, full publication of Nagy et al. (2012), therefore there were nine unique cost-effectiveness studies.

The cost-effectiveness studies are summarised in Table 37.

Table 37 Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Badiani	2018	Effectiveness data were derived from the randomised-controlled trial PEARL-1, a Markov model was employed. Ulipristal acetate 5 mg for presurgical therapy was estimated to be associated with an incremental cost of €351 per patient	Women with symptomatic fibroids, excessive uterine bleeding and anaemia (haemoglobin level of ≤10.2 g per decilitre)	Ulipristal acetate: 0.22058 placebo: 0.20127	€3836 for UPA €3485 for placebo	€18,177 per QALY gained
Choi	2016	Abstract presenting a Markov model. Developed to assess cost-utility of UPA for duration of 3 months. Leuprolide acetate (LA) 3.75mg, a GnRH-agonist was selected as an alternative of UPA 5mg UA is a cost-effective treatment with significant improvement in quality of life compared to GnRH-agonist	Patients with reproductive age of 18-50, who can undergo fibroid surgery as alternative of GnRH-agonists in Korea	NR	NR	₩9,372,003 per QALYs
Lorenzovici	2014	Abstract presenting a Markov model. Developed using a 10-year time horizon. Ulipristal acetate was compared with pre-surgical observation and immediate hysterectomy. adding UPA treatment to standard pre-surgical therapy represents a good value for money in Romania. The inclusion of societal benefits may considerably reduce the cost-effectiveness ratio	Adult women of reproductive age with moderate to severe symptoms of UF	3-month course of UPA to pre-operative observation: 0.21 QALY 3 months UPA therapy was compared with immediate hysterectomy: NR	3-month course of UPA to pre-operative observation: €367 3 months UPA therapy was compared with immediate hysterectomy: NR	Pre-operative: ICER €17,749 /QALY Hysterectomy: ICER €2,300 /QALY
Maratea	2016	Comparing repeated-intermittent use of UPA 5 mg with presurgical use of UPA 5 mg in a cost effectiveness analysis. Repeated intermittent use of 5mg UPA has a favourable outcome and may be cost-saving	Management of symptomatic UF	NR	Total costs/ patient for pre-surgical use with UPA 5mg: €826.25. Total costs/patient for repeated-intermittent +UPA 5mg: up to €3,729.69 (10 cycles)	Pre-surgical use with UPA 5mg: - repeated-intermittent +UPA 5mg: €31,905.93
Nagy	2012	Abstract presenting a Markov state-transition economic model. Developed over 10 year time horizon. Ulipristal acetate was compared to 1) pre-surgical observation, and 2) immediate hysterectomy	Adult women of reproductive age with moderate to severe symptoms of UF	3 month UPA + standard pre-operative therapy 0.019 QALYs Vs observation 3 month UPA + Vs hysterectomy: NR	3 month UPA + standard pre-operative therapy €376, Vs observation 3 month UPA + Vs hysterectomy: NR	UPA + pre op vs observation 20,180€ per QALY UPA + Vs hysterecomy:6,095 €/QALY
Nagy	2014	Full publication of Nagy 2012 paper. Adding ulipristal treatment to standard pre-surgical	Women with symptomatic UF and	UPA V pre op	UPA V pre op	UPA V pre op

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		therapy represents a good value for money in Hungary	excessive uterine bleeding who are eligible to undergo fibroid surgery at the end of the treatment period	UPA: 6.32 Pre op: 6.30 UPA v hysterectomy UPA:3.32 Immediate hysterectomy: 6.14	UPA: 12.38 Pre op: 842 UPA v hysterectomy UPA:12.38 Immediate hysterectomy: 609	19,200€/QALY UPA v hysterectomy 3575€/QALY
Paladio-Hernandez	2015	Abstract presenting a decision tree approach over a 1 year time horizon. Ulipristal acetate vs leuprolide acetate. Ulipristal acetate is a cost-effective alternative when compare to leuprolide acetate	Patients eligible to undergo fibroid surgery in Mexico	NR	NR	NR
Paquete	2016	Abstract presenting a Markov model. Developed using a life-time horizon, long term UPA vs surgery. The use of long term treatment with UPA 5 mg for moderate to severe symptoms of uterine fibroids incurs added costs per QALY which are generally accepted in Portugal.	NR	Long term UPA vs surgery 0.134	UPA costs in the Societal perspective decrease from € 3,194 to € 2,525 (incl indirect)	versus surgery range from € 18,862 to € 23,85 per QALY
Tsoi	2015	probabilistic decision tree was used to estimate expected costs QALYs: UPA (5 mg orally daily) compared to leuprolide (3.75 mg)	Women with moderate-to-severe symptoms of UF eligible for surgery	leuprolide: 0.165 UPA: 0.177	leuprolide:CD $1365.58 UPA: CD $1,273.44	UPA: CD$92.13 / QALY
Geale	2017	A decision-analytic model for UPA followed by surgery vs iron and NSAID followed by surgery. versus the use of UPA as a repeated, intermittent treatment for women with moderate to severe symptoms of UF wishing to avoid surgery is likely to be a cost-effective intervention when compared to BSC	Women with moderate to severe symptoms of uterine fibroids (UFs) who wish to avoid surgery.	UPA: 6.696 BSc:6.610	UPA: £6,669 BSc: £5,555	UPA: £12,850/QALY

Abbreviations: BSc: best supportive care; GnRH: gonadotrophin releasing hormone; ICER: incremental cost-effectiveness ratio; LA: leuprolide acetate; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; NSAID: non-steroidal anti-inflammatory drug; QALY: quality adjusted life year; UPA: ulipristal acetate; UF: uterine fibroid

B.3.2 Economic analysis

No cost-effectiveness studies for relugolix CT were identified in the SLR. A *de novo* cost-effectiveness model was thus constructed to evaluate the cost-effectiveness of relugolix CT for the treatment of moderate to severe symptoms associated with UF.

Patient population

The patient population considered in the analysis is premenopausal women with moderate to severe symptoms associated with UF who have failed or are unsuitable for conventional hormonal therapy including contraceptives. The model patient population is informed by the pooled patient characteristics from LIBERTY 1 and LIBERTY 2 trials of relugolix CT (41). The LIBERTY 1 and LIBERTY 2 patient characteristics are considered to be generalisable to those of patients anticipated to receive relugolix CT in the NHS in England and Wales according to clinical expert opinion.

Model structure

The cost-effectiveness model takes the form of a Markov cohort model consisting of 6 states as shown in Figure 29. All patients enter the model in the 'pharmacological treatment' state, initiating treatment with either relugolix CT or a gonadotrophin-releasing hormone (GnRH) agonist. From this state treatment withdrawal can occur to best supportive care (BSC) or the patient can be referred immediately for surgery. In the BSC state patients are not treated with active pharmacological treatment and any treatments taken are for symptom management such as pain control. The model also includes a health state for pre-surgery waiting time. This is in practice an extension of the BSC state but intended to separate those patients waiting for surgery from those who have not been referred to surgery yet. The waiting time before surgery is 15 months in the model base-case, reflecting current waiting times for procedures in the UK, as informed by clinical expert opinion (Table 45). Costs and outcomes are measured over a lifetime horizon using monthly cycles.

The surgery state is a tunnel state that patients remain in for one cycle. This state includes different types of surgery which are each explicitly modelled to describe the distribution of patients currently undergoing surgery by surgery type and to allow correct application of surgery related mortality risks and adverse events. Following

surgery, patients move to a post-surgery state that is divided in two – reflecting patients who received hysterectomies and those who did not. Patients who did not receive hysterectomies can then transition to a second surgery state following the completion of further waiting time. The waiting time is again equal to being on BSC.

When patients reach the mean age of menopause (specified in the model as 51 years) all patients transition to the menopause state. In the menopause state patients who received hysterectomies are again differentiated from those who did not.

From all states, transition is possible in all cycles to the death state. No excess mortality is present in the pharmacological state, BSC state, pre-surgery waiting time state, post-surgery state or menopause state. Surgery-related mortality is applied as an excess mortality in the surgery state during the cycle patients receive surgery. In all other states the population background mortality is applied.

The analysis was conducted from the perspective of the NHS and personal social services (PSS) in England and Wales, in line with current NICE guidelines (77). The base-case analysis thus considers only direct healthcare costs. Costs and outcomes are discounted at an annual rate of 3.5%, in line with the NICE reference case (77).

Figure 29: Model structure

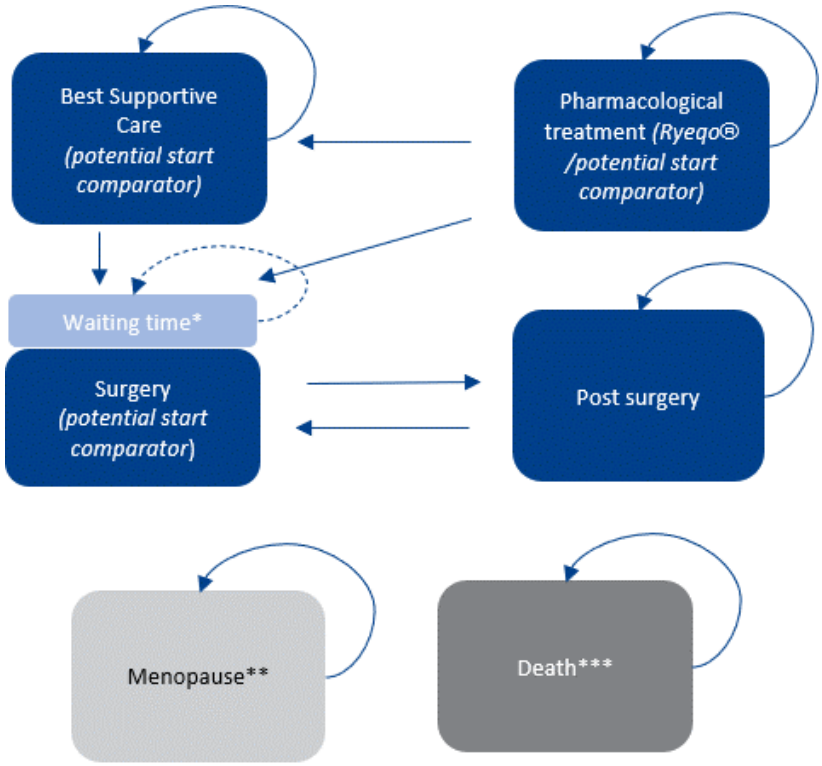


Table 38 Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon	Lifetime	Although treatment is only provided up to menopause, hysterectomies may have a lifetime impact.
Treatment waning effect?	No	There is a lack of data from key clinical studies that would support a treatment waning effect for either relugolix CT or any of the GnRH agonist comparators.
Source of utilities	Mapped from MBL values in LIBERTY 1, 2 and 3 phase 3 studies of relugolix CT	Although EQ-5D-5L data was collected in the LIBERTY trials, this was deemed unsuitable for several reasons. Firstly, an EQ-5D assessment on a singular day may not truly reflect patients' overall quality of life, as the patient may feel very different depending on exactly which timepoint in their menstrual cycle this is taken. Furthermore, during the LIBERTY clinical trials, the EQ-5D was only administered at baseline and at the Week 24 assessment, whereas the disease-specific UFS

		QoL was administered at baseline, week 12 and week 24. Finally, the UFS QoL includes questions that relate directly to symptoms experienced during days of menstrual bleeding, when some symptoms may be at their most severe.
Source of costs	British National Formulary (BNF) (78), NHS Reference costs 2019/20 (79), PSSRU 2020 (80), Hospital episode statistics, KOL (key opinion leader) expert opinion	Cost inputs were sourced from the British National Formulary (BNF), NHS reference costs, Hospital Episode Statistics (HES) and the literature. Where possible, costs were obtained from UK national resources to reflect the UK NHS/PSS perspective. Due to lack of published healthcare resource use (HRU) data specific to the population of interest, HRU frequencies for disease management and regular monitoring and tests or examinations was informed by KOL expert opinion.

Intervention technology and comparators

The modelled intervention is relugolix CT. As relugolix CT maintains oestradiol and progestogen concentrations in a range that maintains BMD and endometrial health, it can be used for as long as is required without interruption. Thus, no maximum treatment duration is implemented in the model other than cessation at menopause. Patients who discontinue treatment cannot return to treatment with relugolix CT.

The comparators are GnRH agonists that are used for the treatment of UF, as outlined in the final NICE scope (23). GnRH agonists and UPA (Esmya®) are second line pharmacological options that have an approved indication for UF. However, Esmya® is only indicated for moderate to severe UF when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed (30,31) and its usage has been commonly replaced with GnRH agonists in the absence of other pharmacological options.

The GnRH agonists that are licensed for the treatment of UF in the UK are leuprorelin acetate, goserelin and triptorelin. All 3 GnRH agonists are also available as long-acting (3-monthly) formulations, but only long-acting leuprorelin acetate and triptorelin are licensed for the treatment of UF. However, based on clinical expert opinion, gynaecologists often use long-acting goserelin ‘off-license' and prescribe this to women with moderate to severe symptoms of UF. It was therefore deemed a relevant comparator for relugolix CT. The model thus includes 6 comparators which are the short and long-acting formulations of leuprorelin acetate, goserelin and

triptorelin. The model base-case assumes that patients who are treated with long-acting GnRH agonists will first receive 3 months of short-acting (monthly) GnRH agonist treatment before transitioning to the long-acting formulation. This assumption was based on clinical expert opinion.

Although GnRH agonists are only licensed for use for up to 3 to 6 months of continuous therapy, clinician feedback is that they are often used for longer than this where there is a need to delay or avoid surgery. This has become more common following the COVID-19 pandemic where long surgery waits have necessitated longer treatment courses. When GnRH agonists are given for longer than 3 months hormonal add-back therapy is often administered to reduce BMD loss and vasomotor symptoms. In the UK tibolone or raloxifene may be used as add-back therapy (81).

The scope for this appraisal lists hormonal treatments such as cyclical oral progestogens and contraceptives as comparators, however these treatments are not included as comparators in the economic model as the anticipated positioning of relugolix CT in clinical practice aligns with those patients who have failed or are unsuitable for these treatments.

B.3.3 Clinical parameters and variables

The cohort starting age is 42 years, based on the mean age in the LIBERTY trials. Mean age at menopause is 51 years, based on the mean age of the natural menopause in the UK population (82). The mean MBL of the cohort is 229.1 mL, based on the mean MBL at baseline in the LIBERTY trials.

The principal sources of data used to inform the effectiveness of relugolix CT are MBL and withdrawal rates in the LIBERTY (1, 2 and 3) clinical trials. LIBERTY 1 and LIBERTY 2 were two replicate double-blind phase 3 trials of relugolix CT vs. placebo (41). LIBERTY 3 was a phase 3, open-label, single-arm, long-term efficacy, and safety extension study that enrolled eligible patients who had completed participation in LIBERTY 1 or LIBERTY 2 (44). The primary efficacy endpoint in the LIBERTY trials was treatment response defined as both a volume of MBL of less than 80 ml and a reduction of at least 50% from the baseline volume of MBL, as measured by the AH method, over the last 35 days of the treatment period (41).

The model assumes equal efficacy for all GnRH agonists comparators as reported in a systematic review by Lethaby et al., 2001 (50), thus the clinical inputs are the same for each individual GnRH agonist. There is no clinical trial evidence directly comparing relugolix CT against GnRH agonists either with or without add-back therapy, thus an ITC bridging to the PEARL II study, which included a GnRH agonist arm, is the primary source of evidence used to inform the effectiveness of GnRH agonists (53) (see section B.2.9). PEARL II was a randomised, parallel-group, double-blind, double-dummy, active-comparator-controlled, phase 3 noninferiority trial to assess the efficacy and safety of daily-oral ulipristal acetate (UPA) compared with leuprolide acetate in the preoperative treatment of symptomatic UF (53). Treatment was started within 4 days after the start of the menstrual period and was continued until week 13, after which patients could go on to have surgery (53). Although PEARL II does not provide data for a direct comparison of GnRH agonist CT vs. relugolix CT, it is the most appropriate source to inform clinical inputs for the GnRH agonist arm of the model considering the limited evidence base. The LIBERTY trials and PEARL II comprised similar study populations, with key baseline characteristics such as age aligned between the studies. Furthermore, only 45.1% of patients in PEARL II went on to have surgery at the end of the 13-week treatment period, with the rest transferring to BSC. GnRH agonist was therefore not used solely as a pre-operative treatment, thus making outcomes for this treatment arm more comparable to the LIBERTY populations.

In the BSC state patients are not treated with active pharmacological treatment. It is assumed that patients take NSAIDs for pain management and iron supplements due to high blood loss. The model does not explicitly model the treatment effect of concomitant medication, but as the clinical effect data for the placebo arm from the LIBERTY 1 and LIBERTY 2 trials is used in the BSC state and patients in the LIBERTY and PEARL II trials used concomitant medications such as NSAIDs and iron supplements, it is accounted for indirectly.

Due to a lack of data to inform certain clinical and healthcare resource use parameters, several inputs are informed by clinical expert opinion. 3 KOLs engaged in primary research interviews in the form of a questionnaire (83). Additional responses to selected key clinical questions from the questionnaire, including GnRH

agonist treatment duration and waiting time for surgery, were also elicited *ad hoc* via direct communication with other KOLs. This resulted in a sample size of n=7 responses for questions relating to GnRH treatment duration (see section 'GnRH agonist treatment duration from 6 months onwards') and n=5 responses for queries related to surgery waiting time (see section 'Type of surgery').

Treatment withdrawal

A key clinical outcome of interest that is used to assess the efficacy of relugolix CT vs. GnRH agonists is duration of treatment (treatment withdrawal). Whilst patients are on active pharmacological treatment, they cannot have surgery, as this is modelled as a separate health state. Duration on treatment is thus indicative of surgical events avoided.

For each cycle that patients spend on either relugolix CT or a GnRH agonist there is a probability that they will discontinue treatment. Transitions to BSC or surgery health states are modelled as conditional on discontinuing treatment in the base-case. A fixed proportion of the patients who withdraw are assumed to be immediately referred for surgery (explained in detail in sub-section 'Surgery'), with the remaining patients transitioning to BSC. In addition, to account for patients who may be referred to have surgery at a later date, a small background surgery rate is included within the BSC state.

Relugolix CT

Withdrawal rates for relugolix CT were calculated based on patient-level data on the reason for discontinuation from the CSRs of LIBERTY 1 (42) and LIBERTY 2 (43) for months 1-6, LIBERTY 3 (44) for months 7-12 and the randomised withdrawal study (RWS) (56) for months 13-24. For months 1-6, data for patients in the LIBERTY 1 and LIBERTY 2 clinical trials were pooled. Clinicians who attended an advisory board stated they felt that discontinuation in the LIBERTY studies was higher than would be expected in real-world settings due to the alkaline hematin method that was used to measure MBL in the studies. The alkaline hematin method involves chemically measuring the blood content of used sanitary products and is considered the 'gold standard' for measuring MBL (84). However, the method requires patients to retain their used sanitary products, with KOLs stating that patients describe this as

both unpleasant and a hindrance to their daily life as they feel they cannot continue with regular activities such as going to eat at a restaurant. Patients cannot simply dispose of their used sanitary product when changing their sanitary product whilst outside of their home and they must keep this on their person until they reach home. KOLs that were interviewed (n=3) all agreed that they felt retention on treatment would be much higher in the real-world due to the removal of the procedures associated with the alkaline hematin method. It is thus assumed that from the list of the potential discontinuation reasons reported in the LIBERTY study CSRs, protocol deviations and patients lost to follow-up would remain on treatment in a real-life setting.

The descriptions of the reasons for patient withdrawal from the LIBERTY studies were examined to deem whether such reasons would lead to discontinuation of treatment in clinical practice. For patients who discontinued due to adverse events, the description of the adverse event was examined to determine the severity of the adverse event and whether it was drug-related. If adverse events were mild for instance, mood swings, or if it was categorised as non-drug related, such as a lack of energy, then it was assumed that these patients would remain on treatment in clinical practice. Most of the reasons provided for discontinuations categorised under ‘withdrawal by patient’ were not related to the study drug. For instance, several participants stated that they simply did not wish to participate in the trial any longer and most of these patients under this category cited life changes such as moving out of the state or starting a new job as their reason for withdrawal from the study. In these instances, it was assumed that patients would remain on treatment in clinical practice and thus they were not included in the proportion discontinuing treatment in the model. The same approach was followed for discontinuations categorised as ‘other’ in all of the LIBERTY studies.

The numbers of patients discontinuing in each study and the respective reasons why are reported in Table 39. The numbers discontinuing once the assumptions detailed above were applied are reported in Table 40.

Withdrawal rates were converted to monthly probabilities using standard methods for converting rates to probabilities (85). The resultant withdrawal rates applied for each model cycle in the relugolix CT arm are presented in Table 40.

Table 39 Treatment withdrawals reported in LIBERTY studies

	LIBERTY 1	LIBERTY 2	LIBERTY 3	LIBERTY withdrawal study
N	128	126	163	115
Discontinuation reason				
Adverse event	7	2	[redacted]	[redacted]
Protocol deviation	1	1		
Lost to follow-up	1	4		
Withdrawal by patient	10	13		
Lack of efficacy	4	2		
Pregnancy	0	0		
Other	5	1		
Total	**28**	**23**	[redacted]	[redacted]
% withdrawing	**22%**	**18%**	[redacted]	[redacted]

Source: LIBERTY study CSRs; (42), (43), (44), (57)

Table 40 Modified treatment withdrawals applied in the model

	LIBERTY 1	LIBERTY 2	LIBERTY 3	LIBERTY withdrawal study
N	128	125	163	115
Discontinuation reason				
Adverse event	3	1	[redacted]	[redacted]
Protocol deviation	0	0		
Lost to follow-up	0	0		
Withdrawal by patient	1	1		
Lack of efficacy	4	0		
Pregnancy	0	0		
Other	0	0		
Total	**8**	**2**	[redacted]	[redacted]
% withdrawing	**6%**	**2%**	[redacted]	[redacted]

Source: Gedeon Richter data on file

Table 41 Rates of withdrawal from relugolix CT

Timepoint	Source	Proportion of patients withdrawing – study data	Follow-up time	Monthly probability of withdrawal
Month 1-6	Pooled LIBERTY 1 & 2	4.74%	24 weeks	0.86%
Month 7-12	LIBERTY 3	[redacted]	24 weeks	[redacted]

Month 13 onwards	LIBERTY withdrawal	[redacted]	52 weeks	[redacted]

*Study follow-up time applied in probability to rate conversions to derive monthly probabilities of withdrawal

GnRH agonist

To maintain consistency with the MBL outcomes, the PEARL II study was used as a source of withdrawal rates in the GnRH agonist arm for the first 6 months of the model. Given that GnRH agonist has to be administered by healthcare professionals and that treatment past 3 to 6 months is off-licence, clinician opinion was used to estimate withdrawal rates after the first 6 months of treatment, as described in section '*GnRH agonist treatment duration from 6 months onwards*'.

Model base-case for GnRH agonist – first 6 months

Withdrawal rates in the first 6 months of the GnRH agonist arms of the model were derived from patient-level information on the reason for discontinuation of GnRH treatment in the PEARL II study (53). During the 13-week treatment period in PEARL II, 6 out of 101 subjects in the GnRH agonist arm withdrew due to either AE or patient request. One subject was assumed to transfer to surgery (AE: worsening of bleeding) and the other 5 (4 AE and 1 subject request) were assumed to transfer to BSC. As the data were not disaggregated by time-point i.e. we do not know at which week each individual withdrawal occurred, the 13-week withdrawal rates were converted to a monthly probability of 1.91%. This monthly probability was applied at each cycle over the first 6 months of the model, including months 4-6, during which the PEARL II 13-week data was extrapolated. Thereafter, the proportion of patients remaining on GnRH agonist treatment was capped by the KOL responses implemented in the model at each cycle, described in section '*GnRH agonist treatment duration from 6 months onwards*' later below. The withdrawal rates implemented in the model base case are summarised below.

Table 42 GnRH agonist withdrawal rates per model cycle, base case

Timepoint	Proportion of patients discontinuing treatment	Discontinuation rate source
Months 1-6	1.913%	PEARL II
Months 7-119	Time-varying	KOL opinion
Months 120 onwards	100%	KOL opinion

Scenario for GnRH agonist - first 6 months

As part of a scenario analysis, withdrawal rates in the in the first 6 months of the GnRH agonist arms of the model were assumed equal to the modelled withdrawal rates for relugolix CT. The withdrawal rates per cycle for this scenario are presented below. As per the model base-case, the proportion of patients remaining on GnRH agonist treatment after 6-months was capped by the KOL responses implemented in the model at each cycle as per the base case. Based on the KOL feedback described in earlier sections, no patients receive GnRH agonist treatment for more than 10 years, thus by cycle 120, the cycle probability of discontinuation is fixed at 100%.

Table 43 GnRH agonist withdrawal rates per model cycle, scenario analysis

Timepoint	Proportion of patients discontinuing treatment	Discontinuation rate source
Months 1-6	0.86%	Identical to relugolix CT arm
Months 7-119	Time-varying	KOL opinion
Months 120 onwards	100%	KOL opinion

GnRH agonist treatment duration from 6 months onwards

The licence indications for all the GnRH agonists comparators impose a limit on treatment duration, ranging from 3 to 6 months, due to adverse effects such loss of BMD and vasomotor symptoms. However, interviews with key opinion leaders (KOLs) (n=7) revealed that these treatments are often used in combination with HRT (add-back) beyond 6 months in clinical practice. KOLs stated that the majority of patients would remain on treatment for up to a year and for subsequent time periods there would be a decline in proportion of patients on treatment. The KOL responses regarding the proportion of patients remaining on treatment with GnRH agonist at various time points is summarised in Table 44. An average of the 7 responses for each time point was applied in the model.

Table 44 KOL responses regarding proportion of patients remaining on GnRH agonist treatment beyond 6 months

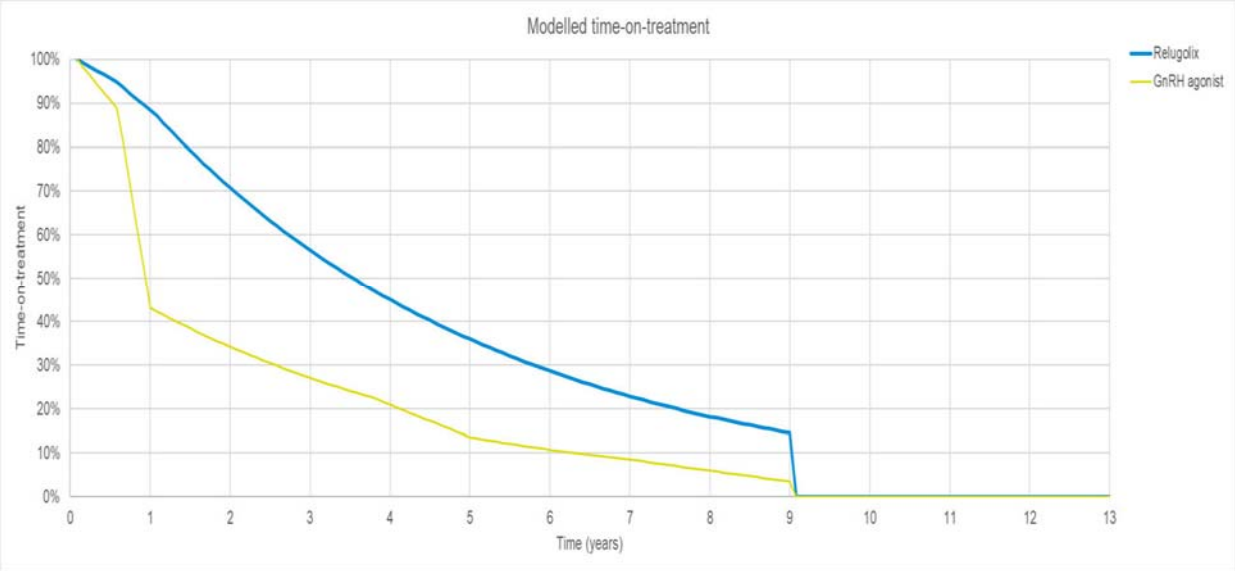
Timepoint	KOL 1	KOL 2	KOL 3	KOL 4	KOL 5	KOL 6	KOL 7	Proportion applied in model (average)
6 months	PEARL II (in base case)	PEARL II (in base case)	PEARL II (in base case)	PEARL II (in base case)	PEARL II (in base case)	PEARL II (in base case)	PEARL II (in base case)	PEARL II (in base case)
1 year	80%	5%	60%	12.5%	50%	15%	80%	43.2%
5 years	10%	0%	20%	5%	0%	5%	55%	13.6%
10 years	0%	0%	0%	0%	0%	0%	5%	0.7%

KOL: key opinion leader

The discontinuation rates for the intermediate timepoints for which there were no KOL responses e.g. cycles in between 1 year and 5 years, were calculated by assuming that a constant number of patients would withdraw at each cycle between timepoints for which was a KOL response. For instance, equally distributing the total number of patients that discontinued from year 1 to year 5 across all the cycles between year 1 and year 5. This ensured a 'smooth' discontinuation curve.

A trace of the time on treatment on relugolix CT and GnRH agonist in the model base case is shown in Figure 30. As expected, discontinuation is faster at all timepoints in the GnRH agonist arm and few patients remain on GnRH agonist over the longer term.

Figure 30 Time on pharmacological treatment in the model base case



Surgery

The model assumes that patients cannot have surgery whilst on active pharmacological treatment. Based on KOL opinion, the model base-case also assumes that patients who are within 5 years of menopause do not receive referrals to surgery. This assumption was explored in a scenario analysis where it is assumed that surgical referrals are possible up until the age of menopause (51 years).

Patients can be referred to surgery at the timepoint at which they discontinue treatment or can transition to surgery from the BSC state, where a background rate

is assumed. The latter is intended to capture patients who did not opt for surgery upon discontinuation but choose to at a later date. Once patients are referred for surgery the model includes a waiting time which is explored via scenario analyses.

Surgery rates upon pharmacological treatment discontinuation

The proportion of patients discontinuing treatment and subsequently going on to have surgery was not available from the LIBERTY studies of relugolix CT. The rate of surgery in those women who discontinue pharmacological treatment was thus informed by the proportion of patients who went on to have surgery at the end of the 13-week treatment period in PEARL II. The study reported that 45.1% of patients went on to have surgery. This proportion was therefore applied to those coming off all modelled pharmacological treatments.

Surgery rates once on BSC

Transition to surgery from BSC was estimated based on patients included in the observational PREMYA study (86). There were 1139 patients that received no treatment, iron supplements, or NSAIDs prior to beginning PREMYA, corresponding to BSC (87).Of these patients, 142 received a UF related surgery before the start of PREMYA. The average time between previous diagnosis of the 1139 patients and the beginning of PREMYA was 26.6 months, which is interpreted as the average time at risk of all 1139 patients (87). The percentage of patients receiving a surgery following a UF diagnosis was calculated as 142/1139 (12.5%). This risk was converted from 26.6 months to an annual risk assuming constant rates of surgery over time, to give an annual transition rate for BSC to surgery of 5.83%. This was then converted to a monthly risk to accommodate the monthly cycle length, resulting in a probability of 0.5% per cycle for transitioning from BSC to surgery.

Type of surgery

There are a range of surgery options that are available to women with moderate to severe symptoms associated with UF. These include a non-invasive procedure, uterine artery embolisation (UAE), and invasive options comprising myomectomy or a complete hysterectomy. According to KOLs that were interviewed, the choice of surgery type may be dependent on a range of factors such as the wish to preserve

fertility or wish to avoid a hysterectomy due to personal preferences that may also be influenced by cultural factors.

The waiting time before surgery is assumed the same for all treatments and is 15 months in base-case, regardless of the health state from which the surgery is assumed to occur (after withdrawal from pharmacological treatment, from BSC, or following a first surgery). Waiting time was informed by KOL opinion. Clinical experts advised that at present, due to the COVID-19 pandemic, waiting time for all surgical procedures had increased significantly. The value of 15 months is an average of the responses that were received, as detailed in Table 45.

Table 45 Summary of KOL responses for surgery waiting time (months)

	KOL 1	KOL 2	KOL 3	KOL 4	KOL 5	Average applied in model
Waiting time before surgery (months)	12	10.5 (average of 9-12)	18	15 (average of 12-18)	18	15

The model allows for patients to undergo up to 2 surgeries, with the exception of those who undergo hysterectomies as the first procedure, as symptoms of UF will no longer persist after this. The risk of re-surgery was calculated on an annual basis for each individual surgery based on proportions reported in the literature. The annual risk of re-surgery for each surgery (excluding hysterectomy) is presented in Table 46.

Table 46 Re-surgery rate per first surgery

Re-surgery	Myomectomy	UAE	MRgFUS
Annual risk of re-surgery	3.5%	11%	6.10%
Source	Gupta et al., 2014 (70)	Gupta et al., 2014 (70)	Gorny et al., 2017 (71)

MRgFUS: Magnetic resonance-guided focused ultrasound; UAE: uterine artery embolisation

The annual risk of re-surgery was summed for each surgery in Table 46 (20.6%) and then converted to a monthly probability, resulting in a risk of 1.72% of re-surgery per cycle. The proportion of patients assumed to be cured after surgery was calculated by converting the monthly risk of re-surgery to a 10-year probability. 10 years was chosen as this is the maximum possible duration of GnRH agonist treatment. This

resulted in a total of 87.48% of patients having a second surgery over 10 years. The probability of the first surgery being curative is thus 12.52% (1-87.48%). This parameter informed the utility assigned to patients after surgery (non-hysterectomy). Among patients who did not receive hysterectomy, 12.52% were considered cured and incurred general population utility, while 87.48% were not considered cured and incurred BSC utility.

The distribution of patients by type of surgery was assumed to be the same for all treatment arms, however the distribution differed for the first vs. second surgery. No single data source was found with hysterectomy, myomectomy, and UAE procedures performed in England or the UK that differentiated by surgery type and approach. Thus Hospital Episode Statistics (HES) data from 2013 (88) were combined with a US study conducted by Carls et al., 2008 (89) of a claims database of patients treated for UF to calculate the distribution of surgeries. The HES data is used as the base value and is differentiated according to the approach described by Carls et al. (89) where necessary. The reporting of surgery types in the most recent HES data published for 2019/20 precludes the stratification of all categories of surgery appropriately in this indication. For example, some of the surgeries, such as myomectomy, are not disaggregated into the various types of procedure (open, laparoscopic or vaginal) and thus it is not possible to derive proportions for each surgery type from the latest releases of HES, hence 2013 HES data (90) were used. These HES data were further stratified into subtype (according to the approach by Carls et al. (89) when necessary.

The distribution of patients amongst second surgeries was calculated from the long-term follow-up trial conducted by Moss et al., 2011 (91) (partly presented in Edwards and colleagues (92)), where a total of 24 patients had their first re-surgery, excluding two women that never received the index intervention and one woman that had a second re-surgery. Eight women received UAE and 12 women received hysterectomy at the time of re-surgery. No patients received a myomectomy as a re-surgery. The proportions sourced from the various data sources are presented in Table 47. The proportions of re-surgeries are presented in Table 49.

Table 47 Sources of surgery distribution data

Surgery	HES 2013 data	Carls et al., 2008 data	Moss et al., 2011 and Edwards et al., 2007 data (second surgery only)
Abdominal hysterectomy	61.2%	75.7%	70.4%
Laparoscopic hysterectomy		10.4%	
Vaginal hysterectomy		13.9%	
Abdominal myomectomy	8.5%	Not used	No records of myomectomy
Laparoscopic myomectomy	25.5%	32.4	
Vaginal myomectomy		67.6	
UAE	4.8%	Not used	29.6%

HES: Hospital Episode Statistics; UAE: uterine artery embolisation

Table 48 Distribution of patients for first surgery

Surgery	Proportion of patients
Abdominal hysterectomy	43.36%
Laparoscopic hysterectomy	6.36%
Vaginal hysterectomy	8.48%
Uterine artery embolisation	4.82%
Abdominal myomectomy	8.51%
Laparoscopic myomectomy	8.24%
Vaginal myomectomy	17.23%
MRgFUS	3.00% (assumption, 3% of proportion subtracted from abdominal hysterectomy)

MRgFUS: Magnetic resonance-guided focused ultrasound

Table 49 Distribution of patients for second surgery

Surgery	Proportion of patients
Abdominal hysterectomy	53.30%
Laparoscopic hysterectomy	7.30%
Vaginal hysterectomy	9.80%
Uterine artery embolisation	26.60%
MRgFUS	3.00%

MRgFUS: Magnetic resonance-guided focused ultrasound

Adverse events

Treatment-related adverse events

Short-term adverse events related to treatment (relugolix CT or GnRH agonists) are applied each cycle while on treatment and are assumed to last for a total of one month (model cycle). Treatment-related adverse events were sourced from relevant clinical trials and studies. Only adverse events that occurred in 5% or more patients were included. Adverse events rates were sourced from the relugolix CT arm of LIBERTY 1 and LIBERTY 2 for relugolix CT and from the placebo arm for patients in

the BSC health state. Adverse events for GnRH agonists were derived from the CSR of the PEARL II study and included if they occurred in 5% or more of patients (93).

Combining GnRH agonists with hormonal add-back therapy may decrease BMD loss and vasomotor symptoms, namely hot flushes (73). An SLR assessing the short-term (within 12 months) effectiveness and safety of add-back therapy for women using GnRH agonists for uterine fibroids reports a risk ratio of 0.38 for vasomotor symptoms (73) from tibolone, a commonly used add-back therapy in the UK. To adjust for the impact of add-back therapy on vasomotor symptoms in the GnRH agonist arm, the risk ratio of 0.38 was multiplied by the monthly risk of hot flushes estimated from the GnRH agonist arm of PEARL II (20.56%), resulting in a proportion of 7.81% per model cycle. This adjusted adverse event rate was applied to reflect those situations where GnRH is given longer term in combination with HRT. In the scenario where treatment is assumed to be administered as per the SmPC, for a maximum of 6 months pre-surgery, it is assumed that no add-back is given, therefore no risk ratio is applied. The adjusted adverse event rate is applied from month 0 in the model base-case as it is assumed that add-back HRT is administered alongside GnRH agonists from the onset of treatment.

Adverse event probabilities from the clinical studies were converted to cycle probabilities and are reported below.

Table 50 Adverse event rates applied for each treatment arm and BSC health state, model base-case

Adverse event	Relugolix CT	GnRH agonists	BSC
Cough	0.00%	0.00%	0.73%
Upper respiratory tract infection	0.00%	0.00%	0.66%
Headache	1.72%	1.92%	2.38%
Hot flush	1.44%	7.81%	1.01%
Anaemia	0.00%	0.00%	0.93%
Insomnia	0.00%	1.20%	0.00%
Hypertension	0.81%	0.00%	0.00%
Nausea	0.00%	0.00%	1.07%

Sources: LIBERTY 1 (42), LIBERTY 2 (43), PEARL II CSR (93)

Surgery-related adverse events

The incidence of surgery-related adverse events was sourced from the literature for each individual surgery. Surgery-related short-term adverse events occur only in the cycle that the surgery is performed and not in subsequent cycles. The reported rates of adverse events for each surgery were converted to monthly (cycle) probabilities, these are reported in Table 51.

Table 51 Risk of short-term adverse events related to surgery

	Abdominal hysterectomy	Laparoscopic hysterectomy	Vaginal hysterectomy	Myomectomy	Uterine artery embolisation	MR-guided focused ultrasound
Bowel obstruction	0.00%	0.00%	0.00%	1.37%	0.00%	0.00%
Febrile event	2.50%	1.40%	0.90%	0.00%	0.00%	0.00%
Fibroid expulsion	0.00%	0.00%	0.00%	0.00%	1.35%	0.00%
Groin haematoma	0.00%	0.00%	0.00%	0.00%	2.70%	0.00%
Haemorrhage	8.30%	5.70%	4.40%	1.37%	0.00%	0.00%
Ileus	0.00%	0.00%	0.00%	1.37%	0.00%	0.00%
Pelvic infection, haematoma or abscess	0.80%	3.20%	2.20%	0.00%	0.00%	0.00%
Pneumonia	0.00%	0.00%	0.00%	1.37%	0.00%	0.00%
Post embolisation syndrome	0.00%	0.00%	0.00%	0.00%	8.11%	0.00%
Pulmonary embolus	0.00%	0.00%	0.00%	1.37%	0.00%	0.00%
Sepsis	0.00%	0.00%	0.00%	1.37%	1.35%	0.00%
UTI	2.20%	0.70%	1.50%	10.96%	0.00%	0.00%
Urticaria	0.00%	0.00%	0.00%	0.00%	1.35%	0.80%
Wound infection	2.40%	1.50%	0.90%	0.00%	0.00%	0.00%
Abdominal oedema	0.00%	0.00%	0.00%	0.00%	0.00%	17.70%
Pain	0.00%	0.00%	0.00%	0.00%	0.00%	3.80%
Source	Brummer et al., 2011 (94)	(94)	(94)	Manyonda et al., 2012 (95)	(95)	Gorny et al., 2011 (71)

Long-term complications following surgery were only incorporated for those patients who had hysterectomies. The incidence of these complications was sourced from a prospective cohort study conducted in a sample of Turkish women (96). Adverse

effects were only reported at 3- and 6-months post-hysterectomy, thus the model base-case assumes that duration of each long-term complication is 12 months.

Table 52 Long-term adverse events related to hysterectomies

Adverse event	Duration (months)	Proportion of patients
Hot flushes	12	27.30%
Fatigue	12	6.06%
Urinary problems	12	3.03%
Abdominal distention	12	9.08%
Insomnia	12	15.10%
Housework problems	12	9.06%
Anxiety	12	6.06%
Vaginal irritation and pruritus	12	3.03%

Mortality

All-cause mortality is applied using a background mortality rate applied to all patients. The background mortality represents the risk of dying of any cause at a given age and is sourced from national life tables provided by the Office for National Statistics (97). Annual mortality was adjusted to a monthly rate to accommodate the monthly cycle length. No treatment-related excess mortality has been reported for relugolix CT or GnRH agonists, thus there is no treatment-related mortality included in the model.

Surgery specific risk of mortality is attributed to certain surgical procedures and is applied only in the cycle that surgery is performed, on top of the background mortality. The risk of mortality is applied at the time of surgery and is independent on whether surgery is first surgery or re-surgery. It was assumed that due to the invasive nature of abdominal surgery the abdominal approach for myomectomy would have the same risk of procedure-related mortality as abdominal hysterectomy. The mortality risks associated with each surgery are presented in Table 53.

Table 53 Surgery-specific risk of mortality

Surgery	Risk of mortality	Source
Abdominal hysterectomy	0.0028%	Settnes et al., 2020 (98)
Laparoscopic hysterectomy	0.0020%	Settnes et al., 2020 (98)
Vaginal hysterectomy	0.0031%	Settnes et al., 2020 (98)
Abdominal myomectomy	0.0028%	Assumed same as abdominal hysterectomy

Laparoscopic myomectomy	0.0000%	Assumption
Vaginal myomectomy	0.0000%	Assumption
Uterine artery embolisation	0.0200%	Zowall et al., 2008 (99)
MR-guided focused ultrasound	0.0000%	Gorny et al., 2011 (71)

B.3.4 Measurement and valuation of health effects

Each state in the model is associated with a utility weight specific to that state. For all patients (apart from those on surgery), utility weights are calculated through a utility function with inputs for bleeding, described below. Patients receiving surgery carry the population baseline utility adjusted for surgery specific utilities and adverse event utilities where applicable. Utility weights sourced as annual utilities are applied each cycle (corresponding to one month) as one twelfth of the annual utility.

Age dependent population utility

Population baseline utility is the mean utility experienced by the average person in the population. The model uses UK population utility weights stratified by age-bands sourced from a study published by Szende et al., 2014 (100).

Table 54 UK population utility weights

Age band	EQ-5D utility weight
18-24	0.940
25-34	0.927
35-44	0.911
45-54	0.847
55-64	0.799
65-74	0.779
75+	0.726

Health-related quality-of-life data from clinical trials

Quality of life (QoL) was measured prospectively in the LIBERTY (1, 2 and 3) clinical trials using several self-reported QoL measures. These were the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire, the EuroQol 5 Dimension 5 Level (EQ-5D-5L) and the patient global assessment (PGA) tools.

The UFS-QoL is a validated, disease-specific questionnaire that assesses symptom severity and QoL in patients with UF. It consists of an 8-item symptom severity scale and a 29-item QoL scale, comprising six subscales: Concern, Activities,

Energy/Mood, Control, Self-consciousness, and Sexual Function (42). All items are scored on a 5-point Likert scale, ranging from "not at all" to "a very great deal" for symptom severity items and "none of the time" to "all of the time" for the quality-of-life items. Symptom severity and QoL scale scores are summed and transformed into a 0- to 100-point scale (42). Higher QoL scale scores indicate better QoL whilst increased Symptom Severity scores indicate greater severity.

The EQ-5D-5L measures quality of life across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems (101).

The PGA was used to assess symptoms and functions in study participants. The PGA for symptoms and the PGA for function are single-item questions used to capture patients' perception of the severity of symptoms or the impact on function in relation to UF (42).

In both LIBERTY 1 and LIBERTY 2, mean UFS-QoL total scores in the relugolix CT arms showed a considerable improvement at week 24 compared to baseline (increases ranging from 36.8 to 44.1). The improvement in UFS-QoL total scores in the placebo arms of these RCTs was considerably lower, at 11.4 and 13.7 in LIBERTY 1 and LIBERTY 2, respectively. In both studies, the difference in UFS-QoL scores between the relugolix CT and placebo groups was statistically significant. The improvement in quality of life observed for relugolix CT at Week 24 was sustained through Week 52 in LIBERTY 3 (44).

Across all 3 of the LIBERTY RCTs, overall changes in EQ-5D-5L scores were similar across treatment groups. Most patients (75% - 85%) had no change or improvement from baseline to week 52 for any of the 5 domains of the EQ-5D and the mean change from baseline ranged from 2.7 to 8.3 in LIBERTY 1 and LIBERTY 2. Of note, the trial investigators reported that the time point of administration of the EQ-5D instrument was not appropriate to measure the impact of UF on patients' quality-of-life. Since the EQ-5D-5L has a recall of "today," i.e. patients assess their state of health on the day the questionnaire is completed only, the EQ-5D-5L only reflects

what a patient experienced on the day of the administration (i.e. the study visit), which generally did not occur during menstruation (42).

Given the complex nature of fibroids and the subsequent effect on HMB, a singular EQ-5D assessment on a single day may not truly reflect patients' overall QoL, as the patient may plausibly report differently depending on exactly which timepoint in their menstrual cycle they complete the measure. These issues raise questions as to the degree of internal validity and thus reliability of the EQ-5D scores from the LIBERTY RCTs. Furthermore, during the LIBERTY trials, the EQ-5D questionnaire was only administered at baseline and at the Week 24 assessment, thus any data from this assessment will only reflect how the patient was feeling on one day after up to 6 months of treatment. The disease specific UFS-QoL was however administered at baseline, week 12 and week 24, thus the full study time horizon and in turn the assessment of QoL was fully covered with these 3 questionnaires. As a result, it was felt that the UFS-QoL was a much more reliable and valid scale to use in the assessment of patient QoL.

Mapping

OLS Regression model

An unpublished algorithm (102) is available that allows mapping from the UFS-QoL and MBL to EQ-5D. This was used in a published economic model of Esmya® (UPA) vs. BSC in the UK (87).

The clinical effect of treatment with relugolix CT is estimated in the model using a symptom-based algorithm that converts MBL volume (mL) for each treatment arm to EQ-5D utility weights. The algorithm is parameterised using ordinary least squares (OLS) regression on patient-level data from LIBERTY 1, LIBERTY 2, and LIBERTY 3. UFS-QoL data from these studies was first mapped to the EQ-5D and an OLS regression was then carried out using MBL and baseline age as the explanatory variables. EQ-5D weights in the LIBERTY-studies have been generated using a previously estimated mapping regression from the UFS-QoL disease specific measure to EQ-5D weights (87). The OLS model is outlined in the equation below.

$$EQ-5D = \alpha + \beta_1 MBL\ volume + \beta_2 Age\ at\ baseline + \varepsilon$$

In the equation above, α is the intercept, $EQ-5D$ is the UFS-QoL mapped EQ-5D values, $MBL\ volume$ is the absolute MBL volume (measured in mL) recorded in LIBERTY 1, LIBERTY 2, and LIBERTY 3. $Age\ at\ baseline$ is the age recorded at the baseline visit in LIBERTY 1 and LIBERTY 2, and ε is the error term.

Predicted EQ-5D score is thus a function of patients' MBL score (measured in mL) over all time points and their age at baseline. The difference in MBL volume between relugolix CT and GnRH agonist is the primary driver of differences in predicted EQ-5D since age at baseline is equal between treatment arms.

The OLS model is fitted using 1,706 observations where multiple observations over time for the same patient are used. Only patients randomised to relugolix CT or Placebo in LIBERTY 1 and LIBERTY 2, who had UFS-QoL data (mapped EQ-5D) and non-missing observed MBL volume for at least one visit were included in the analysis. The following visits were included in the analysis: Baseline, Week 12, Week 24, Week 36, and Week 52; where visits at Week 36 and Week 52 were part of the LIBERTY 3 open-label extension.

There is an obvious source of bias in the OLS model since multiple observations over time for the same patient are included. The within-patient correlation is not accounted for, which makes the estimated standard error biased. Thereby, the estimated OLS model should not be used for inference, and the corresponding p-values and confidence intervals should not be used. However, predictions of the EQ-5D weights are only based on the estimated coefficients, which should not be subject to the same bias and thereby produce accurate predictions of the mean EQ-5D weights.

The estimates from the OLS regression are presented in below. The estimated coefficients from the OLS model show that 100 mL increase in MBL volume gives approximately a 0.04 decrease in EQ-5D weight. On the other hand, a one-year increase in the baseline age corresponds to approximately a 0.003 increase in EQ-5D weight.

Table 55 OLS model used to generate predicted EQ-5D weights

Coefficient	Point estimate
Intercept (α)	0.69568
MBL volume in mL (β_1)	-0.0003877
Age at baseline in years (β_2)	0.00296

MBL volume input

The treatment effect of relugolix CT in the model is measured via reported MBL volume as the main driver of differences in predicted EQ-5D between relugolix CT and the comparator. MBL volume for relugolix CT and the BSC state (i.e., the placebo arm in the LIBERTY 1 and LIBERTY 2 trials) are extracted from the CSR and are presented below. A weighted mean of the MBL volume at baseline for the relugolix CT and placebo is calculated from the numbers reported in the CSR to have similar MBL at baseline between treatment arms in the model. For all other visits, the treatment-arm specific MBL volumes are used. Corresponding MBL volume for GnRH agonists are not readily available, thus MBL volume for the comparator are derived from an ITC (described in section B.2.9), also presented in the table below. The estimated mean difference (MD) from the ITC between treatments is used to convert MBL volume in the relugolix CT and placebo arm to corresponding values in the GnRH agonist arm.

Table 56 MBL estimates in mL for relugolix CT and comparators

<table>
<tr><th rowspan="2">Time point</th><th colspan="3">MBL (mL)</th></tr>
<tr><th>Relugolix CT</th><th>BSC (Placebo)</th><th>GnRH agonist</th></tr>
<tr><td>Baseline</td><td>229.1</td><td>229.1</td><td>229.1</td></tr>
<tr><td>Week 4</td><td>115.8</td><td>180.8</td><td>231.6</td></tr>
<tr><td>Week 8</td><td>51.3</td><td>187.8</td><td>32.2</td></tr>
<tr><td>Week 12</td><td>37.8</td><td>184.2</td><td>58.9</td></tr>
<tr><td>Week 16</td><td>39.8</td><td>164.1</td><td rowspan="14">58.9
(Extrapolation based on last value carried forward)</td></tr>
<tr><td>Week 20</td><td>39.2</td><td>171.0</td></tr>
<tr><td>Week 24</td><td>42.2</td><td>159.9</td></tr>
<tr><td>Week 28</td><td>38.9</td><td rowspan="13">159.9
(Extrapolation based on last value carried forward)</td></tr>
<tr><td>Week 32</td><td>29.5</td></tr>
<tr><td>Week 36</td><td>27.7</td></tr>
<tr><td>Week 40</td><td>26.8</td></tr>
<tr><td>Week 44</td><td>22.6</td></tr>
<tr><td>Week 48</td><td>24.8</td></tr>
<tr><td>Week 52</td><td>25.6</td></tr>
<tr><td>Week 53+</td><td>25.6
(Extrapolation based on last value carried forward)</td></tr>
</table>

QoL algorithm output

The estimated OLS coefficients and the mean MBL volume were combined to generate predicted EQ-5D weights, assuming a mean baseline age equal to 42 years, for each respective treatment arm in the model, presented below.

Table 57 Predicted EQ-5D for all treatment arms

Timepoint	Relugolix CT	BSC (Placebo)	GnRH agonist
Baseline	0.731	0.731	0.731
Week 4	0.775	0.750	0.730
Week 8	0.800	0.747	0.808
Week 12	0.805	0.749	0.797
Week 16	0.805	0.756	0.797 (Extrapolation based on week 12 value carried forward)
Week 20	0.805	0.754	
Week 24	0.804	0.758	
Week 28	0.805	0.758 (Extrapolation based on week 24 value carried forward)	
Week 32	0.809		
Week 36	0.809		
Week 40	0.810		
Week 44	0.811		
Week 48	0.810		
Week 52	0.810		
Week 53+	0.810		

Disutilities associated with surgery

Surgery related utilities are calculated as a utility decrement applied to the population baseline utility or to the BSC utility, based on the proportion of patients assumed to be cured on uncured after surgery. An annual EQ-5D utility decrement per year for each surgery was sourced from a cost-effectiveness study of UPA in the treatment of UF (87). These values are reported below.

Table 58 Surgery-related disutilities reported in the literature

Surgery	EQ-5D QoL decrement/year	Source
Abdominal approach	-0.07	Sculpher et al. (2004) (15)
Laparoscopic approach	–0.04	(15)
Vaginal approach	–0.02	(15)
UAE	-0.02	(15)

EQ-5D: EuroQol 5 Dimension; QoL: quality of life; UAE: uterine artery embolisation

The disutility associated with surgery is assumed to be present for longer than the cycle that the event occurs, thus the annual disutility reported is adjusted for the number of months that the disutility will be applied. In the base-case, the duration of surgery-related disutility is 12 months. The annual disutilities reported in the literature were divided by 12 to calculate a disutility per monthly cycle and are reported below.

Disutility for MR-guided focused ultrasound procedures were not reported in the study thus it assumed that the same disutility applies as for UAE.

Table 59 Surgery-related disutilities applied in the model

Surgery	Disutility applied per monthly cycle
Abdominal hysterectomy	-0.005
Laparoscopic hysterectomy	-0.003
Vaginal hysterectomy	-0.002
Abdominal myomectomy	-0.005
Laparoscopic myomectomy	-0.003
Vaginal myomectomy	-0.002
UAE	-0.002
MRgFUS	-0.002

MRgFUS: Magnetic resonance-guided focused ultrasound; UAE: uterine artery embolisation

Waiting for surgery

Patients in the 'waiting for surgery' state are attributed a surgery anticipation disutility. This state assumes that patients have experienced treatment failure. When patients wait for their second surgery, they are assumed to have recurrent symptoms. Consequently, their utility and costs incurred would be equal to patients in the BSC state who are without specific treatment besides concomitant medication. It is assumed that the disutility when waiting for surgery arises from worrying, thus a disutility value equivalent to that of anxiety (-0.01) is applied (103).

Loss of uterus

The loss of the uterus may be associated with negative feelings and perceived loss of for example, femininity. According to the World Health Organisation (WHO) the loss of the uterus is associated with an annual disutility of -0.18, (104) thus the model applies one twelfth of this each month to patients in the post-hysterectomy state. The resultant disutility of -0.015 is applied per model cycle up until patients reach menopause.

Health-related quality-of-life studies

Refer to "Appendix H: Health-related quality-of-life studies" for a description of the search methodology and findings.

A literature review was performed to gather quality of life data, 12 papers were identified that collected QoL data outcomes including one paper which specified

utility values based off time trade off methods, six that used EQ-5D, one paper did not specify a tool and the remaining papers used SF-36. In two of the papers found the intervention was ulipristal acetate, for the remaining papers the interventions were types of surgery, ranging from ablations to hysterectomy. While some of these papers gathered EQ-5D, none of the quality-of-life assessments were specific to menstrual blood loss values, therefore they were not able to be used in the model. Health state utilities in the cost-effectiveness model came from an algorithm.

One of the studies found was used to inform the disutility associated with hot flushes as an adverse event (14) and a further *ad hoc* literature search informed the remaining disutilities.

Adverse reactions

Disutilities associated with treatment-related adverse events

Disutilities for treatment-related adverse events are applied for each individual treatment-related AE (reported in section B.3.3). Disutilities related to short term adverse events are applied in the model in the cycle they occur and the duration of the disutility is thus one month. Disutility values were sourced from the literature and adjusted to reflect a monthly cycle length.

Table 60 Disutilities for treatment-related adverse events

Adverse event	Disutility	Source
Hot flush	-0.005	Hux et al., 2015 (14)
Headache	0.000	Assumption of no disutility
Hypertension	0.000	Assumption of no disutility
Cough	0.000	Assumption of no disutility
Nausea	-0.011	Assumption that same disutility as reported for influenza in Lloyd et al., 2006 (105)
Upper respiratory tract infection	-0.011	Assumption that same disutility as reported for influenza in Lloyd et al., 2006 (105)
Anaemia	-0.009	Del Rio et al., 2006 (106)
Insomnia	-0.010	Assumption that same disutility as for fatigue in Lloyd et al., 2006 (105)

Surgery-related adverse events

Utility decrements for surgery-related adverse events are reported in Table 61 and Table 62 below. Disutilities for surgery related short-term adverse events are applied for one month. Disutilities for long-term complications from hysterectomies are applied for a duration of 12 months.

Table 61 Disutilities for surgery-related short-term adverse events

Surgery-related adverse event	Disutility	Source
Bowel obstruction	-0.017	Earnshaw et al., 2010 (107)
Febrile event	0.000	Assumption of no disutility
Fibroid expulsion	-0.001	Assumption that same as pain, reported in Anderson et al., 1985 (108)
Groin haematoma	0.000	Assumption of no disutility
Haemorrhage	-0.017	Freeman et al., 2011 (109)
Ileus	-0.017	Earnshaw et al., 2010 (107)
Pelvic infection, haematoma or abscess	-0.016	Tolley et al., 2013 (110)
Pneumonia	-0.008	Assumption that same disutility as reported for influenza in Lloyd et al., 2006 (105)
Post embolisation syndrome	-0.012	Assumption that same as sum of pain and nausea
Pulmonary embolus	-0.002	Blondon et al., 2010 (111)
Sepsis	-0.010	Karlsson et al., 2009 (112)
Urinary tract infection	-0.006	Lourenco et al., 2008 (113)
Urticaria	0.000	Assumption of no disutility
Wound infection	-0.016	Tolley et al., 2013 (110)
Oedema	-0.005	Assumption that same as pain (108)
Pain	-0.001	(108)

Table 62 Disutilities for long-term adverse events for hysterectomies

Surgery-related adverse event	Disutility	Source
Hot flushes	-0.005	Hux et al., 2015 (14)
Fatigue	-0.010	Lloyd et al., 2006 (105)
Urinary problems	-0.006	Assumption: same as UTI (113)
Abdominal distention	-0.008	Groeneveld et al, 2001 (114)
Insomnia	-0.010	Assumption: same as fatigue (105)
Housework problems	-0.005	Dolan, 1997 (115)
Anxiety	-0.013	Stein et al., 2005 (103)
Vaginal irritation and pruritus	-0.001	Assumption that same as pain (108)

Health-related quality-of-life data used in the cost-effectiveness analysis

Table 63 Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
On treatment - Relugolix CT	Mapped from MBL	Mapped from MBL	MBL volume input (Page 150)	EQ-5D data failed to capture changes in quality-of-life (QoL) that were observed using other self-reported QoL measures in the LIBERTY studies.
On treatment - GnRH agonist	Mapped from MBL	Mapped from MBL	MBL volume input (Page 150)	EQ-5D data failed to capture changes in quality-of-life (QoL) that were observed using other self-reported QoL measures in the LIBERTY studies.
BSC	Mapped from MBL	Mapped from MBL	MBL volume input (Page 150)	EQ-5D data failed to capture changes in quality-of-life (QoL) that were observed using other self-reported QoL measures in the LIBERTY studies.
Waiting for surgery	Mapped from MBL	Mapped from MBL	MBL volume input (Page 150)	EQ-5D data failed to capture changes in quality-of-life (QoL) that were observed using other self-reported QoL measures in the LIBERTY studies.
Surgery	Mapped from MBL	Mapped from MBL	MBL volume input (Page 150)	EQ-5D data failed to capture changes in quality-of-life (QoL) that were observed using

				other self-reported QoL measures in the LIBERTY studies.
Post-surgery	Mapped from MBL	Mapped from MBL	MBL volume input (Page 150)	EQ-5D data failed to capture changes in quality-of-life (QoL) that were observed using other self-reported QoL measures in the LIBERTY studies.
Menopause	Mapped from MBL	Mapped from MBL	MBL volume input (Page 150)	EQ-5D data failed to capture changes in quality-of-life (QoL) that were observed using other self-reported QoL measures in the LIBERTY studies.
Disutilities for treatment-related adverse events				
Hot flush	-0.005	(-0.004, -0.006)	Hux et al., 2015 (14) (Adverse reactions, Page 153)	Literature
Headaches	0.000	NA	(Adverse reactions, Page 153)	Assumption of no disutility due to the very mild nature of this event
Hypertension	0.000	NA	(Adverse reactions, Page 153)	Assumption of no disutility due to the very mild nature of this event
Cough	0.000	NA	(Adverse reactions, Page 153)	Assumption of no disutility due to the very mild nature of this event
Nausea	-0.011	(-0.009, -0.013)	Lloyd et al., 2006 (105) (Adverse reactions, Page 153)	Assumption that same disutility as reported in the literature for influenza
Upper respiratory tract infection	-0.011	(-0.009, -0.013)	Lloyd et al., 2006 (105) (Adverse	Assumption that same disutility as reported in

			reactions, Page 153)	the literature for influenza
Anaemia	-0.009	(-0.007, -0.011)	Del Rio et al., 2006 (106) (Adverse reactions, Page 153)	Literature
Disutilities for surgery-related short-term adverse events				
Bowel obstruction	-0.017	(-0.013, -0.020)	Earnshaw et al., 2010 (107) (Adverse reactions, Page 154)	Literature
Febrile event	0.000	NA	(Adverse reactions, Page 154)	Assumption of no disutility
Fibroid expulsion	-0.001	(-0.001, -0.001)	Anderson et al., 1985 (108) (Adverse reactions, Page 154)	Literature
Groin haematoma	0.000	NA	(Adverse reactions, Page 154)	Assumption of no disutility
Haemorrhage	-0.017	(-0.013, -0.020)	Freeman et al., 2011 (109) (Adverse reactions, Page 154)	Literature
Ileus	-0.017	(-0.013, -0.020)	Earnshaw et al., 2010 (107) (Adverse reactions, Page 154)	Literature
Pelvic infection, haematoma or abscess	-0.016	(-0.013, -0.020)	Tolley et al., 2013 (110) (Adverse reactions, Page 154)	Literature
Pneumonia	-0.008	(-0.007, -0.010)	Lloyd et al., 2006 (105) (Adverse reactions, Page 154)	Assumption that same disutility as reported in literature for influenza
Post embolisation syndrome	-0.012	(-0.010, -0.014)	Sum of disutilities for pain and nausea (Adverse reactions, Page 154)	Calculation
Pulmonary embolus	-0.002	(-0.001, -0.002)	Blondon et al., 2010 (111) (Adverse	Literature

			reactions, Page 154)	
Sepsis	-0.010	(-0.008, -0.012)	Karlsson et al., 2009 (112) (Adverse reactions, Page 154)	Literature
Urinary tract infection	-0.006	(-0.005, -0.007)	Lourenco et al., 2008 (113) (Adverse reactions, Page 154)	Literature
Urticaria	0.000	NA	(Adverse reactions, Page 154)	Assumption of no disutility due to the very mild nature of this event
Wound infection	-0.016	(-0.013, -0.020)	Tolley et al., 2013 (110) (Adverse reactions, Page 154)	Literature
Oedema	-0.005	(-0.004, -0.007)	Anderson et al., 1985 (108) (Adverse reactions, Page 154)	Literature
Pain	-0.001	(-0.001, -0.001)	Anderson et al., 1985 (108) (Adverse reactions, Page 154)	Literature
Disutilities for hysterectomy-related long-term adverse events				
Hot flushes	-0.005	(-0.004, -0.006)	Hux et al., 2015 (14) (Disutilities associated with surgery, Page 145)	Literature
Fatigue	-0.010	(-0.008, -0.012)	Lloyd et al., 2006 (105) (Disutilities associated with surgery, Page 145)	Literature
Urinary problems	-0.006	(-0.005, -0.007)	Lourenco et al., 2008 (113) (Disutilities associated with surgery, Page 145)	Assumption that same as UTI
Abdominal distention	-0.008	(-0.006, -0.009)	Groeneveld et al, 2001 (114) (Disutilities associated with surgery, Page 145)	Literature

Insomnia	-0.010	(-0.008, -0.012)	(Disutilities associated with surgery, Page 145)	Assumption: same as fatigue
Housework problems	-0.005	(-0.004, -0.007)	Dolan, 1997 (115) (Disutilities associated with surgery, Page 145)	Literature
Anxiety	-0.013	(-0.011, -0.017)	Stein et al., 2005 (103) (Disutilities associated with surgery, Page 145)	Literature
Vaginal irritation and pruritus	-0.001	(-0.001, -0,001)	Anderson et al., 1985 (108) (Disutilities associated with surgery, Page 145)	Literature
Loss of uterus	-0.015	-0.012, -0.018)	WHO (104) (Disutilities associated with surgery, Page 145)	Literature
Utility decrements due to surgery event				
Abdominal hysterectomy	-0.005	(-0.004, -0.007)	Sculpher et al. (2004) (15) (Disutilities associated with surgery, Page 151)	Literature
Laparoscopic hysterectomy	-0.003	(-0.003, -0.004)	Sculpher et al. (2004) (15) (Disutilities associated with surgery, Page 151)	Literature
Vaginal hysterectomy	-0.002	(-0.001, -0.002)	Sculpher et al. (2004) (15) (Disutilities associated with surgery, Page 151)	Literature
Abdominal myomectomy	-0.005	(-0.004, -0.007)	Sculpher et al. (2004) (15) (Disutilities associated with surgery, Page 151)	Literature
Laparoscopic myomectomy	-0.003	(-0.003, -0.004)	Sculpher et al. (2004) (15) (Disutilities associated with	Literature

			surgery, Page 151)	
Vaginal myomectomy	-0.002	(-0.001, -0.002)	Sculpher et al. (2004) (15) (Disutilities associated with surgery, Page 151)	Literature
UAE	-0.002	(-0.001, -0.002)	Sculpher et al. (2004) (15) (Disutilities associated with surgery, Page 151)	Assumed to be same as disutility for vaginal procedures
MRgFUS	-0.002	(-0.002, -0.002)	Sculpher et al. (2004) (15) (Disutilities associated with surgery, Page 151)	Assumed to be same as disutility for vaginal procedures
Abbreviations: HS, health state; AR, adverse reaction				

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Refer to “Appendix I: Cost and healthcare resource identification, measurement and valuation” for details on how cost and resource use studies were identified.

Intervention and comparators’ costs and resource use

Drug acquisition costs

The drug acquisition cost for relugolix CT is the accepted list price of £72 for a 28-pack of 40 mg/1 mg/0.5 mg tablets. Given the monthly cycle length, the drug costs for relugolix CT are calculated assuming a cycle duration of 30.5 days, as opposed to 28 days. This results in a cost per model cycle of £78.43 (£72*(30.5/28)).

As requested by the ERG during the Decision Problem Meeting, although all GnRH agonists are assumed to have equal efficacy, cost effectiveness is calculated for each GnRH agonist individually to enable an incremental analysis. Costs for the GnRH agonist comparators were sourced from the NHS drug tariff (116). A weighted average price was calculated using prescription cost analysis (PCA) data (114) for monthly Triptorelin as two brands of the short-acting formulation were listed on the BNF. The weighted average was calculated as the sum of the costs for the 2

different brands divided by the sum of their respective market share. Costs of short-acting GnRH agonists are incurred at each monthly cycle, whereas the costs for the long-acting formulations are only applied once every 3 months. That is, the acquisition costs are incurred at the beginning of the 3-month treatment cycle, and the costs are incurred over 4 time points within a year.

Treatment costs for the GnRH agonist comparators also include the acquisition costs of add-back therapy (HRT) which is taken whilst patients are on active GnRH agonist treatment. The model includes two HRT options which are tibolone and raloxifene. The model assumes an equal split of use amongst the 2 HRTs, that is, 50% are assumed to receive tibolone whilst the other 50% are assumed to receive raloxifene. Drug acquisition costs for these treatments were obtained from the NHS drug tariff (117) and converted to a cost per monthly cycle, assuming a length of 30.5 days per month. The breakdown of add-back therapy costs applied for GnRH agonist patients is provided in Table 66. The 50/50 split of patients between the two HRTs resulted in a cost per cycle of £7.13. The treatment acquisition cost of HRT is incurred for each month that patients are on active treatment with GnRH agonist, as it was assumed that even those who are on long-acting (3-monthly) GnRH agonist would have monthly prescriptions of HRT. The cost calculations assume 100% dose intensity for GnRH agonist and add-back therapies.

Table 64: Intervention and comparator drug acquisition costs for monthly treatments

Drug	Pack price	Doses per pack	Doses used per monthly cycle	Total cost per monthly cycle
Relugolix CT	£72.00	28	30.5	£78.43
Leuprorelin acetate monthly formulation	£75.24	1	1	£75.24
Triptorelin monthly formulation	£72.32	1	1	£72.32
Goserelin monthly formulation	£70.00	1	1	£70.00

Table 65 Comparator drug acquisition costs of long-acting GnRH agonist

Drug	Pack price	Doses per pack	Doses used per monthly cycle*	Total cost per monthly cycle*
Leuprorelin acetate 3-monthly formulation	£225.72	1	1/3	£75.24

Triptorelin 3-monthly formulation	£207.00	1	1/3	£69.00
Goserelin 3-monthly formulation	£235.00	1	1/3	£78.33

* the cost per dose is applied every 3 months in the model (in line with treatment dosing schedule)

Table 66 Add-back therapy costs applied for GnRH agonist patients

Drug	Pack price	Doses per pack	Doses used per monthly cycle	Cost per monthly cycle
Tibolone 2.5 mg tablets	£7.44	28	30.5	£8.10
Raloxifene 60mg tablets	£5.65	28	30.5	£6.15

Administration costs

Relugolix CT is self-administered orally and thus there are no additional administration costs. KOLs advised that an appointment with a gynaecologist would be required to initiate the first prescription for relugolix CT, as is currently standard practice for GnRH agonists. This is applied as a one-off cost to both treatment arms (relugolix CT and GnRH agonist) in the model, incurred in the first cycle. GnRH agonists are administered as a subcutaneous injection and KOLs advised that these treatments are typically administered by a nurse based within a GP practice. The unit cost of an hour of practice nurse time is £38 (80) and it was assumed that only 10 minutes of nurse time would be required for injection administration, thus the cost applied in the model is £6.33 (£38*10/60).

Table 67 Drug administration costs

Resource category	Unit cost	Source
Gynaecologist visit	£144.98	Gynaecology, Non-Admitted Face-to-Face Attendance, Follow-up, Consultant Led, NHS reference costs 2019-20. Currency code: WF01A (79)
Nurse administration of GnRH agonists	£6.33	Calculated as 10 minutes of practice nurse time (80)

Monitoring costs

HRU frequency in terms of routine monitoring and disease management was informed by KOL expert opinion. Interviews were conducted with gynaecologists (n=3) based in UK hospitals who routinely treat women experiencing moderate to

severe symptoms associated with UF. The KOLs provided frequencies of HRU for each treatment strategy included in the model. These are listed below.

Table 68 Monitoring frequency for each treatment, KOL responses

Resource use	Frequency - relugolix CT	Frequency – GnRH agonist	Frequency - BSC
Gynaecologist	Once every 6 months	Once every 6 months	None
GP visits	None	None	Once every 3 months

Table 69 Monitoring frequency applied in cost-effectiveness model

Resource use	Frequency per monthly cycle - relugolix CT	Frequency per monthly cycle – GnRH agonist	Frequency per monthly cycle - BSC
Gynaecologist	0.167	0.167	0.000
GP visits	0.000	0.000	0.333

Table 70 Examinations and test frequency for each treatment, KOL responses

Resource use	Frequency - relugolix CT	Frequency – GnRH agonist	Frequency - BSC
DEXA scan	Once after the first year	Once a year	None
Ultrasound	Once a year	Once a year	Once a year
Full blood count	Once a year	Once a year	Once a year
Hysteroscopy	Required once a year in only 25% of patients	Required once a year in only 25% of patients	Required once a year in only 25% of patients
MRI	Required once a year in only 20% of patients	Required once a year in only 20% of patients	Required once a year in only 20% of patients

BSC: best supportive care; DEXA: dual-energy x-ray absorptiometry; GnRH: gonadotrophin releasing hormone; MRI: magnetic resonance imaging

Table 71 Examinations and tests, frequencies applied in cost-effectiveness model

Resource use	Frequency per monthly cycle - relugolix CT	Frequency per monthly cycle – GnRH agonist	Frequency per monthly cycle - BSC
DEXA scan	0.00	0.08	0.00
Ultrasound	0.08	0.08	0.08
Full blood count	0.08	0.08	0.08
Hysteroscopy	0.02	0.02	0.02
MRI	0.02	0.02	0.02

Table 72 Unit costs of monitoring and examinations

Resource use	Unit cost	Source
Gynaecologist	£144.98	Gynaecology consultant Non-Admitted Face-to-Face Attendance, Follow-up (79)
General Practitioner	£39.23	Per surgery consultation lasting 9.22 minutes, PSSRU 2020 (80)
DEXA scan	£63.12	Outpatient DEXA scan, Currency code: RD50Z (79)
Ultrasound	£164.03	Transvaginal Ultrasound, Currency code: MA36Z (79)
Full blood count	£2.53	Haematology, Currency code: DAPS05 (79)
Hysteroscopy	£212.06	Diagnostic Hysteroscopy, Currency code: MA31Z (79)
MRI	£173.38	MRI, Outpatient procedures, Currency code: DIM004 (79)

DEXA: dual-energy x-ray absorptiometry; MRI: magnetic resonance imaging; PSSRU: Personal Social Services Research Unit

Costs of surgery

The model includes a range of surgery options that patients may opt for, as detailed in section B.3.3. Unit costs for surgical procedures were sourced from NHS reference costs and are presented in Table 73. The total cost of surgeries was calculated as the product of the proportion of patients receiving each type of surgery and the unit costs for the respective surgery. Surgery costs were applied as one-off costs.

Table 73 Unit costs of surgical procedures

Surgical procedure	Unit cost	Source
Abdominal hysterectomy	£4,878.31	Major Open Upper Genital Tract Procedures, average of CC scores 0-5+, currency codes MA07G, MA07F, MA07E; weighted average of elective, day case, and outpatient unit costs (79)
Laparoscopic hysterectomy	£4,220.52	Major, Laparoscopic or Endoscopic, Upper Genital Tract Procedure, average of CC scores 0-2+, currency codes MA08B, MA08A; weighted average of elective, day case, and outpatient unit costs (79)
Vaginal hysterectomy	£4,878.31	Major Open Upper Genital Tract Procedures, average of CC scores 0-5+, currency codes MA07G, MA07F, MA07E; weighted average of elective, day case, and outpatient unit costs (79)
Uterine artery embolisation	£2,230.70	Uterine Artery Embolisation, currency code YR55Z, weighted average of elective, day case, and outpatient unit costs (79)
Abdominal myomectomy	£3,300.82	Intermediate Open Upper Genital Tract, currency code MA12Z, weighted average of elective, day case, and outpatient unit costs (79)

Laparoscopic myomectomy	£3,300.82	Intermediate Open Upper Genital Tract, currency code MA12Z weighted average of elective, day case, and outpatient unit costs (79)
Vaginal myomectomy	£3,300.82	Intermediate Open Upper Genital Tract, currency code MA12Z, weighted average of elective, day case, and outpatient unit costs (79)
MRgFUS	£976.77	Radiofrequency Ablation or Cryoablation, for Pain Management, currency code AB15Z, weighted average of elective, day case, and outpatient unit costs (79)

Adverse reaction unit costs and resource use

Treatment-related adverse events

Only costs of moderate-to-severe adverse events occurring in ≥5% of patients were incorporated into the model. Unit costs were combined with the monthly rates of each treatment-related adverse event (Table 58) to derive costs per treatment cycle. Unit costs for each treatment-related adverse event are reported in Table 74.

Table 74 Unit costs of treatment-related adverse events

Adverse event	Unit cost	Assumptions and source
Hot flush	£0.00	No cost incurred as it is assumed that this will be self-managed and no treatment sought
Cough	£0.00	No cost incurred as it is assumed that this will be self-managed and no treatment sought
Hypertension	£39.23	Assumption that cost incurred is a GP appointment (80)
Headache	£0.00	No cost incurred as it is assumed that this will be self-managed and no treatment sought
Upper respiratory tract infection	£39.23	Assumption that cost incurred is a GP appointment (80)
Acne	£39.23	Assumption that cost incurred is a GP appointment (80)
Anaemia	£39.23	Assumption that cost incurred is a GP appointment (80)
Anxiety	£39.23	Assumption that cost incurred is a GP appointment (80)
Nausea	£0.97	Treatment with Metoclopramide (118)
Insomnia	£39.23	Assumed to be the cost of a GP appointment

Surgery-related adverse events

Short-term adverse events relating to surgery are incorporated as one-off costs incurred during the same cycle in which the surgery is performed. The costs of long-term adverse effects of hysterectomies are incurred over a 12-month period post-surgery. The unit cost of each surgery-related adverse event are presented in Table 75. Unit costs of surgery-related adverse events were multiplied by the proportion of patients experiencing each adverse event for each individual surgery, as reported in Table 51 and Table 52 to derive total cost of surgery-related adverse events.

Table 75 Unit costs of surgery-related adverse events

Adverse event	Unit cost	Source
Bowel obstruction	£5,748.41	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+, currency code WH07C, Non-elective long stay, (79)
Febrile event	£2,103.38	Infections or Other Complications of Procedures, with Single Intervention score 0-1, currency code WH07D, Non-elective short stay (79)
Fibroid expulsion	£5,748.41	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+, currency code WH07C, Non-elective long stay (79)
Groin haematoma	£2,103.38	Infections or Other Complications of Procedures, with Single Intervention score 0, currency code WH07D, Non-elective short stay (79)
Haemorrhage	£3,640.02	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+, currency code WH07C, Non-elective short stay (79)
Ileus	£0.00	Assume no cost
Pelvic infection, haematoma or abscess	£2,103.38	Infections or Other Complications of Procedures, with Single Intervention score 0, currency code WH07D, Non-elective short stay (79)
Pneumonia	£2,103.38	Infections or Other Complications of Procedures, with Single Intervention score 0, currency code WH07D, Non-elective short stay (79)
Post embolisation syndrome	£3,640.02	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+, currency code WH07C, Non-elective short stay, (79)
Pulmonary embolus	£3,640.02	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+, currency code WH07C, Non-elective short stay, (79)
Sepsis	£5,748.41	Infections or Other Complications of Procedures, with Single Intervention, with

		CC Score 2+, currency code WH07A, Non-elective long stay, (79)
UTI	£2,103.38	Infections or Other Complications of Procedures, with Single Intervention score 0, currency code WH07D, Non-elective short stay (79)
Urticaria	£0.00	Assume no cost
Wound infection	£2,103.38	Infections or Other Complications of Procedures, with Single Intervention score 0, currency code WH07D, Non-elective short stay (79)
Abdominal oedema	£0.00	Assume no cost
Pain	£0.00	Assume no cost
Urinary problems	£0.00	Assume no cost
Abdominal distention	£0.00	Assume no cost
Insomnia	£39.23	Assumed to be the cost of a GP appointment
Vaginal irritation and pruritus	£0.00	Assume no cost
Anxiety	£39.23	Assumed to be the cost of a GP appointment

Concomitant medications

Patients with moderate to severe UF may require supplementary drugs to combat persistent symptoms such as pain and blood loss, as observed in the LIBERTY trials. The model thus also accounts for the costs associated with concomitant medications for these breakthrough symptoms. NSAIDs are included for pain management whilst iron supplements are included for blood loss.

The proportion of patients requiring concomitant medication in the relugolix CT is informed by the proportions reported in the relugolix + E2/NETA arm of LIBERTY 3 (44). The proportions requiring iron supplements and NSAIDs in the placebo arm of LIBERTY 3 were applied for BSC patients. For GnRH agonists, the proportions of patients requiring concomitant medication is informed by the proportion reported in the PEARL II study report (93). The usage per patient per month (in mgs) for concomitant medication was calculated as the proportion of patients requiring the medication multiplied by the number of doses required per day e.g. 4 times for NSAIDs, and by the number of days in a month. The resultant usage per patient per month is reported in Table 79. Given that concomitant medication usage for each comparator were sourced from different studies, a scenario was explored where concomitant usage was assumed equal between the relugolix CT and GnRH agonist arms.

Table 76 Concomitant medication dose assumptions

Medication	Dosage information	Source
NSAIDs	200-400 mg given as a single dose or 3-4 times a day with an interval of 6 hours as required	Dosage for primary dysmenorrhoea reported in ibuprofen SmPC (119)
Iron supplement	200 mg daily for iron deficiency anaemia	BNF (120)

BNF: British National Formulary; NSAID: Non-steroidal anti-inflammatory drug; SmPC: summary of product characteristics

Table 77 Concomitant medication costs applied in the model

Medication	Pack price	Cost per tablet	Cost per dosing episode
NSAIDs	£1.17 for a 24-pack of 200mg ibuprofen tablets, NHS drug tariff price (121)	£0.05	£0.60 (assuming 200mg taken 3 times a day for 4 days)
Iron supplement	£1.27 for 28-pack of ferrous sulfate 200 mg tablets, NHS drug tariff price (120)	£0.05	£1.50 per monthly cycle (assuming daily treatment)

NHS: National Health Service; NSAID: Non-steroidal anti-inflammatory drug

Table 78 Proportion of patients requiring each concomitant medication, per treatment arm

Medication	Relugolix CT	GnRH agonist	BSC
NSAIDs	61.3%	27.7%	70.7%
Iron supplement	30.1%	24.8%	30.5%

BSC: best supportive care; GnRH: gonadotrophin releasing hormone; NSAID: Non-steroidal anti-inflammatory drug

Table 79 Usage (mg) of each concomitant medication, per treatment arm, per month

Medication	Relugolix CT	GnRH agonist	BSC
NSAIDs	68.66	31.02	79.18
Iron supplement	8.43	6.94	8.54

BSC: best supportive care; GnRH: gonadotrophin releasing hormone; NSAID: Non-steroidal anti-inflammatory drug

B.3.6 Summary of base-case analysis inputs and assumptions

Base case inputs

Please see Table 111 in Appendix J: Summary of base-case analysis inputs for the summary of input parameters.

Table 80 Assumptions applied in the model

Assumption	Justification
Waiting time before surgery is 15 months	Waiting time was informed by KOLs who advised that at present, due to the COVID-19 pandemic, waiting time for all surgical procedures had increased substantially. KOL responses provided a range of waiting times, thus an average of the responses was taken
Treatment duration of GnRH agonists is based on 'off-label' use and exceeds label restriction	KOL feedback was that GnRH agonists are often used in combination with HRT (add-back) beyond 6 months in clinical practice. KOLs stated that the majority of patients would remain on treatment for up to a year and for subsequent time periods there would be a decline in proportion of patients on treatment. An average of the 3 KOL responses for each time point was thus applied in the model
Withdrawal to surgery is conditional on discontinuing treatment	Relugolix CT is positioned as a treatment for patients who wish to avoid having surgery and is not a pre-surgical treatment. The same assumptions apply for GnRH agonists. Patients on active pharmacological treatment cannot have surgery, thus transitions to surgery are only possible from the BSC health state Patients cannot discontinue directly from treatment to the surgery health state due to the 14-month waiting time before surgery and would thus be treated with BSC during this time
Second surgery is possible for all surgical procedure except hysterectomy	Once patients have undergone a hysterectomy, they do not experience uterine fibroids

Once patients are within 5 years of the age of menopause (51 years), they can no longer opt for surgery	KOL feedback was that patients who are close to menopause do not receive referrals to surgery, as the moderate-severe symptoms associated with uterine fibroids will cease once they reach menopause

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

The incremental cost-effectiveness results are reported in Table 81. Relugolix CT is associated with greater total costs compared to the GnRH agonist comparators, as total costs for relugolix CT are £9,967 compared to a range of £7,995 to £9,967 for GnRH agonists, mainly due to the longer time during which patients remain on active treatment with relugolix CT. However, relugolix CT is also more effective, with an incremental QALY gain of 0.178 QALYs. Goserelin monthly is the least expensive treatment and dominates all GnRH agonist comparators, as it achieves the same QALYs at lower cost. The ICER for relugolix CT vs. Goserelin monthly is £11,069 per QALY. This lies below the NICE cost-effectiveness threshold of £20,000 to £30,000 per QALY.

Table 81 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,995	21.522	16.878	-	-	-	
Triptorelin 3-monthly	8,050	21.522	16.878	55	0.000	0.000	Dominated
Triptorelin monthly	8,052	21.522	16.878	57	0.000	0.000	Dominated
Leuprorelin monthly	8,124	21.522	16.878	129	0.000	0.000	Dominated
Leuprorelin 3-monthly	8,200	21.522	16.878	205	0.000	0.000	Dominated
Goserelin 3-monthly	8,255	21.522	16.878	260	0.000	0.000	Dominated
Relugolix CT	9,967	21.524	17.057	1,972	0.002	0.178	11,069
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Note: Refer to Appendix J for a summary of the base-case analysis inputs and Appendix K for clinical outcomes from the model and disaggregated results of the base-case incremental cost effectiveness analysis.

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model parameters. PSA was conducted by varying these parameters using their upper and lower bound values and a distribution was assigned to these parameters (Table 111). 1000 PSA iterations were deemed sufficient to derive a stable estimate of the mean model results, represented by the probabilistic ICER.

Output from the PSA iterations is presented as scatter points on the cost-effectiveness plane in Figure 31. All points lie in the northeast quadrants of the plane, indicating that relugolix CT is more costly and more effective compared to GnRH agonists. The cost-effectiveness acceptability curve (Figure 32) shows that the probability of relugolix CT being cost-effective increases at willingness to pay (WTP) thresholds of approximately £8,000 and above. The probability of cost-effectiveness for relugolix reaches 100% at a willingness to pay (WTP) of £17,100 per QALY and remains at 100% at higher thresholds. When compared against the NICE cost-effectiveness threshold (£20,000 to £30,000 per QALY), the probability of cost-effectiveness for relugolix CT is thus 100%.

The probabilistic cost-effectiveness results are reported in Table 82. The results reiterate the base-case results, as relugolix CT remains slightly more costly compared to the GnRH agonists comparators (incremental costs ranging from £1,697 to £1,961), but it is also more effective with an incremental QALY gain of 0.178 QALYs, as in the model base-case. The incremental costs for relugolix CT vs. goserelin monthly (£1,961) are identical to the model base-case. The probabilistic ICER is however slightly lower than the base-case (£11,009 vs. £11,069) due to a very small difference in the incremental QALYs compared to the base-case (0.1782 vs. 0.1781).

Figure 31 Cost-effectiveness plane

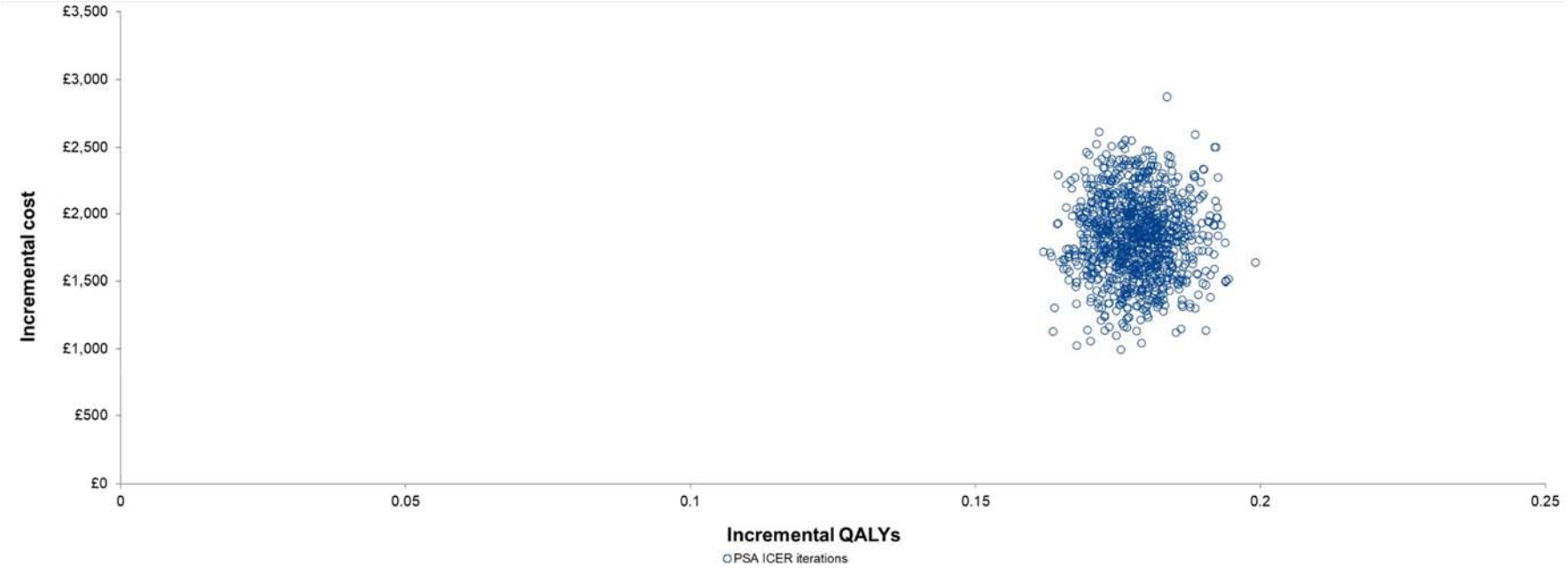


Figure 32 Cost-effectiveness acceptability curve, relugolix CT vs. comparators

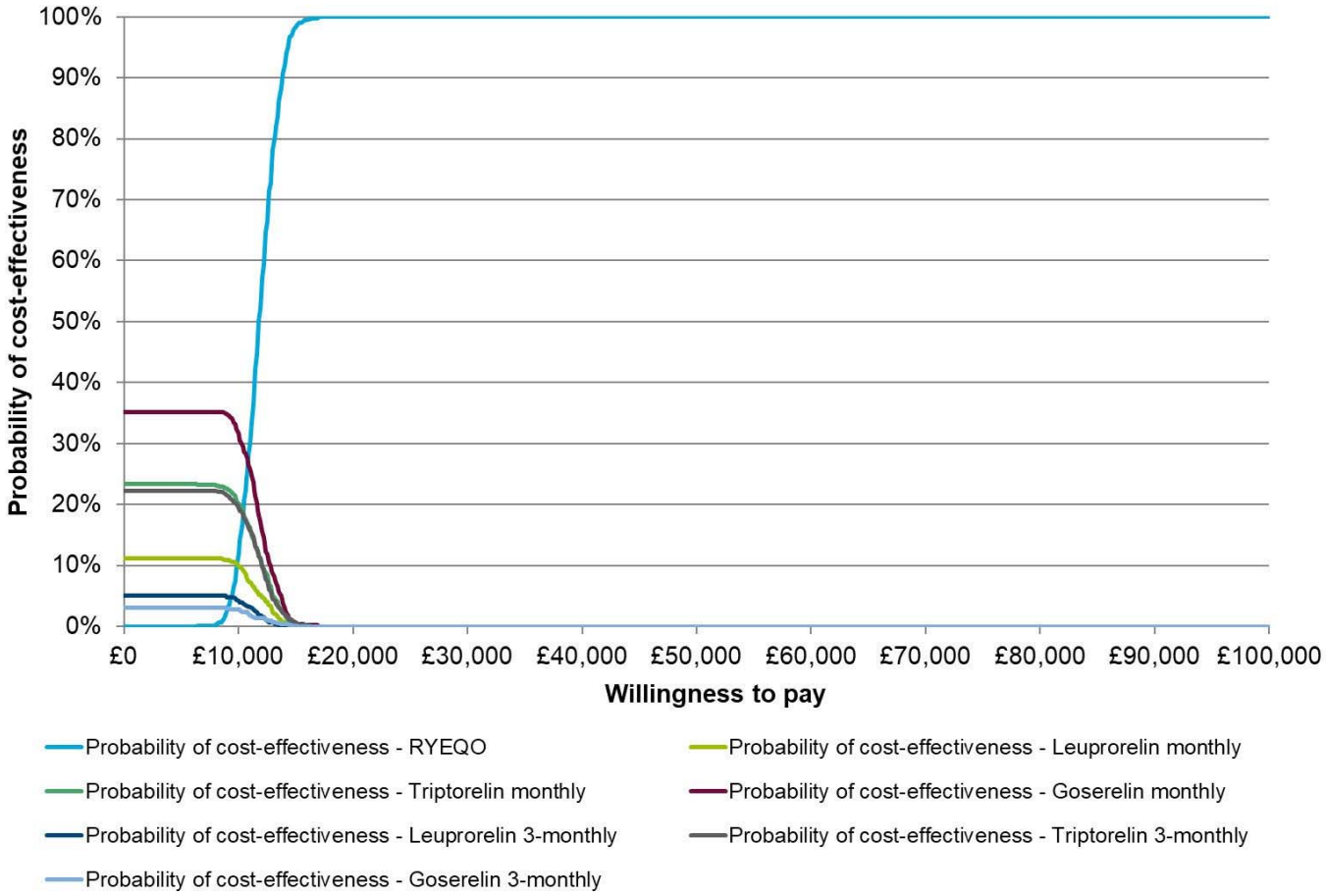


Table 82 Probabilistic cost-effectiveness results

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,995	16.878	-	-	-
Triptorelin 3-monthly	8,045	16.878	50	0.000	Dominated
Triptorelin monthly	8,048	16.878	53	0.000	Dominated
Leuprorelin monthly	8,126	16.878	131	0.000	Dominated
Leuprorelin 3-monthly	8,200	16.878	205	0.000	Dominated
Goserelin 3-monthly	8,260	16.878	265	0.000	Dominated
Relugolix CT	9,956	17.056	1,961	0.178	11,009

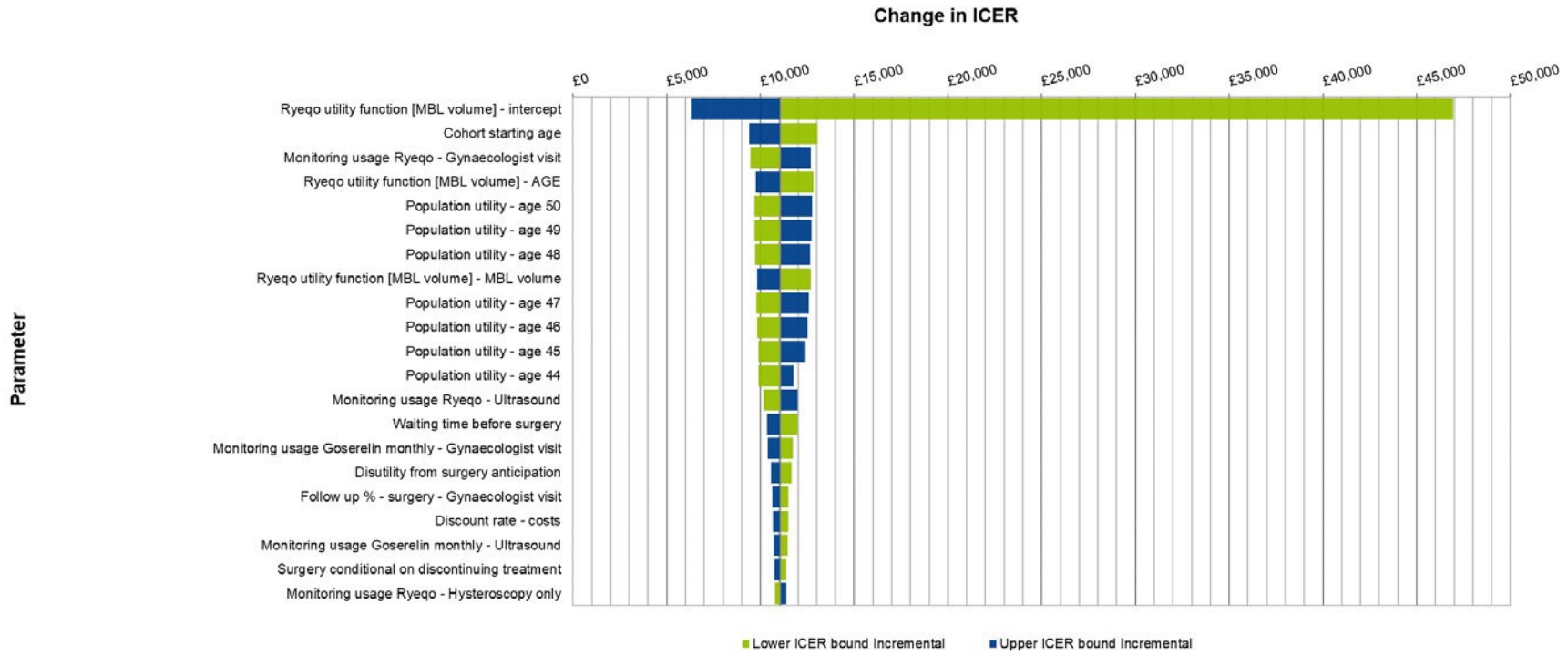
Deterministic sensitivity analysis

One-way deterministic sensitivity analyses (OWSA) were conducted to examine the sensitivity of the model result to lower and upper estimates for parameter values. In cases where no upper or lower estimate for a parameter value was available, parameters were varied by 20% of the mean. The upper and lower parameter estimates that were used in the OWSA are presented in appendix Table 111. Given that the incremental QALY gain for relugolix CT vs. GnRH agonists is identical for each individual GnRH agonist, OWSAs are only presented vs. the least costly comparator (goserelin monthly). The results are presented in the tornado diagram (Figure 33) where each parameter (y axis) is ranked (highest to lowest) by its impact on the model result. Only the 20 parameters that had the largest impact on the results are included in the tornado diagrams. The results show that the parameter that had the most sizeable impact upon the ICER when varied was the intercept term of the regression model applied in the utility algorithm for relugolix CT. Other parameters that have the most sizeable impact upon the ICER when varied are the frequency of gynaecologist monitoring appointments for relugolix CT patients, baseline age and the age parameter in the regression model used in the utility algorithm. The parameters that had the least impact on the ICER when varied in the OWSA were the HRU frequencies for hysteroscopy in the relugolix CT arm, the frequency of ultrasounds in the GnRH agonist arm and the rate of surgery once patients withdraw from pharmacological treatment.

Table 83 OWSA results, relugolix CT vs. goserelin monthly

Parameter	Lower bound ICER	Upper bound ICER	Difference
Ryeqo utility function [MBL volume] - intercept	£46,935	£6,274	-£40,661
Cohort starting age	£13,037	£9,390	-£3,646
Monitoring usage Ryeqo - Gynaecologist visit	£9,458	£12,680	£3,223
Ryeqo utility function [MBL volume] - AGE	£12,820	£9,739	-£3,081
Population utility - age 50	£9,664	£12,743	£3,079
Population utility - age 49	£9,681	£12,715	£3,034
Population utility - age 48	£9,716	£12,661	£2,945
Ryeqo utility function [MBL volume] - MBL volume	£12,697	£9,811	-£2,887
Population utility - age 47	£9,769	£12,580	£2,811
Population utility - age 46	£9,826	£12,496	£2,670
Population utility - age 45	£9,889	£12,405	£2,516
Population utility - age 44	£9,892	£11,752	£1,860
Monitoring usage Ryeqo - Ultrasound	£10,157	£11,981	£1,823
Waiting time before surgery	£11,964	£10,343	-£1,621
Monitoring usage Goserelin monthly - Gynaecologist visit	£11,739	£10,399	-£1,340
Disutility from surgery anticipation	£11,645	£10,547	-£1,097
Follow up % - surgery - Gynaecologist visit	£11,495	£10,643	-£851
Discount rate - costs	£11,488	£10,670	-£817
Monitoring usage Goserelin monthly - Ultrasound	£11,448	£10,690	-£758
Surgery conditional on discontinuing treatment	£11,382	£10,738	-£644
Monitoring usage Ryeqo - Hysteroscopy only	£10,774	£11,364	£589
BSC - monthly risk of withdrawal to surgery - RYEQO®	£11,375	£10,794	-£580
Monitoring usage BSC - Ultrasound	£11,356	£10,782	-£575
Monitoring usage BSC - GP visit	£11,344	£10,794	-£550
Monitoring usage Ryeqo - MRI	£10,828	£11,310	£482
Discount rate - benefits	£10,830	£11,308	£478
Concomitant med units/month - Ryeqo - NSAID 200mg tablet	£10,846	£11,292	£446
Monthly re-surgery risk	£11,297	£10,891	-£405
Post-hysterectomy disutility	£11,245	£10,898	-£347
Monitoring usage Goserelin monthly - Dexa scan	£11,215	£10,923	-£292

Figure 33 Tornado diagram, analysis relugolix CT vs. goserelin monthly



Scenario analysis

The sensitivity of the model results to changes in key assumptions or parameters underpinning the model base-case was examined through several scenario analyses. The scenarios analyses results are presented below, with pairwise ICERs presented for relugolix CT vs. the least costly short-acting and long-acting GnRH agonist comparators respectively (goserelin monthly and triptorelin 3-monthly). The ICERs estimated in each of the scenario analyses lie closely to the base-case ICERs, as they are typically in the range of £10,000 to £16,000 per QALY, compared to the base-case ICER of £11,069 per QALY against goserelin monthly. None of the scenarios resulted in ICERs above £20,000 per QALY. The scenario that had the largest impact upon the ICERs was the scenario where GnRH plus HRT dose intensity was reduced to 50%. This is a proxy for assuming that treatment breaks are taken for those on GnRH, with a 50% reduction in GnRH plus add back costs but no reduction in efficacy. ICERs for relugolix CT vs. goserelin monthly and triptorelin 3-monthly were £16,414 and £16,255 per QALY respectively. Other scenarios that had the most impact upon the ICERs were applying a fixed maximum duration of 6 months for GnRH agonist, excluding surgery health states and reducing the waiting time before surgery from 15 months in the base-case to 6 months.

Assuming a fixed maximum duration of 6 months for GnRH agonists resulted in ICERs of £14,845 and £14,805 vs. goserelin monthly and triptorelin 3-monthly respectively. Excluding surgery health states increased both the incremental QALYs for relugolix CT (0.194 vs. 0.178 in the base-case), but also increased incremental costs (£3,016-£3,070), thus resulting in higher ICERs of £15,798 and £15,516 per QALY vs. goserelin monthly and triptorelin 3-monthly. Reducing the waiting time before surgery to 6 months led to a reduction in the incremental QALYs, which reduced from 0.178 in the base-case to 0.132. This therefore resulted in increased ICERs for relugolix CT vs. goserelin monthly and triptorelin 3-monthly, which were £11,964 and £11,628 per QALY.

Table 84 Results of scenario analyses

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. relugolix CT
Base-case			**Goserelin monthly**	**£1,972**	**0.178**	**£11,069**
			Triptorelin 3-monthly	**£1,917**	**0.178**	**£10,761**
Modelling of treatment withdrawal in GnRH agonist arm	Withdrawal rates estimated from GnRH agonist arm of PEARL II for the first 6 months and from KOL expert opinion after the first 6 months	Withdrawal for GnRH agonist assumed equal to the modelled withdrawal rates for relugolix CT for the first 6 months of treatment and from KOL expert opinion after the first 6 months	Goserelin monthly	£1,928	0.178	£10,854
			Triptorelin 3-monthly	£1,874	0.178	£10,548
Modelling of adverse events	Adverse events for relugolix CT informed by LIBERTY studies. Adverse events for GnRH agonist informed by PEARL II	Assume identical adverse event profile for relugolix CT and GnRH agonists	Goserelin monthly	£1,976	0.167	£11,799
			Triptorelin 3-monthly	£1,921	0.167	£11,471
MBL volume input for utility algorithm	MBL volume for GnRH agonists derived from ITC	Mean MBL in the GnRH agonist arms assumed the same as relugolix CT for the utility algorithm	Goserelin monthly	£1,972	0.154	£12,825
			Triptorelin 3-monthly	£1,917	0.154	£12,468
Concomitant medication usage	Informed by proportions in LIBERTY 3 for relugolix CT arm and PEARL II for GnRH agonist arm	Assumed equal for relugolix CT and GnRH agonist arms	Goserelin monthly	£1,859	0.178	£10,435
			Triptorelin 3-monthly	£1,804	0.178	£10,127
Induction period of short-acting GnRH	Yes	No	Goserelin monthly	£1,972	0.178	£11,069
			Triptorelin 3-monthly	£2,037	0.178	£11,434

agonist required before receiving long-acting GnRH agonist						
Duration of short-acting GnRH agonist required before receiving long-acting GnRH agonist	3 months	1 month	Goserelin monthly	£1,972	0.178	£11,069
			Triptorelin 3-monthly	£1,922	0.178	£10,788
Inclusion of surgery health states	Included	Excluded	Goserelin monthly	£3,070	0.194	£15,798
			Triptorelin 3-monthly	£3,016	0.194	£15,516
Referral to surgery upon discontinuation of treatment	No referrals within 5 years of menopause	Referrals possible up until menopause (51 years of age)	Goserelin monthly	£2,071	0.174	£11,919
			Triptorelin 3-monthly	£2,016	0.174	£11,603
Waiting time before surgery	15 months	6 months	Goserelin monthly	£1,924	0.132	£14,570
			Triptorelin 3-monthly	£1,869	0.132	£14,154
Waiting time before surgery	15 months	12 months	Goserelin monthly	£1,955	0.163	£11,964
			Triptorelin 3-monthly	£1,900	0.163	£11,628
GnRH agonist and HRT dose intensity	100%	50%	Goserelin monthly	£2,924	0.178	£16,414
			Triptorelin 3-monthly	£2,896	0.178	£16,255
Add-back therapy costs and effect on AEs for GnRH agonist	Included	Excluded	Goserelin monthly	£2,148	0.194	£11,079
			Triptorelin 3-monthly	£2,093	0.194	£10,795
GnRH agonist treatment duration and inclusion of add-back therapy	Cap on % remaining on treatment at multiple periods based on KOL opinion; add-back therapy included	Fixed maximum duration of 6 months as per SmPC, add-back therapy costs and effect on AEs excluded	Goserelin monthly	£3,144	0.212	£14,845
			Triptorelin 3-monthly	£3,135	0.212	£14,805
GnRH agonist treatment duration (including add-back)	Cap on % remaining on treatment at multiple periods based on KOL opinion	Fixed maximum duration of 12 months; PEARL II withdrawal rates applied throughout	Goserelin monthly	£2,753	0.210	£13,104
			Triptorelin 3-monthly	£2,742	0.210	£13,050

Summary of sensitivity analyses results

The results of sensitivity analysis show the probability of relugolix CT being cost-effective at a WTP threshold of £20,000 to £30,000 per QALY is 100%. In all iterations of the probabilistic analysis, relugolix CT was more costly than GnRH agonists but relugolix CT also accrued more QALYs than GnRH agonists. The ICERs for relugolix CT vs. GnRH agonists increase when certain assumptions are varied, however none of these scenarios increase the ICER above £20,000 per QALY.

B.3.9 Subgroup analysis

No subgroup analyses have been performed.

B.3.10 Validation

Validation of cost-effectiveness analysis

The model has undergone thorough internal validation. The model was developed internally by a team of health economists. The structure and clinical assumptions of the model were discussed and ratified as part of an advisory board which included UK clinical experts, industry representatives and a Professor of Clinical Epidemiology & Biostatistics. In addition to the advisory board, KOL engagement was enhanced with primary research interviews with consultant gynaecologists where the model assumptions, particularly those pertaining to HRU were discussed in more detail before finalisation. All feedback and external ratification went into the final model and this written submission.

B.3.11 Interpretation and conclusions of economic evidence

Over a lifetime horizon, patients receiving relugolix CT accrued 17.057 QALYs, compared to 16.878 for those receiving GnRH agonist. The incremental cost-effectiveness results show that the ICER for relugolix CT vs. the least costly GnRH agonist is £11,069 per QALY. This indicates that relugolix CT is likely to be cost-effective at the threshold of £20,000 to £30,000 per QALY. The OWSA found that the model was most sensitive to the regression model parameters underpinning the utility algorithm that is used to convert MBL values into EQ-5D scores in the relugolix CT arm. However, the scenario analyses show that even when the MBL values in

the utility algorithm are set equal between treatment arms, the ICERs do not increase significantly, as they remain under £20,000 per QALY. Probabilistic results indicate that the probability of relugolix CT being cost-effective increases in line with increased WTP thresholds and relugolix CT remains more costly but also more effective than GnRH agonists. Scenario analyses found that relugolix CT was more likely to be more cost-effective in scenarios where GnRH agonist is used beyond the 6-month label restriction, which, based on KOL responses is currently standard practice in the treatment of symptomatic UF. Furthermore, relugolix CT is more cost-effective when waiting times before surgery are assumed to be beyond 6 months, which is the case at present, due to increases in waiting times post the COVID-19 pandemic.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

October 2021

File name	Version	Contains confidential information	Date
ID3842 relugolix CT Clarification responses 07.01.22 [ACIC REDACTED]	V2.0	Yes	07.01.2022

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Identification and selection of relevant evidence

A1. Appendix D.1.1, Figures 34 and 35, pages 235-236, and Tables 85, 87 and 89, pages 237, 240, 242. The 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) diagrams show that a total of 205 studies were included in the systematic literature review (SLR [178 from the initial SLR and 27 from the updated SLR]). These 205 articles were further screened, and 3 studies assessing relugolix combination therapy, which were reported in 9 articles (Table 85, page 237) and a further 2 studies related to the indirect treatment comparison, which were reported in 3 articles (Table 87, page 240), were finally included. This means that 193 articles were excluded. However, Table 89 shows only 192 articles. Please clarify this discrepancy.

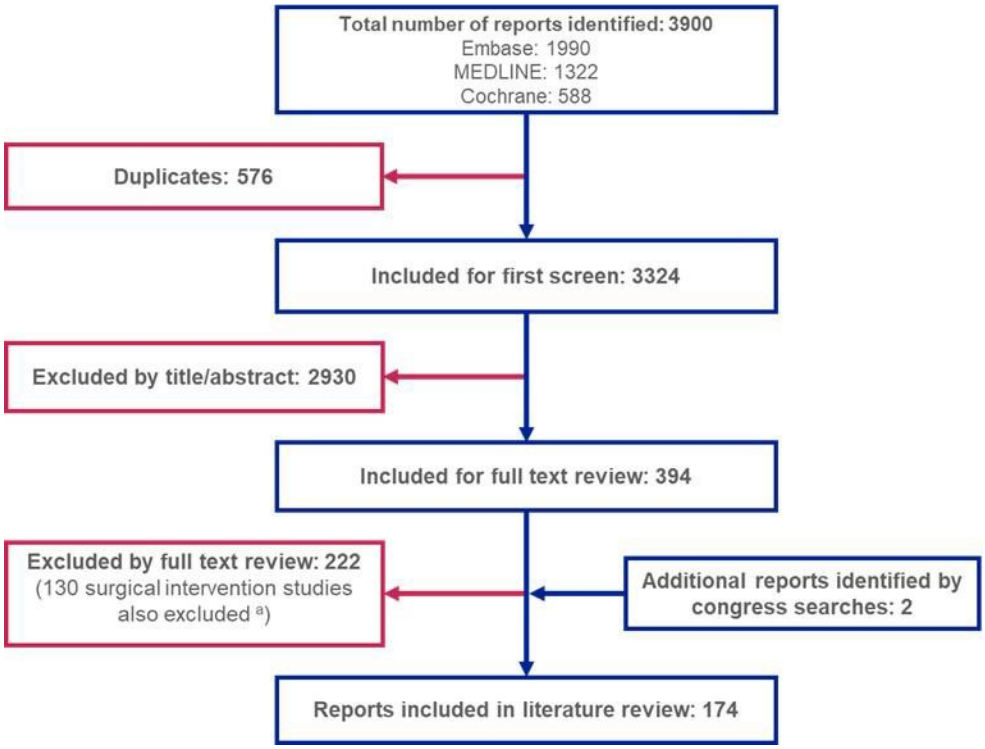
Gedeon Richter response: We have checked and counted the excluded articles in Table 89 and there are 193 articles in total according to our count.

A2. Appendix D.1.1, Figure 34, page 235.

The ERG notes that the numbers in the PRISMA flow diagram for the initial search do not add up; 394 articles were included for full-text screening, 226 were excluded and two further articles were included from congress searches, giving a total of 170 articles and not 174 as reported in Figure 34. Please clarify this discrepancy.

Gedeon Richter response: A review of the initial SLR findings confirms the discrepancy you identified. Apologies for this error. The number of articles excluded by full text review should be 222 (not 226). This is now corrected in the PRISMA below.

Figure 1 Corrected PRISMA for the initial SLR [submission figure 34]



A3. Document B, section B.2.5, page 63 and Appendix D.1.3, Tables 90 to 93, pages 268-275. About the quality assessment of the LIBERTY 1, LIBERTY 2, PEARL I, and PEARL II studies, please clarify the number of reviewers involved in the risk of bias assessment and whether reviewers worked independently.

Gedeon Richter response: Two reviewers conducted the risk of bias assessment. The reviewers worked independently then came together to discuss and agree the assessment findings.

A4. Document B, Appendix D.1, page 234. Please clarify i) the number of reviewers involved in the full-text screening and whether they worked independently;

ii) the number of reviewers involved in data extraction and whether they worked independently.

Gedeon Richter response: In the initial SLR, two reviewers conducted the full-text screening in a double-blind process, working independently. In the update SLR, two reviewers worked independently to perform the citation screening. Differing opinions of the reviewers were solved through discussion, with a senior team member casting a deciding vote on any discrepancies. Two reviewers were involved in data extraction for both the initial and update SLRs and worked independently.

Decision problem – population

A5. PRIORITY. Document B, Section B.1.1, page 16. In the final scope issued by NICE, the population is specified as “people with moderate to severe symptoms associated with uterine fibroids”. The LIBERTY and PEARL studies both use the equivalent of 80ml per cycle for 2 menstrual cycles. In the opinion of the ERG clinical expert, this may exclude some participants with moderate symptoms and no heavy bleeding. Please justify using the LIBERTY and PEARL studies as populations with moderate to severe symptoms.

Gedeon Richter response: Heavy menstrual bleeding (HMB) is the most common symptom associated with uterine fibroids (UF), and around 60% of women with fibroids are reported to suffer from this symptom.(1) In particular, the majority of women classified as suffering from moderate symptoms will have associated heavy bleeding. It is very unusual for a woman to have symptoms classified as being of a moderate level which excludes heavy uterine bleeding.

Furthermore, one of the primary reasons for using the level of HMB as the main indicator of severity of symptoms is it is one of the only symptoms which can be measured objectively and in a quantifiable manner. Many other symptoms associated with UF, such as pain and pelvic discomfort, are very subjective and difficult to interpret. Similarly, even with the measurements of uterine volume and UF size, these can be very operator/machine dependent. Therefore, the level of menstrual blood loss (MBL) is the most accurate indicator for level of severity, with the other symptoms being supplementary and supportive. For all UF studies, irrespective of the population being studied, one of the main criteria for inclusion into the study is the actual level of MBL, whereas for many other symptoms due to the

subjectivity of measurement these are not used as inclusion criteria. Additionally, many of the subjective QOL outcomes are linked (both directly and indirectly) to HMB, for example, energy/mood, concern regarding soiling garments, anxiety about the unpredictable onset of bleeding, etc.

Investigations of the baseline characteristics in both the LIBERTY and PEARL studies showed that patients were classified as having a heavy level of MBL, with mean uterine volume being approximately 300-400 cm^3, had low mean haemoglobin levels (e.g. 11.25g/dL in LIBERTY 1, 11.16g/dL in LIBERTY 2, ≤10.2g/dL in PEARL I) and with scores indicating distress and impact of UF on their lives. The LIBERTY trials baseline showed UFS-QoL BPD scale scores indicative of moderate distress due to bleeding and pelvic discomfort (LIBERTY 1: 68.90 and LIBERTY 2: 70.89), and PGA scores indicative of limitations in function and moderate to extreme symptoms with most patients reporting at least moderate symptoms associated with UF. In PEARL II, the mean baseline symptom severity score was 54.0 and 52.5 for UPA 5mg and GnRH agonist, respectively, and mean HRQL score at baseline was 53.3 and 50.1 for UPA 5mg and GnRH agonist respectively. Baseline pain measures were also moderate to severe in the trials. For example, three-quarters of the LIBERTY 2 cohort had NRS scores at baseline reflecting moderate to severe pain and mean baseline scores for SF-MPQ Parts A and B (McGill pain questionnaire) for the PEARL studies were comparable to values reported for various conditions such as musculoskeletal pain and postoperative pain.

Given the data available for both the LIBERTY and PEARL studies regarding the overall level of blood loss at baseline, in combination with the other baseline characteristics, it can be concluded that the patients included in these studies would be classified as having at least moderate to severe symptoms of UF.

Decision problem – comparators

A6. PRIORITY. Document B, Section B.1.1, Table 1, pages 16-19.
Gonadotrophin-releasing hormone (GnRH) agonists are listed as the relevant comparator treatment to address the decision problem. The ERG notes that treatments currently on the market for uterine fibroid symptoms include GnRH antagonists. Moreover, the NICE final scope lists GnRH analogues as relevant

comparators, which include both agonists and antagonists. Please further clarify the relevance of GnRH agonists to the decision problem and the exclusion of GnRH antagonists.

Gedeon Richter response: Four GnRH antagonists have been identified as part of the SLR (relugolix, elagolix, linzagolix and cetrorelix). Among these four identified compounds, relugolix is the first and only GnRH antagonist with an approved licensed indication for UF in EU/UK. Elagolix is licensed for use in the USA but does not have an approval for use within Europe. Linzagolix is currently under review by the European regulatory authorities but, as of the time of this appraisal, does not have an approval for use in Europe. Cetrorelix is indicated and used for fertility purposes only. Therefore, in Gedeon Richter's view, no other GnRH antagonists are relevant comparators for relugolix CT in this appraisal.

GnRH agonists and Esmya®/UPA are both second-line pharmacological options that have an approved indication for UF. However, as a result of historical safety concerns with sporadic liver injuries, Esmya's licensed indication has become more limited. The product is currently only indicated for intermittent treatment of moderate to severe symptoms of UF in adult women who have not reached menopause when UF embolisation and/or surgical treatment options are not suitable or have failed.

Recently, as a result of its limited indication, Esmya® has been commonly replacedwith GnRH agonists, in the absence of other pharmacological options. For the reasons provided, Gedeon Richter's evidence submission focuses on GnRH agonists as the most relevant comparator for relugolix CT at the anticipated positioning of relugolix CT for moderate to severe symptoms of UF.

A7. Document B, Section B.1.1, Table 1, pages 16-19. Gonadotrophin-releasing hormone (GnRH) agonists are listed as the only relevant comparator treatment. Clinical expert opinion received by the ERG indicates that anti-progesterone drugs such as Esmya® are still widely used for treating uterine fibroid symptoms despite restrictions placed on the label following EU safety reviews (as noted on page 122, Document B of the company submission [CS]) and could therefore be considered as

a relevant comparator. Please clarify the reason for not including Esmya as a relevant comparator.

Gedeon Richter response: Esmya® (UPA 5mg) is not included in the NICE scope for this technology appraisal. Patients who meet the eligibility criteria for relugolix CT are similar to those who would have been prescribed Esmya® prior to the restriction of the label. However, due to the indication restriction, usage of Esmya® is now commonly replaced with GnRH agonists in the absence of other pharmacological options to treat moderate-severe symptoms of UF.

A review of Gedeon Richter Esmya® unit sales data demonstrates that current Esmya® usage is very low. A total of [redacted] units of Esmya® have been sold to trade within the UK in the past 5 months, from June-Oct 2021, once stock became available in the UK after Esmya's temporary suspension was lifted. This figure reflects the number of units sold at the warehouse level, i.e. not what is utilised by patients, which will be less than this figure. Of note, the same 5-month timeframe in 2017, when Esmya's label was broader and before Esmya's PRAC (pharmacovigilance risk assessment committee) review commenced, showed [redacted] units sold; with a total of [redacted] units sold in total in 2017. Low current usage of Esmya® supports the positioning of GnRH agonists as the most relevant comparator to relugolix CT in this technology appraisal.

Description of the technology being assessed

A8. Document B, Section B.1.2, Table 2, pages 20-21. It is stated that the technology being assessed is relugolix in combination with oestradiol (1 mg) and norethisterone acetate (0.5 mg). The ERG notes that oestradiol may be given by titrating the dose to achieve physiological concentrations for individual patients. Please provide the rationale for using a fixed dose of 1 mg, rather than variable doses of oestradiol for all patients, and clarify the primary goal of the 1 mg fixed dose of oestradiol in the management of uterine fibroid symptoms.

Gedeon Richter response: A fixed dose combination (FDC) tablet of relugolix CT was developed by Myovant Sciences consisting of relugolix 40mg, oestradiol 1mg and norethisterone acetate 0.5mg. The doses were selected to complement each other by achieving a balance of reproductive hormones to treat symptoms

associated with UF while also maintaining bone health, minimising the severity and frequency of vasomotor symptoms, and protecting the endometrium from the effects of unopposed oestrogen.

When combined with a 40mg dose of relugolix, a 1mg dose of oestradiol achieves systemic oestradiol concentrations of 10 to <60pg/mL. In the majority of women, this was sufficient to prevent hypoestrogenic symptoms and maintain bone health. Research has shown that hormone therapy should achieve oestradiol concentrations ≥10pg/mL in order to address concerns regarding both the risk for BMD loss and vasomotor symptoms. Data to support correlation between observed oestradiol concentrations and BMD changes in the pivotal phase 3 LIBERTY studies with relugolix CT has helped to further refine the clinically therapeutic range for oestradiol in premenopausal women with oestradiol concentrations ≥20 pg/mL considered adequate to maintain BMD.(2)

The combination of 1mg oestradiol with 0.5mg norethisterone acetate provides the optimal dosing option to ensure oestradiol levels are kept within the pre-follicular phase level of 20-50pg/mL and is therefore able to provide control of UF symptoms whilst minimising side effects such as BMD loss and vasomotor symptoms. Additionally, a fixed dose of 1mg oestradiol manufactured into a single FDC tablet provides convenience to patients and their healthcare professional, avoids complexities associated with variable dosing, and aids medication adherence.

Subgroup analyses

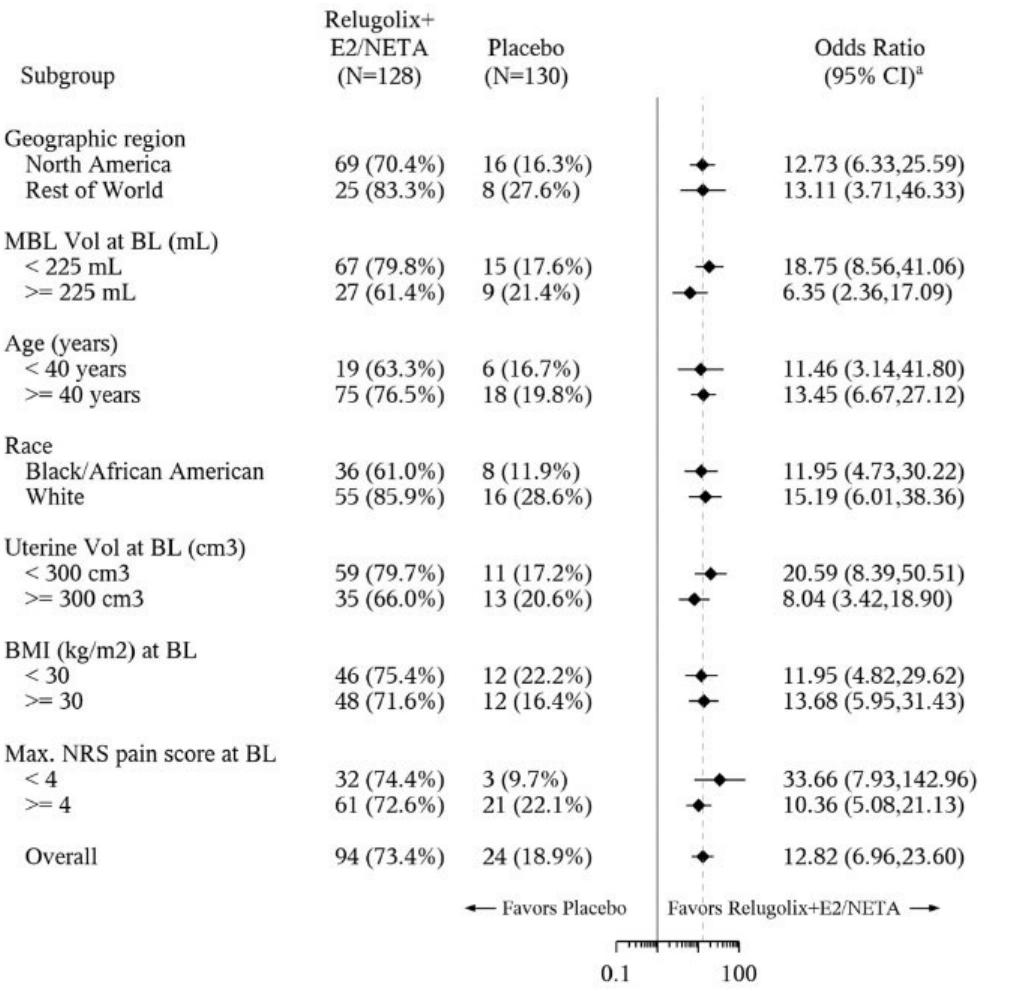
A9. Document B, Section B.2.7, page 88. Text on page 88 indicates that subgroup analyses are described in Section B.2.4 of the CS. Please provide details of the subgroup analyses, as the ERG is unable to find them in Section B.2.4 or elsewhere in the CS.

Gedeon Richter response: For the PEARL I and II trials, no overall subgroup analyses were envisaged and none were performed. For the LIBERTY 1, 2 and 3 trials, subgroup analyses of the primary efficacy endpoint were conducted comparing the relugolix CT group versus the placebo group to assess whether treatment effects were consistent across clinically important subgroups of the study population (including geographical region, age, baseline MBL volume, race, body mass index

(BMI), uterine volume at baseline, maximum NRS score at baseline and history of prior pregnancy). Additionally, LIBERTY 3 also assessed the following subgroups: MBL volume at parent study baseline, uterine fibroid volume, and alcohol use and smoking status. However, please note that no subgroup analysis data were incorporated into the economic analyses.

The odds ratio and its 95% CI based on a logistic regression model were displayed in a forest plot for each subgroup. Across all subgroups, treatment differences were consistent with the primary analysis with a higher proportion of patients who received relugolix CT meeting the definition for responder than patients who received placebo, as indicated by the point estimate and lower bound of the 95% CI for the odds ratios being above 1 favouring relugolix CT over placebo. The magnitude of the responses across these subgroups was generally consistent with that observed in the analysis of the primary efficacy endpoint in the overall population, especially in the subgroups with larger sample sizes.

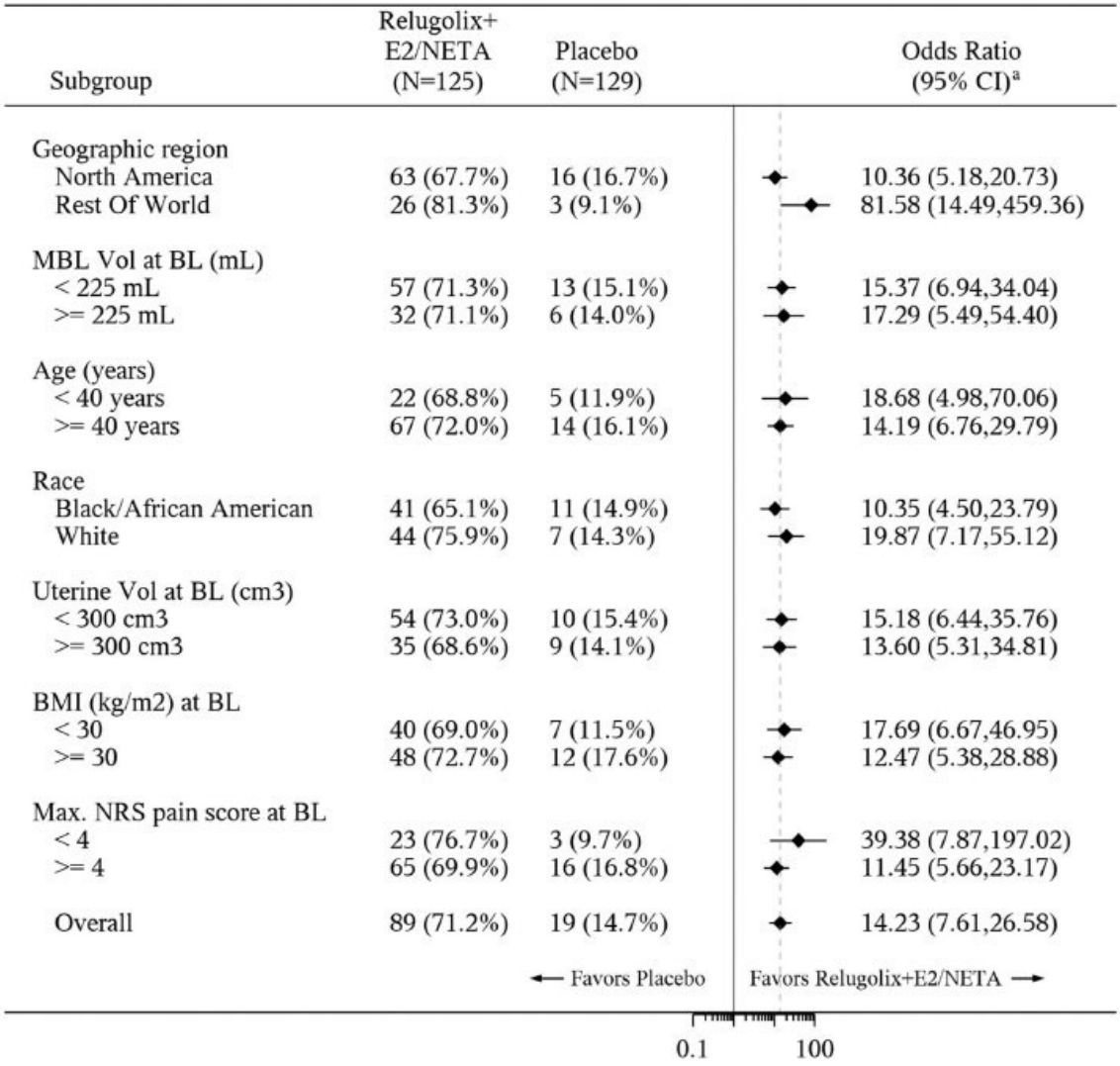
Figure 2 LIBERTY 1: Summary of subgroup analyses for the primary endpoint (mITT) (3)



Abbreviations: BL = baseline; E2 = estradiol; max = maximum; MBL = menstrual blood loss; n = number of patients in subset; NETA = norethindrone acetate.

[a] Odds ratio > 1 favors relugolix + E2/NETA over placebo based on logistic regression with treatment group, baseline MBL volume (< 225 mL or ≥ 225 mL), and geographic region (North America or Rest of World) as covariates.

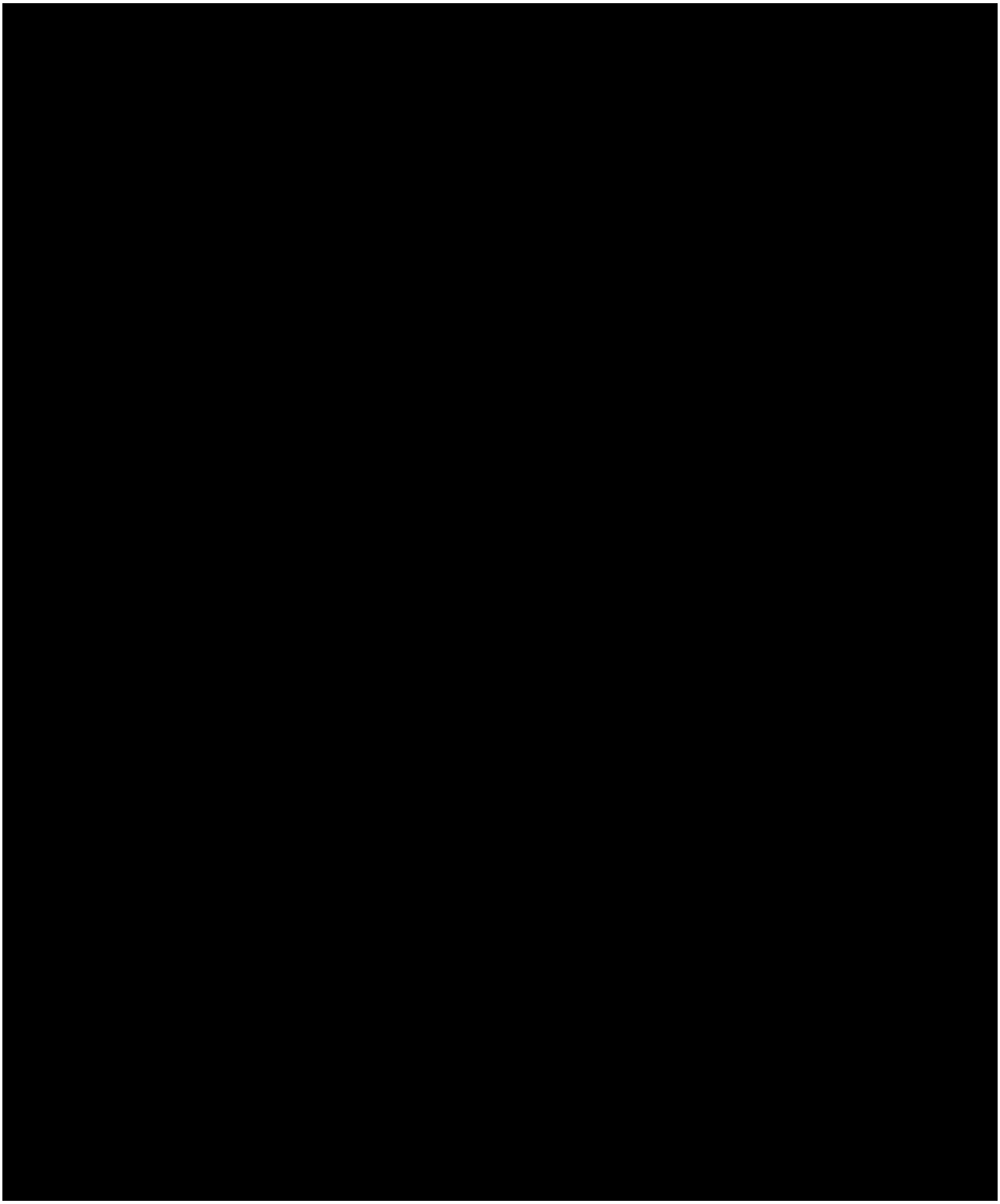
Figure 3 LIBERTY 2: Summary of subgroup analyses for the primary endpoint (mITT) (4)



Abbreviations: BL = baseline; E2 = estradiol; max = maximum; n = number of patients in subset; MBL = menstrual blood loss; NETA = norethindrone acetate.

[a] Odds ratio > 1 favors relugolix + E2/NETA over placebo based on logistic regression with treatment group, baseline MBL volume (< 225 mL or ≥ 225 mL), and geographic region (North America or Rest of World) as covariates.

Figure 4 LIBERTY 3: Summary of subgroup analyses for the primary endpoint (Extension Study Population) (5)



Characteristics of LIBERTY 1 and LIBERTY 2

A10. Document B, Section B.2.3, Tables 10 and 11, pages 49-50. These tables show disease-specific baseline characteristics of patients assessed in LIBERTY 1 and LIBERTY 2, including 'any surgery for uterine fibroids'. The ERG considers uterine artery embolisation (UAE) important in this clinical context. Please provide data on the number and proportion of participants who had received UAE before the initiation of each trial, if available.

Gedeon Richter response: There were only a small number of participants who had received UAE prior to initiation of LIBERTY 1 and LIBERTY 2. These were as follows:

Figure 5 LIBERTY 1 & 2: number and proportion of participants who received UAE prior to initiation

Trial	Participants who received UAE prior to trial initiation N (%)
LIBERTY 1	Relugolix CT: 2 (2.3%) Relugolix-delayed CT: 2 (1.6%) Placebo: 1 (0.8%)
LIBERTY 2	Relugolix CT: 3 (2.4%) Relugolix-delayed CT: 0 Placebo: 0

Characteristics of PEARL I and PEARL II

A11. Figures 41 and 42, Appendix D.1.2, pages 266-267. The flow diagrams for PEARL I and PEARL II based on information from their Clinical Study Reports [references 93 and 136] are not the same as the diagrams reported in the respective publications [reference 51, Donnez et al. 2012; and reference 53, Donnez et al. 2012]. Please clarify the reason for these discrepancies.

Gedeon Richter response: Thank you for raising this question with us. We are still exploring this query with the lead author and will provide you with clarification for the discrepancies as soon as possible.

Network meta-analysis

A12. PRIORITY. Document B, Section B.2.8, page 88. The CS indicates that a meta-analysis was not applicable. Please provide a justification for not undertaking a network meta-analysis.

Gedeon Richter response: The only outcome used by the economic model that was informed by the indirect treatment comparison was MBL, which was subsequently used in the utility algorithm. In the majority of economic models where a network meta-analysis (NMA) is used to inform the model efficacy parameters, this is usually carried out on a small number of outcome measures deemed consistent or similar across studies in the network. Conversely, in order to inform our relugolix CT model, the ITC required several conversion steps; conversion between the MBL measurement method (pictorial bleeding assessment chart [PBAC]) and the alkaline haematin method) followed by calculation of change from baseline (CBL) at multiple timepoints. Even if a broader network could have been constructed using other RCTs, it would not have been possible to synthesize them in an NMA with only

aggregate-level data available. Furthermore, a Bucher ITC carried out in Excel was felt to be both more transparent and intuitive, given the multiple conversions required, and less computationally complex than using statistical software to carry out a full NMA.

Indirect treatment comparisons (ITCs)

A13. PRIORITY. Document B, Section B.2.9, page 89. Text on page 89 indicates that the only outcome assessed through an ITC was the mean menstrual blood loss for relugolix CT versus GnRH agonist. Please clarify the reason for not performing ITC for other outcomes listed in the decision problem addressed by the CS.
Gedeon Richter response: MBL volume was the key outcome measure in the primary efficacy endpoint of both LIBERTY 1 and LIBERTY 2. The primary efficacy endpoint in the PEARL studies also comprised of changes in MBL. Although the PEARL and LIBERTY studies used different MBL measures (PBAC vs. alkaline haematin method, respectively), MBL remains the most comparable outcome between the studies. Other outcomes such as pain may be clinically relevant but were not captured for the full patient population in the LIBERTY studies and were hence excluded from the ITC. Furthermore, MBL, as assessed in the key clinical studies is an objective physical outcome that is one of the only symptoms which can be measured objectively and in a quantifiable manner. Many other symptoms associated with UF, such as pain and pelvic discomfort, are very subjective and difficult to interpret. The latter outcomes, furthermore, were captured in the economic model via the UFS-QoL, which was used to derive utility scores via a mapping algorithm. Importantly, the symptoms of UF are inter-linked and improvements in HMB (i.e. reductions in MBL) were demonstrated in the clinical trials at the same time as improvements in other symptoms of UF (e.g. pain and HRQoL).

The outcome measures, apart from MBL volume, listed in the decision problem (scope) were the following. Below each bullet we have included an explanation why the endpoint was not included in the ITC.

- Time to MBL response
    - Time to MBL response was not included as a defined outcome in the LIBERTY or PEARL trials and timepoints of measurement were not exactly aligned between the studies. During the LIBERTY studies the MBL was measured via the alkaline haematin method which only

reports values on a 4-weekly basis, whereas during the PEARL studies the MBL was reported on a daily basis via the PBAC scoring system. Therefore, a direct comparison of exact time to response cannot be measured. Moreover, the actual classification of a responder was defined differently in the studies.

- Pain
    - The effect on pain was only measured for a subgroup of patients with high baseline pain scores i.e. NRS ≥4 (moderate/severe pain) in the LIBERTY trials and was therefore not included.

- Uterine fibroid volume (UFV) / uterine volume (UV)
    - The method of measurement of uterine fibroid volume was different in the LIBERTY and PEARL trials and thus are not directly comparable.

- Haemoglobin (Hb) levels
    - Hb levels are interesting to detect potential anaemia. However, they are a consequence of HMB; therefore if HMB is controlled then Hb levels should be within normal ranges. Therefore, it is more relevant to focus on MBL than Hb levels
    - Also, in the LIBERTY studies again a sub-group of patients were actually assessed i.e. those with Hb ≤ 10.5 g/dL at baseline who subsequently had an increase of > 2 g/dl. This was a defined endpoint rather than the actual raw change in Hb levels

- Change in bone mineral density (BMD)
    - The trial data used in the ITC covered a period of 3 months which is too short to measure changes in BMD

- Rates and route of surgery
    - This was not collected in the LIBERTY trials

- Impact on fertility and pregnancy and teratogenic effects
    - This was not collected in the LIBERTY trials

- Mortality
    - Mortality was not included as no deaths were reported during the LIBERTY trials

- Adverse effects of treatment, including but not limited to vasomotor symptoms, incontinence and pelvic organ prolapse
    - Safety outcomes were not assessed in the ITC. The trial data used in the ITC covered a period of 3 months and no relevant safety events were observed in the LIBERTY or PEARL studies during this time period

- Health-related quality of life
    - QoL in PEARL I was measured using a subset of UFS-QOL questions and was answered only by a subset of patients. Therefore, comparison of HRQoL was not included.

A14. Document B, Section B.2.9, Figure 25, pages 96. Please clarify which data (extrapolated / raw data) were used to plot the week 24/26 timepoint for the PEARL study in the forest plot.

Gedeon Richter response: Patients in the PEARL I study received treatment for 13 weeks (until the week 13 end-of-treatment visit) and had a closing Week 17 visit which concluded Part A of the study. Subjects were then seen 3 and 6 months after treatment ended (at week 26 and week 38) as part of the follow up part of the study (study Part B).

The bleeding values underlying the week 24/26 timepoints from the PEARL study were calculated from clinical trial results reported from PEARL I Part B, without extrapolation. Note that the forest plot results for week 24/26, presented in Document B, Section B.2.9, Figure 25, pages 96, were used in the ITC results and were not used in the economic model.

A15. PRIORITY. Document B, Section B.2.9, Tables 24 and 25, pages 97-98. The ERG notes that no confidence intervals were provided for the estimates of effect when standard deviation information was available for both the LIBERTY and PEARL studies. Please provide confidence intervals for Tables 24 and 25.

Gedeon Richter response: 95% confidence intervals around the ITC point estimates have been added to Tables 24 and 25, based on a Normal distribution approximation under the Central Limit Theorem. Alternative approaches are significantly more complicated and provide little additional information. Gedeon

Richter notes that these confidence intervals can include values that are less than -100%, which simply reflects high levels of uncertainty and the characteristics of the Normal distribution. Applying a CFB value less than -100% to baseline MBL would result in a follow-up MBL value that is less than 0, a value outside the support of the MBL statistic which is on [0, ∞). While Gedeon Richter has not adjusted any of the confidence intervals, the ERG may wish to disregard any value in the confidence interval that is less than -100%.

Table 1 ITC results: relugolix CT vs. UPA [submission table 24]

	Mean difference %-CFB Week 4	**Mean difference %-CFB Week 8**	**Mean difference %-CFB Week 12**	**Mean difference %-CFB Week 24-no hysterectomy * (UPA patients not on treatment)**	**Mean difference %-CFB Week 24-no surgery** (UPA patients not on treatment)**
Relugolix CT vs. UPA (95% CI)	-19.43% (-55.32%, 16.46%)	+4.53% (-22.62%, 31.69%)	-10.73% (-39.41%, 17.94%)	-77.63% (-119.79%, -35.46%)	-63.06% (-106.93%, -19.18%)
Heterogeneity statistic Chi^2	1.125 (p=0.289)	0.107 (p=0.744)	0.538 (p=0.463)	13.021 (p<0.001)	7.936 (p=0.005)

CFB: Change from baseline
* No hysterectomy or endometrium ablation post treatment in the PEARL trials.
** No surgery post treatment in the PEARL trials.
Note: Treatment in the PEARL I and II trials was discontinued after week 13.

Table 2 ITC results: leuprorelin vs. UPA [submission Table 25]

	Mean difference %-CFB Week 4	**Mean difference %-CFB Week 8**	**Mean difference %-CFB Week 12**	**Mean difference %-CFB Week 24-no hysterectomy***	**Mean difference %-CFB Week 24-no surgery****
Leuprorelin vs. UPA (95% CI)	+31.14% (-52.49%, 114.77%)	-3.79% (-105.03%, 97.45%)	-1.50% (-71.05%, 68.05%)	+23.45% (-91.88%, 138.78%)	+14.12% (-114.80%, 143.04%)

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

A16. PRIORITY. Document B, Section B.2.9, page 98. It is stated that the effect of relugolix CT on reducing menstrual blood loss volume is at least equal to and potentially better than that of the GnRH agonist. Please provide statistical analysis to support this statement.

Gedeon Richter response: It can be seen from the response to question A16 that

there is significant uncertainty associated with the ITC results. In drawing our conclusion, we were referring to the point estimates from the ITC rather than the uncertainty around these estimates. In our submission we acknowledged the uncertainty inherent in the ITC and, as part of the economic analysis, undertook a scenario analysis whereby MBL was assumed to be identical in the GnRH agonist and relugolix CT arms. In this scenario, relugolix CT continued to be highly cost effective against GnRH agonist. In fact, the majority of the economic value of relugolix CT derives not from higher utility gain on treatment relative to GnRH agonist but from the benefit of being able to keep a patient on treatment for longer than is currently possible using GnRH agonists. Being able to remain on effective medical treatment for longer enables patients to avoid or delay the poor quality of life experienced when they discontinue back to current best supportive care, as well as the high costs of surgery.

A17. Document B, Appendix M1.6 page 354. Participants in the LIBERTY studies are reported to have a higher mean body mass index (BMI) compared to those in the PEARL studies. Please explain why a subgroup analysis based on the LIBERTY studies should be used to infer that there is no subgroup treatment effect from BMI within the PEARL studies.

Gedeon Richter response: We understand the ERG's concern that there may be the potential for an imbalance in treatment effect modifiers between the LIBERTY and PEARL studies that may bias the ITC. However, we believe that this is not an issue for the following reasons:

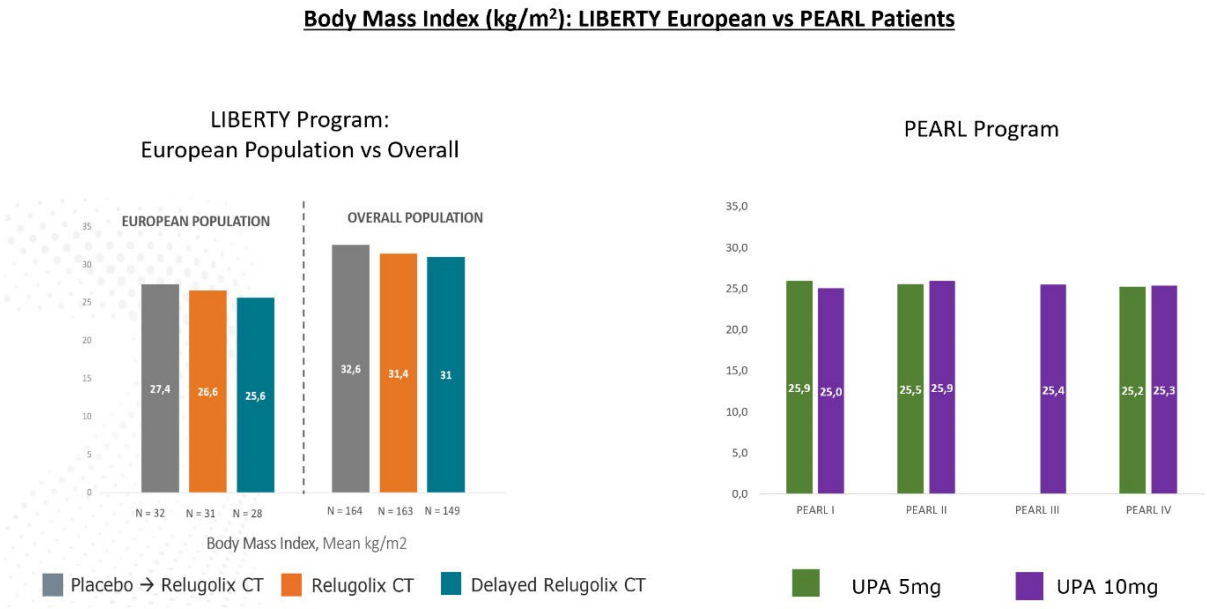
- Firstly, we have already shown that there is no effect on the overall response rate in the LIBERTY studies when different groups of BMI are investigated (see Figure 2 and Figure 3 in response to question A9).

- In addition to this, further analysis was carried out on a subgroup of patients from the LIBERTY study programme who were recruited from only European sites. This analysis showed that the population recruited into the LIBERTY programmes from the European sites were very similar in BMI in comparison to all patients recruited into the PEARL studies. In the LIBERTY European population, for those patients treated with relugolix CT, the average BMI was 26.6 kg/m^2, compared to the PEARL studies where the overall average BMI

for those treated with UPA 5mg (Esmya®) was 25.5 (see Figure 6). Furthermore, on investigation of the BMI reported during the PEARL studies it could be seen that in all studies the upper limit of the BMI was 38-40, which falls within the range seen in the LIBERTY programmes.

As a result of these similarities in the BMI, and the data showing that during the LIBERTY studies there is no effect of BMI on overall outcome, it can be extrapolated that the data from the PEARL program, where patients had similar BMI to the European subgroup in the LIBERTY can be used to infer that BMI is not a potential source of treatment effect modification that could lead to a bias in effect on MBL between the LIBERTY and PEARL studies.

Figure 6 BMI across the European sites in the LIBERTY programme and patients recruited into the PEARL studies



PEARL studies – reporting of results

A18. Appendices, Section M1.6, page 356. The ERG notes that treatment phase duration for PEARL I and PEARL II was shorter and therefore, menstrual blood loss data were extrapolated further to estimate treatment effects at the 24-week time point. Please provide more information on how this extrapolation was performed.

Gedeon Richter response: In the ITC no extrapolation of trial data was performed, instead, the raw data was used. However, since patients in the PEARL studies were not on treatment in week 26, the estimation from the ITC for this week was not used in the model. For the model, the extrapolation was performed based on the last value carried forward, see submission Table 56 (copied in below). The 'last value' was thus based on the last estimate from the ITC at which patients in the PEARL studies were still on treatment (week 12).

Table 3 MBL estimates in mL for relugolix CT and comparators [submission table 56]

<table>
<tr><th rowspan="2">Time point</th><th colspan="3">MBL (mL)</th></tr>
<tr><th>Relugolix CT</th><th>BSC (Placebo)</th><th>GnRH agonist</th></tr>
<tr><td>Baseline</td><td>229.1</td><td>229.1</td><td>229.1</td></tr>
<tr><td>Week 4</td><td>115.8</td><td>180.8</td><td>231.6</td></tr>
<tr><td>Week 8</td><td>51.3</td><td>187.8</td><td>32.2</td></tr>
<tr><td>Week 12</td><td>37.8</td><td>184.2</td><td>58.9</td></tr>
<tr><td>Week 16</td><td>39.8</td><td>164.1</td><td rowspan="13">58.9
(Extrapolation based on last value carried forward)</td></tr>
<tr><td>Week 20</td><td>39.2</td><td>171.0</td></tr>
<tr><td>Week 24</td><td>42.2</td><td>159.9</td></tr>
<tr><td>Week 28</td><td>38.9</td><td rowspan="10">159.9
(Extrapolation based on last value carried forward)</td></tr>
<tr><td>Week 32</td><td>29.5</td></tr>
<tr><td>Week 36</td><td>27.7</td></tr>
<tr><td>Week 40</td><td>26.8</td></tr>
<tr><td>Week 44</td><td>22.6</td></tr>
<tr><td>Week 48</td><td>24.8</td></tr>
<tr><td>Week 52</td><td>25.6</td></tr>
<tr><td>Week 53+</td><td>25.6
(Extrapolation based on last value carried forward)</td></tr>
</table>

A19. Appendices, Section M1.6 pages 349-353. Please explain why the results of the PEARL I and PEARL II studies are only discussed in the text and not tabulated using the information available from the relevant papers.

Gedeon Richter response: Apologies for not providing in tabulated format. The tabulated results for the efficacy endpoints for PEARL I and PEARL II are as follows:

Table 4 PEARL I efficacy results for UPA 5mg and placebo groups (6)

Endpoint	Placebo (N = 48)	UPA 5 mg (N = 95)	Difference, 5 mg UPA − Placebo (95% CI)†	P Value
Primary endpoints at week 13				
PBAC <75 — no./total no. (%)	9/48 (19)	86/94 (91)	73 (55 to 83)	<0.001

% Change from screening in total fibroid volume‡				0.002
Median	3.0	−21.2	−22.6 (−36.1 to −8.2)	
Interquartile range	−19.7 to 23.0	−41.2 to −1.1		
Secondary endpoints at week 13				
Baseline PBAC				
Median	376	386		
Interquartile range	241 to 608	235 to 627		
Wk 9-12 PBAC				
Median	336	0		
Interquartile range	115 to 543	0 to 5		
Change from baseline to wk 9-12 in PBAC				
Median	−59	−329	−291 (−399 to −194)	<0.001
Interquartile range	−216 to 58	−571 to −205		
Amenorrhea, PBAC ≤2, at wk 9–12 — no./total no. (%)	3/48 (6)	69/94 (73)	67 (50 to 77)	<0.001
Total reduction ≥25% in fibroid volume at wk 13 — no./ total no. (%)	8/45 (18)	35/85 (41)	23 (4 to 39)	0.01
% Change from screening in uterine volume at wk 13				0.001§
Median	5.9	−12.1		
Interquartile range	−3.8 to 18.4	−28.3 to 2.9		
Reduction in uterine volume ≥25% at wk 13 — no./ total no. (%)	3/47 (6)	30/88 (34)	28 (11 to 40)	<0.001
Haemoglobin – g/dl				
Baseline	9.55±1.18	9.32±1.50		
Wk 13	12.61±1.30	13.50±1.32		
Change from baseline to wk 13	3.10±1.68	4.25±1.90	0.92 (0.39 to 1.44)	<0.001
Pain assessment with Short-Form McGill Pain Questionnaire				
Baseline				
Median	8.5	6.5		
Interquartile range	3.0 to 18.0	3.0 to 15.0		
Wk 13				
Median	4.2	1.0		
Interquartile range	1.0 to 10.0	0.0 to 4.0		
Change from baseline to wk 13				
Median	−2.5	−5.0	−2.0 (−4.0 to 0.0)	0.10
Interquartile range	−6.3 to 1.0	−8.0 to −2.0		

Measurement of discomfort questionnaire				
Baseline				
Median	16.0	14.0		
Interquartile range	13.5 to 18.0	10.0 to 19.0		
Wk 13				
Median	11.0	3.0		
Interquartile range	4.0 to 15.0	1.0 to 7.0		
Change from baseline to wk 13				
Median	−6.0	−9.0	−4.0 (−6.0 to −1.0)	0.001
Interquartile range	−9.0 to −2.0	−13.0 to −6.0		

* All confidence intervals and P values have been adjusted for multiplicity (Bonferroni correction) because two doses of ulipristal acetate were compared with placebo (i.e., P values were multiplied by 2). PBAC denotes pictorial blood-loss assessment chart.
† The differences in categories with numbers and percents are percentage-point differences. The differences in categories with medians and interquartile ranges are differences in medians, as calculated with the use of the Hodges–Lehmann estimator.
‡ The percent change from screening in total fibroid volume was assessed in 45 patients in the placebo group, 85 patients in the 5-mg ulipristal acetate group, and 80 patients in the 10-mgulipristal acetate group.

Table 5 PEARL II efficacy results for UPA 5mg and leuprolide acetate groups (per protocol population) (7)

	UPA 5mg (N = 93)	**Leuprolide acetate (N = 93)**	**Difference, 5 mg UPA vs. Leuprolide acetate (95% CI)**
Primary efficacy endpoints at week 13			
PBAC <75 — no./total no. (%)	84/93 (90)	82/92 (89)†	1.2 (−9.3 to 11.8)‡
Secondary efficacy endpoints			
Median (IQR)	0 (0 to 2)	0 (0 to 1)	
Change from baseline — median (IQR)	−268 (−412 to −172)	−274 (−430 to −161)	6 (−54 to 63)
≤2, indicating amenorrhea — no./total no. (%)	70/93 (75)	74/92 (80)	−5.2 (−18.7 to 8.6)
Total volume of three largest myomas			
Percent change from baseline — median (IQR)	−36 (−58 to −11)	−53 (−69 to −36)	
Ratio to screening volume — geometric mean	0.66	0.54	1.23 (0.99 to 1.52)
Uterine volume			
Percent change from baseline — median (IQR)	−20 (−40 to −3)	−47 (−57 to −35)	
Ratio to screening volume — geometric mean	0.84	0.57	1.48 (1.25 to 1.74)

Short-Form McGill Pain Questionnaire Score			
Median (IQR)	2.0 (0.0 to 4.0)	0.0 (0.0 to 4.0)	
Change from baseline — median (IQR)	−5.0 (−11.0 to −2.0)	−5.5 (−14.5 to −2.0)	0.2 (−2.0 to 3.0)
Uterine Fibroid Symptom and Quality of Life questionnaire			
Health-related quality of life score	76.4±23.2	73.2±23.0	
Change from baseline	23.7±26.9	23.2±28.2	2.5 (−7.3 to 12.3)
Haemoglobin — g/dl	12.8±1.4	12.7±1.6	−0.02 (−0.3 to 0.3)

† One patient had a missing score on the pictorial blood-loss assessment chart.
‡ A lower limit of the confidence interval of more than −20% (the prespecified noninferiority margin) indicates noninferiority. A lower limit of the confidence interval of more than zero indicates superiority.

Adverse events

A20. PRIORITY. Document B, Section B.2.10, page 99. The ERG notes that the adverse reactions from the PEARL studies are not included in the submission. Please clarify the reason for not providing this information and provide the comparable adverse event numbers for PEARL I and PEARL II.

Gedeon Richter response: An overview of the safety results for the PEARL studies was provided in the text within Section M1.5 of the submission. Apologies for not providing in tabulated format. The tabulated safety results for PEARL I and PEARL II are as follows:

Table 6 PEARL I summary of adverse events in the UPA 5mg and placebo groups (safety population) (6)

Event *	**Placebo (N = 48)** number (%)	**UPA 5 mg (N = 95)** *number (%)*
At least one serious adverse event	3 (6)	2 (2)
Serious adverse event during treatment period	1 (2)	0
Uterine haemorrhage	0	0
Fibroid protruding through cervix	1 (2)	0
Serious adverse event within 4 wk after treatment period	1 (2)	2 (2)
Uterine haemorrhage	0	1 (1)
Breast cancer	1 (2)	0
Ovarian haemorrhage	0	1 (1)
Serious adverse event from wk 17 to wk 38	1 (2)	0
Menometrorrhagia	1 (2)	0
Uterine haemorrhage	0	0
Adverse event leading to discontinuation of study drug†	1 (2)	1 (1)
At least one adverse event‡	22 (46)	47 (49)
Headache	2 (4)	4 (4)
Breast pain, tenderness, or discomfort	0	2 (2)

Abdominal pain	2 (4)	2 (2)
Pyrexia	2 (4)	3 (3)
Hypercholesterolemia	1 (2)	3 (3)
Hypothyroidism	0	2 (2)
Constipation	1 (2)	4 (4)
Hypertriglyceridemia	1 (2)	3 (3)
Influenza	1 (2)	1 (1)
Dizziness	0	1 (1)
Nasopharyngitis	0	3 (3)
Dysmenorrhoea	2 (4)	0

* All serious adverse events and adverse events occurring in at least 3% of the patients in any group are included. Patients could have more than one adverse event of the same type. There were no significant differences between either ulipristal acetate group and the placebo group for any adverse event, with two-sided P values calculated with the use of Fisher's exact test and no adjustment for multiplicity.

† The adverse events leading to discontinuation of the study drug were breast cancer (one patient in the placebo group), endometrial changes (one patient in the 5-mg ulipristal acetate group, with the event initially reported by the local laboratory as hyperplasia but later diagnosed as benign endometrium by three pathologists who were unaware of the study-group assignments).

‡ Adverse events with onset at or after the first dose of study drug and on or before the last assessment date of week 17 (4 weeks after the end of the treatment period) are included.

Table 7 PEARL II summary of adverse events in the UPA 5mg and leuprolide acetate groups (safety population) (7)

Event *	**UPA 5mg (N = 97)** number (%)	**Leuprolide acetate (N = 101)** *number (%)*
At least one event	8 (8)	6 (6)
Any event during treatment	2 (2)	2 (2)
Headache	1 (1)	0
Fibroid protruding through cervix	0	0
Lung infection	0	1 (1)
Thyroid cancer	1 (1)	0
Uterine haemorrhage	0	1 (1)
Within 4 wk after treatment†	3 (3)	2 (2)
From wk 17 to 38‡	3 (3)	2 (2)
Adverse events		
Leading to study-drug discontinuation	1 (1)	6 (6)
At least one event¶	75 (77)	85 (84)
Hot flash	25 (26)	66 (65)
Headache	25 (26)	29 (29)
Procedural pain	9 (9)	9 (9)
Abdominal pain	6 (6)	14 (14)
Nausea	6 (6)	6 (6)
Fatigue	4 (4)	3 (3)
Anaemia	5 (5)	5 (5)
Nasopharyngitis	6 (6)	2 (2)
Acne	0	5 (5)
Breast pain or tenderness	5 (5)	2 (2)
Influenza	2 (2)	5 (5)
Insomnia	2 (2)	5 (5)

Pharyngitis	5 (5)	2 (2)

* Listed are all serious adverse events and adverse events that occurred in at least 5% of patients in each study group, including events that were considered to be unrelated to the study drug. There were no significant between-group differences for any adverse event except hot flashes (P<0.001 for both doses of ulipristal acetate vs. leuprolide acetate). No adjustment for multiplicity was performed.

† These serious adverse events were operative complications in two patients and sarcoma in one patient (retrospectively diagnosed after further review after premature discontinuation of the study drug) in the group receiving 5 mg of ulipristal acetate; endometrial polyp, haemangioma, and operative complications and lymphocytic choriomeningitis in one patient each in the group receiving leuprolide acetate.

‡ These serious adverse events were spontaneous abortion, surgery for suspected ovarian tumour but intraoperative diagnosis corrected to new uterine myoma, and vaginal haemorrhage in one patient each receiving 5 mg of ulipristal acetate; and uterine haemorrhage in two patients receiving leuprolide acetate.

Section B: Clarification on cost-effectiveness data

Treatment withdrawal assumptions

B1. PRIORITY. Document B, Section B.3.3, Tables 39 and 40, page 134. The ERG notes that the treatment withdrawals from the LIBERTY trials were not directly used in the economic model but were instead modified based on the assumption that withdrawals in the trial are an overestimate of clinical practice. The ERG preferred method is to use the data obtained directly from the trial (Table 39). In the economic model, please provide a scenario analysis applying the withdrawal rates directly sourced from the LIBERTY trials.

Gedeon Richter response: We would like to reiterate that all KOLs that were engaged with during interviews and at an advisory board stated that they felt the withdrawal rates in the LIBERTY studies were inflated due to the alkaline haematin method used to measure MBL. The reasoning behind applying the modified withdrawal rates that were applied in our base-case was to align withdrawal in the model to what would be expected in clinical practice. However, as requested, we have updated the model to include a scenario analysis where the unadjusted LIBERTY withdrawal rates are used. The incremental cost-effectiveness results for this scenario are presented below.

Table 8: Incremental cost-effectiveness results, scenario with unadjusted LIBERTY withdrawal rates

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,742	21.525	16.530				
Triptorelin 3-monthly	7,797	21.525	16.530	55	0.000	0.000	Dominated
Triptorelin monthly	7,799	21.525	16.530	57	0.000	0.000	Dominated
Leuprorelin monthly	7,871	21.525	16.530	129	0.000	0.000	Dominated
Leuprorelin 3-monthly	7,947	21.525	16.530	205	0.000	0.000	Dominated
Goserelin 3-monthly	8,002	21.525	16.530	260	0.000	0.000	Dominated
Relugolix CT	8,185	21.525	16.633	444	0.000	0.103	4,311
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

B2. PRIORITY. Document B, Section B.3.3, Tables 41, 42, 44, pages 134, 135, 137. The ERG notes some inconsistencies between the treatment withdrawal probabilities reported in the CS and those applied in the economic model:

A) The monthly probability of treatment withdrawal at months 1-6 for relugolix is reported as being 0.86% in Table 41; however, in the submitted economic model the monthly probability of withdrawal at months 1-6 for relugolix is 0.72% (see: 'clinical' sheet, cells N26-N36). Please clarify which values are correct and provide a revised set of cost-effectiveness results if necessary.

Gedeon Richter response: We would like to apologise for this transcription error. The monthly probability in the submitted economic model (0.72%) is the correct value, the 0.86% figure stated in the CS is thus incorrect.

B) The monthly probability of treatment withdrawal from GnRH analogues is reported as 1.913% between months 1-6 (Table 42) and time varying between months 7-119, based on key opinion leaders (KOLs) responses (Table 44). However, in the submitted economic model, the monthly probability of

withdrawal is set to 1.913% up until month 119 and does not appear to be time varying (see: 'clinical' sheet, cells: E77 and E79). Please clarify which values are correct and provide a revised set of cost-effectiveness results if necessary.

Gedeon Richter response: We would like to apologise for not being clearer in our explanations of discontinuation in the GnRH agonist arm. The monthly probability of discontinuation in the GnRH arm is 1.913%, based on data from PEARL II (which was only of three months duration and therefore within the licensed duration of treatment). This can either be extrapolated forward as a constant rate for a pre-specified time period or can be overridden from 6 months onwards by the KOL responses, which are time-varying and higher than the PEARL II rates. In our model base-case, the rates from PEARL II are applied for the first 6 months, then are overridden by the clinician estimates to a maximum treatment duration of 10 years, based on their feedback For the scenarios where the GnRH treatment duration is capped at 6 months, no KOL-provided proportions of patients remaining on treatment as used and only the constant monthly discontinuation rate of 1.913% is applied. After month 6, all patients come off GnRH agonists.

B3. PRIORITY. Document B, Section B.3.3, Table 44, page 137. The ERG notes that views from KOLs are sought to inform the proportion of patients remaining on GnRH analogues between years one and ten. Please provide further details of the expert elicitation process, specifically:

A) How KOLs were identified and recruited.

Gedeon Richter response: All KOLs that were contacted were clinicians that Gedeon Richter had previously interacted with through previous HTA experience for Esmya® under the original indication for women with UF. KOLs were recruited via either email or telephone communication, initiated by the Medical Director for Gedeon Richter UK and Ireland.

B) Their experience of treating this patient population in clinical practice.

Gedeon Richter response: All KOLs that were contacted were experienced consultant gynaecologists regularly treating patients with uterine fibroids. The KOLs thus had the necessary experience as they are secondary care clinicians who regularly treat those patients who would be eligible for relugolix CT.

C) Their potential conflict of interest.

Gedeon Richter response: Two of the KOLs that were interviewed had previously attended an advisory board for Gedeon Richter and had received consultancy fees for this. One of these KOLs, a Consultant Gynaecologist at Frimley Park Hospital NHS Foundation Trust was nominated by Gedeon Richter as a clinical expert for this technology appraisal. There are no other potential conflicts of interest.

D) Please provide the interview schedule and any questionnaires that were used to elicit the expert's responses.

Gedeon Richter response: Three KOLs participated in a one-hour telephone interview that involved going through a full questionnaire, including questions regarding resource use and monitoring. The questionnaire that was used for these one-to-one calls was provided as data on file as part of the original submission. A further 5 KOLs were contacted to answer a subset of questions from the questionnaire that were considered critical model inputs for which a larger sample was deemed important, such as GnRH agonist treatment duration and surgery waiting times. Questions were asked of these additional KOLs via email and responses were also received via email. A summary of KOL engagement is presented in the table below.

Table 9 Summary of KOL contact methods and questions asked

KOL ID	Method of contact	Questions from questionnaire asked
KOL 1	Phone call	Full questionnaire
KOL 2	Phone call	Full questionnaire
KOL 3	Email	GnRH agonist treatment duration, use of add-back therapy, surgery waiting time
KOL 4	Email	GnRH agonist treatment duration, use of add-back therapy, surgery waiting time
KOL 5	Email	GnRH agonist treatment duration, use of add-back therapy, surgery waiting time
KOL 6	Email	GnRH agonist treatment duration, use of add-back therapy, surgery waiting time
KOL 7	Email	GnRH agonist treatment duration, use of add-back therapy, surgery waiting time
KOL 8	Phone call	Full questionnaire

E) Please clarify if the KOLs were asked to provide estimates of discontinuation considering that add-back therapy would be also be provided with the GnRH treatment in UK clinical practice.

Gedeon Richter response: We can confirm that the KOLs were asked to provide estimates of discontinuation for GnRH plus add-back therapy. Question 6.2 from the clinician survey covers this and is provided below.

"How long do patients wishing to avoid surgery stay on GnRHa plus add-back therapy in clinical practice? Roughly what % would remain on treatment after 6 months, 1 year, 5 years and 10 years?"

F) Please clarify whether uncertainty in the KOLs opinions was incorporated in the probabilistic analyses. If not, please update the probabilistic sensitivity analysis (PSA) to reflect the range of uncertainty in long-term GnRH treatment withdrawal.

Gedeon Richter response: KOL opinion was not incorporated into the PSA in the original model. We have now updated the PSA to reflect the range of uncertainty in the long-term GnRH treatment withdrawal. A summary of the point estimates and their uncertainty is shown below. The PSA results with these updated parameters are provided in the appendix with updated cost-effectiveness results.

Table 10 Point estimates and uncertainty data for KOL responses

Parameter	Mean value	Lower bound	Upper bound
% on GnRH agonist – after 6 months	100%	80%	100%
% on GnRH agonist – after 1 year	43.21%	34.57%	51.86%
% on GnRH agonist – after 5 years	13.57%	10.86%	16.29%
% on GnRH agonist – after 10 years	0.71%	0.57%	0.86%

Adverse events

B4. Document B, Section B.3.3, pages 144-145 & Table 52. The ERG notes that the incidence of long-term adverse events related to hysterectomy is obtained from a prospective cohort study based on a population of Turkish women. Please explain the reason for choosing this specific source and comment on whether any alternative sources were considered. Please confirm whether there are any published UK data on long-term adverse events related to hysterectomy and if so, please provide a scenario analysis where these data are used in the model.

Gedeon Richter response: We would like to draw the ERG's attention to the fact that the model is not very sensitive to these parameters. This was tested by including a scenario where the long-term hysterectomy-related adverse events are excluded . The results for this scenario are reported in the table below. As can be seen the

incremental ICER for relugolix CT vs. Goserelin monthly (£5,996) under this scenario is not much higher than the updated base-case ICER (£5,796).

Table 11: Incremental cost-effectiveness results, scenario with long-term hysterectomy-related AEs removed

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,742	21.525	16.552	-	-	-	-
Triptorelin 3-monthly	7,797	21.525	16.552	55	0.000	0.000	Dominated
Triptorelin monthly	7,799	21.525	16.552	57	0.000	0.000	Dominated
Leuprorelin monthly	7,871	21.525	16.552	129	0.000	0.000	Dominated
Leuprorelin 3-monthly	7,947	21.525	16.552	205	0.000	0.000	Dominated
Goserelin 3-monthly	8,002	21.525	16.552	260	0.000	0.000	Dominated
Relugolix CT	9,854	21.525	16.904	2,112	0.000	0.352	5,996
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

We were not able to identify any published UK-specific data reporting the incidence of long-term AEs related to hysterectomy. The only UK-specific published data we could find were papers reporting long-term effects of hysterectomy on outcomes such as mortality and cancer incidence, as opposed to the AE rates. We felt that these AEs should be accounted for in the model given the plethora of anecdotal evidence such as articles published online, detailing the long-term complications that women who have had a hysterectomy experience. The scope of the search for this data was thus broadened to identify any data (non-UK specific) that provided this information. The Moraloglu et al., 2007 study (8) was selected to inform these parameters because although the study was conducted in a sample of Turkish women, in the absence of UK-specific data, it was the best alternative we could find. Furthermore, the majority (72.7%) of patients in Moraloglu et al., 2007 (8) had a principle diagnosis of leiomyoma (UF) and the mean at baseline was 47, compared to 43 in the relugolix CT arm of LIBERTY 1 and 42 in the same arm of LIBERTY 2. It was thus felt that the patient population in this study was similar to the model population and that the AE incidence was generalisable to the LIBERTY population.

B5. Document B, Section B.3.3, Table 50, page 143. With regards to the inclusion of non-surgical adverse event rates in the model, can the company please:

A) Clarify whether the criteria used was 5% across the pooled studies or 5% in either LIBERTY 1 or LIBERTY 2 and double-check that the data included in the model are consistent with those reported in Table 29 of the submission?

Gedeon Richter response: If an AE was reported in 5% or more during any of the trials, the total reported number of events was pooled between LIBERTY 1 and LIBERTY 2, potentially reducing the pooled proportion to be less than 5%. Arthralgia and Fatigue were stated in table 29 of the submission as having occurred in >5% in any group, however they did not occur in >5% in either of the trials and are thus not included in the cost-effectiveness model.

B) Justify why a cut-off of 5% was chosen for the inclusion of adverse event data in the model. Please provide a scenario analysis incorporating all available adverse event data from the LIBERTY trials.

Gedeon Richter response: We would like to draw the ERG's attention to the fact that the model is not very sensitive to AEs. This has been confirmed by including an additional scenario where all treatment-related AEs are excluded . The incremental cost-effectiveness results for this scenario are reported in the table below. It can be seen that the results are very closely aligned with the model base-case (appendix of cost-effectiveness results, table 2). The ICER for relugolix CT vs. the least costly GnRH agonist (goserelin monthly) is £6,014, compared to £5,796 in the updated base-case.

Table 12: Incremental cost-effectiveness results, scenario with treatment-related AEs removed

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,709	21.525	16.552				
Triptorelin 3-monthly	7,764	21.525	16.552	55	0.000	0.000	Dominated
Triptorelin monthly	7,767	21.525	16.552	57	0.000	0.000	Dominated
Leuprorelin monthly	7,839	21.525	16.552	129	0.000	0.000	Dominated
Leuprorelin 3-monthly	7,915	21.525	16.552	205	0.000	0.000	Dominated
Goserelin 3-monthly	7,970	21.525	16.552	260	0.000	0.000	Dominated
Relugolix CT	9,823	21.525	16.904	2,114	0.000	0.352	6,014
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

With regards to the adverse events reported in LIBERTY 1 and LIBERTY 2, as can be seen from table 24 of the LIBERTY 1 CSR and table 23 of the LIBERTY 2 CSR, there were 35 various adverse events reported in LIBERTY 1 and 38 in LIBERTY 2. This would be an excessive amount of AEs to include in the model. Furthermore, most of these AEs would be categorised as mild-moderate AEs e.g. ‘nasal congestion’ and ‘decreased appetite’ and would thus not incur material cost or QoL impact, if any. A cut-off of 5% was chosen for the inclusion of adverse event data in the model as this is common practice in health economic models. Furthermore, although the NICE methods guide is not prescriptive as to what level of incidence would be required to categorise an event as a common AE of a treatment, the EMA defines ‘very common’ AEs as those occurring in 10% or more patients and ‘common’ AEs as those that have an incidence rate of 1% - 10% (9). Conversely, the FDA defines common AEs using a rate of 10% or more in the treatment group (9). The 5% cut-off in the model is thus considered an appropriate mid-point.

C) Explain why treatment-related adverse event rates were only obtained from LIBERTY 1 and 2 for relugolix and best supportive care (BSC), and not from the LIBERTY 3 or LIBERTY withdrawal studies. Please provide a scenario analysis using all the available data.

Gedeon Richter response: Treatment-related AEs could not be sourced from the LIBERTY withdrawal study as the CSR is not yet available. Furthermore, given that there are no AE data for the GnRH arm beyond 3 months (PEARL II), using long-term data from LIBERTY 3 to inform AEs in the relugolix CT arm while extrapolating only short-term AEs for GnRH agonist would be a biased comparison given the known longer-term tolerance profile of GnRH is the primary reason for its limited treatment duration. Given this and the very limited impact that removing AEs has on the model results (Table 12), the requested scenario has not been conducted as this would not make a material difference to the cost-effectiveness results.

Transition to surgery

B6. Document B, Section B.3.3, page 140. The ERG noted that the waiting time before surgery was assumed to be 15 months based on 5 KOLs opinions, with clinical experts commenting that waiting times are longer because of the COVID-19 pandemic. Please provide an estimate of surgery waiting times that might be expected when services return to normal post-pandemic.

Gedeon Richter response: The model is programmed to allow removal of the waiting time to surgery, and we have run a scenario to investigate its impact. While the model is sensitive to this parameter, even assuming this unrealistic scenario of no waiting time, leads to ICERs below £20,000 per QALY. The incremental cost-effectiveness results for this scenario are presented in the table below.

Table 13 Incremental cost-effectiveness results, scenario with waiting time before surgery removed

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	8,210	21.525	17.013				
Triptorelin 3-monthly	8,265	21.525	17.013	55	0.000	0.000	Dominated
Triptorelin monthly	8,268	21.525	17.013	57	0.000	0.000	Dominated
Leuprorelin monthly	8,340	21.525	17.013	129	0.000	0.000	Dominated
Leuprorelin 3-monthly	8,416	21.525	17.013	205	0.000	0.000	Dominated
Goserelin 3-monthly	8,471	21.525	17.013	260	0.000	0.000	Dominated
Relugolix CT	10,111	21.525	17.116	1,901	0.000	0.103	18,470
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Surgery mortality

B7. Document B, Section B.3.3, page 145 & Company economic model, tab: 'clinical', Cells: 'O238: W244'. The ERG notes that the only mechanism by which differential life year gains can be accrued in the model is through "surgery-related" mortality. However, setting all surgical mortality parameters to '0' in the model does not result in equal life-year gains across all treatments. Please review and clarify whether there are any technical errors within the model file. If any errors are identified, please provide a revised set of cost-effectiveness results with corrections applied.

Gedeon Richter response: Thank you for bringing this to our attention, there was a technical error within the model which has now been corrected. The updated model contains an updated waiting time state that has been added into the Markov traces to eliminate the error. There are no major structural updates that were thus required. A detailed explanation with references to the sheets and cells where these changes have been implemented are provided in the appendix file with updated cost-effectiveness results [ID3842 Appendix_relugolix CT updated cost-effectiveness results 16.11.21]. We provide a revised set of cost-effectiveness results with these

corrections applied in the cost-effectiveness appendix. Of note, all ICERs have reduced under the corrected base-case and the incremental QALY gain has increased from 0.178 (as in the original submission) to 0.364. The base-case ICER for relugolix CT vs. Goserelin monthly (the least costly GnRH agonist) is now £5,796 per QALY.

Utilities

B8. Document B, Page 152. A disutility value during the waiting time for surgery of -0.01 [sourced from Stein, 2005] is applied in the model. Please:

A) Clarify whether there is a risk of double counting the utility already captured for those receiving BSC.

Gedeon Richter response: There is very minimal risk of double counting in the utility mapped from the LIBERTY trials given that one of the trials' main exclusion criteria was that a patient was not planned to undergo surgery for at least the initial 6 months of the study. Furthermore, very few patients in the studies went on to undergo surgery during the full study period, including up to 104 weeks of treatment. For reference, please note that with regards to the PEARL studies, EQ-5D was not captured, thus, utility was derived using MBL outcome.

B) Provide further details of why this study was chosen, how it is appropriate for this patient group, and an assessment of its appropriateness against the NICE reference case (e.g., EQ-5D, UK value set, etc.).

Gedeon Richter response: The study population in Stein were patients enrolled in the baseline phase of the Collaborative Care for Anxiety and Panic (CCAP) Study (http://staff.washington.edu/bmeister/panic/index.html)

Eligible subjects were patients who 1) were between 18 and 70 years old, 2) were English-speaking, and 3) had access to a telephone. 480 people included in sample (63.1% females). The utility metric used was the SF-12 and a UK value set was used to elicit utility values. (Brazier JE, Roberts J. The estimation of a preference-based measure of health from the SF-12. Med Care. 2004 Sep;42(9):851-9.)

The measure was deemed appropriate as the target population was outpatients in primary care with any form of anxiety disorder. Being worried/anxious prior to surgery would fall under this category and it would thus appear reasonable since most surgeries included in the model are more or less invasive and some carry risk of mortality. Thus, this utility was deemed relevant to the patient population in the model as the surgery anticipation anxiety is assumed equivalent "any anxiety disorder" and is not connected per se to the patient's diagnosis of uterine fibroids but surgery.

C) Please provide a scenario analysis where the utility decrement is removed from the "waiting time" state.

Gedeon Richter response: The results for this scenario are presented in the table below. It can be seen that this scenario has very little impact upon the cost-effectiveness results, the incremental QALYs for relugolix CT have decreased very slightly from the updated base-case (0.364 to 0.361). Because this difference is so small, the ICER for relugolix CT vs goserelin monthly is largely unchanged from the new base-case, as reported in the appendix of updated cost-effectiveness results.

Table 14: Incremental cost-effectiveness results, scenario with disutility for waiting time before surgery removed

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,742	21.525	16.536	-	-	-	-
Triptorelin 3-monthly	7,797	21.525	16.536	55	0.000	0.000	Dominated
Triptorelin monthly	7,799	21.525	16.536	57	0.000	0.000	Dominated
Leuprorelin monthly	7,871	21.525	16.536	129	0.000	0.000	Dominated
Leuprorelin 3-monthly	7,947	21.525	16.536	205	0.000	0.000	Dominated
Goserelin 3-monthly	8,002	21.525	16.536	260	0.000	0.000	Dominated
Relugolix CT	9,854	21.525	16.897	2,112	0.000	0.361	5,848
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

B9. PRIORITY. Document B, Section B.3.4, Tables 58-62, pages 151-154. Please provide further details on the approach used to source all disutility parameters from the literature for use in the model. Please add the following additional columns to Tables 58 – 62 to enable an assessment of the sources against the NICE reference case: "Study population", "Measurement tool", "Value set applied", “Justification”.

Gedeon Richter response: We would like to draw the ERG’s attention to the fact that the model is not very sensitive to the disutilities. This was confirmed by setting all disutility values in the model to 0, the results for this scenario are presented below. The ICER for relugolix CT vs. the least costly GnRH agonist (goserelin monthly) is £6,788 compared to £5,796 in the updated base-case. The utility decrements applied thus have very little impact upon the results.

Table 15 Incremental cost-effectiveness results, scenario with all utility decrements removed

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,742	21.525	16.625	-	-	-	-
Triptorelin 3-monthly	7,797	21.525	16.625	55	0.000	0.000	Dominated
Triptorelin monthly	7,799	21.525	16.625	57	0.000	0.000	Dominated
Leuprorelin monthly	7,871	21.525	16.625	129	0.000	0.000	Dominated
Leuprorelin 3-monthly	7,947	21.525	16.625	205	0.000	0.000	Dominated
Goserelin 3-monthly	8,002	21.525	16.625	260	0.000	0.000	Dominated
Relugolix CT	9,854	21.525	16.936	2,112	0.000	0.311	6,788
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

We are happy to provide the additional details regarding the disutility parameters, however we would like to request some additional time to provide this information. We will send over the requested additional information w/c 22 November 2021.

B10. PRIORITY. Document B, Section B.3.4, pages 148-149. Please provide full details of the mapping algorithm used to map from UFS-QoL to EQ-5D.

Gedeon Richter response: The full details of the mapping algorithm are provided in the unpublished paper (Rowen and Brazier, 2011) that was submitted as data on file alongside our submission. The authors evaluated various ordinary least squares (OLS), tobit, and two-part regression models, with the best performing model being the OLS model presented in the equation below:

$$\begin{aligned} EQ5D_i = {} & 0.974 - 0.062 \times I(Q24 = 2)_i - 0.075 \times I(Q24 = 3)_i - 0.243 \times I(Q24 = 4)_i \\ & - 0.151 \times I(Q24 = 5)_i - 0.059 \times I(Q5 = 2)_i - 0.061 \times I(Q5 = 3)_i \\ & - 0.094 \times I(Q5 = 4)_i - 0.323 \times I(Q5 = 5)_i - 0.047 \times I(Q8 = 2)_i \\ & - 0.040 \times I(Q8 = 3)_i - 0.071 \times I(Q8 = 4)_i - 0.100 \times I(Q8 = 5)_i \end{aligned}$$

Where $EQ5Di$ is the estimated utility for patient i based on the EQ5D measure, and I is an indicator function for different levels of questions 25, 5, and 8 from the UFS-QoL. Note panel models that would have accounted for repeated measures were not fitted due to difficulties linking observations at different visits within the estimation dataset that was used.

The report has been submitted previously. No further information was available to Gedeon Richter.

B11. Document B, Section B.3.4, page 149. The CS indicates that standard errors obtained from the ordinary least squares (OLS) model may be biased. The ERG suggests a repeated measures model (with respondent fitted as a random effect) as an alternative approach to generate unbiased estimates of the standard error. Please provide this analysis and incorporate the estimated standard errors into the PSA.

Gedeon Richter response: As requested by the ERG, we have explored a scenario using a repeated measures model to generate standard errors for the utility algorithm parameters. The distributions for these parameters have been updated and the alpha and beta values applied in the PSA have also been recalculated to account for the updated standard errors. These parameters are provided in the table below.

Table 16 Parameter estimates from the repeated measures regression of mapped EQ-5D utilities from UFS-QoL

Parameter	Estimate	Standard error	Distribution	Alpha	Beta
Intercept	0.7035	0.04196	Gamma	281.10	0.003
MBL volume (dL)	-0.0593	0.00350	Negative gamma	287.06	0.000
Age at baseline (years)	0.0030	0.0001	Gamma	9.09	0.000

The incremental cost-effectiveness results with the updated utility values from the repeated measures model applied are reported in Table 17. The model is not very sensitive to these utility parameters as the ICER against goserelin monthly reduces slightly from £5,796 in the base-case to £4,977. The PSA results with the standard errors from the repeated measures model incorporated into the analyses are reported in Table 18. The PSA ICER is very closely aligned with the deterministic ICER (difference of £35), as the incremental QALYs are almost identical (difference of 0.001), whilst the incremental costs for relugolix CT vs. goserelin monthly decrease by a very small amount (£11). The cost-effectiveness acceptability curve (CEAC) is presented in Figure 7 and shows that the probability of relugolix CT being cost-effective increases in line with higher willingness to pay (WTP) thresholds and is 100% at thresholds of £7,400 per QALY and above. It should be noted however that the variance-covariance matrix from the repeated measures model has not been incorporated into the PSA and the results may therefore be subject to change.

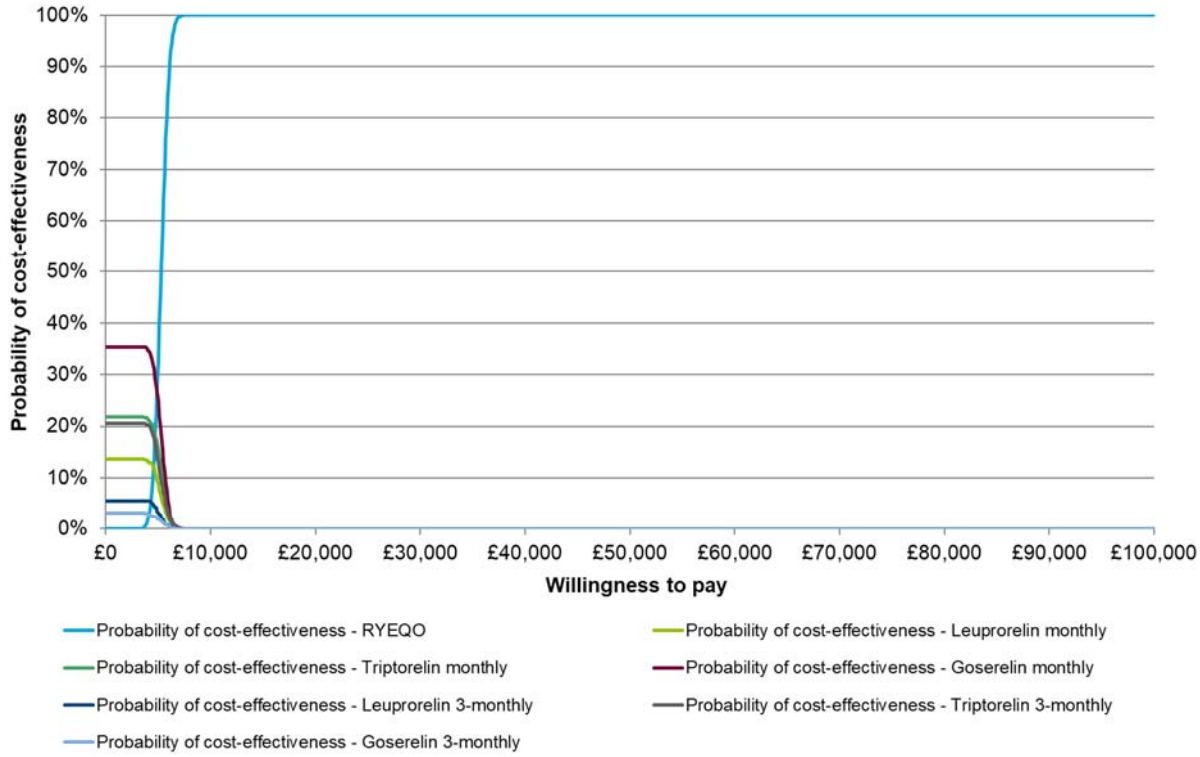
Table 17 Incremental cost-effectiveness results, scenario with utility parameters estimated from repeated measures model

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,742	21.525	16.432	-	-	-	-
Triptorelin 3-monthly	7,797	21.525	16.432	55	0.000	0.000	Dominated
Triptorelin monthly	7,799	21.525	16.432	57	0.000	0.000	Dominated
Leuprorelin monthly	7,871	21.525	16.432	129	0.000	0.000	Dominated
Leuprorelin 3-monthly	7,947	21.525	16.432	205	0.000	0.000	Dominated
Goserelin 3-monthly	8,002	21.525	16.432	260	0.000	0.000	Dominated
Relugolix CT	9,854	21.525	16.856	2,112	0.000	0.424	4,977
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 18 Probabilistic cost-effectiveness results, scenario with utility parameters estimated from repeated measures model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,743	16.432	-	-	-	-
Triptorelin 3-monthly	7,814	16.432	71	0.000	0.000	Dominated
Triptorelin monthly	7,805	16.432	62	0.000	0.000	Dominated
Leuprorelin monthly	7,861	16.432	118	0.000	0.000	Dominated
Leuprorelin 3-monthly	7,948	16.432	205	0.000	0.000	Dominated
Goserelin 3-monthly	8,009	16.432	266	0.000	0.000	Dominated
Relugolix CT	9,844	16.857	2101	0.000	0.425	4,942

Figure 7 Cost-effectiveness acceptability curve, scenario with utility parameters estimated from repeated measures model



We have explored the impact of updating the cost-effectiveness model with the standard errors from the OLS model. These values are reported in the table below. In the model base-case the standard errors for these parameters in the model are calculated as a 20% variation of the mean.

Table 19 Parameter estimates from the OLS regression of mapped EQ-5D utilities from UFS-QoL

Parameter	Estimate	Standard error	95% Lower CL	95% Upper CL
Intercept	0.6957	0.02999	0.6369	0.7545
MBL volume (dL)	-0.0388	0.00238	-0.0434	-0.0341
Age at baseline (years)	0.0030	0.00070	0.0016	0.0043

The OWSA and PSA were re-run with the uncertainty estimates reported in Table 19 applied. The PSA was unaffected by the updated parameters, whilst the OWSA showed more of an impact. With the updated standard errors from the OLS model, the range in the ICERs obtained in the OWSA for utility algorithm intercept

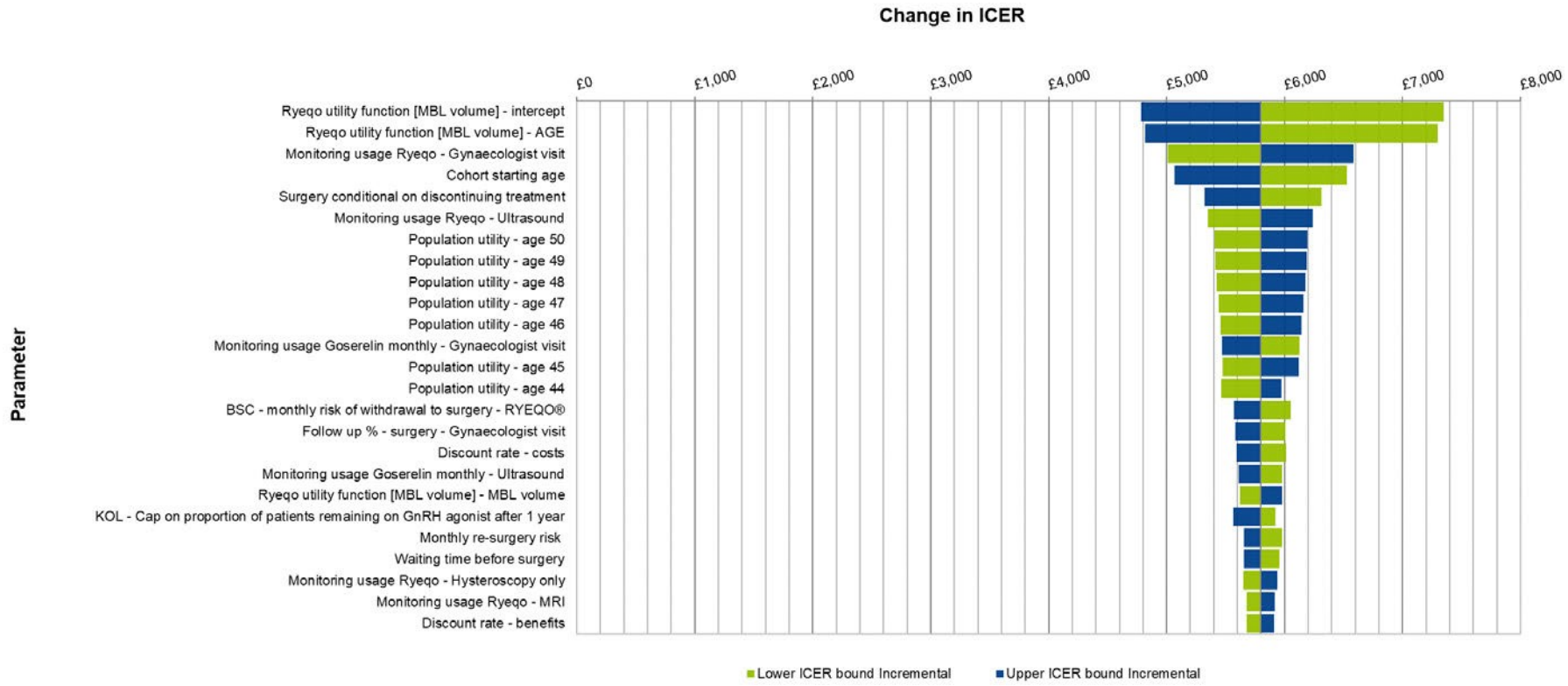
parameter reduced from £7,750 in the model base-case to £2,568. The OWSA results for this scenario are presented in Table 20 and Figure 8.

Table 20 OWSA results scenario with standard errors from OLS regression applied for utility algorithm parameters

Parameter	Lower bound ICER	Upper bound ICER	Difference
Ryeqo utility function [MBL volume] - intercept	£7,351	£4,783	-£2,568
Ryeqo utility function [MBL volume] - AGE	£7,296	£4,819	-£2,477
Monitoring usage Ryeqo - Gynaecologist visit	£5,008	£6,584	£1,576
Cohort starting age	£6,528	£5,067	-£1,460
Surgery conditional on discontinuing treatment	£6,312	£5,320	-£992
Monitoring usage Ryeqo - Ultrasound	£5,350	£6,242	£891
Population utility - age 50	£5,409	£6,196	£787
Population utility - age 49	£5,414	£6,190	£776
Population utility - age 48	£5,423	£6,179	£756
Population utility - age 47	£5,438	£6,162	£723
Population utility - age 46	£5,456	£6,142	£686
Monitoring usage Goserelin monthly - Gynaecologist visit	£6,123	£5,468	-£655
Population utility - age 45	£5,473	£6,122	£648
Population utility - age 44	£5,461	£5,975	£514
BSC - monthly risk of withdrawal to surgery - RYEQO®	£6,052	£5,572	-£480
Follow up % - surgery - Gynaecologist visit	£6,010	£5,582	-£427
Discount rate - costs	£6,011	£5,591	-£420
Monitoring usage Goserelin monthly - Ultrasound	£5,981	£5,611	-£370
Ryeqo utility function [MBL volume] - MBL volume	£5,623	£5,981	£357
KOL - Cap on proportion of patients remaining on GnRH agonist after 1 year	£5,924	£5,568	-£357
Monthly re-surgery risk	£5,977	£5,656	-£321
Waiting time before surgery	£5,954	£5,654	-£300
Monitoring usage Ryeqo - Hysteroscopy only	£5,652	£5,940	£288
Monitoring usage Ryeqo - MRI	£5,678	£5,914	£236
Discount rate - benefits	£5,681	£5,911	£230
Monitoring usage BSC - Ultrasound	£5,906	£5,686	-£220
Concomitant med units/month - Ryeqo - NSAID 200mg tablet	£5,687	£5,905	£218
Monitoring usage BSC - GP visit	£5,901	£5,691	-£210
KOL - Cap on proportion of patients remaining on GnRH agonist after 6 months	£5,940	£5,796	-£144

Monitoring usage Goserelin monthly - Dexa scan	£5,867	£5,725	-£143

Figure 8 OWSA results, scenario with standard errors from OLS regression applied for utility algorithm parameters



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

Clarification response to question B9

Dear Evidence Review Group,

Please find below, in addition to our previous response submitted on the 16th November 2021, further response to question **B9**:

B9. PRIORITY. Document B, Section B.3.4, Tables 58-62, pages 151-154. Please provide further details on the approach used to source all disutility parameters from the literature for use in the model. Please add the following additional columns to Tables 58 – 62 to enable an assessment of the sources against the NICE reference case: "Study population", "Measurement tool", "Value set applied", “Justification”.

Gedeon Richer response (continued from previous response submitted on 16th November 2021):

A pragmatic search was carried out to source disutility parameters for the model. The majority of values had been sourced previously as part of the published cost effectiveness analysis of ulipristal acetate carried out by Geale *et al*. 2017 (1). Tables 58-61 have been updated with the additional column requested below.

Table 58 Surgery-related disutilities reported in the literature

Surgery	EQ-5D QoL decrement/year	Source	Study population	Measurement tool	Value set applied	Justification
Abdominal approach	-0.07	Sculpher et al. 2004 (2)	English-reading Canadian women without fibroids and aged 20–50 years.	EuroQoL-5D-5 level (EQ-5D-5L)	Canadian value set	Generalisable population, measured on valid instrument. Canadian value set produces similar values to UK (3)
Laparoscopic approach	–0.04					
Vaginal approach	–0.02					
UAE	-0.02					

EQ-5D: EuroQol 5 Dimension; QoL: quality of life; UAE: uterine artery embolisation

Table 59 Surgery-related disutilities applied in the model

Surgery	Disutility applied per monthly cycle	Source	Study population	Measurement tool	Value set applied	Justification
Abdominal hysterectomy	-0.005	Sculpher et al. 2004 (2). **Note: see calculations in Geale et al. for more details** (1)**.**	English-reading Canadian women without fibroids and aged 20–50 years.	EuroQoL-5D-5 level (EQ-5D-5L)	Canadian value set	Generalisable population, measured on valid instrument. Canadian value set produces similar values to UK (3). Also see Geale et al. (1)**.**
Laparoscopic hysterectomy	-0.003					
Vaginal hysterectomy	-0.002					
Abdominal myomectomy	-0.005					
Laparoscopic myomectomy	-0.003					
Vaginal myomectomy	-0.002					
UAE	-0.002					
MRgFUS	-0.002					

MRgFUS: Magnetic resonance-guided focused ultrasound; UAE: uterine artery embolisation

Table 60 Disutilities for treatment-related adverse events

Adverse event	Disutility	Source	Study population	Measurement tool	Value set applied	Justification
Hot flush	-0.005	Hux et al., 2015 (4)	English-reading Canadian women without fibroids and aged 20–50 years.	EuroQoL-5D-5 level (EQ-5D-5L)	Canadian value set	The condition reported corresponds to the one used in the CE model.
Headache	0.000	Assumption of no disutility				
Hypertension	0.000	Assumption of no disutility				
Cough	0.000	Assumption of no disutility				
Nausea	-0.011	Assumption that same disutility as reported for influenza in Lloyd et al., 2006 (5)	100 members of the public, living in the greater London area	Standard gamble (SG)	NA	Assumption that same disutility as reported in the literature for influenza
Upper respiratory tract infection	-0.011	Assumption that same disutility as reported for influenza in Lloyd et al., 2006 (5)	100 members of the public, living in the greater London area	Standard gamble (SG)	NA	Assumption that same disutility as reported in the literature for influenza
Anaemia	-0.009	Del Rio et al., 2006 (6)	NR	NR	NR	Estimate from other cost-effectiveness studies
Insomnia	-0.010	Assumption that same disutility as for fatigue in Lloyd et al., 2006 (5)	100 members of the public, living in the greater London area	Standard gamble (SG)	NA	Being sleep deprived would have the same effect as being fatigued

Key: NA, not applicable; NR, not reported

Table 61 Disutilities for surgery-related short-term adverse events

Surgery-related adverse event	Disutility	Source	Study population	Measurement tool	Value set applied	Justification
Bowel obstruction	-0.017	Earnshaw et al., 2010 (7)	724 patients recruited from 170 pharmacies in the Netherlands.	EQ-5D-3L	NR	Difference between utilities reported by patients being constipated and not constipated. Assumed equivalent to having an obstruction in the bowel.
Febrile event	0.000	Assumption of no disutility				Assumption of no disutility
Fibroid expulsion	-0.001	Assumption that same as pain, reported in Anderson et al., 1985 (8)	3,461 refugees at UCMC in San Diego	NA	NA	Fibroid explusion is assumed to be painful but passing.
Groin haematoma	0.000	Assumption of no disutility				Assumption of no disutility
Haemorrhage	-0.017	Freeman et al., 2011 (9)	NR	NR	NR	Assumed to be equivalent to bleeding event in patients with atrial fibrillation. Estimates from CE-analysis, no report on instrument or value set.
Ileus	-0.017	Earnshaw et al., 2010 (7)	724 patients recruited from 170 pharmacies in the Netherlands.	EQ-5D-3L	NR	Assumed same disutility as bowel-obstruction.

Surgery-related adverse event	Disutility	Source	Study population	Measurement tool	Value set applied	Justification
Pelvic infection, haematoma or abscess	-0.016	Tolley et al., 2013 (10)	110 members of the UK general public	Time-trade-off	NA	The reported disutility for infection assumed to be comparable.
Pneumonia	-0.008	Assumption that same disutility as reported for influenza in Lloyd et al., 2006 (5)	100 members of the public, living in the greater London area	Standard gamble (SG)	NA	Assumption that same disutility as reported in literature for influenza
Post embolisation syndrome	-0.012	Assumption that same as sum of pain and nausea				Calculation
Pulmonary embolus	-0.002	Blondon et al., 2010 (11)	NR	NR	NR	Peer reviewed disutility in publication.
Sepsis	-0.010	Karlsson et al., 2009 (12)	470 patients with severe sepsis	EQ5D	NR	Peer reviewed disutility in publication.
Urinary tract infection	-0.006	***Note: incorrect reference was provided in the submission***. Should have been Armstrong et al. (13). Difference between full health and UTI utility/12 months	NR	Standard gamble	NA	Urinary tract infection assumed to carry the same utility decrement in women as in men.
Urticaria	0.000	Assumption of no disutility				Assumption of no disutility due to the very mild nature of this event
Wound infection	-0.016	Tolley et al., 2013 (10)	110 subjects, representative cross-sectional sample of UK population	Time-trade-off	NA	Literature

Surgery-related adverse event	Disutility	Source	Study population	Measurement tool	Value set applied	Justification
Oedema	-0.005	Assumption that same as pain (8)	3,461 refugees at UCMC in San Diego	NA	NA	Oedema is assumed to be painful but passing.
Pain	-0.001	(8)	3,461 refugees at UCMC in San Diego	NA	NA	Literature

Key: NA, not applicable; NR, not reported

Table 62 Disutilities for long-term adverse events for hysterectomies

Surgery-related adverse event	Disutility	Source	Study population	Measurement tool	Value set applied	Justification
Hot flushes	-0.005	Hux et al., 2015 (4)	English-reading Canadian women without fibroids and aged 20–50 years.	EuroQoL-5D-5 level (EQ-5D-5L)	Canadian value set	Literature
Fatigue	-0.010	Lloyd et al., 2006 (5)	100 members of the public, living in the greater London area	Standard gamble (SG)	NA	Literature
Urinary problems	-0.006	Assumption: same as UTI (14)				Assumption that same as UTI
Abdominal distention	-0.008	Groeneveld et al, 2001 (15)	73 patients enrolled in the Study of Management and Costs of Helicobacter pylori Infection (STOMACH)	Time-trade-off	NA	Assumed to be comparable with bloating.
Insomnia	-0.010	Assumption: same as fatigue (5)	100 members of the public, living	Standard gamble (SG)	NA	Assume fatigue as being sleep deprived would

			in the greater London area			have the same effect as being fatigued
Housework problems	-0.005	Dolan, 1997 (16)	2,997 members of the UK public	Time-trade-off	NA	EQ-5D tariff estimation of third dimension incorporates not being able to perform house work acitivites.
Anxiety	-0.013	Stein et al., 2005 (17)	patients enrolled in the baseline phase of the Collaborative Care for Anxiety and Panic (CCAP) Study	SF-12	UK value set	See answer to question B8. Anxiety prior to surgery assumed to be same as any other anxiety and not specifically related to UF.
Vaginal irritation and pruritus	-0.001	Assumption that same as pain (8)	3,461 refugees at UCMC in San Diego	NA	NA	Assumed painful but passing.

Key: NA, not applicable

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ID3842: Appendix – relugolix CT updated cost-effectiveness results

16 November 2021

This appendix provides updated cost-effectiveness results for the model base-case, with the rectification of an error outlined in question B7 of the clarification questions. The error in question was related to surgery mortality and the original submitted model generated faulty results regarding patient survival when all mortalities apart from baseline mortality were set to 0. We have now amended this error by amending the existing surgery waiting time state within the Markov traces of the economic model. Additional columns that have been added into the Markov traces represent each month that the patient is in the waiting before surgery state (an extension of the BSC state). The model 'Settings' sheet has a drop-down (cells I45 to L45) which enables the selection of up to 24 months of waiting time before surgery. The additional columns thus account for up to 24 months of possible waiting time. If the waiting time (months) is greater than or equal to the number of months represented by the column e.g. 2 months for column AB of the Markov trace sheets, then general population mortality is applied for those patients who are in the waiting for surgery health state. No background mortality is applied in months that exceed the waiting time e.g. from month 16 onwards, as patients will have had their procedure at month 15, as waiting time is 15 months in the base-case.

Additional changes have also been made to the model in response to some of the clarifications from the ERG that were received. The changes to the model are summarised in the table below.

Table 1: Updates to the economic model

Clarification question pertaining to change	Model sheet	Cell range	Change applied
B3.F	'Parameters'	A14 to U17	Uncertainty parameters applied to KOL-predicted proportions of patients remaining on GnRH agonist treatment at various timepoints. This was

			done so these estimates could be included in the OWSA and PSA.
B4	'Settings'	I82 to L82	Scenario added in to exclude long-term adverse events related to hysterectomy
B5.B	'Settings'	I74 to L74	Scenario added in to explore the impact of excluding all treatment-related adverse events
B7	'Markov Ryeqo', 'Markov GnRH1', 'Markov GnRH2', 'Markov GnRH3', 'Markov GnRH4', 'Markov GnRH5', 'Markov GnRH6'	AA9 to AX728	Population general mortality applied for those patients who are waiting for their first surgery
	'Markov Ryeqo', 'Markov GnRH1', 'Markov GnRH2', 'Markov GnRH3', 'Markov GnRH4', 'Markov GnRH5', 'Markov GnRH6'	CD9 to DA728	Population general mortality applied for those patients who are waiting for their second surgery
B8.C	'Settings'	I80 to L80	Scenario added in to explore the impact of removing the utility decrement in the 'waiting for surgery' state
B11	'Parameters'	L185 to N187	Scenario added in where standard errors and lower and upper bound for the utility algorithm parameters are replaced with those from the OLS regression mapped EQ-5D utilities from the UFS-QoL

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

The incremental cost-effectiveness results are reported in Table 2. Relugolix CT is associated with greater total costs compared to the GnRH agonist comparators, as total costs for relugolix CT are £9,854 compared to a range of £7,742 to £8,002 for GnRH agonists, mainly due to the longer time during which patients remain on active treatment with relugolix CT. However, relugolix CT is also more effective, with an incremental QALY gain of 0.364 QALYs. Goserelin monthly is the least expensive treatment and dominates all GnRH agonist comparators, as it achieves the same QALYs at lower cost. The ICER for relugolix CT vs. Goserelin monthly is £5,796 per QALY. This lies below the NICE cost-effectiveness threshold of £20,000 to £30,000 per QALY.

Table 2 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,742	21.525	16.530	-	-	-	-
Triptorelin 3-monthly	7,797	21.525	16.530	55	0.000	0.000	Dominated
Triptorelin monthly	7,799	21.525	16.530	57	0.000	0.000	Dominated
Leuprorelin monthly	7,871	21.525	16.530	129	0.000	0.000	Dominated
Leuprorelin 3-monthly	7,947	21.525	16.530	205	0.000	0.000	Dominated
Goserelin 3-monthly	8,002	21.525	16.530	260	0.000	0.000	Dominated
Relugolix CT	9,854	21.525	16.894	2,112	0.000	0.364	5,796
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

B.3.8 Sensitivity analyses

Probabilistic sensitivity analysis

Output from the PSA iterations is presented as scatter points on the cost-effectiveness plane in Figure 1. All points lie in the northeast quadrants of the plane, indicating that relugolix CT is more costly and more effective compared to GnRH agonists. The cost-effectiveness acceptability curve (Figure 2) shows that the probability of relugolix CT being cost-effective increases at willingness to pay (WTP) thresholds of approximately £5,000 and above. The probability of cost-effectiveness for relugolix reaches 100% at a willingness to pay (WTP) of £8,800 per QALY and remains at 100% at higher thresholds. When compared against the NICE cost-effectiveness threshold (£20,000 to £30,000 per QALY), the probability of cost-effectiveness for relugolix CT is thus 100%.

The probabilistic cost-effectiveness results are reported in Table 3. The results reiterate the base-case results, as relugolix CT remains slightly more costly compared to the GnRH agonists comparators (incremental costs ranging from £1,862 to £2,120), but it is also more effective with an incremental QALY gain of 0.365 QALYs, as in the model base-case. The probabilistic ICER for relugolix CT vs. goserelin monthly (£5,808 per QALY) lies very closely to the base-case ICER (£5,796 per QALY).

Figure 1 Cost-effectiveness plane

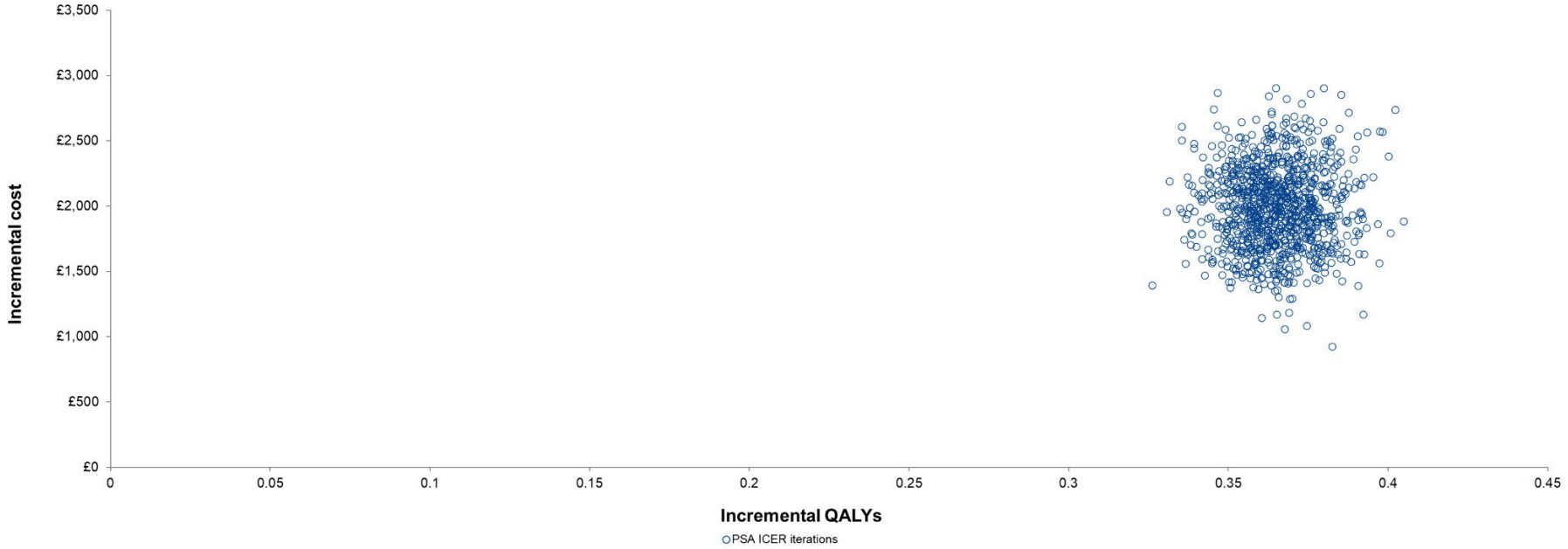


Figure 2 Cost-effectiveness acceptability curve, relugolix CT vs. comparators

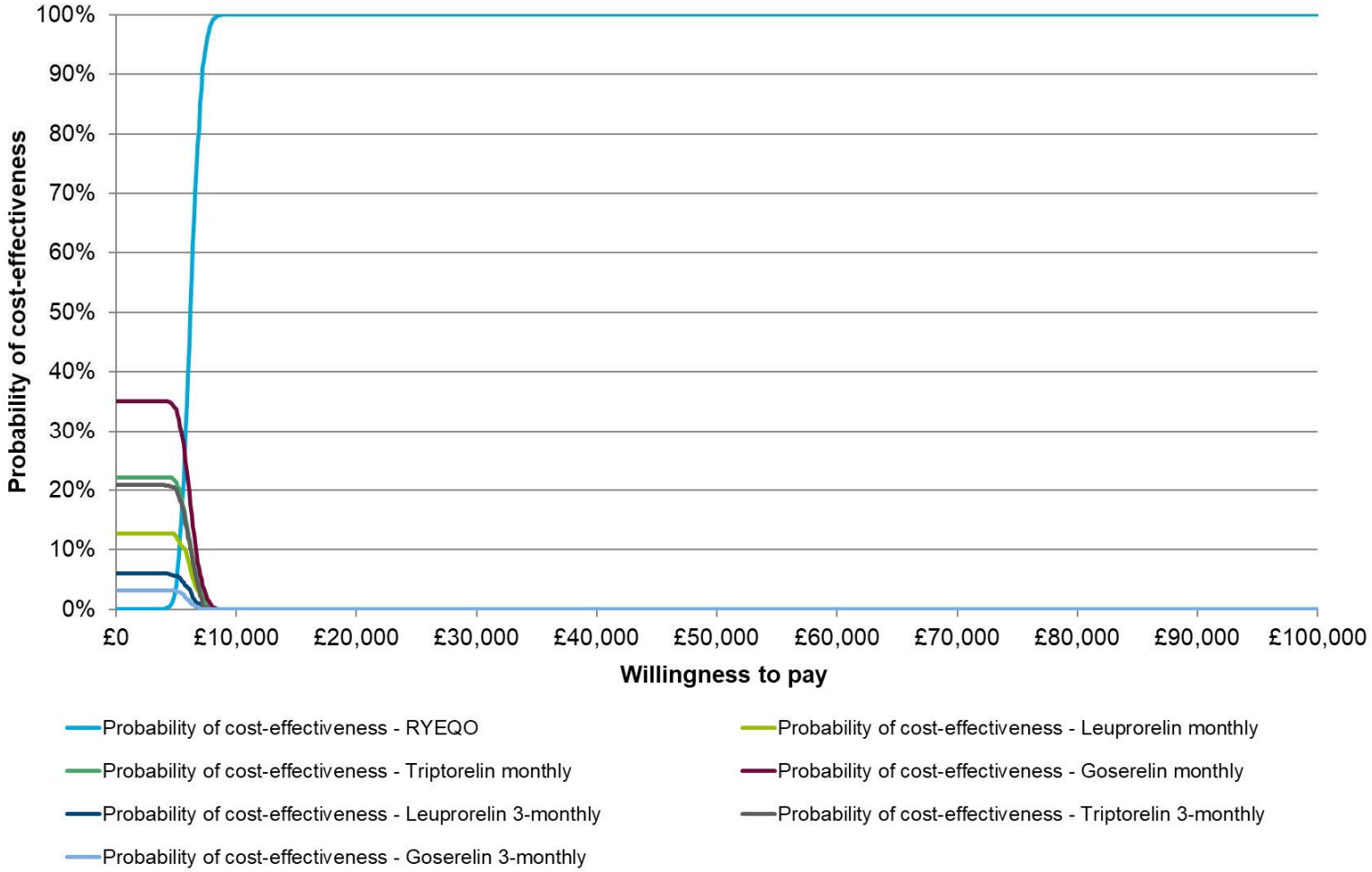


Table 3 Probabilistic cost-effectiveness results

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Goserelin monthly	7,729	16.529	-	-	-
Triptorelin 3-monthly	7,774	16.529	45	0.000	Dominated
Triptorelin monthly	7,791	16.529	62	0.000	Dominated
Leuprorelin monthly	7,857	16.529	128	0.000	Dominated
Leuprorelin 3-monthly	7,927	16.529	197	0.000	Dominated
Goserelin 3-monthly	7,988	16.529	258	0.000	Dominated
Relugolix CT	9,850	16.894	2,120	0.365	5,808

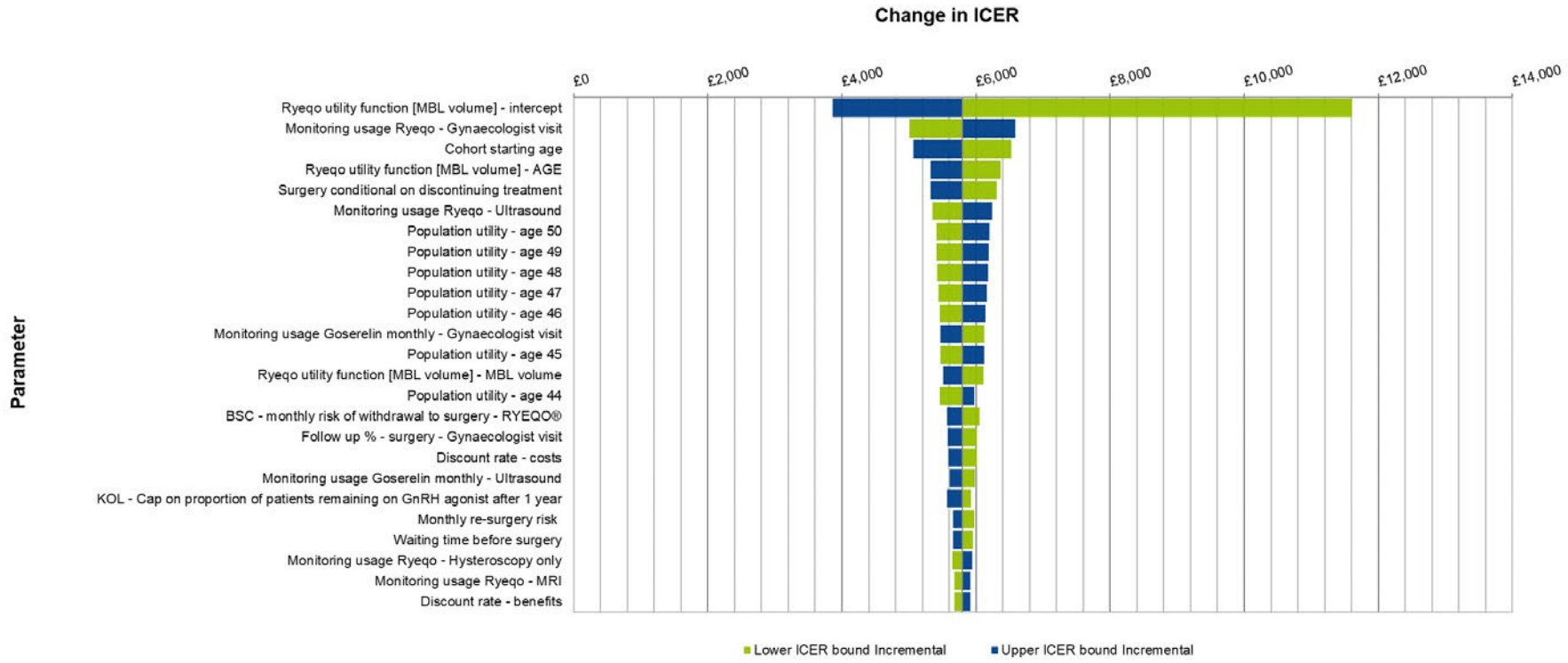
Deterministic sensitivity analysis

The results of the one-way deterministic sensitivity analyses are presented in the tornado diagram (Figure 3) where each parameter (y axis) is ranked (highest to lowest) by its impact on the model result. Only the 20 parameters that had the largest impact on the results are included in the tornado diagrams. The results show that the parameter that had the most sizeable impact upon the ICER when varied was the intercept term of the regression model applied in the utility algorithm for relugolix CT. Other parameters that have the most sizeable impact upon the ICER when varied are the frequency of gynaecologist monitoring appointments for relugolix CT patients, baseline age and the age parameter in the regression model used in the utility algorithm. The parameters that had the least impact on the ICER when varied in the OWSA were the HRU frequencies for DEXA scans in the GnRH agonist arm and GP visits for BSC patients, as well as the KOL-predicted proportion of patients remaining on GnRH agonists beyond 6 months.

Table 4 OWSA results, relugolix CT vs. goserelin monthly

Parameter	Lower bound ICER	Upper bound ICER	Difference
Ryeqo utility function [MBL volume] - intercept	£11,612	£3,862	£7,750
Monitoring usage Ryeqo - Gynaecologist visit	£5,008	£6,584	£1,576
Cohort starting age	£6,528	£5,067	£1,460
Ryeqo utility function [MBL volume] - AGE	£6,366	£5,320	£1,046
Surgery conditional on discontinuing treatment	£6,312	£5,320	£992
Monitoring usage Ryeqo - Ultrasound	£5,350	£6,242	£891
Population utility - age 50	£5,409	£6,196	£787
Population utility - age 49	£5,414	£6,190	£776
Population utility - age 48	£5,423	£6,179	£756
Population utility - age 47	£5,438	£6,162	£723
Population utility - age 46	£5,456	£6,142	£686
Monitoring usage Goserelin monthly - Gynaecologist visit	£6,123	£5,468	£655
Population utility - age 45	£5,473	£6,122	£648
Ryeqo utility function [MBL volume] - MBL volume	£6,110	£5,513	£597
Population utility - age 44	£5,461	£5,975	£514
BSC - monthly risk of withdrawal to surgery - RYEQO®	£6,052	£5,572	£480
Follow up % - surgery - Gynaecologist visit	£6,010	£5,582	£427
Discount rate - costs	£6,011	£5,591	£420
Monitoring usage Goserelin monthly - Ultrasound	£5,981	£5,611	£370
KOL - Cap on proportion of patients remaining on GnRH agonist after 1 year	£5,924	£5,568	£357
Monthly re-surgery risk	£5,977	£5,656	£321
Waiting time before surgery	£5,954	£5,654	£300
Monitoring usage Ryeqo - Hysteroscopy only	£5,652	£5,940	£288
Monitoring usage Ryeqo - MRI	£5,678	£5,914	£236
Discount rate - benefits	£5,681	£5,911	£230
Monitoring usage BSC - Ultrasound	£5,906	£5,686	£220
Concomitant med units/month - Ryeqo - NSAID 200mg tablet	£5,687	£5,905	£218
Monitoring usage BSC - GP visit	£5,901	£5,691	£210
KOL - Cap on proportion of patients remaining on GnRH agonist after 6 months	£5,940	£5,796	£144
Monitoring usage Goserelin monthly - DEXA scan	£5,867	£5,725	£143

Figure 3 Tornado diagram, relugolix CT vs. goserelin monthly



Scenario analysis

The sensitivity of the model results to changes in key assumptions or parameters underpinning the model base-case was examined through several scenario analyses. The scenarios analyses results are presented below, with pairwise ICERs presented for relugolix CT vs. the least costly short-acting and long-acting GnRH agonist comparators respectively (goserelin monthly and triptorelin 3-monthly). The ICERs estimated in each of the scenario analyses lie closely to the base-case ICERs, as they are typically in the range of £5,500 to £9,000 per QALY, compared to the base-case ICER of £5,796 per QALY against goserelin monthly. None of the scenarios resulted in ICERs above £20,000 per QALY. The scenario that had the largest impact upon the ICERs was the scenario where the surgery health states were removed.

GnRH plus HRT dose intensity was reduced to 50%. This is a proxy for assuming that treatment breaks are taken for those on GnRH, with a 50% reduction in GnRH plus add back costs but no reduction in efficacy. ICERs for relugolix CT vs. goserelin monthly and triptorelin 3-monthly were £16,414 and £16,255 per QALY respectively. Other scenarios that had the most impact upon the ICERs were applying a fixed maximum duration of 6 months for GnRH agonist, excluding surgery health states and reducing the waiting time before surgery from 15 months in the base-case to 6 months. Under this scenario, no patients can transition to surgery, therefore the additional benefit with relugolix CT, where less patients transition to surgery, is no longer captured within the model. This reduces the incremental QALYs from 0.364 in the base-case to 0.194 QALYs. There is also an increase in incremental costs as patients remain on pharmacological treatment for a longer duration. The increase in costs coupled with the reduction in QALYs results in increased ICERs of £15,798 and £15,516 per QALY vs. goserelin monthly and triptorelin 3-monthly respectively.

Other scenarios that had the most sizeable impact upon the ICER were a reduction in the waiting time to surgery to 6 months and reducing the GnRH agonist and HRT density from 100% to 50%. Reducing the waiting time before surgery to 6 months reduced the incremental QALYs from 0.364 in the base-case to 0.223 QALYs. This resulted in increased ICERs of £8,947 and £8,700 per QALY vs. goserelin monthly and triptorelin 3-monthly respectively. Reducing the GnRH and HRT dose intensity

from 100% to 50% is a proxy for assuming that treatment breaks are taken for those on GnRH, with a 50% reduction in GnRH plus add back costs but no reduction in efficacy. The incremental costs for relugolix CT thus increase, leading to increased ICERs of £8,409 and £8,331 per QALY for relugolix CT vs. goserelin monthly and triptorelin 3-monthly respectively.

Table 5 Results of scenario analyses

Structural assumption	Base-case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER vs. relugolix CT
Base-case			**Goserelin monthly**	**£2,112**	**0.364**	**£5,796**
			Triptorelin 3-monthly	**£2,057**	**0.364**	**£5,645**
Modelling of treatment withdrawal in GnRH agonist arm	Withdrawal rates estimated from GnRH agonist arm of PEARL II for the first 6 months and from KOL expert opinion after the first 6 months	Withdrawal for GnRH agonist assumed equal to the modelled withdrawal rates for relugolix CT for the first 6 months of treatment and from KOL expert opinion after the first 6 months	Goserelin monthly	£2,067	0.362	£5,706
			Triptorelin 3-monthly	£2,013	0.362	£5,556
Modelling of adverse events	Adverse events for relugolix CT informed by LIBERTY studies. Adverse events for GnRH agonist informed by PEARL II	Assume identical adverse event profile for relugolix CT and GnRH agonists	Goserelin monthly	£2,116	0.354	£5,982
			Triptorelin 3-monthly	£2,061	0.354	£5,827
MBL volume input for utility algorithm	MBL volume for GnRH agonists derived from ITC	Mean MBL in the GnRH agonist arms assumed the same as relugolix CT for the utility algorithm	Goserelin monthly	£2,112	0.340	£6,212
			Triptorelin 3-monthly	£2,057	0.340	£6,050
Concomitant medication usage	Informed by proportions in LIBERTY 3 for relugolix CT arm and PEARL II for GnRH agonist arm	Assumed equal for relugolix CT and GnRH agonist arms	Goserelin monthly	£2,052	0.364	£5,632
			Triptorelin 3-monthly	£1,995	0.364	£5,475
Induction period of short-acting GnRH agonist required before	Yes	No	Goserelin monthly	£2,112	0.364	£5,796
			Triptorelin 3-monthly	£2,177	0.364	£5,974

receiving long-acting GnRH agonist						
Duration of short-acting GnRH agonist required before receiving long-acting GnRH agonist	3 months	1 month	Goserelin monthly	£2,112	0.364	£5,796
			Triptorelin 3-monthly	£2,062	0.364	£5,659
Inclusion of surgery health states	Included	Excluded	Goserelin monthly	£3,070	0.194	£15,798
			Triptorelin 3-monthly	£3,016	0.194	£15,516
Referral to surgery upon discontinuation of treatment	No referrals within 5 years of menopause	Referrals possible up until menopause (51 years of age)	Goserelin monthly	£2,203	0.344	£6,403
			Triptorelin 3-monthly	£2,148	0.344	£6,243
Waiting time before surgery	15 months	6 months	Goserelin monthly	£1,993	0.223	£8,947
			Triptorelin 3-monthly	£1,938	0.223	£8,700
Waiting time before surgery	15 months	12 months	Goserelin monthly	£2,099	0.353	£5,954
			Triptorelin 3-monthly	£2,044	0.353	£5,798
GnRH agonist and HRT dose intensity	100%	50%	Goserelin monthly	£3,064	0.364	£8,409
			Triptorelin 3-monthly	£3,036	0.364	£8,331
Add-back therapy costs and effect on AEs for GnRH agonist	Included	Excluded	Goserelin monthly	£2,288	0.380	£6,019
			Triptorelin 3-monthly	£2,233	0.380	£5,875
GnRH agonist treatment duration and inclusion of add-back therapy	Cap on % remaining on treatment at multiple periods based on KOL opinion; add-back therapy included	Fixed maximum duration of 6 months as per SmPC, add-back therapy costs and effect on AEs excluded	Goserelin monthly	£3,362	0.497	£6,766
			Triptorelin 3-monthly	£3,354	0.497	£6,749
GnRH agonist treatment duration (including add-back)	Cap on % remaining on treatment at multiple periods based on KOL opinion	Fixed maximum duration of 12 months; PEARL II withdrawal rates applied throughout	Goserelin monthly	£2,960	0.488	£6,070
			Triptorelin 3-monthly	£2,949	0.488	£6,047

Summary of sensitivity analyses results

The results of sensitivity analysis show the probability of relugolix CT being cost-effective at a WTP threshold of £20,000 to £30,000 per QALY is 100%. In all iterations of the probabilistic analysis, relugolix CT was more costly than GnRH agonists but relugolix CT also accrued more QALYs than GnRH agonists. The ICERs for relugolix CT vs. GnRH agonists increase when certain assumptions are varied, however none of these scenarios increase the ICER above £20,000 per QALY.

K1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

The disaggregated results of the base-case incremental cost-effectiveness analysis for relugolix CT vs. each individual GnRH agonist comparator are presented in the tables below. For costs, results are only presented versus the least costly GnRH agonist.

Table 6 Summary of QALY gain by health state

Health state	QALY Relugolix CT	QALY GnRH agonists	Increment	Absolute increment	% absolute increment
On treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Waiting for surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Menopause	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life year; HS1, health state 1; HS2, health state 2

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 7 Summary of costs by health state, relugolix CT vs. Goserelin monthly

Health state	Cost relugolix CT	Cost Goserelin monthly	Increment	Absolute increment	% absolute increment
On treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HS1, health state 1; HS2, health state 2

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 8 Summary of predicted resource use by category of cost, relugolix CT vs. Goserelin monthly

Item	Cost relugolix CT	Cost Goserelin monthly	Increment	Absolute increment	% absolute increment
Drug acquisition and administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC drug acquisition administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC AE cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Surgery-related adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-surgery surveillance, hysterectomy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-surgery surveillance, other surgeries	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: Tech, technology; treat, treatment; admin, administration; mon, monitoring					

PEARL I and PEARL II menstrual blood loss results by visits

Table 1 PEARL I summary of PBAC Part A (ITT Population)

		Placebo (N=48)		PEARL I UPA 5 mg (N=95)	
Visit		**Actual**	**CFB**	**Actual**	**CFB**
Inclusion	N	48		95	
(Days 1-8)	Mean	446.00		466.64	
	SD	277.28		306.09	
	Median	376.00		366.00	
	Min, Max	119.0, 1284.0		118.0, 1645.0	
Baseline	N	48		95	
	Mean	459.81		487.44	
	SD	292.80		319.89	
	Median	376.00		386.00	
	Min, Max	119.0, 1284.0		118.0, 1645.0	
Week 5*	N	48	48	94	94
	Mean	508.69	48.88	461.39	-13.74
	SD	397.14	339.39	347.78	289.12
	Median	388.00	46.00	315.50	-22.50
	Min, Max	12.0, 2163.0	-1218.0, 879.0	8.0, 1401.0	-986.0, 1021.0
Week 9	N	48	48	93	93
	Mean	424.42	-35.40	73.42	-401.65
	SD	368.47	327.82	193.82	310.25
	Median	321.50	-34.00	0.00	-333.00
	Min, Max	0.0, 1641.0	-1230.0, 720.0	0.0, 1070.0	-1238.0, 386.0
Week 9 LOCF	N	48	48	94	94
	Mean	424.42	-35.40	85.46	-389.67
	SD	368.47	327.82	225.36	329.70
	Median	321.50	-34.00	0.00	-327.00
	Min, Max	0.0, 1641.0	-1230.0, 720.0	0.0, 1205.0	-1238.0, 724.0
Week 13	N	36	36	82	82
	Mean	350.67	-119.67	36.27	-435.71
	SD	290.17	302.85	144.79	302.70
	Median	309.50	-54.50	0.00	-328.50
	Min, Max	0.0, 1206.0	-1230.0, 409.0	0.0, 1007.0	-1238.0, 13.0
Week 13 LOCF	N	48	48	94	94
	Mean	348.04	-111.77	60.91	-414.21
	SD	268.30	282.83	206.87	324.50
	Median	336.00	-59.00	0.00	-328.50

Source: PEARL I CSR

* Week 5 PBAC scores covers the period of the first menstrual cycle at treatment start
Abbreviations: CFB: changes from baseline; LOCF=Last observation carried forward; SD: standard deviation; UPA: ulipristal acetate

Table 2 PEARL II summary of PBAC Part A (Per protocol population)

		UPA 5mg (N=93)		GnRH-agonist (N=93)	
Visit		**Actual**	**CFB**	**Actual**	**CFB**
Inclusion	N	93		93	
(Days 1-8)	Mean	357.77		391.66	
	SD	273.61		329.79	
	Median	275.00		288.00	
	Min, Max	109.0, 1960.0		102.0, 2104.0	
Baseline	N	93		93	
	Mean	378.92		404.22	
	SD	301.31		338.61	
	Median	286.00		297.00	
	Min, Max	109.0, 1984.0		102.0, 2104.0	
Week 5*	N	93	93	92	92
	Mean	321.13	-57.80	479.57	73.91
	SD	197.51	231.09	455.68	292.58
	Median	275.00	-23.00	331.00	33.00
	Min, Max	0.0, 827.0	-1293.0, 476.0	33.0, 2640.0	-824.0, 1432.0
Week 9	N	93	93	92	92
	Mean	19.71	-359.22	30.12	-375.54
	SD	64.68	305.49	84.31	338.46
	Median	0.00	-278.00	0.00	-269.00
	Min, Max	0.0, 425.0	-1984.0, 58.0	0.0, 521.0	-2104.0, -98.0
Week 9 LOCF	N	93	93	92	92
	Mean	19.71	-359.22	30.12	-375.54
	SD	64.68	305.49	84.31	338.46
	Median	0.00	-278.00	0.00	-269.00
	Min, Max	0.0, 425.0	-1984.0, 58.0	0.0, 521.0	-2104.0, -98.0
Week 13	N	90	90	90	90
	Mean	26.57	-348.49	41.67	-363.10
	SD	92.96	311.48	132.12	342.20
	Median	0.00	-268.50	0.00	-268.00
	Min, Max	0.0, 625.0	-1981.0, 267.0	0.0, 687.0	-2104.0, 204.0
Week 13 LOCF	N	93	93	92	92
	Mean	36.89	-342.03	42.04	-363.62
	SD	131.95	312.68	130.97	338.68
	Median	0.00	-268.00	0.00	-273.50
	Min, Max	0.0, 944.0	-1981.0, 267.0	0.0, 687.0	-2104.0, 204.0
	N	93	93	92	92

Last 28 Days Under Treatment	Mean	32.74	-346.18	37.77	-367.89
	SD	125.24	313.54	123.11	341.48

Source: PEARL II CSR
* Week 5 PBAC scores covers the period of the first menstrual cycle at treatment start
Abbreviations: CFB: changes from baseline; LOCF=Last observation carried forward; SD: standard deviation; UPA: ulipristal acetate

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

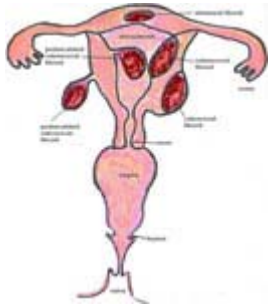
About you	
1.Your name	[redacted]

2. Name of organisation	FEmISA – Fibroid Embolisation, Information, Support & Advice
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	FEmISA was set up by women whose fibroids were successfully treated by embolisation (sometimes referred to as UAE or UFE). Many of us were keen to avoid hysterectomy and we want to ensure that other women have access to embolisation for the treatment of uterine fibroids by: - • informing potential patients/women and GPs and gynaecologists about embolisation and its benefits • promoting embolisation as the treatment for uterine fibroids supporting women with fibroids • helping and lobbying to ensure that all women have access to this treatment FEmISA is a UK based not-for-profit organisation. It is run by volunteers and funded by group members. FEmISA does not receive any financial support through advertising, nor benefit from free website hosting or similar sponsorship.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	No

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	From personal experience of FEmISA members, surveys, contacts via our web site, feedback from clinicians including GPs, interventional radiologists and gynaecologists. FEmISA has carried out a significant amount of research on published clinical papers and meta-analysis of results together with the experiences of women. We have taken part in NICE interventional procedures review of uterine artery/fibroid embolisation [UAE/UFE] where we submitted, reviewed, analysed and appraised 200 clinical papers that NICE had missed and helped overturn NICE's original intention, so that UAE/UFE was declared safe and effective enough for routine patient use. FEmISA has also taken part in the first Clinical Guidelines on Heavy Menstrual Bleeding [HMB][CG44] Published: 24 January 2007, which we supported as it made great progress for women making diagnosis and treatments for HMB and fibroids, safer, less invasive and preserving women's fertility. It banned removal of healthy ovaries and hysterectomy was not a first line treatment for HMB. FEmISA also contributed significantly to a review of these guidelines HMB Clinical Guidelines Review 2018 NG88 which we do not support. It reversed all the progress and safeguarding for women made in the previous version. It increases mortality and morbidity and pain for women as well as significantly

	escalating costs for the NHS. It promoted the interests of gynaecologists in self-referral for diagnosis – hysteroscopy instead of ultrasound as a first line diagnosis, it allowed removal of healthy ovaries and made hysterectomy a first line treatment, at great expense of women's health. In addition, the co-ordinator has spoken at NHS and health conferences, including some for NHS Improvements with Sir Bruce Keogh.
Living with the condition	
6. What is it like to live with the condition? ~~What do carers experience when caring for someone with the condition?~~	Women with symptomatic fibroids do not normally have carers and often struggle on alone without any support**.** As they normally occur at working age it can be particularly stressful combining a job and family life with struggling with the significant impact of fibroid symptoms. **Incidence** Uterine fibroids or leiomyomata are the commonest benign tumours in women of reproductive age having an incidence of up to 80% at post-mortem. [40],[41] The peak incidence occurs between 35 and 40 years old. [42] There is a higher incidence in nulliparous women, Afro-Caribbean women and the obese. There is a lower incidence in those on the contraceptive pill and those who smoke. [42],[43] The aetiology is not known, but thought to be associated with oestrogen and progesterone since fibroids appear in women of reproductive age and can reduce after menopause. [42],[43] The very high incidence of symptomatic fibroids makes their treatment a significant resource and health issue.

Pathology



Fibroids can be classified according to their position:

- **Subserosal**. Symptoms include compression on the surrounding tissues, such as the bladder and bowel pain
- **Intramural**. Symptoms include pressure on the bladder and / or uterus and infertility or miscarriage and menorrhagia
- **Submucosal**. Symptoms include menorrhagia, pain and infertility. [42],[43]

They can also be pedunculated, or non-pedunculated. Women can have a mixture of types of fibroid.

Symptoms

Approximately 25% of women with fibroids have symptoms. These vary with the position, type of fibroid and size. It can be extremely debilitating and make normal life very difficult, especially trying to ignore the

	symptoms while working hard in a career. Fibroids and heavy menstrual bleeding and other symptoms do not involve carers. Women have to struggle on with the symptoms by themselves For younger women fibroids can be a cause of infertility and this is particularly true for Afro-Caribbean and darker skinned women who have fibroids younger, some in their 20s and 30s. The first port of call is the GP, when symptoms get too bad. Some are sympathetic, but others don't even examine patients, saying it is one of the joys of getting older. Common symptoms are: - • Menorrhagia – heavy menstrual bleeding • Iron deficiency anaemia – some women contacting FEmISA have been admitted to A&E as left untreated this has caused fainting • Dysmenorrhea – painful periods • Bladder incontinence/urgency • Infertility or miscarriage • Pressure symptoms on the bowel leading to constipation • Pressure symptoms on the ureters, bladder and/or kidneys sometimes leading to enlarged kidneys • Back pain and sciatica • Abdominal swelling, as in pregnancy • Indigestion, discomfort sitting, etc., as in pregnancy • Dyspareunia • Dyspnoea • Varicose veins and haemorrhoids [42],[43]

- Migraine

Please see the patient stories on our web site –

Zoe - http://www.femisa.org.uk/index.php/zoe

Marianne - http://www.femisa.org.uk/index.php/marianne

Yvonne - http://www.femisa.org.uk/index.php/yvonne

Ginette - http://www.femisa.org.uk/index.php/ginette

HMB and fibroids affect women of working age and it is therefore important that the treatment is not prolonged and they get back to normal life and work as quickly as possible. This is particularly true for the NHS itself which employs a large number of women. Neither NICE nor the NHS measures or monitors the time to return to work/normal life, which is so important to patients and their families of all sexes. In general, women have to work harder to reach senior positions, although this is improving over time and also still bear most of the family and home responsibilities as well.

References –

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Current treatment of the condition in the NHS	
7. What do patients ~~or carers~~ think of current treatments and care available on the NHS?	**Current Treatments for Fibroids** FEmISA has prepared a comparison table of GNRH drugs, Esyma, hysterectomy, myomectomy and uterine artery/fibroid embolisation [UFE] which is copied at the end of this section. **Temporary – Short-Term Treatments -Medicines** There are two main classes of medicines to give temporary relief to symptomatic fibroids – Hormonal treatments and non-hormonal treatments as listed in the original NICE HMB Guidelines CG44 and their main side effects are listed on page 47. (https://www.nice.org.uk/guidance/ng88/evidence/full-guideline-pdf-4782291810) They can control menorrhagia and some dysmenorrhea, but are unlikely to reduce other symptoms or large fibroids. Most are not licensed to treat fibroids. **Hormone treatments** • Intrauterine levonorgestrel-releasing systems (LNG-IUS) the Mirena Coil - This product is licensed for Contraception and Idiopathic menorrhagia ***not*** *for the treatment of symptomatic fibroids*. It must be replaced within 5 -years. The insertion of this device is **extremely painful to women**, and has some mortality,but they are not offered analgesia. This puts women off from having it and from having it replaced. It must be inserted by a suitably qualified and trained clinician. Uterine rupture has been reported at the time of insertion. Women are infertile while it is inserted and suffer menopausal symptoms including – mood swings and psychological disorders and reduction in libido.

	"*Very common undesirable effects (occurring in more than 10% of users) include uterine/vaginal bleeding including spotting, oligomenorrhoea, amenorrhoea (see section 5.1)*." *The frequency of benign ovarian cysts depends on the diagnostic method used (see section 4.4) but has been estimated from clinical trial data to occur in 7% of users."* More are listed in the SPC - Electronic Medicines Compendium SPC https://www.medicines.org.uk/emc/product/1132 • Combined oral contraceptives These are not licensed for fibroid treatments, but can be used to make periods regular and reduce HMB. • Oral progestogens • Injected/depot progestogens These are not licensed for fibroid treatments, but can be used to make periods regular and reduce HMB • Other hormonal treatments for HMB • Hormone replacement therapy (HRT) • Gonadotrophin-releasing hormone analogues fibroids These medicines block oestrogen (and testosterone in men) production and put women into immediate 'chemical castration' – the menopause with all the very unpleasant side effects of menopausal symptoms. Many gynaecologists refuse to prescribe them as their menopausal side effects are unacceptable to women. They cannot be given orally and are administered by injection or implants. They are licensed to treat fibroids prior to surgery i.e., short-term. Zoladex is a commonly used GNRH antagonist. The special warnings and undesirable effects are listed in the SPC but for women include o Loss of bone density o Loss of libido o Clinical Depression o Hypertension o Pituitary tumours o Mood swings

- Psychotic disorders
- Paraesthesia
- Hot flushes
- Dry vagina making intercourse painful

A common and very concerning menopausal symptom is loss of intellect/memory and this is not widely reported, but of great significance to women. The question of whether this might be another very undesirable effect is questioned. A full list of side effects are included in the SPC - https://www.medicines.org.uk/emc/product/1543/smpc

There is a strong concern about liver toxicity – "LiverTox: Clinical and Research Information on Drug-Induced Liver Injury - Gonadotropin Releasing Hormone (GnRH) Analogues" – "*Common side effects of the GnRH agonists and antagonists include symptoms of hypogonadism such as hot flashes, gynecomastia, fatigue, weight gain, fluid retention, erectile dysfunction and decreased libido. Long term therapy can result in metabolic abnormalities, weight gain, worsening of diabetes and osteoporosis*." - https://www.ncbi.nlm.nih.gov/books/NBK547863/

- A newer medicine - ulipristal acetate (Esmya)
  This medicine is a GNRH antagonist and licensed for the treatment of fibroids. Unlike other GNRH antagonists it is given orally in tablet form. In a higher dosage form it is used as the morning after pill. Like other medicines in this category, it causes undesirable menopausal symptoms, although the manufacturer claims that these are less severe than other drugs. The SPC can be found here - https://www.medicines.org.uk/emc/product/3951/smpc However, of more concern than menopausal effects is its affect on liver function. This drug was withdrawn from sale while serious cases of liver failure were investigated see letter - https://www.medicines.org.uk/emc/dhpc/1714/Document
  The medicine was re-introduced in January '21 but with certain restrictions - https://www.medicines.org.uk/emc/dhpc/2004/Document

Non-hormonal pharmaceutical treatments for HMB

- Tranexamic acid
  This is licensed for the treatment of Menorrhagia but the BNF advises – *"Before initiating treatment for menorrhagia, exclude structural or histological causes or fibroids causing distortion of uterine cavity."* This therefore should not be used until a proper diagnosis has been carried out and it is not licensed for the treatment of fibroids and is unlikely to treat any other fibroid symptoms. A link to the SPC lists side effects - https://www.medicines.org.uk/emc/product/2359/smpc
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Etamsylat

Long -Term/Permanent/Semi-Permanent Treatments for Fibroids

Most in-hospital treatments for fibroids, particularly the older ones, have never been formally reviewed for safety or efficacy and it is doubtful if this were to happen that they would continue to be widely available and meet modern standards for safe and effective treatment.

The in-hospital treatments for symptomatic fibroids available –

Those with **no** formal review of safety and efficacy

- Hysterectomy
  Hysterectomy is one of the commonest women's procedures in the NHS and private sector. Over 38,000 hysterectomies are carried out in the NHS in England [HES data] alone each year, with the highest proportion, over 80% being the most invasive abdominal hysterectomy. Hysterectomy is also the commonest procedure in the private sector after joint replacement. Hysterectomy has never been formally reviewed for safety and efficacy as other procedures have. The first hysterectomy was recorded in 1843 when the woman died and it was not until 1853 that a woman managed to survive this operation. Over 180 women die in the NHS in England alone within 3 months of hysterectomy each year [mortality rate 0.6% HES & ONS mortality data] and over 2,000 suffer serious complications. It was not until the VALUE study was published in 2002 [Maresh et al] an audit of outcomes of hysterectomy that the high morbidity rates for hysterectomy were revealed. Even after this publication the safety of hysterectomy has not be formally reviewed and

	has even been recommended as a first line treatment for HMB, in the latest NICE HMB guidelines NG88, which FEmISA condemns. Hysterectomy renders a woman infertile. Her uterus is removed and, in many cases, so are most or all of her reproductive organs, including after recent NICE Clinical Guidelines on HMB, healthy ovaries. Very concerningly there has been **little if any research on sexual dysfunction after hysterectomy.** It is well documented that hysterectomy triggers pre-mature menopause and the Million Women Study showed hysterectomy was the commonest reason for early HRT. Menopause is linked to lack of libido, but women's reproductive organs also play an important part in the enjoyment of sex and orgasm. In fact, it must be questioned how a woman can have a full orgasm when her reproductive organs have been removed. Hysterectomy has a high morbidity rate, with serious complications. The full list of complications and risks are rarely shared with patients. The recent Cumberledge Review of Mesh has shown the considerable suffering of many women after surgical mesh was used to treat prolapse. Prolapse of the uterus is one of the many complications of hysterectomy, previously treated with surgical mesh. **Side effects and safety** The most serious side effects arise because hysterectomy is such an invasive procedure. Urinary tract infection (from the bladder to the kidneys) occurs in 3.3% to 25% of women and wound infections in 25%. Deep vein thrombosis (DVT) occurs in approximately 15-18% of patients having gynae surgery. This is a serious complication where a blood clot occurs in the leg (usually) due to the surgery and subsequent inactivity. This blood clot can move to the heart and lungs causing a potentially fatal pulmonary embolism. Surgical damage can occur to the bladder (1.1-1.7%) resulting in incontinence in some. It can also occur in the urinary tract (0.1-1.7%) and the bowel (gut) (0.5-5%). This kind of damage can have long-term side effects. Surgical damage to the bowel can lead to serious infection. There can also be surgical damage to the nerves supplying the vagina, which will affect the woman's enjoyment of sex considerably.

The overall surgical complication rate is 9-16%. ***Please see the comparison table for more detailed information.***

- Myomectomy
  This is the surgical removal of the fibroid(s) alone, normally only offered to younger women, wishing to preserve their fertility, although many older women also wish to do so. This procedure has never been formally reviewed for safety and efficacy and there is little information on the morbidity and mortality associated with this procedure. This is unacceptable. Fibroids can and do regrow after myomectomy and there is a high incidence of adhesions requiring surgical intervention – ***see comparison table***.

  FEmISA has written a clinical article in support of the FEMME trial comparing UFE and myomectomy on fertility, in which many gynaecologists refused to take part – http://www.femisa.org.uk/images/women%20need%20femme%20-%20article%20from%20femisa%202014.pdf

- Therapeutic Hysteroscopy
  This was introduced as a first line diagnosis in the NICE HMB review, instead of ultrasound, although it has never been reviewed for safety and efficacy.

  This procedure is performed as an outpatient procedure, but is extremely controversial as it is very painful and no analgesia is offered. The morbidity and mortality rates are unacceptably high. 180 women a year die in the NHS in England from hysteroscopy and a further 3,000 women suffer serious complications. If hysteroscopy is to be used as a first line hospital diagnosis these deaths and serious complications could double or triple to over 500 deaths and over 8,000 serious complications each year. Ultrasound and MRI are much safer, cheaper and quicker and visualise the whole abdomen. Hysteroscopy can be used therapeutically to remove some small fibroids.

[1] NHS – HES ONS hospital mortality data
[1] The incidence of fluid overload - 1.6% and 2.5% (Agostini A 2002a; Overton 1997), uterine perforation is 0.014%, and infectious complications account for 0.3% to 1.6% of cases (Bradley 2002) average 3.14%
[iii]

Hysteroscopy	No. Procedures p.a. [HES]	Mortality @ 90 days [i]	Mortality Rate [i]	No. Serious Complications - rate 3.14% [ii]
Current				
Diagnostic	55,377	148	0.3%	1,739
Therapeutic	31,573	32	0.1%	991
Total	86,950	**180**		**2,956**
Projected x 2				
Diagnostic	110,754	296	0.3%	3,478
Therapeutic	63,146	64	0.1%	2,147
Total	173,900	**360**		**5,913**
Projected x 3				
Diagnostic	166,131	444	0.3%	5,648
Therapeutic	94,719	128	0.1%	3,220
Total	260,850	**572**		**8,869**

- Endometrial Ablation for Fibroids >3cm
  The new HMB Guidelines NG88 recommend endometrial ablation should be used to treat fibroids >3cm, when this has only been formally assessed for safety and efficacy for small fibroids <3cm. Fertility status after this procedure is unknown.

Treatments for Symptomatic Fibroids with a formal review of safety and efficacy

- Uterine Artery/Fibroid Embolisation
  [UAE/UFE] – is newer treatment performed by Interventional Radiologists since 1980s. It has been formally, positively reviewed by NICE for safety and efficacy - Interventional procedures guidance [IPG367] Published: 24 November 2010 - https://www.nice.org.uk/Guidance/IPG367 It is minimally invasive and has a very low mortality rate – no reported deaths at all in recent years. A woman retains her fertility. The hospital stay is overnight and the return to work much sooner than hysterectomy or myomectomy. (unlike hysterectomy and myomectomy) - ***see comparison table***

- Endometrial Ablation for fibroids <3cm
  This has been formally reviewed by NICE, but does not preserve fertility. Fluid-filled thermal balloon and microwave endometrial ablation techniques for heavy menstrual bleeding Technology appraisal guidance [TA78] Published: 28 April 2004 - https://www.nice.org.uk/guidance/ta78

- MRI Focused Ultrasound
  This is an Interventional Radiology minimally invasive treatment reviewed positively by NICE for safety and efficacy. Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids Interventional procedures guidance [IPG413]Published: 23 November 2011 - https://www.nice.org.uk/guidance/ipg413 This is only available at a few hospitals in England.

COMPARISON OF FIBROID TREATMENTS - UPDATED 6.21

	Drugs	Esmya (Ulipristal acetate)	Hysterectomy	Myomectomy	Embolisation

		SAFETY				
	Formal Safety Review	All medicines are licensed by MHRA for safety and the safety is continually monitored	All medicines are licensed by MHRA for safety and the safety is continually monitored- in March '20 the marketing authorisation for Esmya was suspended by EMA but reinstated with caveats in early '21	There has never been a a formal review of the safety and efficacy of hysterectomy	There has never been a a formal review of the safety and efficacy of myomectomy, the mortality and morbidity rates i.e. the risk to women is unknown despite the fact that myomectomy has been used for many decades	**Embolisation was been formally reviewed by the NICE Interventional Procedures process and found to be safe and efficacious enough for general use [58]**

	Mortality Rate	Unknown but little risk	Unknown but risk of liver failure some requiring transplant	Abdominal Hysterectomy - 43 deaths (0.17%) within 30 days; 119 deaths (0.6%) within 90 days, overall mortality 180 deaths within 90 days of procedure for all types of hysterectomy in the NHS in England and ONS [1]	Unknown may be similar to hysterectomy	**No known deaths internationally in last decade**
		SHORT-TERM MORBIDITY - SIDE EFFECTS AND COMPLICATIONS				
	General anaesthetic	N/A	N/A	Yes	Yes -for abdominal, for hysteroscopic - general or local	**No - local and light sedation**
	Major surgery	No	No	Yes	Yes for abdominal, hysteroscopic less invasive	**No**

	Haemorrhage	No	No	Yes - 370-796ml [2],[3] Risk increases with large fibroids >500ml in 55.3% [4]	Yes - 450ml [1], more than hysterectomy [5]	**No** [6],[7],[8],[9],[10],[11]
	Blood transfusion	No	No	Yes 2.2-7.5% [12],[13]	Yes, higher than hysterectomy [14]	**No**
	Painful	No	No	Very	Very	**Variable -none - very [15], [16], [17]**
	Duration of pain	No	No	3-10 days [18] women report "some degree of pain for several months post-op, although many women report that their significant pain diminished by around the fourth week." [19]	3-10 days [18]	**1-2 days [6],[7],[8],[9], [11]**

Infection	No	No	Urinary tract 3.3% -25% [20],[21] wound 25% [21]	Similar to hysterectomy	**Less likely- 1- 2.9%** [6], [7], [8], [9], [10], [11], [22]	
Surgical damage to bladder	No	No	Possible 1.1-1.7 % [2], [13], [23]	Less likely	**No**	
Surgical damage to urinary tract	No	No	Possible 0.1-1.7 % [2], [13], [23]	Less likely	**No**	
Surgical damage to bowel	No	No	Possible 0.5-5% [2], [13], [23]	Less likely	**No**	
Surgical Complications	No	No	Surgical complication rate increases to 61.7% with very large fibroids [24]	Very little data on complications, but the complication rate will increase with large fibroids as with hysterectomy	Complications 5% [68], [74]	

	Liver failure	Rare	5 reported cases requiring liver transplant,19 suspected adverse drug reaction reports of liver disorders in UK [25]	No	No	**No**
	DVT	Unlikely	Unlikely	Possible 15-18% (for all gynae surgery) [25],[26],[27]	Possible 15-18% (for all gynae surgery) [25],[26],[27]	**Much less likely**
	Unexplained fever	Hot flushes likely [28]	Hot flushes, amenorrhea, pelvic and abdominal pain, nausea [29]	Possible 14-49% [2], [3]	Possible 32% [2]	**Possible - post embolization syndrome 1-4%** [15], [16], [17], [11], [22]

	Overall complications	Very unpleasant side effects in most [5], [19], [20]	Liver failure [25], hot flushes, amenorrhea, pelvic and abdominal pain, nausea [29]	Overall short-term complications - 9-16% [30],[31], >50% had worse symptoms [32], serious complication rate 5%, higher complication that UAE 26.1% [56]	Little information 1.8-25%	**No permanent injuries or disease Complications 14.3 % of which only 0.14 % were serious [22] Lower rate than hysterectomy 17.6% [56]**
	Further Hospital Treatment	Yes, this is only a temporary treatment for up to 6 months. Further treatment will be necessary	Yes, only licensed for short-term intermittent treatment [29]	Repair to surgical trauma, in longer term prolapse etc	Hysterectomy and adhesions	**2.7 - 10% go on to hysterectomy usually due to infection , overall re-treatment rate 10.8% including re-embolisation [22]**

		MORBIDITY - MEDIUM AND LONG-TERM COMPLICATIONS AND SIDE EFFECTS				
	Fertility post-op	Infertile while on treatment	N/A	Infertile	Maintains fertility	**Maintain fertility 1-7% developed amenorrhoea** [10],[11]
	Pregnancy post procedure	Unlikely while being treated		No, infertile	Yes, 27-75.6% slightly higher than UAE [21], [22], [57]	**Awaiting results of FEMME study comparing UAE with Myomectomy [55] pregnancy rate 60% slightly lower than myomectomy [57]**

	Side Effects	Hot flushes and menopausal symptoms, memory loss, bone loss, insomnia, osteoporosis, vaginitis [29],[34]	Hot flushes, amenorrhea, pelvic and abdominal pain, nausea [29]	Menopause 5 years earlier, clinical depression, cardiovascular incidents more likely [35], [36], [37]	Pain, pelvic adhesions and re-growth of fibroids 51% in 5 years [39]	**Flu-like symptoms, expulsion or removal of fibroids (5-7%), discharge (1-20%) which resolves spontaneously or following hysteroscopy** [29], [30], [31], [60], [64], [65], [68]	
	Surgical Complication Rate	None	None	Surgical complication rate increases to 61.7% with very large fibroids [70] Longer term disease - depression, urinary incontinence, sexual dysfunction	Adhesions 55-100%, at a rate of 94-55% [38], [39] and 80% for open myomectomy, [41], [42]	Complications 5% [11], [22]	

	Further surgery	Possible - not an effective treatment long term, only licensed for short-term use [43]	Liver transplant to treat liver failure, not licensed for long-term treatment [25]	To correct any damage or bleeding [32] and in the longer term for post-hysterectomy prolapse, incidence range 0.2-43% [46]	Most go on to UAE or hysterectomy due to fibroid re-growth - 20-51% after 5 years [40], [43], [38], [41]	**0.25-7% go on to hysterectomy** [6], [7], [8], [10], [11]	
	Effectiveness	Ineffective 24 weeks after drug ceases fibroids return to original size [43]	Improves symptoms - bleeding and reduces fibroid size in 34%, but only licensed for pre-surgery or intermittent use [46]	Yes	Yes, in the shorter-term, but other treatment is very likely due to fibroid re-growth and adhesions [5], [38], [40], [42], [47]	**84-97%** [8], [10],[15], [16], [48]	

	Fibroid re-growth	Yes returns to normal after 24 weeks [43]	Likely after one-off or intermittent treatment is stopped	No	Yes requiring surgery in 51% of cases for re-growth [40]	**Less likely - 1%** [10], [15], [16], [17]
	Enjoyment of sex/ sexual dysfunction	Can reduce libido, lubrication and cause soreness [29],[34]	Not reported	Can reduce libido (in 42-74%) [51], lubrication, genital sensation, orgasm (in 33-35%) [51] and cause soreness, difficulty in penetration [33],[37], [49], [52]	No known effects after recovery	**No adverse effect reported- may improve In one study 53% - no change, 26% - improved, 10% - a deterioration** [53], [54], [48], [55]
	Psychological effect	Mood swings and possible depression [29],[34]	Anxiety and emotional disorders are 'uncommon' [30]	Loss of femininity, possible clinical depression [37], [49]	None reported	**No adverse effects reported**

	Ability to have HRT if desired/required	No - will counteract effects of drug, fibroids will re-grow	Likely to be the same as other drugs	Yes, required if ovaries removed, also menopause 5- years earlier after hysterectomy	Not affected	**Not affected**
		SOCIAL AND ECONOMIC ISSUES				
	Length of hospital stay	N/A	N/A	5 days - 2 weeks	2 days-2 weeks	**1 night** [10],[15],[16],[17],[22], [50]
	Home care after procedure	No	No	Yes, need personal care for many weeks	Yes, need personal care for many weeks	**None to 4 weeks**
	Driving	Not affected	N/A	Not for 6 weeks post-op	Not for 6 weeks post-op	**Not affected**
	Scar	No	No	Yes	Yes	**None**
	Lifting and physical exercise	No restriction	No restriction	None until at least 6 weeks post-op	None until at least 6 weeks post-op	**No restriction**

Time back to work	N/A - but side effects may affect ability to work	N/A	2-3 months	2-3 months	**1-5 weeks [6], [7], [8], [10]**
Time to full recovery	24 weeks	Unreported	Up to 6 months	Up to 6 months	**1-2 months [6], [7], [17]**
Resumption of sex	No restriction		After 6 weeks	After 6 weeks	**No restriction**

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Cost Comparison of Fibroid Treatment

Although not a question asked FEmISA has carried out some economic appraisal of some of the current in-hospital treatments for fibroids which can be found here –

When we consider the cost of a treatment we must look at the cost to the NHS in the short and longer term, the cost to the patients and their families, who may have to take time off work to look the woman and the costs to employers and society. It is important to people that they recover quickly and get back to normal life as soon as possible. Most women cannot afford to take 3 months off work, especially if they run their own business, have a senior position, are on piece work or have family responsibilities. NICE has not considered the costs to patients, their families and society in the past.

The NHS has a tariff which is an average cost of treatment in England. The table below shows the current tariff and there are considerable savings to be made for the NHS.

Each year the NHS introduces new NHS Tariffs, which are the average cost of a procedure across the NHS in England. The Tariff costs below are for financial year 17/18 The Department of Health wants to encourage less hysterectomies and more less invasive treatments such as UFE.

Cost Comparisons			
Procedure	Hysterectomy	Myomectomy	Embolisation
NHS Tariff 17-18	£3,275	£2,609	£2,400
Cost Saving Comparison with UAE/UFE per procedure	£875	£209	

In the table below we show how much the NHS could save if all the 60% of hysterectomies performed for fiobroids in England each year were converted to UFE. FEmISA does not advocate this as all women should have a choice in treatment, but most do not as they are not told of alternatives to hysterectomy.

Here is an analysis for England as a whole, on the savings that could be made if women had fully informed choice of their treatment options from a multi-disciplinary fibroid outpatients' clinic run by interventional radiologists and gynaecologist working together for the benefit of

women with fibroids. There are few of these clinics in the country, but one is at Heartlands Hospital in Birmingham. Here 60% of women with fibroids opt for UFE. This is a benchmark for the rest of the UK.

Potential Saving on In-Patient Costs from Treatments with Embolisation instead of Hysterectomy

Savings Under Current 17-18 NHSTariff		
Total number of Hysterectomies in England in the NHS		31,624
60% for fibroids		18.974
In-patient cost of Hysterectomy (MA07E-F £3,275- 4,259) using lower tariff	£	103,568,600
If 60% of hysterectomies for fibroids were treated by UFE - costs	£	27,323,136
(60% e.g. Heart of England)(YR54Z UFE £2,400)		
Potential Cost saving by treating 60% with embolisation	**£**	**51,389,000**
Number of potential bed days saved		**139,145**

Further potential cost savings

- Reduction in HRT usage from early menopause associated with hysterectomy
- Reduction in short and longer term readmissions and morbidity

It is also important to look at some of the costs to patients and their families and employers.

Reduction in cost of patients and their families

- Less need for care at home from family member
- Return to work/normal life 1-2 weeks with embolisation c.f. Hysterectomy 10 weeks
- Early HRT use much less likely - prescription charges per hormone so at least double normal charge
- Reduction in cost to the economy, employers, society

Reduction in Cost to the Economy, Employers and Society

Return to work/normal life 1-2 weeks with embolisation c.f. Hysterectomy 10 weeks

	2 weeks off work versus 10 weeks - working days saved **151,795** Average weekly earnings May '17[Office for National Statistics] £ 503.00 **Potential economic saving from earlier return to work from UFE** **£ 76,352,986** **Estimated Full Annual Costs of Fibroids in USA** A clinical study from USA on the total costs of fibroids to the healthcare system and to the economy as a whole has been publishedrecently. [The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH - Am J Obstet Gynecol. 2012 Mar;206(3):211.e1-9. Epub 2011 Dec 11] Estimated annual direct costs (surgery, hospital admissions, outpatient visits, and medications) $4.1-9.4 billion Estimated lost work-hour costs - annually $1.55-17.2 billion Obstetric outcomes that were attributed to fibroids $238m - $7.76 bn **Total costs attributed to fibroids annually** **$5.9-34.4 billion**
8. Is there an unmet need for patients with this condition?	Symptomatic fibroids affect such a large number of women world-wide and in the UK, that a non-invasive, safe and effective treatment that preserved fertility, sexual function, with minimal side effects and return to work/normal life as quickly as possible would be welcome. Medicines currently in use for the treatment of symptomatic fibroids can only be used short-term before hospital treatment. The GNRH antagonists cause immediate chemical menopause with all the

	unacceptable side-effects associated with menopause. Many gynaecologists will not use them and many women find them unacceptable. GNRH antagonists are also associated with liver failure. An oral form Esmya was withdrawn from the market because of this, but has since returned with caveats for use. It is unlikely that any medicine will be able to treat large fibroids, especially symptoms associated with bulk such as pressure on surrounding organs, sciatica etc as they are unlikely to shrink sufficiently. Women want a non-invasive treatment for fibroids with a short recovery time, low morbidity and mortality, which maintains their fertility (even if they do not want to become pregnant) and sexual function. They do not want to suffer menopausal symptoms. If a medicine could deliver a high safety profile, a high efficacy profile with minimal side effects it would be welcome. The other issue with GNRH antagonists is fertility and contraception and the effects on women. However, the disadvantages of drug treatments are that they need to be taken over a long time and if they cannot be administered at home i.e. injected, this requires many visits to the GP. Hospital treatments for fibroids are more permanent than medicines, but hysterectomy and endometrial ablation do not maintain fertility. Hysterectomy and myomectomy are very invasive with high or unknown (in the care of myomectomy) morbidity and mortality. Women are rarely advised fully about possible complications and there is ageism about what women are offered. Many women feel bullied into an unwelcome hysterectomy when they don't want one. Older women are rarely offered myomectomy. 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 recovery from a very invasive operation, such as hysterectomy, especially if they run their own business. Less invasive treatments such as UFE and MR guides focused ultrasound offer maintenance of fertility and a much quicker recovery time. The safety of UFE is far greater than hysterectomy and that of myomectomy is unknown. There have been no reported recent deaths world-wide at all for UFE.

Advantages of the technology	
9. What do patients ~~or carers~~ think are the advantages of the technology?	Very little evidence about Relugolix with oestradiol and norethindrone acetate has been provided. This medicine does not have a product license/marketing authorisation and so there is no SPC available. It has been licensed in Japan for the treatment of fibroids, but is licensed in USA for treatment of prostate cancer. **FEmISA conclusions from cited papers -See below** The trials cited below were only short-term for 6 months and did not establish safety and efficacy over a longer period, but just pre-treatment for in-hospital permanent fibroid treatment. The medicine appeared to treat symptoms of HMB, pain and reduce fibroid size, but the abstracts do not contain enough detail to assess the side effects especially the menopausal symptoms normally associated with GNRH antagonists. In a literature search 7 clinical papers were found. One was in mice and will not be reviewed. - 1. **Relugolix, a novel oral gonadotropin-releasing hormone antagonist, in the treatment of pain symptoms associated with uterine fibroids: a randomized, placebo-controlled, phase 3 study in Japanese women**. Osuga Y, Enya K, Kudou K, Hoshiai H. Fertil Steril. 2019 Nov;112(5):922-929.e2. doi: 10.1016/j.fertnstert.2019.07.013. Epub 2019 Oct 6. PMID: 31594635 Free article. Clinical Trial. Objective: To investigate the efficacy and safety of the oral gonadotropin-releasing hormone receptor antagonist, relugolix, in patients experiencing uterine fibroid-associated pain. Design: Phase 3, multicenter, randomized, double-blind, placebo-controlled study. Patient(s): Premenopausal Japanese women (N = 65) experiencing moderate-to-severe uterine fibroid-

	associated pain with a maximum Numerical Rating Scale (NRS) score of ≥4 were randomized and completed the study. Intervention(s): Once-daily 40 mg relugolix (n = 33) or placebo (n = 32) for 12 weeks. Main outcome measure(s): Primary end point: proportion of patients with a maximum NRS score of ≤1 during the 28-day period before the final dose of study drug. Secondary end points: proportion of patients with no pain (NRS = 0) and percentage of days without pain during the 28-day period before the final dose of study drug; adverse events. Result(s): More patients receiving relugolix versus placebo achieved a maximum NRS score of ≤1 during the 28-day period before the final dose of study drug (57.6% vs. 3.1%). Similarly, more patients receiving relugolix versus placebo achieved a maximum NRS score of 0 (48.5% vs. 3.1%) and experienced more days without pain (96.4% vs. 71.4%). More patients receiving relugolix versus placebo experienced treatment-emergent adverse events (TEAEs; 87.9% vs. 56.3%); however, the rate of treatment discontinuation was low and not different between groups. Most TEAEs were mild to moderate in intensity. TEAEs (≥10%) included hot flush, metrorrhagia, hyperhidrosis, and menorrhagia, consistent with relugolix's mechanism of action, and viral upper respiratory tract infection. Conclusion(s): Relugolix improved uterine fibroid-associated pain and was well tolerated. **FEmISA Analysis and comments –** The patient numbers are very small only 65 in all. The medicine was only taken for 12 weeks and while the conclusion was that pain was relieved none of the other fibroid symptoms was measured e.g. heavy menstrual bleeding, fibroid size etc. 2. **Oral Gonadotropin-Releasing Hormone Antagonist Relugolix Compared With Leuprorelin Injections for Uterine Leiomyomas: A Randomized Controlled Trial**. Osuga Y, Enya K, Kudou K, Tanimoto M, Hoshiai H. Obstet Gynecol. 2019 Mar;133(3):423-433. doi:

	10.1097/AOG.0000000000003141. PMID: 30741797 Clinical Trial. Objective: To investigate the noninferiority of relugolix compared with leuprorelin acetate in reducing heavy menstrual bleeding associated with uterine leiomyomas. Methods: In a double-blind, double-dummy trial, premenopausal women with uterine leiomyomas and heavy menstrual bleeding defined as a pictorial blood loss assessment chart score of at least 120 were randomized in a 1:1 ratio to relugolix (40 mg, oral, once daily) or leuprorelin acetate (1.88 mg or 3.75 mg, monthly injection) for 24 weeks. The primary endpoint was the proportion of patients with a total pictorial blood loss assessment chart score of less than 10 for weeks 6-12. Secondary endpoints included myoma and uterine volumes, and hemoglobin levels. A sample size of 144 patients per group (n=288) was estimated to provide at least 90% power to demonstrate noninferiority (prespecified noninferiority margin -15%; one-sided 0.025 level of significance). Results: From March 2016 to September 2017, 281 patients were randomized (relugolix, n=139, leuprorelin n=142). Demographic and baseline characteristics were well balanced; mean pictorial blood loss assessment chart score was 254.3 in the relugolix group and 263.7 in the leuprorelin group. The proportion of patients with total pictorial blood loss assessment chart score of less than 10 for weeks 6-12 was 82.2% in the relugolix group and 83.1% in the leuprorelin group, demonstrating noninferiority of relugolix compared with leuprorelin (relugolix-leuprorelin difference -0.9%; 95% CI: -10.10 to 8.35; prespecified noninferiority margin -15%; P=.001). Reductions in myoma and uterine volumes and increases in hemoglobin levels were comparable in the two groups. Relugolix was associated with an earlier effect on menstrual bleeding than leuprorelin (pictorial blood loss assessment chart score of less than 10, 64.2% vs 31.7% [relugolix-leuprorelin difference 32.5%; 95% CI: 20.95-44.13%] for weeks 2-6 and pictorial blood loss assessment chart score of 0, 52.6% vs 21.8% [30.7%; 95% CI: 19.45-42.00%] for weeks 2-6) and faster recovery of menses after treatment discontinuation (relugolix median [Q1, Q3], 37 days [32.0, 46.0]; leuprorelin median, 65 days [54.0, 77.0]). Adverse events and bone mineral density loss were similar between relugolix and leuprorelin treatment groups.

	Conclusion: In women with uterine leiomyomas, once-daily treatment with relugolix, an oral gonadotropin-releasing hormone antagonist, demonstrated noninferiority to monthly leuprorelin for improvement of heavy menstrual bleeding at 6-12 weeks of treatment, had a more rapid effect on menstrual bleeding, and was generally well tolerated. **FEmISA Analysis and comments –** N= 144 patients per group. Duration – 24 weeks – 6 months Measuring the treatment of heavy menstrual bleeding comparing relugolix with leuprorelin acetate Adverse events and bone mineral density loss were similar between relugolix and leuprorelin treatment groups. Conclusion – Relugolix…….. demonstrated noninferiority to monthly leuprorelin for improvement of heavy menstrual bleeding at 6-12 weeks of treatment The duration was short and Relugolix appears to be no worse than leuprorelin, which is not a ringing endorsement. 3**. Suppression of the hypothalamic-pituitary-gonadal axis by TAK-385 (relugolix), a novel, investigational, orally active, small molecule gonadotropin-releasing hormone (GnRH) antagonist: studies in human GnRH receptor knock-in mice.** Nakata D, Masaki T, Tanaka A, Yoshimatsu M, Akinaga Y, Asada M, Sasada R, Takeyama M, Miwa K, Watanabe T, Kusaka M. Eur J Pharmacol. 2014 Jan 15;723:167-74. doi: 10.1016/j.ejphar.2013.12.001. Epub 2013 Dec 11. PMID: 24333551 TAK-385 (relugolix) is a novel, non-peptide, orally active gonadotropin-releasing hormone (GnRH) antagonist, which builds on previous work with non-peptide GnRH antagonist TAK-013. ...TAK-385 may provide useful therapeutic interventions in hormone-dependent diseases includ …

	4. **Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy**. Al-Hendy A, Lukes AS, Poindexter AN 3rd, Venturella R, Villarroel C, Critchley HOD, Li Y, McKain L, Arjona Ferreira JC, Langenberg AGM, Wagman RB, Stewart EA. N Engl J Med. 2021 Feb 18;384(7):630-642. doi: 10.1056/NEJMoa2008283. PMID: 33596357 Clinical Trial. Background: Uterine fibroids are a common cause of heavy menstrual bleeding and pain. Treatment with the combination of relugolix (an oral gonadotropin-releasing hormone-receptor antagonist), estradiol, and norethindrone acetate, administered once daily, may have efficacy in women with uterine fibroids and heavy bleeding while avoiding hypoestrogenic effects. Methods: We conducted two replicate international, double-blind, 24-week, phase 3 trials involving women with fibroid-associated heavy menstrual bleeding. Participants were randomly assigned in a 1:1:1 ratio to receive once-daily placebo, relugolix combination therapy (40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethindrone acetate), or delayed relugolix combination therapy (40 mg of relugolix monotherapy, followed by relugolix combination therapy, each for 12 weeks). The primary efficacy end point in each trial was the percentage of participants with a response (volume of menstrual blood loss <80 ml and a ≥50% reduction in volume from baseline) in the relugolix combination therapy group, as compared with the placebo group. Key secondary end points were amenorrhea, volume of menstrual blood loss, distress from bleeding and pelvic discomfort, anemia, pain, fibroid volume, and uterine volume. Safety and bone mineral density were assessed. Results: A total of 388 women in trial L1 and 382 in trial L2 underwent randomization. A total of 73% of the participants in the relugolix combination therapy group in trial L1 and 71% of those in trial L2 had a response (primary end point), as compared with 19% and 15%, respectively, of those in the placebo groups (P<0.001 for both comparisons). Both relugolix combination therapy groups had significant improvements, as compared with the placebo groups, in six of seven key secondary end points, including measures of menstrual blood loss (including amenorrhea), pain, distress from bleeding and pelvic discomfort, anemia, and uterine volume, but not fibroid volume. The incidence of adverse events was similar with relugolix combination therapy and placebo. Bone mineral density was similar with relugolix

	combination therapy and placebo but decreased with relugolix monotherapy. Conclusions: Once-daily relugolix combination therapy resulted in a significant reduction in menstrual bleeding, as compared with placebo, and preserved bone mineral density in women with uterine fibroids. **FEmISA Analysis and comments –** N= 388 and 382 Duration 24 weeks Measuring reduction in HMB, secondary - distress from bleeding and pelvic discomfort, anemia, pain, fibroid volume, and uterine volume. Safety and bone mineral density were assessed. Conclusions: Once-daily relugolix combination therapy resulted in a significant reduction in menstrual bleeding, as compared with placebo, and preserved bone mineral density in women with uterine fibroids Again a short-term study and the conclusion does not give details of the side effects. 5. **Prolapse of a pedunculated uterine leiomyoma through the cervix during GnRH antagonist treatment: Case report and literature review**. Ishizawa C, Hirota Y, Urata Y, Morishima K, Fujii T, Osuga Y.J Obstet Gynaecol Res. 2020 Sep 10. doi: 10.1111/jog.14479. Online ahead of print. PMID: 32911575 We here describe a case of the prolapse of pedunculated submucosal leiomyoma through the cervix during the treatment of a gonadotropin-releasing hormone (GnRH) antagonist relugolix. We also present the literature review of the cases of leiomyoma prolapse duri … Not relevant, not analysed 6. **Elagolix in the treatment of heavy menstrual bleeding associated with uterine fibroids in premenopausal women**. Ali M, A R S, Al Hendy A. Expert Rev Clin Pharmacol. 2021 Apr;14(4):427-437. doi:

	10.1080/17512433.2021.1900726. Epub 2021 Mar 15.PMID: 33682578 Review. INTRODUCTION: Uterine fibroids (UFs) are the most common benign tumor arising from myometrium of reproductive age women, with significant financial burden estimated in hundreds of billions of dollars. ...AREAS COVERED: Authors reviewed the literature available for elagolix … Abstract Introduction: Uterine fibroids (UFs) are the most common benign tumor arising from myometrium of reproductive age women, with significant financial burden estimated in hundreds of billions of dollars. Unfortunately, there are limitations in available long-term treatment options. Thus, there is a large unmet need in the UF space for noninvasive therapeutics. Areas covered: Authors reviewed the literature available for elagolix; an orally bioavailable, second-generation, non-peptide gonadotropin-releasing hormone (GnRH) antagonist recently approved by the US Food and Drug Administration (FDA) in combination with estradiol/norethindrone acetate for the management of heavy menstrual bleeding associated with UFs in premenopausal women. Expert opinion: The utility of new-generation oral GnRH-antagonists, such as elagolix, relugolix and linzagolix, is offering a new potential opportunity for the future therapy of UFs: elagolix has been the most studied drug of this class for treating benign gynecological diseases, including endometriosis and UFs, for which it has been US FDA-approved in 2018 and 2020, respectively. **FEmISA Analysis and comments –** This is a different molecule, but of the same new-generation of GNRH antagonists 7. **Oriahnn for fibroid-associated heavy menstrual bleeding**. [No authors listed] Med Lett Drugs Ther. 2021 Apr 5;63(1621):51-52. PMID: 33830967 No abstract available. From a literature it is very unlikely that

Disadvantages of the technology	
10. What do patients ~~or carers~~ think are the disadvantages of the technology?	From the analysis of the abstracts there is no evidence that Relugolix has any benefits over other GNRH antagonists. There needs to be evidence on - • Long-term studies to show safety over many years • Effect on liver function • Reduction of all or most of fibroid symptoms not just HMB, pain and fibroid size • Lack of side effects and menopausal symptoms • Ability for women to have HRT at menopause if required
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	It would not be a suitable treatment for younger women with fibroids unless as pre-treatment before myomectomy. (Pre-treatment before UFE is contraindicated). It may be useful for older women near menopause, but it would need to be established if the use of HRT to treat menopausal symptoms would bring back fibroid symptoms.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	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.
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	
From the analysis of the abstracts there is no evidence that Relugolix has any benefits over other GNRH antagonists. There needs to be evidence on - • Long-term studies to show safety over many years • Effect on liver function • Reduction of all or most of fibroid symptoms not just HMB, pain and fibroid size • Lack of side effects and menopausal symptoms • Ability for women to have HRT at menopause if required	

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

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to disclose.

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Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contribution of authors

Mari Imamura and Moira Cruickshank summarised and critiqued the clinical effectiveness evidence; David Cooper and Thenmalar Vadiveloo checked and critiqued the statistical analyses presented in the company submission; Dwayne Boyers and Elisabet Jacobsen reviewed and critiqued the cost-effectiveness evidence; Paul Manson checked and critiqued the company's search strategies; Kevin Cooper provided clinical guidance and comments on the draft report. Miriam Brazzelli oversaw and coordinated all aspects of this appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

AE	Adverse event
AH	Alkaline haematin
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
CT	Combination therapy
DECA scan	Dual-energy X-ray absorptiometry scan
EMA	European Medicines Agency
EQ-5D	European quality of life five dimension
ERG	Evidence review group
GnRH	Gonadotropin-releasing hormone
GnRHa	Gonadotropin-releasing hormone analogue
HMB	Heavy menstrual bleeding
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
KOL	Key opinion leader
LNG-IUS	Levonorgestrel-releasing intrauterine system
LS	Least squares
MBL	Menstrual blood loss
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	Modified intention to treat
NHS	(UK) National Health Service
NICE	National Institute for Health and Care Excellence
NRS	Numerical rating scale
NSAID	Non-steroidal anti-inflammatory drug
OLS	Ordinary least squares
PSSRU	Personal social services research unit
QALY	Quality adjusted life year

QoL	Quality of life
RCT	Randomised controlled trial
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short form 36-item survey
SmPC	Summary of product characteristics
TEAE	Treatment emergent adverse event
TTO	Time trade off
UAE	Uterine artery embolisation
UF	Uterine fibroids
UFS-QoL	Uterine fibroid health and symptom-related quality of life
UPA	Ulipristal acetate
UFV	Uterine fibroid volume
UV	Uterine volume
WTP	Willingness to pay

1. Executive Summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

The focus of the submission received from Gedeon Richter is relugolix with oestradiol and norethisterone acetate (referred to throughout as relugolix combination therapy or relugolix CT) for treating moderate to severe symptoms associated with uterine fibroids (UF).

The clinical evidence submitted by the company consists of two recent multicentre Phase-3 trials, LIBERTY 1 and LIBERTY 2, and one Phase-3 open-label extension study of LIBERTY 1 and LIBERTY 2, LIBERTY 3. The clinical outcomes used in the economic model are menstrual blood loss (MBL) volume, change in MBL volume, adverse effects, and quality of life. In LIBERTY 1 and LIBERTY 2 bleeding control was achieved by a higher proportion of participants treated with relugolix CT (73.4% in LIBERTY 1 and 71.2% in LIBERTY 2) compared with those treated with placebo (18.9% and 14.7%, respectively; $p<0.0001$ for both comparisons). Similarly, amenorrhea was achieved by 52% and 50% of participants treated with relugolix CT in LIBERTY 1 and LIBERTY 2, respectively, compared with 6% and 3% of those treated with placebo ($p<0.001$ for both comparisons).

Since the absence of head-to-head RCTs comparing relugolix CT with GnRH agonists, the company conducted an ITC. Apart from LIBERTY 1 and LIBERTY 2,

the other trials included in the ITC were two Phase-3 RCTs: PEARL I and PEARL II that assessed women who were waiting for surgery. PEARL I compared UPA versus placebo and PEARL II UPA versus leuprolide acetate. The company present the results of an ITC of relugolix CT versus UPA but not of relugolix CT versus GnRHa. Results were only presented for the mean difference in percentage change from baseline in MBL and hence uncertainty surrounding the treatment effect was not incorporated into the economic model, substantially under estimating uncertainty in the ICER. The ITC results suggest that relugolix CT and UPA are equally effective in reducing MBL volume. The ERG notes, however, that the patient populations in the LIBERTY and PEARL I trials are different in terms of planned surgery. The company did not present any other comparisons for relugolix CT apart from that versus placebo despite several other outcomes being listed in their scope.

The cost-effectiveness evidence presents a Markov state transition model to calculate expected costs and quality-adjusted life-years (QALYs) associated with relugolix CT or GnRH agonists for the medical management of moderate or severe symptomatic fibroids in pre-menopausal women (average age 42). The cohort enters the model in the 'on treatment' state where they receive either relugolix CT or GnRH agonists. Upon treatment discontinuation, informed by the LIBERTY study (relugolix CT) and PEARL II study / clinical expert opinion (GnRHa) the cohort either enter best supportive care (defined as minimal treatment with iron supplements and NSAIDs) or are listed for surgery. The company base case model assumes that patients can only be listed for surgery following treatment discontinuation and must enter a waiting list of 15 months before surgery is delivered. A maximum of two rounds of surgery are modelled. After age 51, the full cohort enters the menopause health state where they are assumed to be cured, incurring general population utility values, and can only exit this state to enter the "death" state based on all-cause mortality rates. The ERG raises several key issues of uncertainty surrounding the company's modelling approach and data inputs (See Section 1.5 and Chapter 4 of the ERG report).

Table 1 presents a summary of the key issues identified by the ERG.

Table 1 Summary of the key issues identified by the ERG

Issue no.	Summary of key issues	Report sections
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.	Section 2.3 & 4.2.3.
Issue 2	Lack of formal comparison between relugolix CT and GnRH agonsits.	Section 3.4, 3.5, 4.2.6 and 5.1
Issue 3	The appropriateness of using "treatment" rather than "health" states in the economic model structure.	Section 4.2.2
Issue 4	The most appropriate assumptions about treatment discontinuation in UK clinical practice for both relugolix CT and GnRH agonists	Section 4.2.6
Issue 5	The appropriateness of a 'waiting time' health state post-treatment discontinuation	Section 4.2.2 and 4.2.6
Issue 6	The role of surgery in the treatment pathway and the lack of data to inform transitions to the surgery health state	Section 4.2.2 and 4.2.6
Issue 7	Uncertainty surrounding the utility function	Section 4.2.7
Issue 8	Monitoring and follow up resource use in UK clinical practice	Section 4.2.8

The key differences between the company's preferred assumptions and evidence, and the ERG's preferred assumptions and evidence are:

- The company have provided a cost-effectiveness case that appears to be primarily for a group of women who are not scheduled to have surgery but to inform the economic model use data from the comparator study (PEARL II) where women are scheduled for surgery at baseline. The ERG would have preferred these two populations to be considered separately in the economic model.

- The company's ITC only considers one outcome (% change in menstrual blood loss from baseline) for the comparison between relugolix CT and GnRH

agonists but fails to provide estimates or measures of uncertainty surrounding the treatment effect. The ERG is of the opinion that more complete ITCs should have been undertaken to assess relugolix CT versus GnRH agonists, including all relevant clinical outcomes and with results accompanied by appropriate confidence intervals.

- The company prefers an economic model structure based on 'treatment' states whereas the ERG prefers an economic model structure based on 'health' states, defined according to symptom control.

- The company prefers to modify treatment discontinuation data from the LIBERTY study, based on the assumptions of clinical expert opinion that discontinuation in the trial over-estimates discontinuation in real-world clinical practice. The ERG prefers the use of relugolix CT treatment discontinuation data sourced directly from the LIBERTY study because it is more consistent with the costs required to deliver the modelled treatment benefit and also ensures consistency with the data collected in the PEARL II study for GnRH agonists.

- The company prefers a modelling assumption where women can only be listed for surgery after treatment discontinuation, when they enter a 'waiting time' state of duration 15 months. The ERG considers it more appropriate to remove the waiting time state because, in clinical practice, most women listed for surgery would continue to receive the primary treatment in preparation for surgery.

- The company has included the key clinical outcome from the ITC (MBL) as a fixed-point estimate in the economic model, but the ERG prefers full incorporation of uncertainty surrounding the treatment effects for relugolix CT vs. GnRH agonists and relugolix CT vs. BSC into the probabilistic analyses.

- The company uses a mapping algorithm to transform disease-specific quality of life (UFS-QoL) to generic EQ-5D and uses a linear (OLS) utility function to model the impact of MBL on mapped EQ-5D values. The ERG would prefer more details in support of the chosen model structure and how it was derived.

Based on the currently available information, the ERG considers data from the repeated measures model provided by the company in response to clarification queries (with reporting error corrected post FAC) to be more appropriate to allow estimation of appropriate standard errors for inclusion in the probabilistic analysis.

- The company assume that all patients (whether on active treatment or BSC) will receive annual examination scans, but only patients on active treatment will receive gynaecologist appointments (6-monthly). The ERG would ideally prefer a model structure that allows follow-up resource use to be linked to the patient's symptom control ('health' states) rather than their 'treatment' received (other than for Dexa- scans). In a 'treatment' state model, the ERG prefers lower resource use: a one-off gynaecologist appointment and scan to make a treatment plan whenever treatment is started or discontinued.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life-year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing quality of life associated with improved symptom control (MBL) over a longer treatment duration on relugolix CT compared to GnRHa (obtained from a linear additive utility function estimating the effect of changes in MBL on EQ-5D mapped utilities).
- Reducing the proportion and duration of BSC treatment (with lower utility compared to active treatment) for relugolix CT compared to GnRHa.
- Reducing disutilities associated with surgery-related health states, including surgery waiting time, experience of surgery, surgery adverse events, loss of uterus by treating people with active treatment for longer, until menopause. Lower utilities are partially offset by applying general population utilities in the proportion of people assumed to be cured after surgery.

- A negligible impact on QALYs of treatment-related adverse events and a slightly reduced risk of surgical mortality in the relugolix CT arm due to longer treatment duration preventing surgery, but the impact on total QALYs is negligible.

Overall, the technology is modelled to affect costs by:

- Increasing the treatment acquisition costs, due to longer treatment duration with relugolix CT compared to GnRH agonists
- Reducing the costs of BSC and surgery due to longer time on treatment.

The modelling assumptions that have the greatest effect on the ICER are:

- Decisions about the role of surgery in the treatment pathway.
- Assumptions regarding treatment discontinuation for both relugolix CT and GnRHa over time.
- The assumption that people can only be listed for surgery after treatment discontinuation and must enter a waiting time state of duration = 15 months prior to surgery where no active treatment is provided.
- The uncertainty surrounding the menstrual blood loss treatment effect for relugolix CT versus GnRH agonists and versus best supportive care.
- Decisions about the most appropriate utility function used to estimate the impact of MBL on mapped utility values.
- Assumptions about the most appropriate follow-up resource use for patient monitoring and what constitutes BSC in UK clinical practice.

1.3 The decision problem: summary of the ERG's key issues

The ERG notes that the patient population in the LIBERTY trials does not match that of the PEARL trials in terms of planned surgery (see Issue 1 below).

Issue 1 Differences between the LIBERTY and PEARL trials in terms of the patient population

Report section	Section 2.3 (Table 3) & Section 4.2.3.
Description of issue and why the ERG has identified it as important	The patient population assessed in the LIBERTY trials does not match that assessed in the PEARL trials. In the PEARL trials, all women had surgery planned after 13 weeks while planned surgery was an exclusion criterion for the LIBERTY trials and, therefore, it is unlikely that in the LIBERTY trials women would be receiving surgery and certainly not within 13 weeks. The company submission suggests that the company wish to position relugolix CT as a treatment for women who wish to delay or avoid surgery which is similar to the LIBERTY trials (relugolix CT), but the ERG note that it may also be used in clinical practice as a 'pre surgery' treatment which would be more consistent with the population in the PEARL II study (GnRHa).
What alternative approach has the ERG suggested?	As the trials have been conducted in different patient populations the ERG does not have an alternative approach to suggest. However, as the results of the ITC are used in the economic model there are possible scenarios analyses to consider addressing this concern (see Issue 6 below)
What is the expected effect on the cost-effectiveness estimates?	It is difficult to judge the exact impact on the ICER, but the ERG notes that scenarios that remove "waiting time" and "surgery" states from the economic model (approximates subgroup A) increase the ICER substantially. For subgroup B, short-term treatment for 6 months pre-surgery, the company submission provides no evidence of a difference in clinical effectiveness, so it would be reasonable to consider an analysis assuming equal effectiveness. In this case, the alternative with the lowest treatment acquisition cost is likely to be the optimal treatment strategy.
What additional evidence or analyses might help to resolve this key issue?	There is nothing the company can do to address the differences in the study populations. The ERG has provided several scenarios that may help to approximate the likely impact on the ICER in different subgroups. The ERG accepts that the company wish to seek a recommendation for relugolix CT for women who wish to avoid or delay surgery, but the ERG would welcome further consultation with a range of clinical experts to help determine whether relugolix CT would also be used as a 'pre-surgery' treatment in clinical practice.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The CS does not provide a full account of the clinical effectiveness evidence. The company present the results of ITCs of relugolix CT versus UPA and UPA versus leuprolide acetate GnRH agonist but not of relugolix CT versus GnRH agonist. Results were only presented for the mean difference in percentage change from baseline in MBL but not for other relevant clinical outcomes (see sections 3.4 and 3.5 of this report).

Issue 2 Lack of formal comparison between relugolix CT and GnRH agonists

Report section	Section 3.4, 3.5, 4.2.6 and 5.1
Description of issue and why the ERG has identified it as important	Lack of formal comparison between relugolix CT and GnRH agonists. The company present the results of an ITC of relugolix CT versus UPA and UPA versus leuprorelin acetate but not of relugolix CT versus GnRHa. Results were only presented for MBL volume despite several other outcomes were listed in their scope. Furthermore, uncertainty surrounding the treatment effect was no reported or included in the economic model.
What alternative approach has the ERG suggested?	An NMA would have been the most appropriate method for addressing this issue. The ERG has attempted to illustrate the impact of incorporating uncertainty surrounding the treatment effect by re-creating the ITC and approximating standard errors for the comparison of relugolix CT versus BSC for inclusion in the probabilistic analysis of the economic model.
What is the expected effect on the cost-effectiveness estimates?	There is unlikely to be any direct impact on the deterministic ICER as the ERG has been able to back calculate the MBL data used in the model from the ERG's reproduction of the company's ITC for MBL. However, uncertainty surrounding point estimates of MBL treatment effect for relugolix CT vs. GnRH agonists and versus. BSC (from the LIBERTY trials) were not incorporated into the economic model's probabilistic analysis. Therefore, the company's model substantially under-estimates the uncertainty surrounding the company's preferred base case ICER.
What additional evidence or analyses might help to resolve this key issue?	A more complete presentation of the evidence from the company, including an NMA, that estimates a treatment effect and standard error for MBL should be incorporated into the economic model. A pooled estimate of MBL effect for relugolix CT compared to BSC from the LIBERTY study should also be provided and fully incorporated into the model probabilistic analysis. Given that the company have access to the relevant trials data, it would be preferable if they provided a complete set of ITC results (and standard errors) for inclusion within the probabilistic analyses.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

The ERG raises several issues surrounding the appropriateness of the company's base case model structure (the choice of treatment rather than health states and the appropriateness of assuming listing for surgery can only take place after discontinuation, with a further waiting time of 15 months), assumptions about treatment discontinuation in clinical practice, uncertainty surrounding clinical effectiveness parameters used in the model (i.e., MBL), resource use assumptions for routine follow up, and the utility function used to estimate the impact of MBL on utilities mapped from UFS-QoL to EQ-5D. These issues would benefit from the company providing further data from their studies where possible as well as broader engagement with clinical experts around the use of relugolix CT in UK clinical practice and the associated role of surgery within the treatment pathway.

Issue 3 The appropriateness of using "treatment" rather than "health" states in the economic model structure.

Report section	Section 4.2.2
Description of issue and why the ERG has identified it as important	The model structure is built around 'treatment' states (relugolix CT / GnRH agonist and best supportive care) to reflect the treatment pathway. The ERG would have preferred a model built around "health" states defined according to symptom control because it would a) allow the model clinical effectiveness inputs to more closely reflect the trial data (i.e., avoiding the application of MBL data from the trial's mITT analysis directly to an 'on treatment' cohort) and b) allow routine monitoring to reflect patient health / symptom control rather than treatment received and thus would be more reflective of patient management in UK clinical practice. This is potentially an important driver of the ICER, but further modelling would be required to determine the impact.
What alternative approach has the ERG suggested?	The ERG believes adopting a model structure defined according to 'health' rather than 'treatment' states would generate a more accurate estimate of the ICER and would more appropriately reflect decision-making in UK clinical practice.
What is the expected effect on the cost-effectiveness estimates?	The direction and magnitude of any biases are unclear, but it is likely that MBL data used in the company base case analysis, based on an intention to treat analysis of the LIBERTY trial data, would over-estimate the MBL in an on-treatment cohort. However, the cost savings of avoiding BSC may be overestimated in the company's model. The net impact is unclear, and it could bias in favour or against relugolix CT.
What additional evidence or analyses might help to resolve this key issue?	The ERG would ideally like to see a model structured around 'health' rather than 'treatment' received states but appreciates this would be a significant undertaking. If this is not possible, an alternative, second-best option would be for the company to provide a more accurate estimate of the MBL in an 'on treatment' cohort from both LIBERTY and PEARL II studies to help determine the likely magnitude of any bias.

Issue 4 The most appropriate assumptions about treatment discontinuation in UK clinical practice for both relugolix CT and GnRH agonists

Report section	Section 4.2.6
Description of issue and why the ERG has identified it as important	The company preferred base case analysis has modified relugolix CT treatment discontinuation data from the LIBERTY study (up to 24 months of follow-up data available), based on clinical expert opinion and subjective judgment about whether study withdrawals would have continued treatment in clinical practice. No such adjustments were made to GnRH agonist discontinuation up to 3 months, sourced from the PEARL II study. This is important because it impacts on treatment acquisition costs, the costs of follow-on treatment (BSC / surgery), and the duration with which the cohort receives the benefits of relugolix CT. Therefore, it has an important impact on the ICER.
What alternative approach has the ERG suggested?	The ERG prefers the application of treatment discontinuation rates from the trial to ensure that the costs incurred are consistent with the use of relugolix CT that was required to deliver the modelled treatment benefit.
What is the expected effect on the cost-effectiveness estimates?	The implication of applying unmodified discontinuation rates is to increase the discontinuation rate for relugolix CT relative to the company's base case ICER following clarification, reducing treatment acquisition costs, and increasing the proportion receiving BSC or surgery. The magnitude of the impact on the ICER, therefore, depends on the most appropriate assumptions about other modelling parameters (e.g., resource use incurred in BSC and utilities).
What additional evidence or analyses might help to resolve this key issue?	The ERG is satisfied that the company has provided all the necessary evidence on which to make an informed judgment about the most appropriate treatment discontinuation data to apply in the model.

Issue 5 The appropriateness of a 'waiting time' health state post-treatment discontinuation

Report section	Section 4.2.3 and 4.2.6
Description of issue and why the ERG has identified it as important	Transition to the 'surgery' health states is conditional on A) having discontinued medical treatment prior to being listed for surgery and B) having transitioned through a 15-month waiting time state where no active treatment is provided. The ERG's clinical expert advice is that, in clinical practice, patients remain on their primary treatment whilst waiting for a scheduled surgery to ensure maximum fibroid shrinkage to improve chances of surgical success. Different assumptions about the inclusion/removal of the waiting time state and its duration if included lead to substantial variation in the ICER.
What alternative approach has the ERG suggested?	The ERG prefers the removal of the waiting time state to better reflect the use of treatment in UK clinical practice.
What is the expected effect on the cost-effectiveness estimates?	Removal of the 'waiting time' state, therefore, leads to a substantial increase in the ICER.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert advice from a range of clinicians experienced in treating fibroids to confirm whether patients would usually remain on treatment up until they receive surgery. Further validation of the assumption that surgery would not be scheduled past the age of 46 would also be useful.

Issue 6 The role of surgery in the treatment pathway and the lack of data to inform transitions to the surgery health state

Report section	Section 4.2.2 and 4.2.6
Description of issue and why the ERG has identified it as important	The ERG considers that some effect on surgery rates may be plausible because of longer treatment duration with relugolix CT compared to GnRHa, but the magnitude of reduction in surgery rates is not evidence-based, and highly uncertain given the data presented. Issues include: • Patient preference plays an important role in the decision to have surgery • Surgery rates were not collected in the LIBERTY studies • Transitions to surgery informed by the PEARL II study where all patients were considered for surgery are unlikely to be generalisable to a cohort of women who are unable or do not wish to have surgery (see Issue 1). The role of surgery in the treatment pathway, and the rates of transition to surgery are important drivers of cost-effectiveness.
What alternative approach has the ERG suggested?	The company has provided sensitivity analyses removing surgery and the ERG conducts further exploratory sub-group analyses in patients: A: who don't wish to or cannot have surgery B: who wish to receive treatment in preparation for surgery
What is the expected effect on the cost-effectiveness estimates?	Group A: removal of surgery states favours GnRHa, increasing the ICER substantially Group B: equalising treatment effectiveness favours relugolix CT
What additional evidence or analyses might help to resolve this key issue?	A comprehensive review of the literature to identify the rates of surgery that might be expected in a patient population similar to that included in the LIBERTY study would help resolve some uncertainty about the likely transitions to surgery following longer-term use of medical treatment. A more complete ITC, particularly around uterine or fibroid volume, would help validate the ERG assumption of equal effectiveness between relugolix CT and GnRH agonists as a treatment in preparation for surgery used for the exploratory subgroup analysis.

Issue 7 Uncertainty surrounding the utility function

Report section	Section 4.2.7
Description of issue and why the ERG has identified it as important	The company have mapped disease-specific quality of life data from the UFS-QoL, collected in the LIBERTY studies, to EQ-5D using an algorithm from a previous assessment. An OLS linear regression model, adjusting for age and MBL, is then used to predict the impact of MBL on mapped EQ-5D utilities to generate time varying utilities while on treatment or BSC. The company have not provided any details about what alternative model specifications were explored, or why the chosen model was used. This is an issue because the ICER is sensitive to changes in the co-efficient on MBL obtained from the utility function.
What alternative approach has the ERG suggested?	The ERG requested and was provided with the results of a repeated measures model at the clarification stage, and a corrected clarification response post FAC, where the co-efficient on MBL was somewhat higher than in the original OLS model. However, the most appropriate specification for the utility function remains unclear. In the absence of a full exploration of the advantages and disadvantages of different approaches, the ERG prefers the repeated measures model because it allows more appropriate exploration of uncertainty and generates utilities closer to general population averages when MBL is low.
What is the expected effect on the cost-effectiveness estimates?	The repeated measures model, with corrected reporting post FAC, generates a slightly higher reduction in utility for every unit increase in MBL compared to the company preferred OLS model. The implication is lower QALYs in both arms of the model, higher incremental QALY gains for relugolix CT and hence a slightly lower ICER compared to the company preferred base case model.
What additional evidence or analyses might help to resolve this key issue?	A complete assessment of the relative advantages and disadvantages of alternative utility functions, including, for example, exploration of squared terms to explore non-linearities in the impact of MBL on utility, discussion of the face validity and model fits of alternative utility functions.

Issue 8 Monitoring and follow up resource use in UK clinical practice

Report section	Section 4.2.8
Description of issue and why the ERG has identified it as important	The ERG considers the company's base case routine monitoring and resource use to be an over-estimate of UK clinical practice. In addition to dexa-scans to monitor BMD, the company assumes all patients would have annual scans (ultrasound [100%], MRI [25%], hysteroscopy [25%]) whether on or off treatment. A six-monthly gynaecologist consultation was assumed for those on treatment, but not for those on BSC. This is important because the frequency of scanning and consultations leads to important changes to the ICER, particularly when these differ between the on and off treatment cohorts.
What alternative approach has the ERG suggested?	The ERG's clinical expert considers the company's use of dexa-scans to be appropriate, but the remaining examinations and consultations to be an over-estimate. The ERG considers a one-off consultation with a gynaecologist and a scan to assess progress and make a long-term treatment plan would be more appropriate and would be applied whether on treatment or after discontinuation (i.e., upon entry to the BSC state).
What is the expected effect on the cost-effectiveness estimates?	The ERG preferred resource use reduces total costs in both arms of the model, and also reduces the incremental costs associated with relugolix CT, by removing the additional six-monthly gynaecologist consultation compared to BSC. The impact is a reduction in incremental costs and a reduction in the ICER compared to the company's preferred base case.
What additional evidence or analyses might help to resolve this key issue?	The ERG would consider it more appropriate to link resource usage to symptom control rather than on/off treatment and believe this could be incorporated into a model defined by 'health' states (See Issue 3). The ERG is of the opinion that further engagement with a wide range of clinical experts would help to better understand the heterogeneity in how frequently patients have contact with hospital services in UK clinical practice.

1.6 Summary of ERG's preferred assumptions and resulting ICER

Table 2 below outlines the ERG's preferred modelling assumptions. The table demonstrates the impact of changing each assumption from the company's base case individually. There are several uncertainties that the ERG has not been able to resolve at this stage and the ERG's preferred ICER may therefore change following technical engagement if further evidence is provided by the company. The ERG notes that there are many uncertainties surrounding modelling assumptions, and limited data to inform the model. Several assumptions are associated with advantages and disadvantages. Whilst the ERG provides some suggested alternative assumptions, it may be more appropriate to consider a plausible range of ICERs that more appropriately reflect the uncertainty in the underlying assumptions. The magnitude of uncertainty is more appropriately captured using the ERG's revised probabilistic analyses.

Given that the ERG agrees with the company's assumption that all GnRH agonists have equal effectiveness, the cheapest GnRHa (goserelin monthly) dominates all other GnRH agonists at current list prices. For simplicity of reporting, ICERs are only reported for relugolix CT versus goserelin monthly.

Table 2 Summary of ERG's preferred assumptions and ICER (relugolix CT vs. Goserelin monthly)

Scenario	Incremental cost (£)	Incremental QALYs	ICER (£ / QALY)
Company's base case, submitted following clarification	2112	0.364	5,796
+ Application of unmodified treatment discontinuation rates from the LIBERTY study (Issue 4)	444	0.103	4,311
+ Removal of waiting time state for surgery (Issue 5)	407	0.046	8,784
+ Utilities sourced from a repeated measures model (Issue 7)	407	0.07	5,846
+ Female specific UK general population utility norms	407	0.069	5,866
+ Resource use adapted to reflect UK clinical practice (Issue 8)	194	0.069	2,795
ERG's suggested base case deterministic	194	0.069	2,795
ERG's suggested base case probabilistic (including Issue 2)	197	0.069	2,833

Further details of the ERG's additional exploratory and sensitivity analyses, including a full set of updates to the probabilistic analyses can be found in Chapter 6.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Gedeon Richter Limited is moderate to severe symptoms associated with uterine fibroids (UF). The company's description of this health condition in terms of prevalence and complications appears generally accurate and in line with the decision problem. However, the company's focus on heavy menstrual bleeding as "moderate to severe symptoms" is questioned by the ERG's clinical expert, who is of the opinion that pressure symptoms are relevant in this context and should have been specified in the company's inclusion criteria. The relevant intervention for this submission is relugolix in combination with oestradiol and norethisterone (Ryeqo®, Gedeon Richter Limited).

2.2 Background

The company submission (CS) describes uterine fibroids (UF) as benign tumours that develop in or around the uterus. The majority of UF (correctly known as leiomyomas or myomas)[1] are asymptomatic but, for those people who do experience symptoms, treatment can be necessary. There are three distinct classes of symptoms: prolonged or heavy menstrual bleeding, pelvic pressure and pain, and reproductive dysfunction. Bleeding symptoms can be related to the location of the UF, with submucosal the most likely cause. Pelvic pressure is due to increase in the size of the uterus.[2] Other symptoms experienced by some people include abdominal pain, frequent need to urinate, constipation and pain or discomfort during sex.[3] Although the aetiology of UF is not currently known, their development has been linked to oestrogen;[3-5] accordingly, UF tend to develop in people aged between 16 and 50 years, when oestrogen levels are high and shrink after the menopause, when oestrogen levels drop.[3, 5]

Risk factors for UF include race (in particular, black women are disproportionately affected, with UF being three times more common in black women than white women, and more severe symptoms in black women), age, obesity (which increase the risk of UF due to the metabolic function of adipose tissues), having never been pregnant (with each subsequent child possibly lowering the risk further in multiparous women), hypertension, and vitamin D deficiency and diet.[5-7]

Uterine fibroids may be discovered during routine gynaecological examinations, otherwise, diagnosis is usually by tests such as ultrasound scan, hysteroscopy, or laparoscopy.[8]

Uterine fibroids are the most common neoplasms in women worldwide[6] but their actual incidence is difficult to estimate because they are often asymptomatic.[4, 9] Hospital Episode Statistics for the year 2020-21 in England report a total of 15,646 finished consultant episodes for leiomyoma of the uterus (codes D25.0: Submucous leiomyoma of uterus, D25.1: Intramural leiomyoma of uterus, D25.2: Subserosal leiomyoma of uterus, D25.9: Leiomyoma of uterus, unspecified).[10]

The CS cites the NICE pathway for managing heavy menstrual bleeding as the most relevant clinical pathway (presented in Document B, Figure 3 of the CS and reproduced as Figure 1 below).[11]

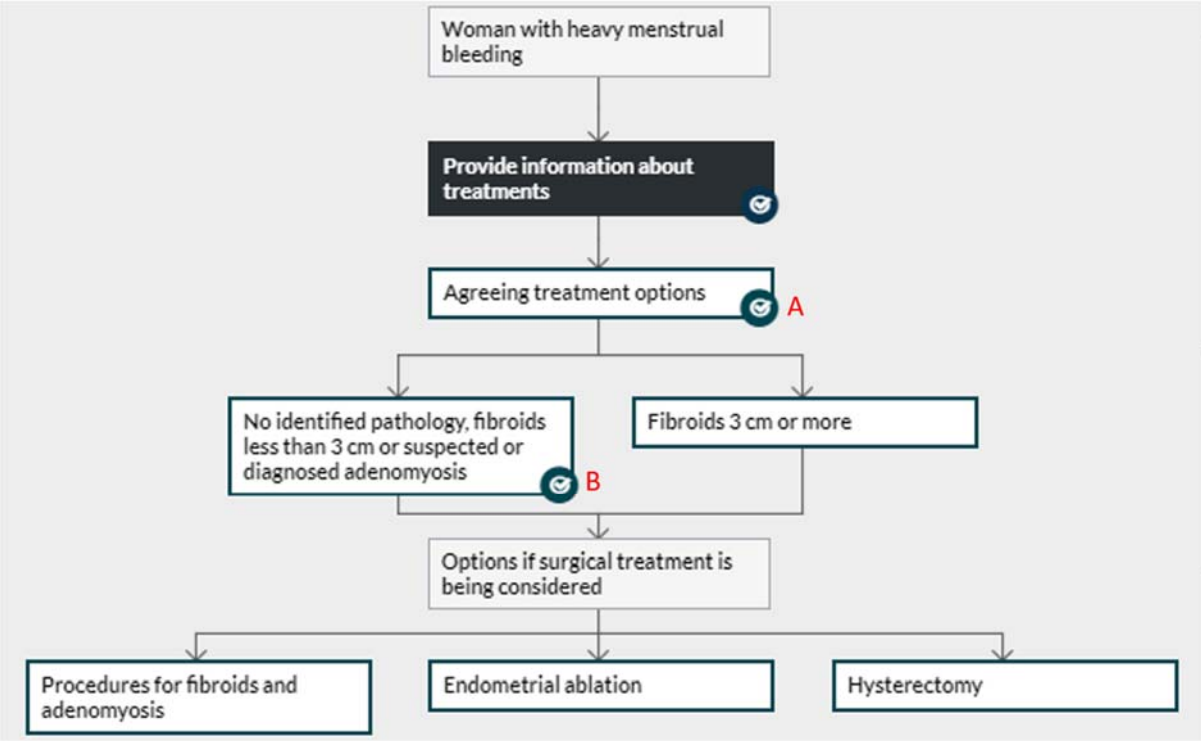


Figure 1 NICE pathway for managing heavy menstrual bleeding [reproduced from Figure 3, Document B of the CS]

The NICE pathway makes the following recommendations:

No identified pathology, fibroids <3cm in diameter which are not causing any distortion of the uterine cavity or suspected or diagnosed adenomyosis.

The NICE pathway recommends levonorgestrel-releasing intrauterine system (LNG-IUS) as the first treatment for heavy menstrual bleeding (HMB) in these women.
For women who decline LNG-IUS, or for whom it is not suitable, pharmacological treatments should be considered:

- Non-hormonal:
    - Tranexamic acid
    - Non-steroidal anti-inflammatory drugs (NSAID)
- Hormonal:
    - Combined hormonal contraception
    - Cyclical oral progestogens.

If treatment is unsuccessful, pharmacological treatment is declined or symptoms are severe; referral to specialist care should be considered:

- Investigations to diagnose the cause of HMB, if needed, taking account of any investigations already undergone and
- Alternative treatment choices, including:
    - Pharmacological options not already tried
    - Surgical options:
        - Second generation endometrial ablation
        - Hysterectomy.

For women with submucosal fibroids, hysteroscopic removal should be considered.

Fibroids 3cm or more in diameter

Taking into account the size, location, and number of fibroids, and severity of symptoms, the following treatments should be considered:

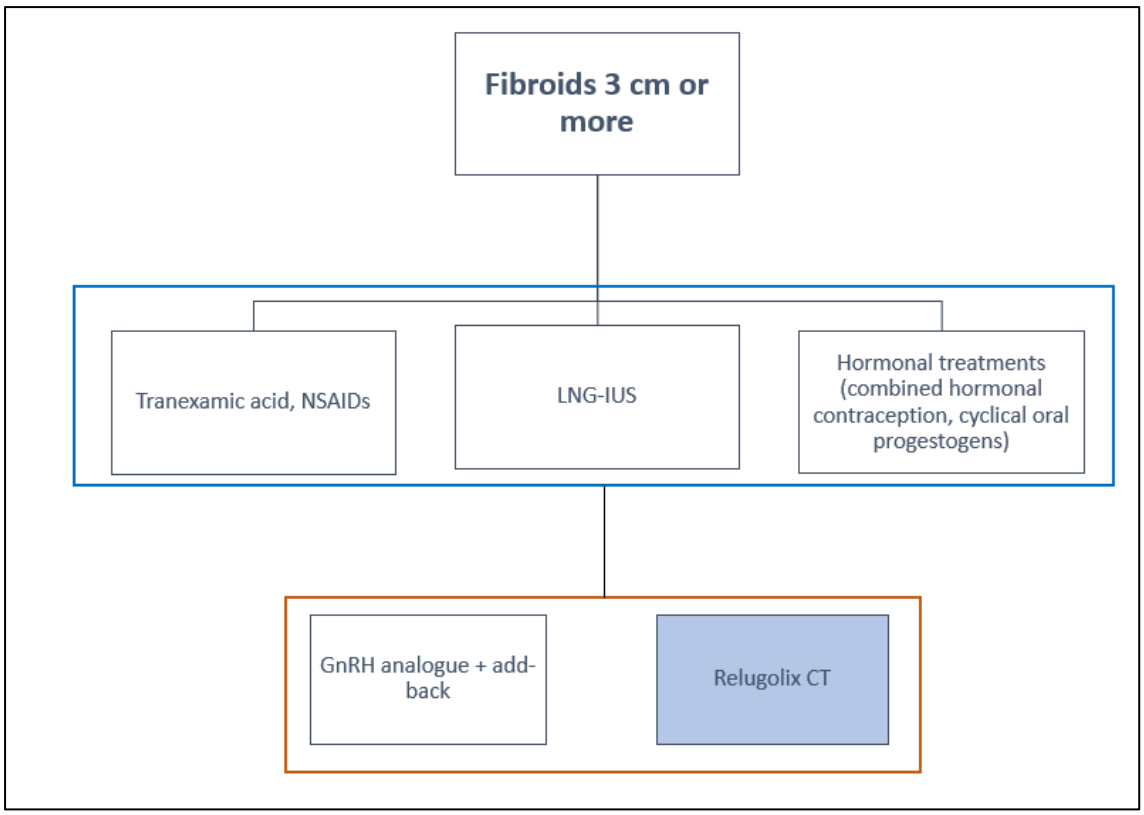
- Non-hormonal (tranexamic acid and/or NSAIDs) should be offered whilst investigations and definitive treatment are being organised; use of these treatments should be continued for as long as they are found to be beneficial
- Hormonal treatment (LNG-IUS, combined hormonal contraception, cyclical oral progestogens, ulipristal acetate [UPA])
- Uterine artery embolisation (UAE)

- Surgical: myomectomy or hysterectomy
- UPA should only be considered for the intermittent treatment of moderate to severe symptoms of UF in premenopausal women if surgery and UAE are not suitable, declined, or have failed surgery or UAE
- Second-generation endometrial ablation should be considered for those who meet the criteria
- Pre-treatment with gonadotropin-releasing hormone (GnRH) analogues before hysterectomy and myomectomy should be considered if UF are causing an enlarged or distorted uterus.

The CS states that there is a current unmet need for pharmacological treatments for moderate to severe UF due to a lack of satisfactory medical treatments. The CS further states that there is no other treatment currently available that meets the unmet need and with an indication that is not time restricted in premenopausal women with moderate to severe UF. The ERG's clinical expert agrees with the company's position.

The CS provides a description of the relevant intervention for this appraisal, relugolix CT (relugolix in combination with oestradiol and norethisterone acetate) in Document B, Table 2 of the CS. Then company describes relugolix as a non-peptide GnRH antagonist that binds to, and inhibits, GnRH receptors in the anterior pituitary gland. Such inhibition results in a dose-dependent decrease in the release of luteinizing hormone and follicle stimulating hormone. By reducing their circulating concentrations, follicular growth and development are prevented and ovulation and development of the corpus luteum are prevented, resulting in reduction of oestrogen production and progesterone, respectively. Relugolix CT was granted marketing authorisation from the EMA on 16th July 2021 and from the MHRA on 9th August 2021.

The proposed place of relugolix CT in the treatment pathway is presented in Document A, Figure 1 of the CS, and is reproduced below as Figure 2. The ERG agrees that the company's proposed pathway is representative of current clinical practice and the anticipated positioning of relugolix CT is within its licensed indication.



NSAIDs; non-steroidal anti-inflammatory drugs, LNG-IUS; levonorgestrel-releasing intrauterine system, GnRH; gonadotrophin-releasing hormone

Figure 2 Company's proposed treatment pathway and positioning of relugolix CT for treating uterine fibroids [reproduced from Figure 1, Document A of the CS]

2.3 Critique of company's definition of the decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with moderate to severe symptoms associated with uterine fibroid(s) (UF)	Same as scope	N/A	The ERG agrees that the population included in the LIBERTY trials is appropriate for this appraisal. The ERG notes, however, that the patient population of the LIBERTY trials does not match that of the PEARL trials, which were used for the ITC with UPA. In the PEARL trials, all women had surgery planned after 13 weeks while planned surgery was an exclusion criterion for the LIBERTY trials. The ERG believes that it may be relevant to consider the clinical and cost-effectiveness of relugolix CT within two different settings to reflect the differing treatment goals: a) in women who wish to improve symptoms but do not intend to undergo surgery, and b) in women who have already been listed for surgery (see Section 4.2.2 for a critique of the populations used in the economic modelling). The ERG notes that symptoms associated with UF include both menstrual- and pressure-related. At

				clarification, the company reiterated that HMB is the most common symptom of UF and most people with "moderate symptoms" will have heavy bleeding. The company further stated that HMB is one of the only symptoms which can be assessed in an objective and quantifiable way and is the most accurate indicator of severity, with other symptoms being supplementary and supportive. Nonetheless, the ERG's clinical expert is of the opinion that some participants with moderate to severe symptoms, in particular, pressure symptoms, may have been excluded from this population.
Intervention	Relugolix with oestradiol and norethisterone acetate (also known as norethindrone acetate), alone, or as an add on to non-hormonal pharmacological treatments *[Please note that relugolix in combination with oestradiol and norethisterone acetate is referred to as 'relugolix CT' throughout this submission; 'CT' is the abbreviation for 'combination therapy']*	Same as scope	N/A	The ERG questioned the fixed 1 mg dosage of oestrogen in the relugolix CT as titrating the dose of oestrogen to gain vasomotor symptom relief for individual patients is current clinical practice. At clarification, the company explained that the dosages of relugolix 40 mg, oestradiol 1mg and norethisterone 0.5 mg were selected to achieve a balance of reproductive hormones to treat the UF symptoms whilst maintaining bone health, minimising vasomotor symptoms and protecting the endometrium from the

				effects of unopposed oestrogen. The company further stated that the combined doses of 40 mg relugolix and 1mg oestradiol achieves systemic oestradiol concentrations of 10 to <60 pg/ml which was sufficient to prevent hypoestrogenic symptoms and maintain bone health in most people. In addition, combining 1mg oestradiol and 0.5 mg norethisterone ensures oestradiol levels are within the pre-follicular phase level of 20 to 50 pg/mL, providing control of UF symptoms whilst minimising side effects. The ERG's clinical expert is of the opinion that the 1 mg dose of oestradiol in the company's combined therapy would be effective in addressing the osteoporosis side effects. However, using a static dose control, vasomotor symptoms is not considered reasonable as people metabolise at different rates and, in current clinical practice, the oestrogen dose is varied to the level required to control symptoms. The dose of 1mg of oestrogen is that which protects against BMD loss and will help control vasomotor symptoms in some, but not all, users.

Comparator(s)	Hormonal treatments, including: • levonorgestrel-releasing intrauterine system (LNG-IUS; off-label for some LNG-IUS) • combined hormonal contraception (off-label for some combined hormonal contraceptives) • cyclical oral progestogens gonadotrophin-releasing hormone analogues (off-label for some gonadotrophin-releasing hormone analogues)	The submission will focus on gonadotrophin-releasing hormone (GnRH) agonists as the relevant comparator for relugolix CT.	N/A	The ERG's clinical expert notes that GnRH antagonists, as opposed to GnRH agonists, would be relevant in this context. At clarification, the company stated that GnRH agonists were the most relevant comparators for relugolix CT, and that these are the existing treatment options that are expected to be displaced by relugolix CT in the NICE pathway for managing HMB. The company further reported that four GnRH antagonists were identified in its systematic literature review (relugolix, elagolix, linzagolix and cetrorelix) and provided justification for the latter three antagonists as not being relevant comparators for this appraisal. The ERG agrees that it is justifiable to exclude these treatments. The ERG's clinical expert also questions the omission of Esmya as a comparator, given that it is an oral preparation that targets symptoms and causes fibroid shrinkage. At clarification, the company stated that Esmya's indication has become limited due to safety concerns about liver injuries and is currently only indicated for intermittent treatment in

				this population when UF embolisation and/or surgery are not suitable or have failed. The company further stated that use of Esmya is currently low, a fact which supports GnRH as the most relevant comparators in this appraisal. The ERG agrees with the company's position in that it is unlikely that many people with UF requiring treatment would agree to randomisation to Esmya, given the level of monitoring required and potential risks of liver damage.
Outcomes	The outcome measures to be considered include: • change in menstrual blood loss (MBL) volume • time to MBL response • pain • uterine fibroid volume (UFV) / uterine volume (UV) • haemoglobin levels • change in bone mineral density (BMD) • rates and route of surgery • impact on fertility and pregnancy and teratogenic effects • mortality • adverse effects of treatment, including but not limited to	The outcome measures in the clinical effectiveness section include: • change in MBL volume • time to MBL response • pain • UFV/UV • haemoglobin levels • adverse effects of treatment, including but not limited to vasomotor symptoms, incontinence and pelvic organ prolapse • health-related quality of life. The outcome measures in the cost-effectiveness model include:	The following measures are not included in the clinical effectiveness section as they were not collected in the relugolix CT clinical trials: • rates and route of surgery • impact on fertility and pregnancy and teratogenic effects Rates and route of surgery are, however, included in the economic model. Mortality is not included as no deaths were reported during the relugolix CT clinical trials.	The ERG's clinical expert considers the outcomes reported in the CS to be appropriate for addressing the topic of this appraisal. However, for the ITCs the company provides only results for the mean difference in percentage from baseline in MBL and not results for other relevant outcomes. Moreover, they failed to consider the uncertainty of clinical effectiveness results within their economic model, appropriately. Despite the company's assertion that mortality is not included, the CS does indeed report that there were no deaths during the relevant trials.

	vasomotor symptoms, incontinence and pelvic organ prolapse • health-related quality of life	• MBL volume and change in MBL volume (used to derive utility) • Adverse effects • Quality of life	Whilst 'change in BMD' was explored in the relugolix CT clinical trials, it is not a relevant outcome in the economic model. In this submission, BMD is not an outcome in the economic model as it is assumed that BMD may resolve once treatment with GnRH agonist therapy (the comparator for relugolix CT) ceases and thus there may be no additional benefit to favour relugolix CT on this outcome. Despite this assumption, and as stated in section B.2.13, there is evidence to suggest that BMD may not be fully recoverable from GnRH agonist use which may underestimate the potential benefit that relugolix CT would provide to women with UF.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating	Same as scope	N/A	A critique of the company's economic analyses against the NICE reference case is provided in Section 4.2.1.

	clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups	Not specified	Not specified	Not specified	At clarification, the company stated that subgroup analyses of the primary efficacy endpoint were conducted for LIBERTY 1, LIBERTY 2 and LIBERTY 3. The company noted that no subgroups were used in the economic analyses and provided the results of all the analyses at clarification. The ERG is satisfied with the company's response regarding the LIBERTY studies.
Special considerations including issues related to equity or equality		Black African and African-Caribbean origin, who are 2-3 times more likely to develop UF than white women, may be more opposed to surgery due to cultural and religious beliefs.		The ERG's clinical expert is in agreement with the company's position

		Additionally, some women will choose to decline surgery in order to avoid impacting their personal circumstances with respect to work and family commitments such as childcare, etc.		

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The ERG'S appraisal of the company's systematic review methods is summarised in Table 4.

Table 4 ERG's appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research, DARE and CDSR for evidence syntheses. Relevant conference proceedings were also searched. Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	Although the submission focused on GnRH agonists as the comparator, the searches for clinical evidence included all therapeutic options so all relevant results will have been found.
Was study selection conducted by two or more reviewers independently?	Yes	Appendix D1.1, page 234: "*Abstracts and titles were reviewed by two independent reviewers in a double-blind process against the inclusion to identify potentially relevant studies*"
Was data extraction conducted by two or more reviewers independently?	Yes	At clarification: "*Two reviewers were involved in data extraction for both the initial and update SLRs and worked independently*"
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes (for the RCTs)	Document B, page 63: "*LIBERTY 1, LIBERTY 2 and LIBERTY 3 were assessed for quality using*

		the York Centre for Reviews and Dissemination [CRD] guidance for undertaking reviews in healthcare". The ERG considers these criteria to be appropriate. LIBERTY 3 is not an RCT so the CRD criteria are mainly not applicable. The CRD criteria were also used for the assessment of PEARL I and PEARL II.
Was the risk of bias assessment conducted by two or more reviewers independently?	Yes	At clarification: "*Two reviewers conducted the risk of bias assessment. The reviewers worked independently then came together to discuss and agree the assessment findings"*
Was identified evidence synthesised using appropriate methods?	No	The ERG believes a network meta-analysis should have been used for the primary efficacy outcome and that a comparison of relugolix CT versus GnRHa presented for the secondary outcomes. Full details of the ITC for MBL should have been provided and the associated uncertainty incorporated into the economic model.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. The results are presented in Table 5.

Table 5 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies, which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are provided in Document B, Section B.2 of the CS. The company presents clinical effectiveness evidence from two phase-3, multicentre, international, double-blind RCTs, LIBERTY 1, LIBERTY 2, conducted between March 2017 and July 2019 and one phase 3 open-label extension study of the LIBERTY 1 and LIBERTY 2 trials, LIBERTY 3. The methods of the three trials are summarised in Document B, Table 6 of the CS and reproduced in Table 6 below. Details of LIBERTY 1, LIBERTY 2 and LIBERTY 3 are reported in sections B.2.2 and B.2.3 of the CS and the participant flow of the studies are presented in Appendix D.1.2. LIBERTY 1 was conducted at 80 sites (USA, Brazil, Italy, Poland, South Africa and the UK) and LIBERTY 2 at 99 sites (USA, Belgium, Brazil, Chile, Czech Republic, Hungary, Poland and South Africa). All three LIBERTY studies were funded by Myovant Sciences. The objective of LIBERTY 1 and LIBERTY 2 was to assess the effectiveness of relugolix combination therapy (CT) compared with placebo for 24 weeks and the methods used in the two trials were identical. Participants were randomly assigned in a 1:1:1 ratio to receive either:

- relugolix CT for 24 weeks: 40 mg relugolix in combination with 1 mg oestradiol and 0.5 mg norethisterone or
- delayed relugolix CT: 40 mg relugolix monotherapy for 12 weeks followed by relugolix CT (as above) for 12 weeks or
- placebo for 24 weeks.

The purpose of the relugolix delayed arm was to allow for the comparison of BMD and vasomotor symptoms in the combination and monotherapy arms during the first 12 weeks of the trial. This arm is not further considered in the clinical effectiveness evidence for this appraisal, which will focus on the relugolix CT versus placebo comparison, as per the licensed indication for relugolix CT. The key eligibility criteria for LIBERTY 1 and LIBERTY 2 are reported in Document B, Table 7 and the eligibility criteria in full are presented in Appendix M1.1, Table 116 of the CS. The study population in LIBERTY 1 and LIBERTY 2 was premenopausal women aged 18

to 50 years with HMB associated with UF (≥80mL per cycle for two cycles or ≥160mL for one cycle as measured by the alkaline haematin [AH] method during the screening period). People who were expected to undergo gynaecological surgery or ablation procedures for UF within 6 months of enrolment into the study were excluded.

LIBERTY 3 is a 28-week open-label extension to LIBERTY 1 and LIBERTY 2. Eligible participants were those who completed LIBERTY 1 or LIBERTY 2 and all received open-label relugolix CT.

Table 6 Comparative summary of the methodology of the relugolix CT studies [reproduced from Table 6, Document B of the CS]

Trial number (acronym)	MVT-601-3001 (LIBERTY 1)	MVT-601-3002 (LIBERTY 2)	MVT-601-3003 (LIBERTY 3)
Location	80 centres globally, including centres in the USA, Brazil, Italy, Poland, South Africa and the UK. Approximately 25% of patients were enrolled at sites outside of North America.	99 centres globally, including centres in the USA, Belgium, Brazil, Chile, Czech Republic, Hungary, Poland and South Africa. Approximately 25% of patients were enrolled at sites outside of North America.	149 centres in the USA, Belgium, Brazil, Chile, Czech Republic, Hungary, Italy, Poland and South Africa.
Trial design	Phase-3 randomised, double-blind, placebo-controlled trial		Phase-3, open-label, single-arm, long-term efficacy and safety extension study
Eligibility criteria for participants	Premenopausal women 18 to 50 years of age with regularly occurring menstrual periods of <14 days' duration with cycle of 21 to 38 days; who had a diagnosis of fibroids as confirmed on ultrasonography and who had HMB, as assessed by the AH method, were eligible		Women who completed 24 weeks of study drug treatment and study participation in either LIBERTY 1 or LIBERTY 2. They were not expected to undergo gynaecological surgery or ablation procedures for UF within the study period, including during the Safety Follow-up period. Negative urine pregnancy test at Week 24/Baseline visit.
Trial drugs	Participants were randomly assigned, in a 1:1:1 ratio, by means of an interactive website to receive blinded placebo for 24 weeks, relugolix CT (40 mg relugolix in combination with 1 mg oestradiol and 0.5 mg norethisterone acetate) for 24 weeks, or relugolix-delayed CT (relugolix monotherapy followed by relugolix CT, each for 12 weeks).* • LIBERTY 1: 388 randomised: relugolix CT (128), placebo (128), relugolix-delayed CT (132) • LIBERTY 2: 382 randomised: relugolix CT (126), placebo (129), relugolix-delayed CT (127)		477 women enrolled to receive open-label relugolix CT (40 mg relugolix in combination with 1 mg oestradiol and 0.5 mg norethisterone acetate) for 28 weeks. This comprised >75% of patients who completed one of the parent studies (LIBERTY 1 or LIBERTY 2).

	Trial visits occurred at baseline and every 4 weeks for 24 weeks.		
Primary outcomes	The proportion of women 'responding' in the relugolix CT versus the placebo group where a 'responder' was classified as a woman who achieved an MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the AH method.		The proportion of women who achieved or maintained an MBL volume of < 80 mL and at least a 50% reduction from parent study baseline MBL volume to the last 35 days of treatment, as measured by the AH method
Other outcomes used in the economic model/specified in the scope	Outcomes in the model: • MBL volume and change in MBL volume (used to derive utility) • Adverse events • Quality of life Other outcomes in the scope: • Achievement of amenorrhoea • Uterine volume • Uterine fibroids volume • Pain (associated with uterine fibroids) • Change in haemoglobin		Outcomes in the model: • MBL volume and change in MBL volume (used to derive utility) • Quality of life Other outcomes in the scope: • Adverse events • Achievement of amenorrhoea • Uterine volume • Uterine fibroids volume • Pain (associated with uterine fibroids)
Pre-planned subgroups	N/A	N/A	N/A

***** The relugolix-delayed CT group was included to allow for the comparison of BMD and vasomotor symptoms in the combination and monotherapy groups during the first 12 weeks of the trial. This arm does not relate to the licenced indication for relugolix CT.

The company assessed the risk of bias of LIBERTY 1, 2 and 3 using an adapted version of the Centre for Reviews and Dissemination checklist for RCTs and concluded that the LIBERTY 1 and LIBERTY 2 RCTs and the LIBERTY 3 open-label extension study were of good quality.[12] In general, the ERG agrees with the findings of the company's assessment.

Details of the baseline characteristics of the modified ITT (mITT) populations of LIBERTY 1 and LIBERTY 2 (i.e. randomised participants who received any amount of the study drug; efficacy analyses were performed by treatment group as randomised) and the safety population of LIBERTY 3 (i.e. participants who received any amount of open-label study drug; safety data were analysed by parent study treatment group by actual treatment received) are presented in Document B Tables 9, 10, 11 and 14 of the CS and summarised in Table 7 below.

Table 7 Baseline characteristics of participants in the modified ITT populations of LIBERTY 1 and LIBERTY 2 and the safety population of LIBERTY 3 [adapted from Tables 9, 10, 11, and 14, Document B of the CS, and the LIBERTY 3 CSR]

	LIBERTY 1[a]			LIBERTY 2[a]			LIBERTY 3[b]		
	Relugolix CT (n=128)	**Relugolix-delayed CT (n=132)**	**Placebo (n=127)**	**Relugolix CT (n=125)**	**Relugolix-delayed CT (n=127)**	**Placebo (n=129)**	**Relugolix CT (n=163)**	**Relugolix-delayed CT (n=149)**	**Placebo (n=164)**
Age, years, mean (SD)	42.5 (5.0)	41.3 (5.4)	42.2 (5.7)	42.4 (5.4)	42.1 (5.3)	41.8 (5.3)	42.6 (5.1)	42.1 (5.6)	41.9 (5.4)
Race, n (%)									
White	64 (50.0)	53 (40.2)	56 (44.1)	58 (46.4)	50 (39.4)	49 (38.0)	85 (52.1)	51 (34.2)	71 (43.3)
Black or African American	59 (46.1)	67 (50.8)	65 (51.2)	62 (49.6)	66 (52.0)	74 (57.4)	69 (42.3)	81 (54.4)	88 (53.7)
Other	5 (3.9)	12 (9.1)	6 (4.7)	2 (1.6)	8 (6.3)	5 (3.9)	6 (3.7)	15 (10.1)	4 (2.4)
Not reported	0 (0)	0 (0)	(0)	3 (2.4)	3 (2.4)	1 (<1%)	3 (1.8)	2 (1.3)	1 (<1%)
BMI, kg/m^2, mean (SD)	31.4 (7.6)	31.4 (7.3)	32.3 (7.5)	31.0 (6.6)	30.8 (5.7)	32.1 (7.6)	31.4 (7.0)	31.0 (6.4)	32.6 (7.5)
MBL volume, mL, mean (SD)	239.4 (180.3)	228.9 (159.6)	218.8 (125.0)	246.7 (186.0)	227.4 (134.4)	211.8 (129.9)	248.7 (197.0)	238.8 (155.3)	216.0 (123.8)
Haemoglobin, g/dL, mean (SD)	11.2 (1.6)	11.1 (1.7)	11.4 (1.4)	11.3 (1.5)	11.1 (1.6)	11.1 (1.6)	11.4 (1.5)	11.0 (1.6)	11.2 (1.5)
Index UF volume, cm^3, mean (SD)	71.9 (128.1)	93.8 (143.8)	71.8 (124.0)	73.7 (126.7)	78.9 (157.5)	74.1 (123.0)	80.0 (145.1)	91.5 (137.8)	74.2 (128.1)

	LIBERTY 1[a]			LIBERTY 2[a]			LIBERTY 3[b]		
	Relugolix CT (n=128)	**Relugolix-delayed CT (n=132)**	**Placebo (n=127)**	**Relugolix CT (n=125)**	**Relugolix-delayed CT (n=127)**	**Placebo (n=129)**	**Relugolix CT (n=163)**	**Relugolix-delayed CT (n=149)**	**Placebo (n=164)**
Uterine volume, cm^3, mean (SD)	379.1 (316.8)	469.9 (427.9)	397.8 (324.9)	387.7 (344.0)	402.7 (371.1)	407.9 (402.0)	386.7 (320.5)	442.4 (370.9)	401.5 (351.5)
Surgery for UF									
Yes	20 (15.6)	15 (11.4)	13 (10.2)	11 (8.8)	15 (11.8)	11 (8.5)	21 (12.9)	14 (9.4)	17 (10.4)
No	108 (84.4)	117 (88.6)	114 (89.8)	114 (91.2)	112 (88.2)	118 (91.5)	142 (87.1)	135 (90.6)	147 (89.6)
UAE							NR	NR	NR
Yes	2 (1.6)	2 (1.5)	1 (0.8)	3 (2.4)	0 (0)	0 (0)			
No	126 (98.4)	130 (98.5)	126 (99.2)	122 (97.6)	127 (100)	129 (100)			
UFS-QoL (BPD subscale), mean (SD)	66.8 (22.1)	68.5 (22.9)	71.4 (21.3)	70.7 (20.8)	72.0 (22.9)	70.0 (20.3)	67.2 (21.0)	72.7 (19.0)	72.6 (19.7)

Note. [a]mITT population, [b]Safety population
CT: combined therapy, SD: standard deviation, BMI: body mass index, MBL: menstrual blood loss, UF: uterine fibroids, UAE: uterine artery embolisation

In general, baseline characteristics were balanced within and across LIBERTY 1 and LIBERTY 2. Mean age was 42 years in LIBERTY 1 and 42.1 in LIBERTY 2. The majority of participants were Black or African American in both trials. Mean BMI of all randomised groups was ≥30, indicating that participants were generally in the obese range. The ERG's clinical expert is of the opinion that this is not representative of women seen in clinical practice and that women of healthy weight are equally likely to have uterine fibroids (UF). Adipose tissue produces oestrogen and obese women have a greater proportion of adipose tissue than women of healthy weight, but UF treatments targeting oestrogen production tackle only the oestrogen produced by the ovaries and not that produced by adipose tissue. Therefore, in the population of LIBERTY 1 and LIBERTY 2, the effects of relugolix CT may have been attenuated due to the mean BMI of participants being in the obese range.

The CS states that the disease-specific characteristics of participants in LIBERTY 1 and LIBERTY 2 are consistent with the population relevant to this appraisal – in particular, mean menstrual blood loss (MBL) at baseline ranged from 211.8mL (LIBERTY 2, placebo arm) to 246.7mL (LIBERTY 2, relugolix CT arm). Overall, the ERG's clinical expert is satisfied that the disease-specific baseline characteristics of the participants in LIBERTY 1 and LIBERTY 2 are representative of women with UF seen in clinical practice in the UK.

3.2.2 Primary and secondary efficacy endpoints

The outcome measures listed in the NICE final scope for this appraisal were: change in MBL volume; time to MBL response; pain; uterine fibroid volume (UFV) / uterine volume (UV); haemoglobin levels; rates and route of surgery; impact on fertility and pregnancy and teratogenic effects; change in bone mineral density (BMD); mortality; adverse effects of treatment, including but not limited to vasomotor symptoms, incontinence, and pelvic organ prolapse; and health-related quality of life. Rates and route of surgery and the impact on fertility and pregnancy and teratogenic effects were not measured in the CS. Results for the primary and secondary endpoints assessed in the CS are presented below.

Primary endpoint: LIBERTY 1 and LIBERTY 2

The primary endpoint of LIBERTY 1 and LIBERTY 2 was achieving a response, defined as both a volume of MBL of less than 80 ml and a reduction of at least 50% from the baseline volume of MBL, as measured by the alkaline haematin (AH) method, over the last 35 days of the treatment period. In LIBERTY 1, the primary efficacy endpoint was achieved at a higher frequency in the relugolix CT group (94 participants, 73.4%) compared with the placebo group (24 patients, 18.9%), and the difference between the groups was statistically significant (54.5%, 95% CI 44.3% to 64.78%, $p < 0.0001$). Similarly, in LIBERTY 2, a greater proportion of participants in the relugolix CT group achieved the primary endpoint (89 participants, 71.2%) compared with the placebo group (19 participants, 14.7%) with a statistically significant difference between the groups (56.47%, 95% CI 46.45% to 66.49%, $p < 0.0001$).

Secondary endpoint: LIBERTY 1 and LIBERTY 2

The secondary efficacy endpoints reported in the CS are the following:

- MBL volume: Figure 8, Section B.2.6 of the CS, shows that the least-squares (LS) mean percent reduction from baseline to Week 24 in MBL volume was greater in the relugolix CT group than that in the placebo group in both LIBERTY 1 (-84.3% versus -23.2%) and LIBERTY 2 (-84.3% versus -15.1%) and the difference between the groups was statistically significant ($p < 0.001$ for both comparisons). Figure 9, Section B.2.6 of the CS, shows that a significant reduction in MBL volume occurred by Week 4, the first post-baseline assessment, and was sustained through Week 24.
- Time to MBL response (MBL volume < 80 mL and ≥ 50% reduction from baseline): The CSRs report that, based upon a Kaplan-Meier analysis, the median time to achieve a first response (the primary endpoint) in the relugolix CT group was 8.3 weeks in LIBERTY 1 and 8.4 weeks in LIBERTY 2, compared with 25.1 weeks and 27.1 weeks, respectively, in the placebo groups (nominal $p < 0.0001$ for both comparisons) (Figure 8, Section 5.1.2.1.1, page 102 of the LIBERTY 1 CSR; Figure 9, Section 5.1.2.1.1, page 106 of the

LIBERTY 2 CSR).[13, 14] This should be interpreted with caution due to the small number of participants in the analysis.

- Amenorrhoea: 67 (52.3%) and 63 (50.4%) of women who received relugolix CT in LIBERTY 1 and LIBERTY 2, respectively, achieved amenorrhea over the last 35 days of treatment compared with 7 (5.5%) and 4 (3.1%) women who received placebo ($p<0.001$ for both comparisons). Additionally, a greater proportion of participants in the relugolix CT group compared with the placebo group in both trials achieved sustained amenorrhoea, defined as the maintenance of amenorrhea at every subsequent visit after the initial achievement of amenorrhoea, at Weeks 8, 12, 16, 20, and 24 (nominal $p < 0.0001$).
- Bleeding and pelvic discomfort (BPD) was defined as the LS mean change from baseline to Week 24 as measured by the uterine fibroid health and symptom-related quality of life (UFS-QoL) BPD scale score (score range 0-100 with higher score value indicating greater distress). In LIBERTY 1, the UFS-QoL BPD score decreased (improved) by -45.0 points in the relugolix CT group, which was greater than the change observed in the placebo group (-16.1 points) ($p < 0.0001$). Similar results were reported for LIBERTY 2, with a UFS-QoL BPD score reduction of -51.7 points in the relugolix CT group compared with a reduction of -18.3 points in the placebo group ($p < 0.0001$).
- Pain associated with uterine fibroids: Pain associated with uterine fibroids was assessed in the subset of pain evaluable participants who had moderate-to-severe pain at baseline (maximum numerical rating scale [NRS] score ≥ 4). Approximately 50% of the participants were considered evaluable for pain (for relugolix CT and placebo, n = 58 and 69, respectively, in LIBERTY 1; and n = 68 and 82, respectively, in LIBERTY 2). In both trials, the proportions of evaluable participants who had achieved reductions to minimal or no pain (maximum NRS ≤ 1) were higher in the relugolix CT group than in the placebo group (LIBERTY 1: 43.1% versus 10.1%, $p < 0.0001$; LIBERTY 2: 47.1% versus 17.1%, $p < 0.0001$).
- Uterine volume (UV) / Primary uterine fibroid volume (UFV): based on the LS mean percent change from baseline to Week 24, the overall UV reduction in both the LIBERTY 1 and LIBERTY 2 trials was greater for relugolix CT

than placebo (LIBERTY 1: -12.9% versus 2.2%; p<0.001; LIBERTY 2: -13.8% versus -1.5%; p = 0.008). The reduction for primary UFV was numerically favourable for relugolix CT compared with placebo, although the difference between groups did not reach statistical significance (LIBERTY 1: -12.4% versus -0.3%; p = 0.09; LIBERTY 2: -17.4% versus -7.4.0%; p = 0.22)

- Change in haemoglobin levels: Defined as the proportion of women with anaemia (haemoglobin ≤10.5 g/dL) at baseline who achieve an increase of >2 g/dL from baseline to Week 24. Among the participants who had baseline anaemia (30 and 23 women in the relugolix CT group and placebo group, respectively, in LIBERTY 1 and 31 and 37 in LIBERTY 2), the outcome was significantly better with relugolix CT than with placebo (LIBERTY 1: 50.0% vs. 21.7%, p = 0.0377; LIBERTY 2: 61.3% vs 5.4%, p < 0.0001).

A summary of key outcomes in LIBERTY1 and LIBERTY2 is presented in Table 8.

Table 8 Summary of LIBERTY 1 and LIBERTY 2 outcomes [adapted from Table 18, Document B of the CS]

Endpoint	LIBERTY 1		LIBERTY 2	
	Placebo (n=127)	Relugolix CT (n=128)	Placebo (n=129)	Relugolix CT (n=125)
Primary Efficacy Endpoint				
Proportion of women with MBL volume < 80 mL & ≥ 50% reduction*				
n (%) Difference 95% CI (unadjusted) p-value	24 (19%)	94 (73%) 55% (44%, 65%) < 0.001	19 (14.73%)	89 (71%) 56% (46%, 66%) < 0.001
Secondary Efficacy Endpoint				
Proportion of women who achieved amenorrhoea over the last 35 days of treatment				
n (%) Difference (95% CI) p-value	7 (6%)	67 (52%) 47% (37%, 56%) < 0.001	4 (3%)	63 (50%) 47% (38%, 57%) < 0.001
% change in MBL volume (baseline to Week 24)				
LS mean (SD) Difference (95% CI) p-value	-23.2 (±4.6)	-84.3 (±4.7) -61.1 (-73.5, -48.6) < 0.001	-15.1 (±5.5)	-84.3 (±5.5) -69.2 (-84.1, -54.3) < 0.001
Change in UFS-QoL BPD score (baseline to Week 24º)				
LS mean (SD) Difference (95% CI) p-value	-16.1 (±2.8)	-45.0 (±2.9) -28.9 (-36.3, -21.5) < 0.001	-18.3 (±2.9)	-51.7 (±2.9) -33.4 (-41.2, -25.5) < 0.001
Proportion of women with anaemia (i.e. ≤10.5 g/dL) at baseline who achieved a Hb increase of > 2 g/dL (baseline to Week 24)				
n/N (%) Difference (95% CI) p-value	5/23 (22%)	15/30 (50%) 28% (4%, 53%) 0.04	2/37 (5%)	19/31 (61%) 56% (37%, 75%) < 0.001
Proportion of women who achieved a maximum NRS 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 (%) Difference (95% CI) p-value	7/69 (10%)	25/58 (43%) 33% (18%, 48%) < 0.001	14/82 (17%)	32/68 (47%) 30% (16%, 44%) < 0.001
% change in primary UFV (baseline to Week 24)				

LS mean (SD) Difference (95% CI) p-value	-0.3 (±5.40)	-12.4 (±5.62) -12.1 (-26.3, 2.0) 0.09	-7.4 (±5.9)	-17.4 (±5.9) -10.0 (-25.8, 5.8) 0.2153
% change in UV (baseline to Week 24)				
LS mean (SD) Difference (95% CI) p-value	2.2 (±3.01)	-12.9 (±3.1) -15.1 (-23.0, -7.3) <0.001	-1.5 (±3.4)	-13.8 (±3.4) -12.2 (-21.3, -3.2) 0.008

Note: * from baseline MBL volume. º score as measured by the UFS-QoL (Q1, Q2, Q5).
CI: Confidence Interval; CT: Combination Therapy; Hb: Haemoglobin; LS: least-squares; MBL: menstrual blood loss; NRS: numerical rating scale; UFS-QoL BPD: uterine fibroid health and symptom-related quality of life bleeding and pelvic discomfort; UFV: uterine fibroid volume; UV: uterine volume

Primary and secondary endpoints in LIBERTY 3

The company also presents the long-term results of the 28-week LIBERTY 3 extension study, in which women who completed one of 24-week parent studies LIBERTY 1 or LIBERTY 2 entered the open-label phase.

The primary endpoint was the proportion of responders, defined as women who achieved or maintained an MBL volume of < 80 mL and at least a 50% reduction from parent study baseline MBL volume to the last 35 days of treatment, as measured by the AH method. Key secondary endpoints in LIBERTY 3 included achievement of amenorrhoea, improvement of anaemia assessed by changes in haemoglobin concentrations, UFS-QoL score, uterine volume and uterine fibroid volume. Primary and secondary endpoints are summarised in Table 9 below.

Table 9 Summary of outcomes assessed in the LIBERTY 3 extension study

	Randomisation in parent trial	
	Placebo (N = 164)	**Relugolix CT (N = 163)**
Proportion of responders[a] at Week 52, n (%)	[redacted]	[redacted]
Proportion of patients who achieved amenorrhoea at Week 52, n (%)	[redacted]	[redacted]
Proportion of women with anaemia (i.e. ≤10.5 g/dL) at parent study baseline who achieved a Hb increase of > 2 g/dL at Week 52, n/N (%)	[redacted]	[redacted]
Change in UFS-QoL BPD scale score from parent study baseline to Week 52	[redacted]	-51.3 points
Proportion of responders[b] on the UFS-QoL BPD scale at Week 52	[redacted]	[redacted]
Percent change in uterine volume from parent study baseline to Week 52	[redacted]	[redacted]
Percent change in uterine fibroid volume from parent study baseline to Week 52	[redacted]	[redacted]

[a] MBL volume < 80 mL and ≥ 50% reduction from baseline over the last 35 days of treatment
[b] At least a 20-point reduction
CT: Combination Therapy; Hb: Haemoglobin; UFS-QoL BPD: uterine fibroid health and symptom-related quality of life bleeding and pelvic discomfort;

3.2.3 Subgroup analyses related to the primary endpoint

Subgroup analyses were not specified in the NICE final scope. Section B.2.4 of the CS stated that subgroup analyses of the primary efficacy endpoint were conducted in LIBERTY 1, LIBERTY 2, and LIBERTY 3 trials. Details of these subgroup analyses were provided by the company at the clarification stage.

In LIBERTY 1 and LIBERTY 2, subgroup analyses were conducted for the following groups: geographical region, age, baseline MBL volume, race, body mass index (BMI), uterine volume at baseline, maximum NRS score at baseline and history of prior pregnancy (Figure 2 and Figure 3 in the clarification response). LIBERTY 3 included the following four additional subgroups: MBL volume at parent study baseline, uterine fibroid volume, and alcohol use and smoking status (see Figure 4 in the clarification response).

In all three studies, the direction of effect across all subgroups appears generally consistent with that observed in the overall study population. However, across all studies, the size of the effect was smaller for Black/African American women relative to White women, and for women with larger uterine volumes (≥ 300 cm^3) relative to those with smaller uterine volume (<300 cm^3). Smaller effect size was also observed for women with greater MBL volume at baseline (≥ 225 mL) in LIBERTY 1 and 3.

3.2.4 Adverse events

LIBERTY 1 and LIBERTY 2

The safety population of LIBERTY 1 and LIBERTY 2 included all participants who received any amount of study drug (LIBERTY 1: relugolix CT, n = 128; placebo, n = 127; LIBERTY 2: relugolix CT, n = 126; placebo, n = 129). The methods used to assess safety are reported in Sections B.2.4 and B.2.10, Document B of the company submission, and are considered appropriate by the ERG. Tables 28 and 29 in Document B of the CS show adverse events for LIBERTY 1 and LIBERTY 2 and are reproduced as Table 10 below. The ERG's clinical expert considers the overall incidence and the types of adverse events for relugolix CT akin to those expected in clinical practice in this clinical population.

Table 10 Summary of adverse events in the LIBERTY 1 and LIBERTY 2 safety population [reproduced from Tables 28 and 29, Document B of the CS]

Characteristics N (%)	LIBERTY 1		LIBERTY 2	
	Placebo (N=127)	Relugolix CT (N=128)	Placebo (N=129)	Relugolix CT (N=126)
Any	84 (66%)	79 (62%)	76 (59%)	76 (60%)
Leading to discontinuation	5 (4%)	7 (5%)	6 (5%)	3 (2%)
Serious	2 (2%)	7 (5%)	4 (3%)	1(1%)
Fatal outcome	0	0	0	0
Adverse event reported in >5% of participants in any group				
Hot flush	10 (8%)	14 (11%)	5 (4%)	7 (6%)
Headache	19 (15%)	14 (11%)	15 (12%)	11 (9%)
Hypertension	0	7 (5%)	4 (3%)	5 (4%)
Arthralgia	4 (3%)	4 (3%)	4 (3%)	1 (1%)
Cough	7 (6%)	1 (1%)	4 (3%)	0
Nausea	6 (5%)	4 (3%)	10 (8%)	6 (5%)
URTI	3 (2%)	1 (1%)	7 (5%)	6 (5%)
Anaemia	6 (5%)	4 (3%)	8 (6%)	2 (2%)
Fatigue	5 (4%)	4 (3%)	2 (2%)	1 (1%)

CT: combination therapy; URTI: upper respiratory tract infection

In LIBERTY 1, during the 24-week study period, the proportion of women treated with relugolix CT who experienced 'any' adverse events was 62% compared with 66% of those treated with placebo. In LIBERTY 2 the incidence of adverse events was 60% and 59%, respectively. The most frequently reported adverse events in any treatment group included headache and hot flush.

The most frequently reported vasomotor symptom through week 24, by preferred term, was hot flush, which was reported more frequently in the relugolix CT group than in the placebo group in both trials (14 [11%] versus 10 [8%] in LIBERTY 1; 7 [6%] versus 5 [4%] in LIBERTY 2). The hot flush events were reported mostly to be Grade 1 or Grade 2 in severity.[13, 14]

No deaths were reported across both trials.

Least-squares mean percent changes from baseline in BMD at the lumbar spine (L1 - L4) in the relugolix CT group compared with placebo at week 24 were -0.356% versus 0.052% for LIBERTY 1 and -0.126% versus 0.315% for LIBERTY 2, with no

significant difference observed between the groups. Similarly, the percent change to week 24 in BMD at the total hip was similar in the relugolix CT and placebo groups in both trials (LIBERTY 1: 0.023% versus 0.549%; LIBERTY 2: -0.0173% versus 0.044%) (CSR, Table 32, page 145 for LIBERTY 1; Table 29, page 139 for LIBERTY 2).[13, 14] BMD was measured by means of a dual-energy x-ray absorptiometry (DEXA).

Serious adverse events (SAE) in LIBERTY 1 were reported for 7 participants (5.5%) in the relugolix CT group and 2 participants (1.6%) in the placebo group. In the relugolix CT group two SAEs were related to expulsion/prolapse of uterine fibroid, and one of these events was assessed as related to study drugs. In LIBERTY 2, SAEs were reported for 1 woman (0.8%) in the relugolix CT group and 4 women (3.1%) in the placebo group, none of them were considered to be related to the study drug.

LIBERTY 3

Cumulatively over the 52-week treatment period encompassing the parent (24 weeks) and open-label extension (28 weeks) studies, [redacted] of participants in the relugolix CT group reported at least one treatment-emergent adverse event (TEAE). [redacted] of the participants in this group experienced one TEAE during the open-label extension study. Grade 3 or higher events were reported for [redacted] in the relugolix CT group, with the event first occurring in the open-label extension study for [redacted]. Among those in the placebo group in the parent study, at least one TEAE was reported for [redacted] cumulatively and [redacted] during the extension. [redacted] were reported during the study. [redacted] The ERG agrees with the company's conclusions.

A summary of serious adverse events reported during LIBERTY 3 are provided in Table 32 of the CS and reproduced as Table 11 below.

Table 11 Summary of serious adverse events by System Organ Class and Preferred Term from the extension safety population of LIBERTY 3 [reproduced from Table 32, Document B of the CS]

Characteristics	LIBERTY 3 Randomisation in parent trial			
	Placebo (N=164)		Relugolix CT (N=163)	
	Cumulative	Extension	Cumulative	Extension
No. of patients with at least one serious AE n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous detachment	[redacted]	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cholecystitis	[redacted]	[redacted]	[redacted]	[redacted]
Cholecystitis acute	[redacted]	[redacted]	[redacted]	[redacted]
Cholelithiasis	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Appendicitis	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
Ankle fracture	[redacted]	[redacted]	[redacted]	[redacted]
Avulsion fracture	[redacted]	[redacted]	[redacted]	[redacted]
Forearm fracture	[redacted]	[redacted]	[redacted]	[redacted]
Radius fracture	[redacted]	[redacted]	[redacted]	[redacted]
Road traffic accident	[redacted]	[redacted]	[redacted]	[redacted]
Wrist fracture	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Blood pressure increased	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Intervertebral disc protrusion	[redacted]	[redacted]	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts & polyps)	[redacted]	[redacted]	[redacted]	[redacted]
Uterine leiomyoma	[redacted]	[redacted]	[redacted]	[redacted]
Uterine myoma expulsion	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Syncope	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]
Panic attack	[redacted]	[redacted]	[redacted]	[redacted]

Renal and urinary disorders		[redacted]			[redacted]			[redacted]			[redacted]	
Nephrolithiasis		[redacted]			[redacted]			[redacted]			[redacted]	
Reproductive system and breast disorders		[redacted]			[redacted]			[redacted]			[redacted]	
Menorrhagia		[redacted]			[redacted]			[redacted]			[redacted]	
Metrorrhagia		[redacted]			[redacted]			[redacted]			[redacted]	
Ovarian cyst ruptured		[redacted]			[redacted]			[redacted]			[redacted]	
Uterine haemorrhage		[redacted]			[redacted]			[redacted]			[redacted]	

Abbreviations: AE = adverse event; n = number of patients in subset; N = number of patients.
Note: Percentages are based on the total number of patients in each treatment group.
Note: Patients with multiple events for a given preferred term or system organ class were counted only once for each preferred term and system organ class.
Note: Cumulative represents the entire treatment period since randomisation in study LIBERTY 1 or LIBERTY 2. Data in the Extension columns relate to the treatment period since enrolment into LIBERTY 3 only.

3.2.5 Meta-analyses

The company did not perform a meta-analysis.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

For the ITC, the company presents evidence from LIBERTY 1, LIBERTY 2 and two further Phase-3 double-blind RCTs (PEARL I, PEARL II). PEARL I assessed the efficacy and safety of ulipristal (UPA) versus placebo for the pre-operative treatment of symptomatic UF and PEARL II assessed the efficacy and safety of UPA versus the GnRH agonist leuprolide acetate in the pre-operative treatment of symptomatic UF.

The baseline demographic characteristics of participants in PEARL I and PEARL II are presented in Table 121 and Table 122, Document B of the CS and reproduced as Tables 12 and 13 below.

Table 12 Summary of the baseline demographic characteristics of PEARL I [reproduced from Table 121, Appendix M, Document B of the CS]

Characteristic		Treatment Group			Total (N=241)
		Placebo (N=48)	UPA 5 mg (N=95)	UPA 10 mg (N=98)	
Age	**N**	48	95	98	241
	Mean	41.6	41.2	42.0	41.6
	SD	5.6	5.9	5.5	5.7
	Median	42.5	42.0	43.0	43.0
	Min, Max	26, 50	24, 50	23, 50	23, 50
Ethnic Origin	**White**	41 (85.4%)	84 (88.4%)	87 (88.8%)	212 (88.0%)
	Black	0	0	0	0
	Asian	7 (14.6%)	11 (11.6%)	11 (11.2%)	29 (12.0%)
	Hispanic	0	0	0	0
	Other	0	0	0	0
Fertility Status	**Not of Childbearing Potential**	5 (10.4%)	8 (8.4%)	6 (6.1%)	19 (7.9%)
	Of Childbearing Potential	43 (89.6%)	87 (91.6%)	92 (93.9%)	222 (92.1%)
	Missing	0	0	0	0
Weight (kg)	**N**	48	95	98	241
	Mean	64.70	70.05	67.12	67.79
	SD	12.47	13.60	10.25	12.22
	Median	60.40	68.00	66.00	66.00
	Min, Max	45.0, 106.5	42.0, 120.0	48.9, 95.0	42.0, 120.0
Height (cm)	**N**	48	95	98	241
	Mean	162.3	164.3	163.9	163.7
	SD	6.6	6.5	6.1	6.4
	Median	163.5	164.0	164.0	164.0
	Min, Max	143, 176	150, 178	145, 178	143, 178
Body Mass Index (kg/m^2)	**N**	48	95	98	241
	Mean	24.55	25.93	25.03	25.29
	SD	4.37	4.63	3.92	4.32
	Median	24.49	25.39	24.87	24.96
	Min, Max	18.0, 40.1	18.1, 39.2	18.1, 37.6	18.0, 40.1

Table 13 Summary of baseline demographic characteristics of PEARL II [reproduced from Table 122, Appendix M, Document B of the CS]

Characteristic		Treatment Group			Total (N=301)
		UPA 5 mg (N=97)	UPA 10 mg (N=103)	GnRH-agonist (N=101)	
Age	N	97	103	101	301
	Mean	40.1	40.7	40.3	40.4
	SD	6.2	6.3	6.2	6.2
	Min, Max	25, 50	20, 50	24, 51	20, 51
Ethnic Origin	White	83 (85.6%)	88 (85.4%)	85 (84.2%)	256 (85.0%)
	Black	9 (9.3%)	11 (10.7%)	9 (8.9%)	29 (9.6%)
	Asian	1 (1.0%)	1 (1.0%)	0	2 (0.7%)
	Hispanic	3 (3.1%)	2 (1.9%)	5 (5.0%)	10 (3.3%)
	Other	1 (1.0%)	1 (1.0%)	2 (2.0%)	4 (1.3%)
Fertility Status	Not of Childbearing Potential	4 (4.1%)	4 (3.9%)	3 (3.0%)	11 (3.7%)
	Of Childbearing Potential	93 (95.9%)	99 (96.1%)	98 (97.0%)	290 (96.3%)
Weight (kg)	N	97	103	100	300
	Mean	68.26	68.84	67.92	68.35
	SD	12.28	12.72	12.16	12.36
	Min, Max	48.5, 108.0	46.0, 111.0	48.0, 119.0	46.0, 119.0
Height (cm)	N	97	103	100	300
	Mean	163.7	162.3	165.2	163.7
	SD	6.4	6.7	5.9	6.4
	Min, Max	146, 180	146, 180	147, 178	146, 180
Body Mass Index(kg/m^2)	N	97	103	100	300
	Mean	25.44	26.15	24.86	25.49
	SD	4.08	4.74	4.06	4.33
	Min, Max	19.4, 37.8	18.1, 39.8	18.4, 39.3	18.1, 39.8

Disease-specific baseline characteristics of participants in PEARL I and PEARL II are presented in Table 14. The CS presents a comparison of the patient characteristics of the LIBERTY and PEARL studies in section M1.6 of the Appendices. The demographic characteristics are balanced within the PEARL I and PEARL II studies and appear similar between the studies. The percentage of White ethnic origin was much higher in PEARL studies compared to LIBERTY studies. The BMI of the participants in LIBERTY studies were higher compared to PEARL studies which will have a negative effect on the relative effect of relugolix CT. The ERG is concerned though participants in the PEARL studies were expected to receive surgery after 13

weeks while those in the LIBERTY studies appear unlikely to be receiving surgery. While this is not necessarily shown in the baseline characteristics it does suggest two different populations in the respective studies.

Table 14 Baseline disease-specific characteristics of participants in PEARL I and PEARL II [adapted from Table 1 of Donnez 2012a and Table 1 of Donnez 2012b][15, 16]

	PEARL I			PEARL II		
	Placebo (n=48)	**UPA 5mg (n=95)**	**UPA 10mg (n=98)**	**UPA 5mg (n=97)**	**UPA 10mg (n=103)**	**Leuprolide acetate (n=101)**
PBAC score, median (IQR)	376 (241-608)	386 (235-627)	330 (235-537)	286 (190-457)	271 (183-392)	297 (189-443)
Haemoglobin, g/dL, mean (SD)	9.6 (1.2)	9.3 (1.5)	9.5 (1.6)	12.4 (1.6)	12.4 (1.6)	12.1 (1.8)
Total UF volume, cm^3, median (IQR)	61.9 (24.8-158.9)	100.7 (40.0-205.3)	96.7 (31.7-181.3)	79.6 (30.3-151.0)	47.6 (24.1-110.6)	59.2 (27.8-156.3)
Uterine volume, cm^3, median (IQR)	318.8 (216.0-496.3)	337.6 (236.1-502.8)	325.6 (212.6-453.3)	199.4 (149.6-315.0)	197.8 (120.9-297.7)	199.9 (138.2-271.9)
UFS-QoL (symptom severity subscale), mean (SD)	NR	NR	NR	54.0 (20.0)	48.9 (22.1)	52.5 (21.7)

Note. UPA: [a]Total volume of 3 largest myomas, cm^3; UPA: ulipristal acetate; PBAC: pictorial blood loss assessment chart; SD: standard deviation; IQR: interquartile range; NR: not reported

Comparison of the disease specific characteristics suggest that the participants in PEARL I are in poorer health than those in PEARL II. The PEARL II disease specific characteristics are also similar to the participants in the LIBERTY studies, although the uterine volumes were higher in LIBERTY studies compared to PEARL II.

Tabulated results for the efficacy endpoints for PEARL I and PEARL II were provided by the company at clarification and are reproduced in Tables 15 and 16 below.

Table 15 PEARL I efficacy results for UPA 5mg and placebo groups [reproduced from Table 4 of the company's clarification response]

Endpoint	Placebo (N = 48)	UPA 5 mg (N = 95)	Difference, 5 mg UPA − Placebo (95% CI)†	P Value
Primary endpoints at week 13				
PBAC <75 — no./total no. (%)	9/48 (19)	86/94 (91)	73 (55 to 83)	<0.001
% Change from screening in total fibroid volume‡				0.002
Median	3.0	−21.2	−22.6 (−36.1 to −8.2)	
Interquartile range	−19.7 to 23.0	−41.2 to −1.1		
Secondary endpoints at week 13				
Baseline PBAC				
Median	376	386		
Interquartile range	241 to 608	235 to 627		
Wk 9-12 PBAC				
Median	336	0		
Interquartile range	115 to 543	0 to 5		
Change from baseline to wk 9-12 in PBAC				
Median	−59	−329	−291 (−399 to −194)	<0.001
Interquartile range	−216 to 58	−571 to −205		
Amenorrhea, PBAC ≤2, at wk 9–12 — no./total no. (%)	3/48 (6)	69/94 (73)	67 (50 to 77)	<0.001
Total reduction ≥25% in fibroid volume at wk 13 — no./ total no. (%)	8/45 (18)	35/85 (41)	23 (4 to 39)	0.01
% Change from screening in uterine volume at wk 13				0.001§
Median	5.9	−12.1		
Interquartile range	−3.8 to 18.4	−28.3 to 2.9		
Reduction in uterine volume ≥25% at wk 13 — no./ total no. (%)	3/47 (6)	30/88 (34)	28 (11 to 40)	<0.001
Haemoglobin – g/dl				
Baseline	9.55±1.18	9.32±1.50		
Wk 13	12.61±1.30	13.50±1.32		
Change from baseline to wk 13	3.10±1.68	4.25±1.90	0.92 (0.39 to 1.44)	<0.001
Pain assessment with Short-Form McGill Pain Questionnaire				
Baseline				
Median	8.5	6.5		
Interquartile range	3.0 to 18.0	3.0 to 15.0		
Wk 13				
Median	4.2	1.0		

Interquartile range	1.0 to 10.0	0.0 to 4.0		
Change from baseline to wk 13				
Median	−2.5	−5.0	−2.0 (−4.0 to 0.0)	0.10
Interquartile range	−6.3 to 1.0	−8.0 to −2.0		
Measurement of discomfort questionnaire				
Baseline				
Median	16.0	14.0		
Interquartile range	13.5 to 18.0	10.0 to 19.0		
Wk 13				
Median	11.0	3.0		
Interquartile range	4.0 to 15.0	1.0 to 7.0		
Change from baseline to wk 13				
Median	−6.0	−9.0	−4.0 (−6.0 to −1.0)	0.001
Interquartile range	−9.0 to −2.0	−13.0 to −6.0		

* All confidence intervals and P values have been adjusted for multiplicity (Bonferroni correction) because two doses of ulipristal acetate were compared with placebo (i.e., P values were multiplied by 2). PBAC denotes pictorial blood-loss assessment chart.

† The differences in categories with numbers and percents are percentage-point differences. The differences in categories with medians and interquartile ranges are differences in medians, as calculated with the use of the Hodges–Lehmann estimator.

‡ The percent change from screening in total fibroid volume was assessed in 45 patients in the placebo group, 85 patients in the 5-mg ulipristal acetate group, and 80 patients in the 10-mg ulipristal acetate group.

Table 16 PEARL II efficacy results for UPA 5mg and leuprolide acetate groups (per protocol population) [reproduced from Table 5 of the company's clarification response]

	UPA 5mg (N = 93)	Leuprolide acetate (N = 93)	Difference, 5 mg UPA vs. Leuprolide acetate (95% CI)
Primary efficacy endpoints at week 13			
PBAC <75 — no./total no. (%)	84/93 (90)	82/92 (89)†	1.2 (−9.3 to 11.8)‡
Secondary efficacy endpoints			
Median (IQR)	0 (0 to 2)	0 (0 to 1)	
Change from baseline — median (IQR)	−268 (−412 to −172)	−274 (−430 to −161)	6 (−54 to 63)
≤2, indicating amenorrhea — no./total no. (%)	70/93 (75)	74/92 (80)	−5.2 (−18.7 to 8.6)
Total volume of three largest myomas			
Percent change from baseline — median (IQR)	−36 (−58 to −11)	−53 (−69 to −36)	
Ratio to screening volume — geometric mean	0.66	0.54	1.23 (0.99 to 1.52)
Uterine volume			
Percent change from baseline — median (IQR)	−20 (−40 to −3)	−47 (−57 to −35)	
Ratio to screening volume — geometric mean	0.84	0.57	1.48 (1.25 to 1.74)
Short-Form McGill Pain Questionnaire Score			
Median (IQR)	2.0 (0.0 to 4.0)	0.0 (0.0 to 4.0)	
Change from baseline — median (IQR)	−5.0 (−11.0 to −2.0)	−5.5 (−14.5 to −2.0)	0.2 (−2.0 to 3.0)
Uterine Fibroid Symptom and Quality of Life questionnaire			
Health-related quality of life score	76.4±23.2	73.2±23.0	
Change from baseline	23.7±26.9	23.2±28.2	2.5 (−7.3 to 12.3)
Haemoglobin — g/dl	12.8±1.4	12.7±1.6	−0.02 (−0.3 to 0.3)

† One patient had a missing score on the pictorial blood-loss assessment chart.
‡ A lower limit of the confidence interval of more than −20% (the prespecified noninferiority margin) indicates noninferiority. A lower limit of the confidence interval of more than zero indicates superiority.

Tables 15 and 16 show effect sizes favouring UPA 5mg in comparison with placebo and similar benefits from UPA 5mg and leuprolide acetate. In both PEARL I and PEARL II, UPA 5mg can be seen to reduce MBL and uterine volume and increase the haemoglobin level. PEARL II shows GnRHa reduces MBL and uterine volume.

Tabulated safety results for PEARL I and PEARL II were also provided by the company at clarification and are reproduced in Tables 17 and 18 below.

Table 17 PEARL I summary of adverse events in the UPA 5mg and placebo groups (safety population) [reproduced from Table 6 of the company's clarification response]

Event *	**Placebo (N = 48)** number (%)	**UPA 5 mg (N = 95)** number (%)
At least one serious adverse event	3 (6)	2 (2)
Serious adverse event during treatment period	1 (2)	0
Uterine haemorrhage	0	0
Fibroid protruding through cervix	1 (2)	0
Serious adverse event within 4 wk after treatment period	1 (2)	2 (2)
Uterine haemorrhage	0	1 (1)
Breast cancer	1 (2)	0
Ovarian haemorrhage	0	1 (1)
Serious adverse event from wk 17 to wk 38	1 (2)	0
Menometrorrhagia	1 (2)	0
Uterine haemorrhage	0	0
Adverse event leading to discontinuation of study drug†	1 (2)	1 (1)
At least one adverse event‡	22 (46)	47 (49)
Headache	2 (4)	4 (4)
Breast pain, tenderness, or discomfort	0	2 (2)
Abdominal pain	2 (4)	2 (2)
Pyrexia	2 (4)	3 (3)
Hypercholesterolemia	1 (2)	3 (3)
Hypothyroidism	0	2 (2)
Constipation	1 (2)	4 (4)
Hypertriglyceridemia	1 (2)	3 (3)
Influenza	1 (2)	1 (1)
Dizziness	0	1 (1)
Nasopharyngitis	0	3 (3)
Dysmenorrhoea	2 (4)	0

* All serious adverse events and adverse events occurring in at least 3% of the patients in any group are included. Patients could have more than one adverse event of the same type. There were no significant differences between either ulipristal acetate group and the placebo group for any adverse event, with two-sided P values calculated with the use of Fisher's exact test and no adjustment for multiplicity.

† The adverse events leading to discontinuation of the study drug were breast cancer (one patient in the placebo group), endometrial changes (one patient in the 5-mg ulipristal acetate group, with the event initially reported by the local laboratory as hyperplasia but later diagnosed as benign endometrium by three pathologists who were unaware of the study-group assignments).

‡ Adverse events with onset at or after the first dose of study drug and on or before the last assessment date of week 17 (4 weeks after the end of the treatment period) are included.

Table 18 PEARL II summary of adverse events in the UPA 5mg and leuprolide acetate groups (safety population) [reproduced from Table 7 of the company's clarification response]

Event *	**UPA 5mg (N = 97)** number (%)	**Leuprolide acetate (N = 101)** number (%)
At least one event	8 (8)	6 (6)
Any event during treatment	2 (2)	2 (2)
Headache	1 (1)	0
Fibroid protruding through cervix	0	0
Lung infection	0	1 (1)
Thyroid cancer	1 (1)	0
Uterine haemorrhage	0	1 (1)
Within 4 wk after treatment†	3 (3)	2 (2)
From wk 17 to 38‡	3 (3)	2 (2)
Adverse events		
Leading to study-drug discontinuation	1 (1)	6 (6)
At least one event¶	75 (77)	85 (84)
Hot flash	25 (26)	66 (65)
Headache	25 (26)	29 (29)
Procedural pain	9 (9)	9 (9)
Abdominal pain	6 (6)	14 (14)
Nausea	6 (6)	6 (6)
Fatigue	4 (4)	3 (3)
Anaemia	5 (5)	5 (5)
Nasopharyngitis	6 (6)	2 (2)
Acne	0	5 (5)
Breast pain or tenderness	5 (5)	2 (2)
Influenza	2 (2)	5 (5)
Insomnia	2 (2)	5 (5)
Pharyngitis	5 (5)	2 (2)

* Listed are all serious adverse events and adverse events that occurred in at least 5% of patients in each study group, including events that were considered to be unrelated to the study drug. There were no significant between-group differences for any adverse event except hot flashes (P<0.001 for both doses of ulipristal acetate vs. leuprolide acetate). No adjustment for multiplicity was performed.

† These serious adverse events were operative complications in two patients and sarcoma in one patient (retrospectively diagnosed after further review after premature discontinuation of the study drug) in the group receiving 5 mg of ulipristal acetate; endometrial polyp, haemangioma, and operative complications and lymphocytic choriomeningitis in one patient each in the group receiving leuprolide acetate.

‡ These serious adverse events were spontaneous abortion, surgery for suspected ovarian tumour but intraoperative diagnosis corrected to new uterine myoma, and vaginal haemorrhage in one patient each receiving 5 mg of ulipristal acetate; and uterine haemorrhage in two patients receiving leuprolide acetate.

The ERG does not have any concern over the adverse event rates in PEARL I. However, results from PEARL II suggest lower rate of headaches, hot flushes and abdominal pain in relugolix CT.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Based on the data from LIBERTY 1, LIBERTY 2, PEARL I and PEARL II trials, Tables 19 and 20 below show the mean difference in percentage change from baseline in MBL from the ITC for relugolix CT versus UPA and leuprorelin acetate (GnRHa) versus UPA. The ITC results indicate that at week 4 and week 12 relugolix CT had a larger mean percentage decrease in MBL compared with UPA. At 8 weeks UPA showed a larger decrease compared with relugolix CT. In both tables, the confidence intervals are very wide indicating uncertainty around the point estimates.

Table 19 ITC results: relugolix CT versus UPA

	Mean difference %-CFB Week 4	**Mean difference %-CFB Week 8**	**Mean difference %-CFB Week 12**	**Mean difference %-CFB Week 24-no hysterectomy* (UPA patients not on treatment)**	**Mean difference %-CFB Week 24-no surgery** (UPA patients not on treatment)**
Relugolix CT vs. UPA (95% CI)	-19.43% (-55.32%, 16.46%)	+4.53% (-22.62%, 31.69%)	-10.73% (-39.41%, 17.94%)	-77.63% (-119.79%, -35.46%)	-63.06% (-106.93%, -19.18%)
Heterogeneity statistic Chi^2	1.125 (p=0.289)	0.107 (p=0.744)	0.538 (p=0.463)	13.021 (p<0.001)	7.936 (p=0.005)

CFB: Change from baseline
* No hysterectomy or endometrium ablation post treatment in the PEARL trials.
** No surgery post treatment in the PEARL trials.
Note: Treatment in the PEARL I and II trials was discontinued after week 13.

Table 20 Direct comparison: leuprorelin versus UPA

	Mean difference %-CFB Week 4	**Mean difference %-CFB Week 8**	**Mean difference %-CFB Week 12**	**Mean difference %-CFB Week 24-no hysterectomy ***	**Mean difference %-CFB Week 24-no surgery****
Leuprorelin vs. UPA (95% CI)	+31.14% (-52.49%, 114.77%)	-3.79% (-105.03%, 97.45%)	-1.50% (-71.05%, 68.05%)	+23.45% (-91.88%, 138.78%)	+14.12% (-114.80%, 143.04%)

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

The company did not follow the ERG's suggestion of conducting a network meta-analysis (NMA) or ITC to compare relugolix CT with GnRHa. The company's justification for not performing an NMA was not considered satisfactory by the ERG: "*The only outcome used by the economic model that was informed by the indirect treatment comparison was MBL, which was subsequently used in the utility algorithm. In the majority of economic models where a network meta-analysis (NMA) is used to inform the model efficacy parameters, this is usually carried out on a small number of outcome measures deemed consistent or similar across studies in the network*." In the absence of direct trial evidence or the opportunity to link relugolix CT and GnRHa through a common comparator, the ERG believes that a network would have been a more appropriate form of analysis as this would better represent the uncertainty, which exists due to the number of required comparisons and the difference in disease-specific characteristics between the PEARL I study and the LIBERTY and PEARL II trials. The ERG notes that the steps required to perform an NMA are similar to those undertaken by the company to perform the ITC.

The ERG also questioned why MBL volume was the only outcome for which the company attempted an ITC. While the ERG understands there may have been difficulties in comparing outcome measures, they notice that UFV/UV, haemoglobin levels, and health-related quality of life were reported in the LIBERTY and PEARL trials and could have been assessed using an ITC. It is also worth noting that time to MBL response, pain, UFV/UV, haemoglobin levels, and health-related quality of life were listed in both the NICE final scope and the company's decision problem and a comparison between relugolix CT and GnRHa was, therefore, expected. In particular, there is a lack of patient-reported outcomes measures (PROMs) in the CS because health-related quality of life measures were not assessed.

The ERG believes that a comprehensive summary of the clinical effectiveness of the technology is missing in the current CS. Similarly, the company's clarification response focused mainly on aspects related to the economic modelling rather than on aspects related to the clinical effectiveness of the technology.

3.5 Additional work on clinical effectiveness undertaken by the ERG

At clarification, the ERG queried by an NMA on MBL response had not been performed and consider performing this analysis themselves. However, performing an NMA using the currently available data would have required assumptions to be made such as approximating

the mean with median and the standard deviations with an adjustment of the interquartile range. Moreover, there are slight differences in the time points of the available outcome data. For these reasons, the ERG did not attempt the NMA.

Using the ITC results provided by the company, the ERG carried out ITCs comparing relugolix CT versus GnRHa. Results of these comparisons are presented in Table 21.

Table 21 ITC results: relugolix CT versus GnRHa

	Mean difference % - CFB (95% CI)
Week 4	-50.57 (-141.58, 40.44)
Week 8	8.32 (-96.50, 113.14)
Week 12	-9.23 (-84.46, 66.00)

The ERG agrees with the company's assumption that relugolix CT and GnRHa are equally effective for reducing MBL. However, all of the confidence intervals around the point estimates are wide and this observed uncertainty should be fed into the probabilistic analysis of the cost-effectiveness model (see Section 4.2.6).

3.6 Conclusions of the clinical effectiveness section

The company only presented the ITC results for MBL but did not attempt any ITC for other outcomes listed in either the NICE final scope or their decision problem. In particular, the company presented only a comparison between relugolix CT and UPA and a comparison between GnRHa and UPA but not a comparison between relugolix CT and GnRHa. The ERG believes the other outcomes in the scope could have been compared considering it is likely the company have access to data from the LIBERTY trials, which could be matched to the 13-week timepoint data in the PEARL trials.

The ERG has some concerns over the population of PEARL and LIBERTY trials as the 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. This suggests that two different populations were included in the respective trials. The PEARL I trial, which is required to link relugolix CT and GnRHa, appears to include participants who initially have higher MBL and uterine volume and lower haemoglobin levels.

The ERG strongly felt that an NMA should have been conducted by the company for MBL as well as for the other relevant outcomes. The ERG believes that an ITC is suitable when the required comparison can be made by linking two trials through a common comparator but given the evidence presented in the current CS, considers that a network would have been more appropriate. Nevertheless, the ERG agrees with the company's assertion that relugolix CT and GnRHa are equally effective in reducing MBL, even though the wide confidence intervals around the estimates of effect indicate some uncertainty.

The ERG has inspected the adverse events being reported in Table 29 of the CS and Tables 6-7 of the clarification response. The proportion of participants experiencing headaches, hot flushes, and abdominal pain were lower amongst patients receiving relugolix CT. The ERG is not concerned with any differences in serious adverse events or rates of adverse events.

Lastly, the ERG felt that the company did not place enough importance on the clinical effectiveness section of their submission and focused more on the cost-effectiveness section.

4 COST-EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

The company conducted a systematic literature review of cost-effectiveness analyses of pharmacological interventions used to treat fibroids for women who have failed conventional hormone therapy. A total of 63 records were identified, and 14 studies were included after screening and full-text review; 9 of which were unique economic evaluations. Full details of the cost-effectiveness review methods, including search strategies and selection criteria are provided in Appendix G of the company submission. Table 37 of the company submission summarises the identified studies.

The ERG has reviewed the company's search strategies and methodology and are satisfied that robust methods have been used to identify the literature. However, the ERG believes that the characteristics of the identified models (including modelled Markov states) should have been more clearly reported, and their usefulness for the current assessment critiqued. Therefore, the ERG provides further details of the model structures in Table 22 below, focusing on the Markov states included in models and their relevance to the current decision problem.

The ERG agrees with the company's assessment that none of the identified economic evaluations are directly relevant to the current decision problem, with all studies assessing the cost-effectiveness of UPA, often compared to GnRHa, and often using data from the PEARL studies. Half of the identified studies were abstracts of conference presentations and therefore provided limited information that might be useful for the development of the current model structure. Among the five published studies, three were Markov models, two of which defined Markov states according to health[17, 18] (based on bleeding and / or symptom control) prior to surgery, with one structure developed using states defined according to treatment received.[19] The ERG considers the definition of states for the economic model to be an important consideration and feels that further critique of these studies would have been useful in determining and justifying the most appropriate model structure for the assessment.

Table 22. Summary of cost-effectiveness model structures identified in the company literature review.

Study	Year	Intervention / comparators	Model type (e.g., Markov)	Modelled health states	ERG interpretation of relevance to decision problem
Badiani[17]	2018	UPA + surgery vs. Placebo + surgery (PEARL I)	Markov	• controlled bleeding • Uncontrolled bleeding • surgery	• Comparison not directly relevant, • useful for model structure
Choi [20]	2016	UPA vs. GnRH agonist prior to surgery [A]	Markov	NR	• Comparison not directly relevant • Insufficient detail on model structure
Lorenzovici[21]	2014	UPA vs. monitoring and UPA vs. hysterectomy [A]	Markov	• Mild excessive bleeding • Moderate excessive bleeding • Severe or persistent excessive bleeding • Myomectomy • Post myomectomy (mild-moderate bleed), • Post myomectomy (severe bleeding) • Hysterectomy • Post hysterectomy • Post menopause • Death	• Comparison not directly relevant, • Limited information potentially useful for model structure

Study	Year	Intervention / comparators	Model type (e.g., Markov)	Modelled health states	ERG interpretation of relevance to decision problem
Maratea[22]	2016	Repeated UPA vs. one-of pre surgical UPA	Simulation model	Not applicable	• Comparison not directly relevant, • Unlikely to be useful for model structure
Nagy	2012 [A18] and 2014[23]	UPA vs. monitoring and UPA vs. hysterectomy	Markov	• Mild or moderate excessive bleeding • Severe or persistent excessive bleeding • Myomectomy • Post myomectomy (mild-moderate bleed) • Post myomectomy (severe bleeding) • Hysterectomy • Post hysterectomy • Post menopause • Death	• Comparison not directly relevant, • useful for model structure
Paladio-Hernandez[24]	2015	UPA vs. GnRHa [A]	Decision tree	NR	• Comparison not directly relevant, • Unlikely to be useful for model structure
Paquete[25]	2016	UPA vs. Surgery [A]	Markov	Unclear (possibly states of on/ off treatment)	• Comparison not directly relevant, • Limited information potentially useful for model structure

Study	Year	Intervention / comparators	Model type (e.g., Markov)	Modelled health states	ERG interpretation of relevance to decision problem
Tsoi[26]	2015	UPA vs. GnRHa	Decision tree	Decision tree branches for: • Controlled bleeding (with / without hot flushes) • Uncontrolled bleeding (with / without hot flushes)	• Comparison not directly relevant, • Partially useful for model structure
Geale[19]	2017	UPA + surgery vs. BSC + surgery	Markov	Treatment states: • UPA • BSC • Surgery • Post-surgery • Death Health state utilities defined according to bleeding and pain outcomes.	• Comparison not directly relevant, • Useful for model structure

Abbreviations: BSC: best supportive care; GnRHa: Gonadotropin-releasing hormone analogue NR: Not reported; UPA: Ulipristal acetate

[A] Abstract only, limited details available.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 23 below provides the ERG assessment of the company submission against the NICE reference case.

Table 23 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	**Partly.** A two-step approach was followed to derive utilities for the treatment states in the model, where a) UFS-QoL data from LIBERTY were mapped to EQ-5D, and b) an OLS model was used to derive a utility function describing the impact of one-unit changes in MBL on mapped utilities. It is unclear to what extent MBL captures all direct health effects.
Perspective on costs	NHS and PSS	**Yes**. An NHS perspective has been adopted.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	**Yes**.
Time horizon	Long enough to reflect important differences in costs or outcomes between the technologies being compared	**Yes**. For an average age of 42, a life-time horizon is modelled in the base case with a scenario analysis to the average age of menopause (age 51). Note that the current model configuration would not allow sensitivity analyses on starting ages < 42 to reflect a life-time horizon.

Element of health technology assessment	Reference case	ERG comment on company's submission
Synthesis of evidence on health effects	Based on a systematic review	**Partly.** Whilst a systematic review was undertaken, the resultant indirect treatment comparisons for evidence of health effects between relugolix CT and GnRHa were limited to one outcome only (MBL). The company used results from the ITC to derive mean MBL for each treatment arm in the model but did not report these results (including measures of uncertainty around the treatment effects that could be incorporated into the PSA).
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	**Partly.** Health effects were measured in QALYs. Whilst EQ-5D data were available from the LIBERTY study, indirect mapping and regression of MBL on QoL were used in the model because of a lack of sensitivity to measure the impact of patient symptoms on QoL, given inappropriate timing of questionnaires and a single day EQ-5D recall.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	**Yes.** UFS-QoL data were reported directly from the LIBERTY trial, but the mapped values have not been reported. The ERG would have appreciated seeing the incremental effect of randomised treatment on the mapped utilities.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	**Yes.**

Element of health technology assessment	Reference case	ERG comment on company's submission
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	**Yes.**
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	**Partly.** Resource use required for routine monitoring was based on clinical expert input, but the ERG considers the resource use requirement to be an over-estimate of routine monitoring in UK clinical practice.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	**Yes.** Though the ERG notes that the discount rate was not varied in sensitivity analyses.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company has submitted a Markov cohort model developed in Microsoft® Excel to determine the cost-effectiveness of relugolix CT compared to GnRHa for the treatment of moderate to severe symptomatic fibroids in adults. The model captures the cost and QALY implications associated with the cohort's transition through a set of mutually exclusive "treatment" states in monthly cycles over a life-time horizon, informed by treatment discontinuation assumptions. The cohort enters the model in the "on treatment" relugolix CT or GnRHa health states. The cohort can then remain on treatment in any given cycle or can discontinue where they immediately enter the BSC state or can be scheduled for surgery. Once a treatment has been discontinued, a second course of pharmacological treatment is not allowed within the model structure. The proportion of those discontinuing that are scheduled for surgery immediately enter the "waiting time" state of assumed duration 15 months before progressing to the surgery state. The waiting time state is essentially an extension of the BSC state

where patients remain off active treatment whilst waiting for surgery. Entry to the 'waiting time' state, and hence scheduling for surgery is therefore modelled to be conditional on treatment discontinuation in the company base case analysis.

The surgery state is a tunnel state that patients remain in for one cycle. This state includes different types of surgery which are each explicitly modelled to describe the distribution of patients currently undergoing surgery by surgery type and to allow correct application of surgery related mortality risks and adverse events. Following surgery, patients move to a post-surgery state that is divided in two – reflecting patients who received hysterectomies and those who did not. Patients who did not receive hysterectomies can then transition to a second surgery state following the completion of further waiting time. For all women, resolution of fibroid symptoms is assumed to have occurred by the point of menopause (age 51), where the cohort all enter the 'menopause' state of the model and receive general population utilities and all-cause mortality risks. The cohort can enter the death state from any other model state according to age and sex-adjusted general population mortality risks. There is an added mortality risk applied from the surgery state to reflect a small additional risk of surgical mortality. The model structure is re-produced from the company submission in Figure 3 below.

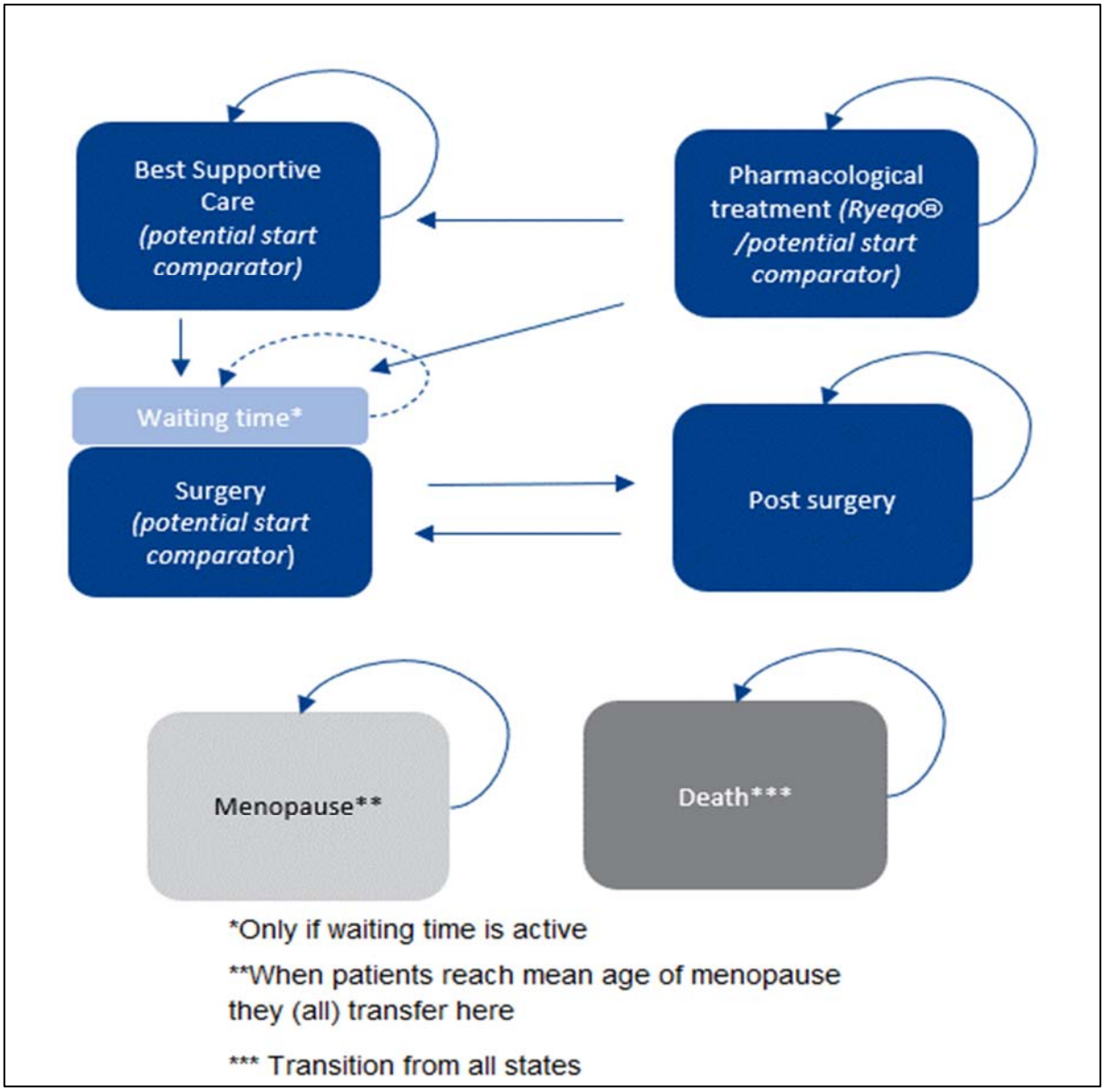


Figure 3 Model structure [reproduced from Figure 29, Document B of the CS].

Decision to model 'treatment' rather than 'health' states

The model structure is built to reflect the treatment pathways that might be experienced in clinical practice, with Markov states defined according to treatment received at any given time point "on-treatment: relugolix CT / GnRHa, off-treatment: BSC, waiting for surgery and surgery.

The ERG does not consider the company's decision to model "treatment" states rather than states defined by "health" outcomes to be sufficiently explained or justified in the submission. The ERG would have considered a more appropriate

model structure to be one, like that of Nagy et al 2014, where the cohort transition through a series of mutually exclusive health outcomes states.[23] Such states might be defined according to bleeding symptoms: such as 'mild', 'moderate' or 'severe' bleeding, or symptom control: 'uncontrolled', 'controlled'. In model states defined by 'health' outcomes, a proportion of the cohort in those states could be modelled to be 'on' or 'off' treatment, according to available treatment discontinuation data from LIBERTY for relugolix CT and from PEARL II / clinical expert opinion for GnRHa. Such an approach would have two key advantages, especially in the pre-surgical states, namely:

1) *MBL effectiveness data from the LIBERTY and PEARL II studies could be linked directly to treatment received, as opposed to the company's approach which applies intention to treat effectiveness (i.e., MBL) data to an 'on treatment' cohort. The approach likely under-estimates MBL and QALY gains in the 'on treatment' proportion of the cohort in both model arms. The overall direction of any bias though is unclear, and dependent on other modelling assumptions. The implications for the effectiveness and QALY gains are discussed in Section 4.2.7.*

2) *Resource use requirements in terms of patient management, investigations, examinations, and follow-up are linked to treatment received in the model. The ERG's clinical expert considers this to be inappropriate, because, in clinical practice, decisions about patient management are more likely to be based on clinical need, which is determined by whether a patient's symptoms are adequately controlled and not necessarily depending on whether they are 'on' or 'off' treatment. The ERG considers that a model based on 'health' states would enable application of more appropriate monitoring and symptom management assumptions. The implications for resource use and costs are discussed in Section 4.2.8.*

Pre-surgery waiting time state

All patients scheduled for surgery first enter a "waiting time" state, of the assumed duration of 15 months. Entry to the waiting time, and hence surgery health states is conditional on treatment discontinuation. The cohort is assumed to only enter the

'waiting time' state if the transition would occur before age 46, on the assumption that patients would not be listed for surgery within five years of menopause (age 51).

The ERG's concern with the company's approach is that, in clinical practice, patients would be unlikely to discontinue treatment before being listed for surgery. Similarly, patients would be unlikely to discontinue treatment whilst waiting for surgery. Indeed, the ERG's clinical expert advisor is of the view that it is advantageous for people to remain on treatment in preparation for surgery to ensure maximum fibroid shrinkage at the point of surgery to improve the chance of surgery success, and potentially even enabling surgeons to conduct surgery via less invasive routes. The ERG, therefore, does not consider the structural assumption to be appropriate, or evidence based.

The implication of the 'waiting time' state is to delay the time point of transition to the surgery state in both arms of the model. However, the combination of three modelling assumptions: A) that listing for surgery is conditional on treatment discontinuation and B) that the cohort can only be listed for surgery between the ages of 41 and 46 and C) given that the relugolix CT treated cohort remains on treatment for longer than GnRHa means that the impact of removing the waiting time state has a much greater relative impact on the relugolix CT arm of the model than the GnRHa arm. Removal of the 'waiting time' state, therefore, leads to a substantial increase in the ICER. The implications for state transitions are discussed in Section 4.2.6.

Surgery model states

The ERG notes that the premise of the company's value case is that longer treatment duration with relugolix CT can maintain adequate response for longer than GnRHa, thus preventing the need for surgery by allowing women to reach the age of menopause where symptoms tend to resolve naturally.

Whilst the ERG accepts that longer duration of a successful medical treatment may lead to some reduction in the need for surgery, there are no data presented by the company to indicate the magnitude of surgery reduction that might be achievable for relugolix CT compared to GnRHa. The company has provided scenario analyses removing the surgery states from the model. The ERG considers that this scenario may reflect the cost-effectiveness of relugolix CT versus GnRHa for the treatment of

fibroids solely in a group of women who will not receive surgery. The scenario analysis would also represent a conservative approach where no differences in surgery outcome would be achieved and based on the assumption that a decision to have surgery is based predominantly on patient preference, rather than whether medical treatment was discontinued or not. On balance, the ERG considers that some effect on surgery may be plausible, particularly in women who do not continue long-term off-licence use of GnRHa, but the magnitude of any effect on surgery reduction is unclear, not evidence-based, and highly uncertain given the available data to inform these transitions.

4.2.3 Population

The company state that their modelled population is informed by the pooled patient characteristics in the LIBERTY 1 and LIBERTY 2 studies of relugolix CT. This results in a model cohort starting age of 42. The company states that the modelled population is reflective of how relugolix CT would be used in UK clinical practice.

The ERG can confirm that the starting age of the model cohort is consistent with that of the pooled LIBERTY study populations. Most characteristics of the LIBERTY study appear to be a reasonable reflection of the population in which relugolix CT might be used in clinical practice, with two exceptions. The first is that the ERG's clinical expert confirms that the model starting age is appropriate but that some women may start treatment at a younger age, especially those who have had their families. There is likely to be substantial variability among the characteristics of the treated population in clinical practice. The second concern relates to treatment goals, and the role of surgery. The ERG notes that the goal of treatment in the LIBERTY study (relugolix CT) is substantially different from the goal of treatment in the PEARL II study used to inform the model comparator (GnRHa). Participants in the LIBERTY studies were not intended to receive surgery and indeed planned surgery was a trial exclusion criterion. In contrast, participants in the PEARL II study were all listed for surgery at baseline. The ERG's view is that the study populations are not comparable with respect to the role of surgery in the treatment pathway. The ERG is concerned that mixing the trial populations to parameterise the economic model without adequate consideration of these different treatment goals is an important limitation of the company's approach. Given that transitions to the surgery states are an important

driver of the ICER, the ERG would have considered it appropriate to model two groups of patients separately, according to their desire to have surgery:

A) *Group A: women who are listed for surgery who receive medical treatment to ensure maximum fibroid shrinkage pre-surgery to improve surgical outcomes (consistent with the population enrolled in the PEARL II study) and*
B) *Group B: women who do not wish or cannot receive surgery, who receive medical treatment to manage fibroid symptoms, such as to reduce blood loss (consistent with the population enrolled in the LIBERTY study).*

This distinction has important implications for the model structure and in particular the role of the surgery model health states. In group A, one could reasonably assume equivalence in transitions to surgery and the decision problem becomes one of cost-minimisation over short term (e.g., 3 months of treatment) prior to surgery. For group B, transitions to surgery may be much lower in both model arms, given that women have already expressed a preference to avoid surgery by initiating treatment with a long-term goal of symptom management.

4.2.4 Interventions and comparators

Intervention: relugolix CT

The intervention under assessment is relugolix CT, containing 40mg relugolix, 1mg estradiol (as hemihydrate) and 0.5mg norethisterone acetate. The drug is self-administered by the patient, orally, as one tablet taken daily. A Dexa-scan is recommended after 52 weeks of treatment to assess bone mineral density and osteoporosis risk. There are no specified treatment stopping rules in the marketing authorisation, other than to recommend cessation of treatment at menopause. The company model treatment to continue indefinitely unless discontinued.

Whilst the clinical community do not have experience of long-term treatment of their patients with relugolix CT, the ERG's clinical expert is satisfied that so long as bone mineral density is monitored through Dexa scans, its modelled usage, which is in line with the marketing authorisation, broadly reflects how relugolix CT would be intended for use in clinical practice, though as noted in Section 4.2.3, some patients

may receive treatment in preparation for surgery, which does not appear to be incorporated in the current model, given the additional 'waiting time' state. There are no modelled stopping rules, other than menopause (age 51), where all treatment is stopped on the assumption that fibroids will shrink without treatment at this point. The modelled cessation of treatment is also in line with the marketing authorisation for relugolix CT and its likely use in clinical practice.

Comparator: GnRHa

The company considers GnRHa to be the most appropriate comparator for use in the model. Six different types of GnRHa are included, based on the treatments currently licensed for use in the UK (goserelin, leuprorelin acetate, and triptorelin) as short acting monthly and long-acting 3 monthly formulations. GnRHa may be used within their licence for the treatment of moderate to severe fibroids up to 3-6 months, but the company's clinical expert opinion is that they are often used off-licence for longer in clinical practice, especially where there is a need to delay or avoid surgery. Long term use requires the addition of add-back HRT to reduce BMD loss.

The ERG agrees that GnRHa are an appropriate comparator for the cost-effectiveness model, as they are the most commonly used medical treatments in UK clinical practice in this setting. Other available medical treatments, such as those included in the NICE scope, target symptom management rather than the underlying fibroids. The ERG's clinical expert is also in agreement that longer term usage of GnRHa is common in clinical practice but given that its usage beyond six months is off-label, duration of treatment in UK clinical practice is likely to vary substantially. The ERG agrees with the company that all GnRHa would likely have similar effectiveness.[27] The ERG therefore considers it appropriate to select the GnRHa with the lowest treatment acquisition costs for calculation of the ICER because all other GnRHa will be dominated (less costly and of equal effectiveness) and thus excluded from the fully incremental analysis. Goserelin monthly has the lowest treatment acquisition cost, and the ERG considers this the most appropriate comparator against which to compare relugolix CT.

Whilst other treatments from the NICE scope have not been included directly as comparators, the ERG's clinical expert is of the view that their role in symptom

management may have an important role to play in best supportive care following treatment discontinuation. This is further addressed in Section 4.2.8.

4.2.5 Perspective, time horizon and discounting

The company submission used an NHS and personal social services (PSS) perspective for costs. The economic model includes functionality that would enable exploration of wider productivity and non-healthcare costs, but these have not been included in the assessment.

The ERG is satisfied that the costing perspective meets the requirements of the NICE reference case.[28]

The model time horizon runs for a maximum of 719 monthly cycles, up to a maximum age of 102 for a starting cohort of age 42. A shorter time horizon, of 9 years, from start age to an assumed average menopause age of 51 is explored in sensitivity analyses, after which point the incremental benefits of treatment are less clear.

In the case of this assessment, a time horizon up to the point of menopause may be sufficient to capture all the costs and benefits of treatment and could be considered as a scenario analysis. The ERG's clinical expert is of the view that post menopause, any incremental benefits of treatment would be difficult to measure with accuracy and the majority of additional health service resource use and quality of life benefit will be accrued prior to menopause. The ERG cautions that any amendments to the model starting age to explore, for example, treatment in younger age groups would not reflect a full lifetime horizon in the current model framework.

Costs and QALYs were discounted by 3.5% per annum in the model.

The ERG is satisfied that discounting has been correctly implemented within the company's economic model and that the base case discount rate applied is in accordance with the NICE reference case.[28] *However, the company has not provided the recommended scenario analyses that vary the discount rate between 0% and 6%*

for both costs and QALYs. The ERG provides scenario analyses that illustrate the impact of different discount rates on the ICER in Section 6.2.

4.2.6 Treatment effectiveness and extrapolation

The following LIBERTY (relugolix CT) and PEARL II (GnRHa) trial data are used to inform the economic model:

A) Treatment discontinuation over time. For relugolix CT, treatment discontinuation is based on the withdrawal rates from the LIBERTY 1-3 studies and the LIBERTY withdrawal study, but with modification to reflect clinical expert opinion that discontinuation in the trials over-estimates discontinuation that might be expected in clinical practice. For GnRHa, data from the PEARL II clinical trial up to three months are supplemented with clinical expert opinion regarding off-licence usage in the longer term.
B) Treatment effectiveness, in terms of menstrual blood loss (MBL) obtained from the LIBERTY studies for relugolix CT and via an indirect treatment comparison (ITC) to the comparator arm of the PEARL II study for GnRH analogues. MBL data are obtained from an ITT analysis of LIBERTY data and applied to an 'on treatment' cohort in the model.
C) Adverse events from LIBERTY 1 and LIBERTY 2 studies and PEARL II studies for relugolix CT and GnRHa respectively, with adverse events beyond trial follow up assumed to equal the rate in the follow up period for the duration of time on treatment.
D) UFS-QoL data mapped to EQ-5D and regressed on MBL to estimate time varying treatment specific health state utility values (See Section 4.2.7).

Summary of model transition probabilities

The ERG note that the company has not directly used transition matrices to govern progression through the model states, with health state occupancy instead determined according to time-varying treatment discontinuation data and assumptions. The ERG has approximated average implied transition matrices from the company base case analysis in Tables 24 and 25 below for relugolix CT and GnRHa respectively. The purpose of this information is to describe the model flow and the differences in health state occupancy over time. Cohort traces are provided in the company submission

Table 24 Summary of approximate transition probabilities among surviving health states (relugolix CT)

	Time (Month)	Treatment	BSC	Waiting for surgery 1	Surgery 1	Post-surgery 1	Waiting for surgery 2	Surgery 2	Post-surgery 2	Menopause
Treatment	Month 1-6	R	0.004	0.0033	-	-	-	-	-	Age< 51: 0 Age 51+: 1
	Month 7-12	R	[redacted]	[redacted]	-	-	-	-	-	
	Month 13-24	R	[redacted]	[redacted]	-	-	-	-	-	
	Month 24 +	R	[redacted]	[redacted]	-	-	-	-	-	
BSC	All	-	R	0.005	-	-	-	-	-	
Waiting for surgery 1	All	-	-	-	1	-	-	-	-	
Surgery 1	All	-	-	-	-	1	-	-	-	
Post-surgery 1	All	-	-	-	-	R	0.0172	-	-	
Waiting for surgery 2	All	-	-	-	-	-	-	1	-	
Surgery 2	All	-	-	-	-	-	-	-	1	
Post-surgery 2	All	-	-	-	-	-	-	-	1	
Menopause	All	-	-	-	-	-	-	-	-	1

Abbreviations: BSC: Best supportive care; R: Remainder

Notes: 1) Proportion transitioning into Surgery state are first on a 15-month waiting list; 2) Everyone transitions into Menopause state aged 51; 3)Patients can enter the Death state from any state according to the general population all-cause mortality; 4) The post-surgery state splits into two sub-states: post-surgery (hysterectomy) and post-surgery (non-hysterectomy), divided according to the proportion having hysterectomy in the model (58.2%); 5) Re-treatment with medical management is not possible. For example, the model does not allow patients to receive GnRHa if relugolix CT is unsuccessful; 6) Patients are not allowed to have more than two surgeries. Once patients enter the Post-surgery 2 state they cannot leave (unless they transition to the Death state) until they reach menopause.

Table 25 Summary of approximate transition probabilities among surviving health states (GnRHa)

	Time (Month)	Treatment	BSC	Waiting for surgery 1	Surgery 1	Post-surgery 1	Waiting for surgery 2	Surgery 2	Post-surgery 2	Menopause
Treatment	Month 1-6	Remainder	0.0105	0.0086	-	-	-	-	-	Age< 51: 0 Age 51+: 1
	Month 7-12	~0.905	~0.052	~0.043	-	-	-	-	-	
	Month 13-60	~0.994	~0.003	~0.003	-	-	-	-	-	
	Month 60+	0.998	0.001	0.001	-	-	-	-	-	
BSC	All	-	Remainder	0.005	-	-	-	-	-	
Waiting for surgery 1	All	-	-	-	1	-	-	-	-	
Surgery 1	All	-	-	-	-	1	-	-	-	
Post-surgery 1	All	-	-	-	-	R	0.0172	-	-	

	Time (Month)	Treatment	BSC	Waiting for surgery 1	Surgery 1	Post-surgery 1	Waiting for surgery 2	Surgery 2	Post-surgery 2	Menopause
Waiting for surgery 2	All	-	-	-	-	-	-	1	-	
Surgery 2	All	-	-	-	-	-	-	-	1	
Post-surgery 2	All	-	-	-	-	-	-	-	1	
Menopause	All	-	-	-	-	-	-	-	-	1

Abbreviations: BSC: Best supportive care; R: Remainder

Notes: 1) Proportion transitioning into Surgery state are first on a 15-month waiting list; 2) Everyone transitions into Menopause state aged 51; 3)Patients can enter the Death state from any state according to the general population all-cause mortality; 4) The post-surgery state splits into two sub-states: post-surgery (hysterectomy) and post-surgery (non-hysterectomy), divided according to the proportion having hysterectomy in the model (58.2%); 5) Re-treatment with medical management is not possible. For example, the model does not allow patients to receive GnRHa if relugolix CT is unsuccessful; 6) Patients are not allowed to have more than two surgeries. Once patients enter the Post-surgery 2 state they cannot leave (unless they transition to the Death state) until they reach menopause.

Treatment discontinuation – relugolix CT

Treatment discontinuation for relugolix CT was obtained from the LIBERTY 1-2 trials (pooled data for months 1-6), LIBERTY 3 study (months 7-12), and the LIBERTY withdrawal study (months 13-24). Clinical expert opinion obtained by the company from N=3 KOLs indicated that the number of patients discontinuing treatment in the LIBERTY studies exceeded what might be expected in UK clinical practice. The company base case model, therefore, assumes that patients discontinuing treatment in the LIBERTY studies for the following reasons would remain on treatment in UK clinical practice.

A) mild (e.g., mood swings) or non-drug-related adverse events,
B) protocol deviations and loss to follow up,
C) most patients that withdrew from the study,
D) some patients that withdrew due to lack of efficacy, given that the MBL measurement used in the trials would not be used in clinical practice and
E) patients withdrawing for several other unspecified reasons

Modified and unmodified discontinuation data are compared in Table 26 below.

Table 26 Relugolix CT modelled treatment discontinuation rates [reproduced from Tables 39 and 40, Document B of the CS].

	LIBERTY 1		LIBERTY 2		LIBERTY 3		LIBERTY withdrawal study	
	Unmodified (ERG preferred)	**Modified (Co. preferred)**	**Unmodified (ERG preferred)**	**Modified (Co. preferred)**	**Unmodified (ERG preferred)**	**Modified (Co. preferred)**	**Unmodified (ERG preferred)**	**Modified (Co. preferred)**
N	128	128	126[A]	125[A]	163	163	115	115
Discontinuation reason								
Adverse event	7	3	2	1	[redacted]	[redacted]	[redacted]	[redacted]
Protocol deviation	1	0	1	0	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	1	0	4	0	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal by patient	10	1	13	1	[redacted]	[redacted]	[redacted]	[redacted]
Lack of efficacy	4	4	2	0	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	0	0	0	0	[redacted]	[redacted]	[redacted]	[redacted]
Other	5	0	1	0	[redacted]	[redacted]	[redacted]	[redacted]
Total	**28**	**8**	**23**	**2**	[redacted]	[redacted]	[redacted]	[redacted]
% withdrawing	**22%**	**6%**	**18%**	**2%**	[redacted]	[redacted]	[redacted]	[redacted]
Cycle specific probabilities of discontinuation								
Months 1-6 [B]	**4.00%**	**0.72%**	**4.00%**	**0.72%**	-	-	-	-
Months 7-12	-	-	-	-	[redacted]	[redacted]	-	-
Month 13 onwards	-	-	-	-	-	-	[redacted]	[redacted]

[A] The ERG notes that the total number of patients in LIBERTY 2 (n=126) and for the modified withdrawal rates (n=125) do not match. The ERG assumes this is a typo.

[B] Data pooled across LIBERTY 1 and LIBERTY 2 studies.

The ERG notes that the company submission provided insufficient detail and explanation to justify the exact modifications applied to the LIBERTY study data for use in the model. The company mention that cases were reviewed to decide which discontinuers reflected clinical practice, but it is unclear how this was done, whether clinical experts were involved, and if so, how many, and how consensus was achieved. It was also unclear how decisions were reached regarding which discontinuers categorised as 'other' and 'patient withdrawal' were deemed transferable to UK clinical practice.

Whilst the ERG appreciates that some patients discontinuing treatment may do so because of trial processes, it is very difficult to accurately identify which discontinuers are non-generalisable. The ERG prefers the use of unmodified treatment relugolix CT discontinuation rates, as observed in the LIBERTY trials for the following reasons:

- *A) The ERG's clinical expert sees no strong evidence that the discontinuations are inappropriate for clinical practice. Whilst adverse events may appear mild, patients may still discontinue treatment for these reasons.*
- *B) The data from the LIBERTY studies are the best available evidence on relugolix CT discontinuation over time,*
- *C) GnRHa discontinuations from the PEARL II study were not modified. Modifying discontinuations for relugolix CT but not GnRHa may generate further bias*
- *D) MBL data from the LIBERTY trials reflect the discontinuation as observed in the studies. Adapting the costs, without any corresponding adjustment to treatment benefit is inappropriate.*

For all of these reasons, the ERG prefers the use of unmodified treatment discontinuation data.

Treatment discontinuation - GnRH analogues

Treatment discontinuation for GnRH analogues was informed using a combination of data from the PEARL II study and assumptions based on clinical expert opinion as follows:

- **Months 1-3**: Data from the PEARL II study show that, by 13 weeks of follow up, 6/101 (5.9%) of participants discontinued treatment. The company converted this to a monthly probability of treatment discontinuation of 1.91%
- **Months 4-6:** The monthly probability of treatment discontinuation was assumed equal to that observed in the PEARL II study up to week 13 (i.e., 1.91%). A scenario analysis assumed 6-monthly discontinuation rates equal to relugolix CT.
- **Months 7-119**: The company use expert opinion from N=7 KOLs to determine the proportion of patients that would remain on treatment at 1, 5 and 10 years, reflecting that GnRHa may be used off-licence, with add-back HRT beyond the current licence of 6-months. On average, the KOLs predicted that 43.2% (range: 5% to 80%), 13.6% (range: 0% to 55%) and 0.7% (range: 0 to 5%) would remain on treatment at 1, 5 and 10 years respectively. Monthly transition probabilities out of the GnRHa state are calculated using interpolation between these time points.
- **Month 120 onwards**: All patients are assumed to have discontinued treatment.

The ERG was unable to exactly reproduce the probability of discontinuing treatment on GnRHa (1.91%) given that the probabilities are hard coded in the model file rather than showing the underlying calculations. The ERG considers it important to embed all calculations within the model file for transparency to enable reproduction of data. However, the ERG is satisfied that any discrepancies are most likely due to rounding and would only have a negligible impact on the ICER.

The ERG notes that there is substantial variation in the KOL responses regarding long-term off-licence use of GnRHa beyond 6 months (See Table 44 of the company submission). The ERG's clinical expert opinion is that wide variation in UK clinical practice is to be expected, given that the use of GnRHa longer term is off-licence, and that the expert opinion sought by the company likely provides a plausible range. The ERG notes that the longer-term proportion of patients discontinuing treatment has important implications for costs and hence the ICER in the economic model. The ERG does not consider the company's base case approach of including a point estimate of

the mean across clinical experts to adequately reflect this uncertainty. In response to a clarification query (QB3), the company updated the PSA to incorporate uncertainty, assuming a standard error (SE) equal to 10% of the mean. The ERG is not convinced that the approach taken adequately captures the uncertainty, given that a standard error could have been calculated using the available KOL responses. The ERG preferred probabilistic analysis, therefore, incorporates standard errors obtained from the KOL data provided by the company and further deterministic analyses explore using the minimum and maximum values of the ranges provided. The company preferred standard errors are 4.32%, 1.36%, and 0.07% for the proportion on treatment at 1, 5, and 10 years respectively. In contrast, the ERG preferred standard errors are 12.18%, 7.38% and 0.71%.

Treatment discontinuation – Relugolix CT versus GnRH

Treatment discontinuation for relugolix CT and GnRHa under different assumptions is depicted in Figure 4. The company's base case assumes that the modified withdrawal rates from the LIBERTY trials are applied, but the ERG prefers unmodified data as described above. The ERG and company preferred treatment discontinuation assumptions are aligned; however, the graph shows the impact of applying the minimum and maximum proportions remaining on treatment as per the KOL input sought by the company. If GnRHa was used strictly within its licence, then all patients would discontinue at 6 months. The large differences in the areas between the curves illustrate the substantial variation when applying alternative plausible assumptions. The impact of this variation on the ICER is explored by the ERG in further scenario analyses (See chapter 6). The ERG notes that treatments which are discontinued earlier in the model are more likely to be cost-effective. This is likely due to savings in treatment acquisition costs, which are proportionally greater than the reductions in treatment benefit, especially given that the company's base case model assumes costly monitoring for BSC and general population utilities for a successful surgery. Further elaboration from the company regarding the face validity of these findings would be useful.

Figure 4 Treatment discontinuation over time

Transition to BSC or surgery following treatment discontinuation

Transition to surgery is conditional on treatment discontinuation from relugolix CT or GnRHa. The proportion of those who discontinue that immediately transition to surgery (and thus enter the waiting time state) is informed by the PEARL II study which reported that 45.1% of GnRHa patients required surgery at 13 weeks of follow up. The remaining 54.9% had planned surgery cancelled in the PEARL II study but were assumed to transition to BSC in the company's model. Therefore, the company base case assumes that that 45.1% and 54.9% of discontinuers in each model cycle transition into the surgery and BSC states, respectively. The resultant monthly transitions to surgery (i.e., first entering the waiting state) were 0.33%, and [redacted] at ≤6 months, 7-12 months, and 13 months onwards respectively for relugolix CT and 0.86% for GnRHa. The remainder of discontinuers transition to BSC as follows: 0.40%, 0.81%, 0.50% at ≤6 months, 7-12 months, and 13 months onward for relugolix CT, respectively, and 1.05% for GnRHa.

The ERG is concerned that the long-term transitions into the surgery state are not evidence-based and that the use of data from PEARL II is inappropriate. The data from the PEARL II study reflect the proportion of patients (45.1%) in that study who did not have a planned surgery cancelled by week 13 of follow-up. The ERG does not consider these data to be transferrable to the modelled cohort, who did not wish to or were unable to have surgery at the point of medical treatment initiation. The company assumed that this proportion (assumed to have surgery) would be applied to the proportion of women who discontinued pharmacological treatment in each cycle (where discontinuation is informed by withdrawal data from the LIBERTY studies and PEARL II respectively). However, this decision appears to be arbitrarily chosen without any appropriate justification. The ERG considers that the company's approach may therefore substantially over-estimate the proportion of the modelled cohort that enters the surgery states after treatment discontinuation. Furthermore, it is unclear what proportion of people would receive surgery in the relugolix CT arm of the model. It is feasible that it may be less than GnRHa given a longer duration of treatment under the company's base case assumptions. However, any proportion would be hypothetical and not evidence based as rates of surgery were not collected as an outcome from the LIBERTY studies.

The ERG does not consider the company's approach to be plausible. The ERG is concerned that the assumptions used in the model generate results that are inconsistent with the quoted data and it is unclear how accurately they may reflect transition to surgery in UK clinical practice. For example, the model predicts that at 3 months 94% of the GnRHa cohort are on treatment, 3% on BSC, 3% waiting for surgery, with 0% receiving surgery. This contrasts with data from PEARL II where almost 45.1% had surgery immediately after the end of treatment. This mismatch illustrates why it is inappropriate to use data from PEARL II study, from a subgroup who were listed for surgery, to populate the risk of surgery in a different group who were not initially intended to receive surgery. As discussed in Section 4.2.3 above, the ERG queries whether it may be appropriate to consider a separate subgroup analysis in a population of people for whom surgery is intended and medical management is used to prepare for surgery. In this short-term treatment (3 months) scenario, the data from the PEARL II study may be more appropriate to enable a comparison of relugolix CT versus GnRHa. Chapter 6 shows the impact on the ICER of the ERG's exploratory analysis around the potential cost-effectiveness of relugolix CT vs. GnRHa in this setting.

In summary, the ERG accepts that some patients may transition to surgery if symptoms are not controlled whilst on medical treatment. Whilst it is plausible that the proportion would be lower for medical treatments that enable longer treatment duration, the rates of transition to surgery are highly uncertain and the chosen sources for the company's base case analysis are likely to generate an overestimate. The ERG believes that the company should have conducted a more thorough review of the literature to identify rates of surgery in a population for whom surgery was not originally intended. Such data would more closely match the setting in which the company appears to be positioning relugolix CT.

In addition to the immediate transition to surgery (waiting list state) for discontinuers, the model also applies a background risk of transition to surgery from the BSC state. The risk is obtained from the PREMYA study, a cohort of 1139 patients, 142 of whom had previously received UF surgery with an average time to surgery of 26.6 months. This resulted in a monthly transition probability of 0.5%.

The ERG considers the calculation approach applied to be reasonable but are concerned that the application of a further transition to the surgery state from BSC may partially double count some of the surgery transitions following treatment discontinuation. An alternative approach would have been to apply the 0.5% monthly transition to surgery for both treatment discontinuers and those entering surgery from BSC.

Waiting time duration prior to surgery

Once a patient has been listed for surgery, they enter the waiting time state for 15 months prior to receiving surgery. KOL advice sought by the company indicated that considering the covid-19 pandemic waiting times for surgery are significantly longer than pre-pandemic. Five expert opinions were obtained, and the company took the average duration from the 5 responses which ranged from 9 to 18 months.

At the clarification stage, the ERG asked the company to provide an estimated waiting time in a world without covid-19, highlighting that the pandemic and its implications on waiting times would not apply indefinitely. The company referred to their scenario removing waiting time altogether but did not provide an estimate of likely waiting times. The ERG notes that NHS England guarantees an 18-week referral time period for non-urgent treatments. As noted in Section 4.2.2, the ERG prefers the removal of the waiting time state from the model as it does not reflect how patients are managed in clinical practice. However, even if waiting time was considered appropriate, the ERG considers an average waiting time of 5 months to be a more appropriate representation of how services might be delivered in the future.[29]

Surgery outcomes (transitions to the post-surgery states)

Surgical outcomes are dependent on the type of surgery received. The proportion of patients that receives hysterectomy have one surgery only, after which point they are assumed cured. The proportion having other surgeries (myomectomy, UAE, and MRgFUS) may have up to two surgeries. Table 36 of the CS details the pre-surgery rates, obtained from Gupta et al. 2014 and Gorny et al 2017 resulting in a monthly chance of re-surgery of 1.72%.[29, 30] The proportion of patients that are assumed to be cured after having surgery was calculated by converting the annual risk of re-surgery (20.60%) to a 10-year probability (where 10 years is based on the maximum time you

can remain on GnRH treatment). The resulting proportion of patients that were cured after surgery was 12.52% while 87.48% [1-EXP(-monthly rate of 1.73%*120 cycles)] were assumed to have a second surgery.

The ERG considers this to be a substantial overestimate of the risk of re-surgery. In general, the ERG queries the appropriateness of allowing more than one round of surgery given that listing for surgery is only assumed to occur between ages 42 (model start age) and 46 (five years before menopause). As a result, the proportion of the cohort entering the second surgery states is very small and amendments to these parameters have only a negligible impact on the ICER. The ERG explores a scenario where only one round of surgery is allowed within the model structure (i.e., pre-surgery rates assumed = 0%).

Clinical-effectiveness parameters in the model: menstrual blood loss (MBL) volume

MBL volume was the main clinical outcome from the LIBERTY and PEARL II studies used in the economic model and is used to estimate utilities for the relugolix CT, GnRHa, and BSC states of the model. Data are obtained directly from the LIBERTY 1 and LIBERTY 2 trials (up to month 12) for relugolix CT and BSC (placebo arm of LIBERTY studies), and the company's ITC for GnRH analogues. Data from the last MBL measurement time point (week 52 for relugolix CT, week 28 for BSC (placebo), and week 12 for GnRHa) were assumed to be carried forward for the remainder of the patient's time on treatment. Table 56 in the CS reports the time-varying MBL data applied in the model, reproduced graphically in Figure 5. The implications of using MBL data to inform QALY gains are critiqued in Section 4.2.7.

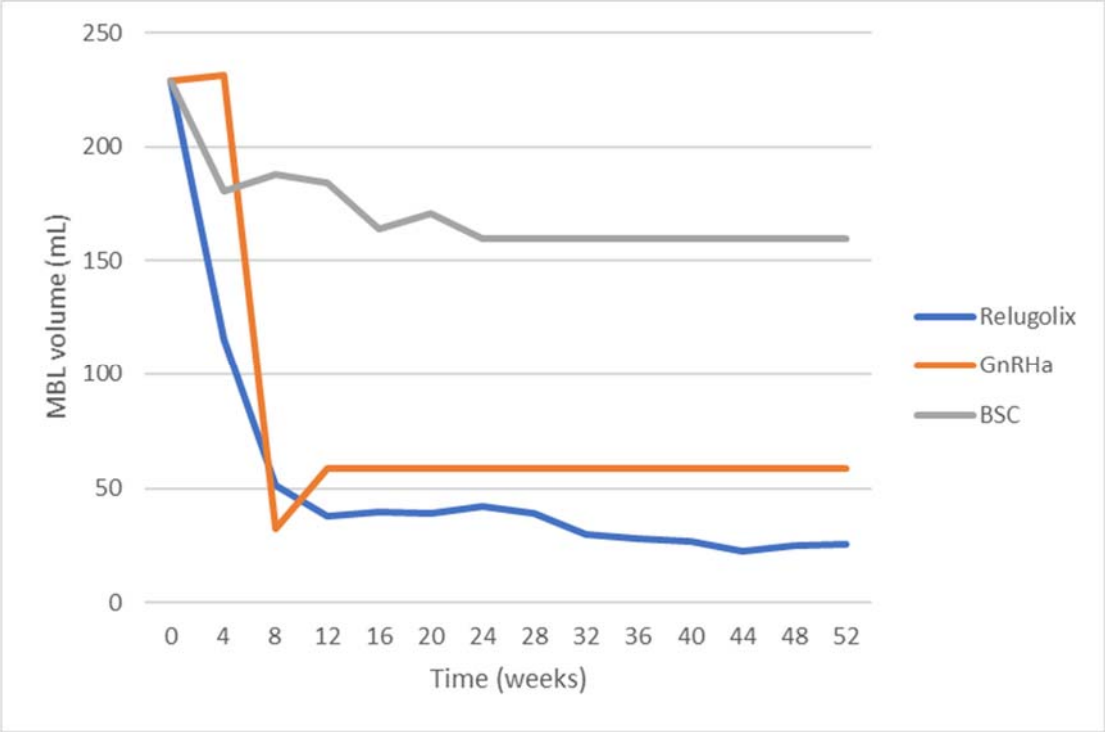


Figure 5 MBL volume over time

The ERG has several concerns regarding the data and assumptions used to integrate MBL data into the economic model:

1) *The ERG's full critique of the company's ITC methodology, and in particular concerns about limited reported data can be found in Sections 3.4 and 3.5 of this report. The points raised in this critique are also relevant considerations for the economic model. The ERG would have preferred to see more clinical outcomes included in the ITC to determine whether the model incorporates sufficient information on patient benefit from which to derive all impacts on quality of life and hence QALY gains.*

2) *Assuming that MBL data are sufficient, the ERG's main concern is that the company did not provide details of the results of the ITC of MBL for relugolix CT versus GnRHa within their submission. The ERG attempted to re-run the company's ITC and was able to generate similar data to those reported in Table 56 of the CS and included in the economic model. The ERG is therefore satisfied that the mean MBL data are indeed sourced from the ITC. However, importantly, no measure of uncertainty surrounding the estimated ITC*

treatment effects was reported or included within the economic model. The ERG's replication of the ITC indicates wide confidence intervals for the comparison of relugolix CT vs GnRHa and hence substantial uncertainty which has not been considered in the economic model. The ERG considers this to be an important omission and one that results in substantial underestimation of the uncertainty surrounding the ICER derived from the company base case probabilistic analysis. The ERG, therefore, uses standard errors derived from our reproduction of the ITC within an updated probabilistic analysis.

3) *Similarly, for BSC MBL, the company include a fixed parameter from what appears to be a pooled analysis of the LIBERTY 1 and* LIBERTY *2 studies. However, again, no estimate of uncertainty has been provided surrounding the pooled MBL treatment effect. The ERG explores applying an approximated standard error obtained from the LIBERTY 1 study, obtained from Table 18 of the CS to incorporate some uncertainty into the probabilistic analysis.*

4) *For the proportion of the cohort in both model arms that discontinue relugolix CT or GnRH analogues and progress to BSC, an immediate increase in MBL is assumed. The ERG's clinical expert considers this to be unreasonable as BSC in clinical practice may still maintain lighter blood loss. It may also take some time for the blood loss levels to revert to placebo following discontinuation. Because a higher proportion of patients come of treatment with GnRH analogues and therefore incur the blood loss levels of someone on BSC (close to pre-GnRHa / relugolix CT levels), any bias would likely be in favour of relugolix CT. Whilst this is an issue of uncertainty that should be considered, the ERG does not have sufficient data to provide a more robust set of assumptions in the model.*

5) *ITT analysis results were used to generate MBL data applied in the economic model. This approach contradicts the model structure which is defined according to treatment received health states. Whilst the ERG would prefer a model structured around 'health' states (see Section 4.2.2), an alternative approach may be to provide a per-protocol analysis of MBL data to apply to*

the 'on treatment' cohort in the current model structure. The implication is that MBL may be underestimated in the 'on treatment' cohorts of both arms of the model. The net impact of any bias depends on the preferred treatment discontinuation assumptions, but in the company's base case analysis any bias is likely to favour GnRHa.

In summary, the ERG would prefer a model structure built on 'health' states that incorporates MBL obtained from the ITC of relugolix CT vs. GnRHa with appropriate standard errors to enable a full assessment of uncertainty in the probabilistic analyses.

Adverse events

Treatment-related adverse events that occurred in ≥5% of patients in the trials (LIBERTY 1-2 and PEARL II) were included in the model (see Table 50 in the CS). The ERG sought further clarification from the company regarding the incorporation of adverse event data in the model. The ERG queries, company clarification and ERG comments on the response are summarised in Table 27.

Whilst there are some uncertainties and the ERG notes that longer-term treatment-related AE data may subsequently become available from the longer-term LIBERTY studies, the ERG is satisfied with the company responses and agree that any impact on the ICER of amending the AEs included in the model is likely to be negligible.

Table 27 Summary of the issues surrounding treatment related adverse events

ERG query	Company response at clarification	ERG comments
Unclear why the company only use adverse event rates from LIBERTY 1-2 and not LIBERTY 3 or the withdrawal studies.	Adverse event data were not available from LIBERTY 3/withdrawal study and therefore could not be used in the economic model.	The ERG is satisfied with the company's clarification response and notes that adverse event rates are not a major driver of the ICER.
Unclear why the company have not included all adverse events in the model and not just those occurring in 5% or more of patients.	1) A total of 35 adverse events were reported in LIBERTY 1 and LIBERTY 2 and including all those adverse events in the economic model would take considerable effort with little impact on the ICER. 2) This would be a biased comparison because of the longer-term data available from LIBERTY compared to GnRHa with 3 months of data from PEARL II. Also, it would be an unfair comparison given the tolerance issues of GnRHa in the longer term. Therefore, extrapolating PEARL II adverse event data for GnRHa and using longer-term adverse event data for relugolix CT might not be appropriate.	The ERG would have preferred to include all adverse events in the trials but appreciates that the impact on the ICER is negligible. The ERG is satisfied that the company's approach to modelling adverse events, whilst not ideal, is sufficient for decision making.

The model also includes adverse events associated with surgery for the proportion of the cohort that enters the surgery health states. Monthly probabilities of short-term surgery-related adverse events were obtained from three studies (Brummer et al. 2011, Manyonda et al. 2012 and Gorny et al. 2011). Details are reported in Table 51 of the CS. The incidence of long-term adverse events related to hysterectomy are reported in Table 52 of the CS.

The ERG noted that no justification was provided for the choice of sources used to obtain short-term adverse events for surgery or their applicability to the modelled population. Whilst further information and a more systematic approach to identifying adverse events would have been preferable, the ERG is satisfied that removing both the short-term and long-term surgery-related adverse events only has a minor impact on the ICER when applied to the company base case analysis. However, in any scenarios in which incremental QALYs are smaller for relugolix CT compared to GnRHa, decisions about these parameters may become more important.

Survival and probability of transition to death state

The company used general population, sex-specific all-cause mortality rates from national life tables to inform transition to the death state in the model. For the proportion of the cohort receiving surgery an excess mortality risk was applied to reflect the risk of surgical mortality. The additional risk was obtained from Settnes et al. 2020, a Danish cohort study.[34] The surgery-specific mortality risks are reported in Table 53 of the CS.

No details were provided regarding how the chosen source was identified or whether a UK source was available. However, the ERG notes that there are minimal incremental life-year gains in the company's base case analysis. Therefore, the impact of surgical mortality only has negligible impact on the ICER.

4.2.7 Health-related quality of life

Section 4.2.6 describes life year gains for relugolix CT in the economic model achieved via lower rates of surgery, and hence a lower overall risk of surgical mortality. However, the predominant driver of quality-adjusted life years (QALYs) within the economic model is through assumed gains in quality of life (utilities) for

relugolix CT compared to GnRHa. There are several routes to utility gain for relugolix CT within the company's economic model:

1) Treatment arm specific health state utility gains associated with lower MBL whilst on treatment with either relugolix CT or GnRHa compared to BSC.
2) Utility decrements due to anxiety and depression associated with being placed on a waiting list for surgery.
3) Disutilities associated with treatment-related adverse events and
4) Gains in utility associated with successful surgery (assumed equal to the general population) offset by utilities equal to the BSC state for unsuccessful surgery, disutilities associated with surgical adverse events, and loss of uterus following hysterectomy applied up to the point of menopause.
5) After menopause (model age 51), the whole cohort receives general population age, but not sex-adjusted utilities.

The ERG's critique of these issues is presented in the following sections.

Treatment state utility values

The model includes treatment-specific utilities that are informed by MBL from the relugolix CT and BSC arms of the LIBERTY studies, and for GnRHa via an ITC with the PEARL II study. Three measures of QoL were included in the LIBERTY studies: EQ-5D-5L, Uterine fibroid symptom and quality of life (UFS-QoL), and patient global assessment (PGA). The LIBERTY studies demonstrated significantly higher improvements in UFS - QoL from baseline for relugolix CT, compared to placebo (BSC), but there was no evidence of any differences between the groups in terms of EQ-5D-5L utilities, with little differences between baseline and follow up in either arm of the trial. The company highlight two concerns that limit the potential for EQ-5D-5L data from the LIBERTY studies to adequately capture QoL benefits of relugolix CT. The first is that EQ-5D data were only collected at baseline and once over follow-up, at 24 weeks. The second is that a recall point of "today" for completing the EQ-5D-5L would likely have failed to capture the QoL implications for women unless the questionnaire happened to be completed during menstruation, which the company state was rare. The company argue therefore that UFS-QoL, which was administered at baseline and twice over follow-up at weeks 12 and 24 and

had a recall time covering the whole follow-up time frame, is a more appropriate measure of QoL.

The ERG agrees that the available EQ-5D-5L data are likely to be insufficient to capture and QoL benefits of treatment. The ERG's main concern with the use of EQ-5D-5L in this context relates to how the instrument was used in the trial, rather than concerns with the instrument's validity per se. The ERG notes that the company could have administered EQ-5D-5L more frequently in their study and could have asked respondents for a mix of responses both during menstruation and at other points in their menstrual cycle. Such an approach would have provided a much richer dataset that would likely have been sufficiently sensitive to measure QALY gains directly in the trial. The company claim that the study visits where EQ-5D-5L was completed rarely occurred during menstruation, but no evidence to support this claim has been provided. Given how EQ-5D-5L was administered in the trial, the ERG generally agrees that UFS-QoL may be a more appropriate measurement tool.

Due to a lack of a valuation tariff for UFS-QoL that would allow estimation of disease-specific QALYs, the company use an unpublished algorithm from Rowen et al to map from the UFS-QoL to EQ-5D-3L.

The ERG is generally satisfied that the underlying mapping process is reasonable, and notes that predicted utilities from the algorithm are generally higher than those of EQ-5D-3L, particularly for more severe health states. The ERG is satisfied that the mapping algorithm may give a conservative estimate of utility decrements associated with uterine fibroids. However, the ERG would have liked to see an estimate of the treatment effect of relugolix CT on mapped EQ-5D values from the LIBERTY studies. This would have helped to validate the company's argument and the ERG opinion that mapped utilities are an appropriate approach to generating treatment state utilities for the economic model.

The company then use a further OLS linear additive regression model as a utility function to predict treatment state utility values based on MBL and baseline age. The model was fitted to the LIBERTY trial data. The following utility function is applied to MBL data for relugolix CT, GnRHa and BSC in the company's base case analysis:

$$EQ - 5D_{mapped} = \alpha + \beta_1 MBL\ Volume + \beta_2\ Baseline\ Age + \varepsilon$$

The resultant utilities at each MBL measurement timepoint for relugolix CT, BSC (placebo) and GnRHa are detailed in Table 57 of the company submission.

The ERG raises several concerns with the company's approach to the estimation of treatment state utility values using their OLS regression.

The first issue is that the company has provided insufficient detail regarding the process of specifying the appropriate utility function, including choices regarding the included explanatory variables and functional form. For example, it is unclear whether non-linearities for age and MBL were explored, for example using squared terms in the OLS model. The company refers to a conference presentation where PBAC bleeding and VAS pain scores were used to directly predict EQ-5D. However, the utility function used in that study is not consistent with the one used in the current submission. The ERG is therefore not satisfied that sufficient information has been provided in the company submission on which to determine the most appropriate utility function

The second issue is that the original company submission did not include standard errors from the OLS regression model, and it was therefore not possible to incorporate the information into the probabilistic analyses. The company raised a concern that SEs from OLS models may be biased due to the repeated measures nature of the UFS-QoL and MBL data. The ERG suggested a repeated measures model at clarification. The company subsequently provided further details from both the OLS and repeated measures models that would enable the incorporation of uncertainty into the probabilistic analyses. The available utility function coefficients and standard errors are compared in Table 28. The ERG notes that the co-efficient on MBL in the repeated measures model is somewhat higher than in the OLS model. However, the most appropriate specification for the utility function remains unclear. In the absence of a full exploration of the advantages and disadvantages of different approaches, the ERG prefers the repeated measures model because it allows more appropriate exploration of uncertainty. The implication of applying the repeated

measures model is that there is a slightly higher reduction in utility for every one-unit increase in MBL compared to the company preferred OLS model. This leads to lower QALYs in both arms of the model, slightly higher incremental QALY gains for relugolix CT and hence a lower ICER compared to the company preferred base case model.

Table 28 Comparison of different utility functions used to populate the economic model

Model parameter	Company base case utility function (OLS)		Company scenario analysis utility function post clarification (repeated measures model)	
	Mean	SE	Mean	SE
Intercept	0.69568	0.02999	0.7035	0.04196
MBL volume (dL)	-0.03877	0.00238	-0.0593 [A]	0.00350 [A]
Age at baseline (Years)	0.00296	0.0007	0.003	0.0001

[A] Note that the numbers reported for MBL volume refer to the company's corrected clarification response (post FAC)

Abbreviations: dL: decilitre; OLS: Ordinary least squares; SE: standard error

Utility in the 'waiting time' and 'surgery' states.

The proportion of the cohort in the 'waiting time' state prior to a first or second surgery are assumed to have the same utilitiy as those on BSC. The justification is that people who are listed for surgery have experienced treatment failure. A further disutility of -0.01 is added to reflect concern or worry among people listed for surgery.

The ERG does not consider the inclusion of a waiting time state to be appropriate (See section 4.2.2.). Even if a 'waiting time' state were included, the ERG disagrees that an additional disutility for anxiety should be applied. The source stated by the company does not reflect a population of people waiting for surgery and is instead a disutility for patients suffering from anxiety. These health states are not comparable.

The ERG sees no evidence that a disutility should be applied during waiting time and an argument could equally be made that people who are listed for surgery may gain positive utility from the anticipation of having a successful resolution of theiry symptoms from surgery.

The utility in the surgery state is calculated as an average of the general population and BSC utilities weighted according to the proportion cured (12.52%) or not cured (87.48%) respectively. A further disutility decrement was then applied to reflect a disutility associated with surgery as outlined in Table 59 of the company submission. A further annual disutility of -0.18 associated with loss of uterus was converted to a monthly disutility and applied in each model cycle to the proportion of the cohort receiving hysterectomy up until the point of menopause.

The ERG considers the company's approach to applying different utilities according to surgical outcome to be reasonable, but as noted in Section 4.2.6, the ERG considers the surgery cure rate to be rather low, and it may be plausible that a larger proportion of the cohort who enter the surgery state may achieve the general population utility than that modelled by the company. The ERG is also concerned that applying multiple disutilities in addition to this may risk double counting. For example, the company has not provided any justification that the disutility of loss of uterus applied in the hysterectomy state is not at least partially captured in the disutilities reported in Sculpher et al (Table 58 and 59 of the company submission).

Furthermore, the ERG notes that the utility function applied to active treatment and BSC underestimates the utility of an age and sex matched UK general population cohort when MBL is low. This means that the incremental QALY gains achieved with progression from active treatment or BSC to a successful surgery, where general population utilities are applied, may be over-estimated. The ERG explores the impact of uncertainty surrounding this assumption in scenario analyses.

Disutilities associated with treatment-related and surgery-related adverse events

Disutilities are also applied to treatment-related adverse events in the model. In response to clarification queries the company provided further detail on the disutility sources applied in the model (see the company's clarification response – B9).

The ERG raised a concern at clarification that the approach used to identify adverse event disutilities did not appear to be systematic. However, following the company's clarification response (B9) providing details of utility measures and value sets applied from the sourced studies, the ERG is now satisfied that the disutilities of adverse applied in the model are reasonable. The ERG also notes that these disutilities are not an important driver of cost-effectiveness results.

UK general population utilities - applied in the menopause state

The company has applied UK general population age-adjusted utility norms, as published in Szende et al., based on the UK-TTO value set.[35] General population utility was used as the starting point for application of all utility decrements incurred after the point of menopause (age 51) and were applied regardless of the experience of surgical procedures, or loss of uterus.

The ERG is satisfied that general population utilities have been appropriately incorporated into the by mode age band. However, the ERG would have considered it more appropriate to use the female-specific general population value set for this population. The ERG accepts however that the impact of changing from the full population value set to a female-specific value set has only a minimal impact on the ICER. The ERG and company preferred value sets are compared in Table 29 below for completeness.

Table 29: General population EQ-5D utility weights used in the model

Age band	Company preferred approach (full population)	ERG preferred approach (female only)	Source
18-24	0.940	0.943	Szende et al.[35]
25-34	0.927	0.925	
35-44	0.911	0.909	
45-54	0.847	0.849	
55-64	0.799	0.815	
65-74	0.779	0.777	
75+	0.726	0.712	

4.2.8 Resources and costs

Treatment acquisition costs (relugolix CT and GnRHa)

The treatment acquisition costs for relugolix CT is £72 at the list price, for a 28-pack of 40 mg/1 mg/0.5 mg tablets. At one tablet per day, this results in a monthly (30.5 days) cycle cost of £78.43.

The treatment acquisition cost for GnRH analogues was obtained from the NHS drug tariff (2021).[36] A total of 4 types of GnRH analogues (across 4 brands) were included. GnRH analogues are given as injections, one injection per month for the short-acting formulations and once every 3 months for the long-acting formulations. The costs are provided in Table 64 and 65 in the CS. The monthly formulations for leuprorelin acetate, triptorelin, and goserelin are priced at £75.24, £72.32 (weighted average of two brands obtained from BNF based on Prescription Cost Analysis data from 2017/18), and £70, respectively. The 3-monthly formulations for leuprorelin acetate, triptorelin, and goserelin are priced at £225.72, £207, and £235, respectively.

The ERG is not convinced that the company's decision to use a weighted average approach is appropriate and would have preferred the use of the lowest available cost for Triptorelin (monthly formulation), which is (£69). However, the impact on the ICER for relugolix CT versus triptorelin is minimal.

Two add-back therapies were included in the analysis. The company assumed 50% would be on tibolone (list price: £7.44; monthly cost: £8.10) and 50% on raloxifene (list price: £5.65; monthly cycle cost: £6.15), based on the BNF (2021). The estimated monthly cost is an average of the two: £7.13.

Although the 50:50 split is an assumption, varying this proportion on each add-back therapy has little impact on the cost-effectiveness results.

Best supportive care treatment costs

For treating persistent symptoms (pain and blood loss), a proportion of patients (informed by the LIBERTY 3 study for relugolix CT and BSC, and PEARL II for GnRH analogues) are assumed to be taking concomitant medications. NSAIDs (200mg ibuprofen) for pain and iron supplements (ferrous sulfate 200mg tablets) for

blood loss. Tables 76-79 in the CS present the concomitant dose assumptions, medication costs, proportion on each type of concomitant medication, and usage mg (per month). The resulting monthly cost of concomitant medication for relugolix CT, GnRHa, and BSC are £3.73, £1.83, and £4.25, respectively.

The ERG has 2 comments related to the concomitant medications used in the economic model:

1) *It is unclear to the ERG why only LIBERTY 3 was used to inform concomitant medication use for relugolix CT and BSC and not the other LIBERTY studies. The company has also provided insufficient information within their submission to clarify exactly what treatments were provided as BSC in LIBERTY 1 and 2, and how these reflect the lack of active treatments included as BSC in the economic model. Ideally, the ERG would like to see evidence that the medications taken in the trials are consistent with those incorporated into the economic model.*

2) *The ERG's clinical expert suggests that treatments following discontinuation of relugolix CT or GnRHa might include hormonal treatments or contraceptives to treat patient's symptoms and manage MBL. However, the company's model assumes no such treatments are included in BSC, including only iron supplements and ibuprofen which the ERG's clinical expert considers to be insufficient for treating fibroids in this patient group. The ERG notes that the company has provided insufficient details within their submission regarding the BSC treatments used in the LIBERTY studies, but it is unlikely that they reflect BSC in UK clinical practice. This raises an uncertainty for decision making. Whilst the ERG considers the costs of BSC to be under-estimated, it is likely that the benefits are also underestimated. Adjusting costs of BSC to better reflect UK clinical practice could be considered as a scenario analysis but doing so would generate further bias because it is unclear how the associated benefits should be adjusted.*

Routine monitoring and examination costs

Other treatment-related costs include an initial gynecologist consultation, GnRHa administration by a nurse, routine monitoring, and examinations. Full details of the

company's monitoring resource use can be found in Tables 68 to 71 of the company submission.

The ERG agrees with the company that a one-off and annual Dexa-scan would be required as part of UK clinical practice use of relugolix CT and GnRHa respectively whilst on treatment to monitor bone mineral density. However, the ERG disagrees with the company's base case assumption that patients receiving BSC would receive annual scans but that they would not have an associated gynaecologist consultation. The ERG also disagrees that patients would routinely receive six-monthly appointments either on or off treatment. The ERG, therefore, considers it more appropriate to assume a one-off gynaecologist consultation and scan, with these usually occurring about 3-4 months after treatment initiation to monitor patient progress and develop a longer-term care plan. Whilst there is uncertainty surrounding the type of imaging that might be used and this is likely to vary across UK clinical practice, the ERG considers one scan to be sufficient, and has applied the company's weighting assumptions as follows: Ultrasound (1/1.45); hysteroscopy (0.25/1.45) and MRI (0.20/1.45). The ERG prefers a scenario where this resource use would be incurred again if there was a major change in the patient's circumstances (for example discontinuing treatment). The ERG, therefore, applies the same resource use after entry to the BSC state in the model. The ERG's clinical expert advice is that patients would be monitored in secondary care and so it is not necessary to include the costs of 3-monthly GP consultation for patients on BSC because they would be managed through a one-off consultation with a gynaecologist instead.

The company's and ERG's preferred base cases on the resource use assumptions, a summary of the ERG's comments on the company's approach, and justification for the ERG's alternative approach are provided in Table 30.

Table 30 Resource use assumptions – admin, routine check-ups, and examinations

Resource category	Company preferred resource use (frequency)			ERG preferred resource use (frequency)			Company obtained source	*ERG comment*
	Relugolix CT	GnRHa	BSC	Relugolix CT	GnRHa	BSC		
Admin costs								
Initial gynecologist visit before starting treatment	Once only	Once only	0	0	0	0	Gynaecology, Non-Admitted Face-to-Face Attendance, Follow-up, Consultant Led, NHS reference costs 2019-20. Currency code: WF01A (NHS England, 2021)[37]	*The ERG considers the company's stated approach to be appropriate. However, the one-off cost of a visit to the gynaecologist to initiate the first treatment with relugolix CT or GnRHa does not seem to be applied in the model. However, because this is applied to both arms before treatment commences, there is no impact on the ICER, and the ERG do not consider this issue further.*
Nurse administration of GnRH agonists	0	Once per treatment	0	0	Once per treatment	0	Calculated as 10 minutes of practice nurse time (Curtis and Burns 2020)[38]	*The ERG considers the company approach to be appropriate.*

Resource category	**Company preferred resource use (frequency)**			**ERG preferred resource use (frequency)**			**Company obtained source**	***ERG comment***
	Relugolix CT	**GnRHa**	**BSC**	**Relugolix CT**	**GnRHa**	**BSC**		
Routine monitoring								
Gynaecologist consultation	6-monthly	6-monthly	None	Once only	Once only	Once only	3 KOLs; Gynaecology consultant Non-Admitted Face-to-Face Attendance, Follow-up (NHS England, 2021)[37]	*The ERG's clinical expert suggests a review once after 3-4 months after starting treatment. A visit to the gynecologist would be triggered if symptoms were not controlled. MBL volume for relugolix CT and GnRHa would suggest symptom control (with regards to blood loss) and therefore regular gynecologist visits may not be required. Therefore, the ERG prefers to assume a one-off visit to the gynaecologist to monitor patient progress and develop a longer-term care plan (applied to relugolix CT, GnRHa and BSC states)*

Resource category	**Company preferred resource use (frequency)**			**ERG preferred resource use (frequency)**			**Company obtained source**	***ERG comment***
	Relugolix CT	**GnRHa**	**BSC**	**Relugolix CT**	**GnRHa**	**BSC**		
GP visits	0	0	3-monthly	0	0	0	3 KOLs; Per surgery consultation lasting 9.22 minutes, PSSRU 2020 (Curtis and Burns 2020)[38]	*The ERG's clinical expert suggests that patients would not have regular 3 monthly visits to the GP. A visit would be triggered only if patients experienced poor symptom control. See comment above.*
Examinations								
DEXA scan	Once after the first year	Annual	0	Once after the first year	Annual	0	3 KOLs; Outpatient DEXA scan, Currency code: RD50Z (NHS England, 2021)[37]	*The ERG considers the company approach to be appropriate. A DEXA scan may also be considered before commencing treatment on both relugolix CT and GnRHa. However, as these would apply to both arms of the model, there is no impact on the ICER.*
Ultrasound	Annual (100%)	Annual (100%)	Annual (100%)	Once *(67%)*	Once *(67%)*	Once *(67%)*	3 KOLs; Transvaginal Ultrasound, Currency code: MA36Z (NHS England, 2021)[37]	*The ERG's clinical expert suggests a scan and review would be conducted after 3-4 months to consider treatment options and long-term plan going forward. The ERG considers one scan*

Resource category	**Company preferred resource use (frequency)**			**ERG preferred resource use (frequency)**			**Company obtained source**	***ERG comment***
	Relugolix CT	**GnRHa**	**BSC**	**Relugolix CT**	**GnRHa**	**BSC**		
Hysteroscopy	Annual (25%)	Annual (25%)	Annual (25%)	Once *(17%)*	Once *(17%)*	Once *(17%)*	3 KOLs; Diagnostic Hysteroscopy, Currency code: MA31Z (NHS England, 2021)[37]	*per patient to be sufficient, weighted according to the company resource assumptions:* *Ultrasound: (1/1.5 = 67%)* *Hysteroscopy: (0.25/1.5 = 17%)* *MRI: (0.25 / 1.5 = 17%)*
MRI[A]	Annual (25%)	Annual (25%)	Annual (25%)	Once *(17%)*	Once *(17%)*	Once *(17%)*	3 KOLs; MRI, Outpatient procedures, Currency code: DIM004 (NHS England, 2021)[37]	
Full blood count	Annual	Annual	Annual	Once only	Once only	Once only	3 KOLs; Haematology, Currency code: DAPS05 (NHS England, 2021)[37]	*ERG's clinical expert does not consider routine investigations for patients that have their symptoms under control. Instead, a review meeting is expected with a gynecologist that would trigger a full blood count measure.*

Abbreviations: BSC: Best supportive care; DEXA: Dual-energy X-ray absorptiometry scan, GnRHa: Gonadotropin-releasing hormone analogue, KOL: key opinion leader, MRI: magnetic resonance imaging

[A] Table 70 in the CS Document B reports 20% having an MRI whereas the model assumes 25%. The ERG assumes the model value is correct.

Surgery-related costs

The proportion of patients receiving each type of surgery was based on HES 2013 data and Carls et al. 2008.[32, 33] The HES 2013 data was used instead of the HES 2019/20 data because it contained more details on the proportions having each type of surgery. It provided the proportion having hysterectomy, abdominal myomectomy, laparoscopic/vaginal myomectomy and UAE. To further disaggregate the data, Carls et al. was used to inform the proportions having the different types of hysterectomy and myomectomy (laparoscopic / vaginal).[33] The distribution of patients having the first and second surgery is reported in Tables 48 and 49 of the company's submission. The surgery-related costs are provided in Table 73 in the CS. All surgery-related costs are a weighted average of elective, day case, and outpatient unit costs.

The ERG is concerned that the proportions having each type of surgery would be out of date considering the older data sources used by the company. The ERG prefers the use of the most up-to-date data sources where possible to inform model inputs however understands that the company have obtained the older HES data to obtain a more granular level of detail. The ERG will conduct a scenario analysis using an alternative source for informing the proportion on each surgery option (Strong et al. 2020). The Strong et al. study includes UK (London) hospital data from 2015-2018. The proportion on each surgery option was (re-weighted according to the surgery options included in the model): abdominal hysterectomy: 2% (company: 43.36%), laparoscopic hysterectomy: 27% (company: 6.36%), vaginal hysterectomy: 0% (company: 8.48%), abdominal myectomy 27% (company: 8.51%), laparoscopic myectomy: 43% (company: 8.24%), vaginal myectomy: 0% (company: 17.23%), UAE: 0% (company: 4.82%) and MRgFUS: 0% (company: 3%).

Adverse event-related costs

Treatment-related adverse event unit costs are reported in Table 74 in the CS. The unit costs are obtained from PSSRU 2020 (GP appointment)[38] and BNF 2021 (Metoclopramide).[39]

The company submitted table presents unrelated treatment-related adverse events that do not match the treatment-related adverse events in Table 50 of the CS (e.g., it included acne and anxiety as treatment-related adverse events). On further inspection of the model file, these unrelated adverse events were not applied. The costs associated with treatment-related

adverse events are listed below which the ERG has obtained from the company submitted model file.

Surgery-related adverse event unit costs are reported in Table 75 of the CS. Different sources were used to inform the surgery related adverse events rates: hysterectomy (Brummer et al. 2011),[40] myomectomy (Manyonda et al. 2012),[41] uterine artery embolization (Mayonda et al. 2012),[41] and MR-guided focused ultrasound (Gorny et al. 2011).[31]

No justification was provided by the company for the chosen HRG codes – some were for non-elective long stay and some for a non-elective short stay. This is not likely a driver of the ICER because of the small probability of having a surgery-related adverse event (see Table 31).

Table 31 Summary of adverse event rates and costs included in the economic model

	Unit cost (£)	Source / HRG code	Rates					
Treatment-related adverse events								
			Relugolix CT	*GnRHa*	*BSC*			
Cough	0	-	0.00%	0.00%	0.73%			
Upper respiratory tract infection	39.23	PSSRU 2020	0.00%	0.00%	0.66%			
Headache	0	-	1.72%	1.92%	2.38%			
Hot flush	0	-	1.44%	7.81%	1.01%			
Anaemia	39.23	PSSRU 2020	0.00%	0.00%	0.93%			
Insomnia	39.23	PSSRU 2020	0.00%	1.20%	0.00%			
Hypertension	39.23	PSSRU 2020	0.81%	0.00%	0.00%			
Nausea	0.97	BNF 2021	0.00%	0.00%	1.07%			
Surgery-related adverse events								
			Abdominal hysterectomy	**Laparoscopic hysterectomy**	**Vaginal hysterectomy**	**Myomectomy**	**UAE**	**MRgFUS**
Bowel obstruction	5 748.41	WH07C, non-elective long stay	0.00%	0.00%	0.00%	1.37%	0.00%	0.00%
Febrile event	2 103.38	WH07D, non-elective short stay	2.50%	1.40%	0.90%	0.00%	0.00%	0.00%
Fibroid expulsion	5 748.41	WH07C, Non-elective long stay	0.00%	0.00%	0.00%	0.00%	1.35%	0.00%
Groin haematoma	2 103.38	WH07D, Non-elective short stay	0.00%	0.00%	0.00%	0.00%	2.70%	0.00%
Haemorrhage	3 640.02	WH07C, Non-elective short stay	8.30%	5.70%	4.40%	1.37%	0.00%	0.00%
Ileus	0	Assumption.	0.00%	0.00%	0.00%	1.37%	0.00%	0.00%
Pelvic infection, haematoma or abscess	2 103.38	WH07D, Non-elective short stay	0.80%	3.20%	2.20%	0.00%	0.00%	0.00%
Pneumonia	2 103.38	WH07D, Non-elective short stay	0.00%	0.00%	0.00%	1.37%	0.00%	0.00%

Post embolisation syndrome	3 640.02	WH07C, Non-elective short stay	0.00%	0.00%	0.00%	0.00%	8.11%	0.00%
Pulmonary embolus	3 640.02	WH07C, Non-elective short stay	0.00%	0.00%	0.00%	1.37%	0.00%	0.00%
Sepsis	5 748.41	WH07A, Non-elective long stay	0.00%	0.00%	0.00%	1.37%	1.35%	0.00%
UTI	2 103.38	WH07D, Non-elective short stay	2.20%	0.70%	1.50%	10.96%	0.00%	0.00%
Urticaria	0	Assumption	0.00%	0.00%	0.00%	0.00%	1.35%	0.80%
Wound infection	2 103.38	WH07D, Non-elective short stay	2.40%	1.50%	0.90%	0.00%	0.00%	0.00%
Abdominal oedema	0	Assumption	0.00%	0.00%	0.00%	0.00%	0.00%	17.70%
Pain	0	Assumption	0.00%	0.00%	0.00%	0.00%	0.00%	3.80%

Abbreviations: BSC: Best supportive care; GnRHa: Gonadotropin-releasing hormone analogue; UAE: Urinary artery embolization; UTI: urinary tract infection.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company have provided an updated economic model and set of cost-effectiveness analyses in response to clarification queries, correcting a minor error identified by the ERG in the model calculations of life year gains from the 'waiting time' state. All analyses and model results reported in Chapters 5 and 6 therefore refer to the company's updated economic model.

5.1.1 Determinants of cost-effectiveness - QALYs

QALY gains for each treatment arm across model health states are provided in Table 113, appendix K of the company submission. There are two main drivers of QALY gains in the model, as follows:

a) Patients in the relugolix CT arm of the model spend longer on active treatment as opposed to BSC, compared to GnRHa and thus accrue higher QALY gains in the pre-surgical states through lower MBL and higher utilities. It is important to note that the effectiveness assumptions surrounding both, time on treatment and MBL whilst on treatment, are subject to several assumptions and are highly uncertain (see full critique in Section 4.2.7).

b) The model predicts that the number of surgeries in the relugolix CT arm of the model is approximately half of that in the GnHRa arm. Surgery impacts on QALYs by leading to utility gain associated with successful surgery (general population utilities) compared to unsuccessful surgery (BSC utilities), with the ERG noting that different utility calculation approaches may over-estimate the utility gain of surgery success). These gains are offset through the application of a disutility in the surgery waiting state, surgical adverse event disutilities, and disutility associated with loss of uterus up to the point of menopause for patients receiving hysterectomy. There is also a slightly higher overall life-year gain for relugolix CT compared to GnRHa, due to a lower proportion of the cohort incurring a small surgical-related mortality risk.

The ERG considers the differences in the proportion of the model arms progressing to surgery to be highly uncertain and based on strong assumptions about the applicability of the PEARL II trial data to the relugolix CT treated cohort (See full critique in Section 4.2.8).

5.1.2 Determinants of cost-effectiveness - Costs

Table 114, appendix K of the company submission details the drivers of costs in the model. Treatment acquisition costs with relugolix CT are substantially higher than GnRHa, primarily due to the longer time on treatment. The additional cumulative treatment acquisition costs are partially offset by reductions to time spent in the BSC state where routine examination costs are applied. They are also offset by a lower proportion of the cohort entering the surgery states where they incur the costs of the first surgery, costs of surgical complications, and revision surgery up to the age of menopause.

5.1.3 Company deterministic and probabilistic base case ICER

The company's economic model is structured to provide separate results for six different GnRHa products (goserelin, triptorelin, leuprorelin), either monthly or 3-monthly. The company assume that all GnRHa are equally effective, and the ERG considers this assumption to be appropriate. Based on this assumption, the company have provided a fully incremental analysis where the lowest cost GnRHa dominates all other GnRHa treatments in all cases. In the company's analyses, goserelin monthly is the lowest cost comparator, and is, therefore, the most appropriate comparator for the ICER calculation. Fully incremental analyses are provided in the company's submission but based on this assumption, and the ERG's agreement with its validity, the ERG considers a pairwise comparison between relugolix CT and GnRHa to be sufficient for decision making in the context of the quoted list prices for all comparators. The company's preferred base case deterministic and probabilistic ICERs are re-produced in Table 32.

Table 32 Company base case deterministic and probabilistic ICERs [reproduced from Tables 2 and 3 of the company's revised cost-effectiveness analyses in response to clarification queries]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company base case analysis (deterministic)							
Goserelin monthly	7,742	21.525	16.530	-	-	-	-
Relugolix CT	9,854	21.525	16.894	2,112	0.000	0.364	5,796
Company base case analysis (probabilistic)							
Goserelin monthly	7,729	--	16.529	-	-	-	-
Relugolix CT	9,850	--	16.894	2,120	--	0.365	5,808

Scatter plots and CEACs from the company base case probabilistic analysis are reproduced in Figures 6 and 7 below.

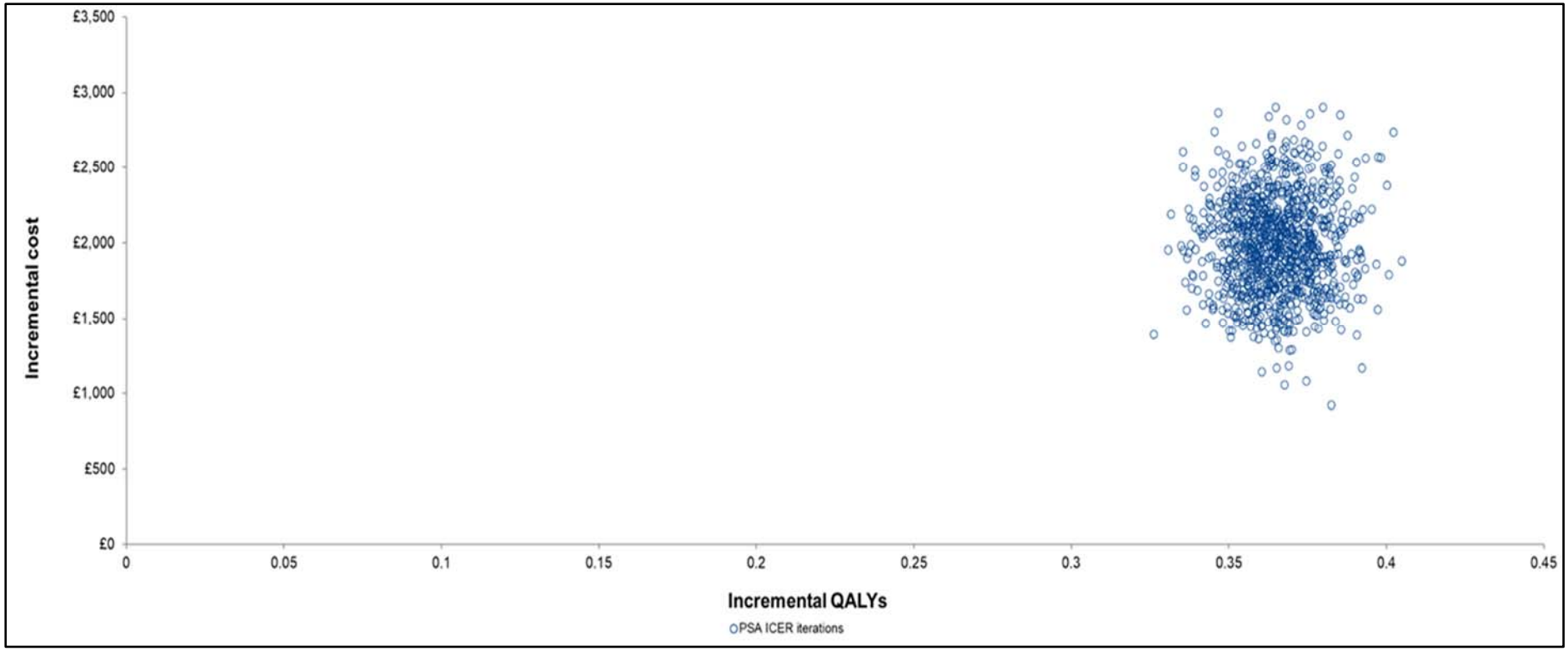


Figure 6 Company probabilistic analysis (scatter plot) - relugolix CT versus GnRHa [reproduced from Figure 1 of the company revised analysis following clarification queries]

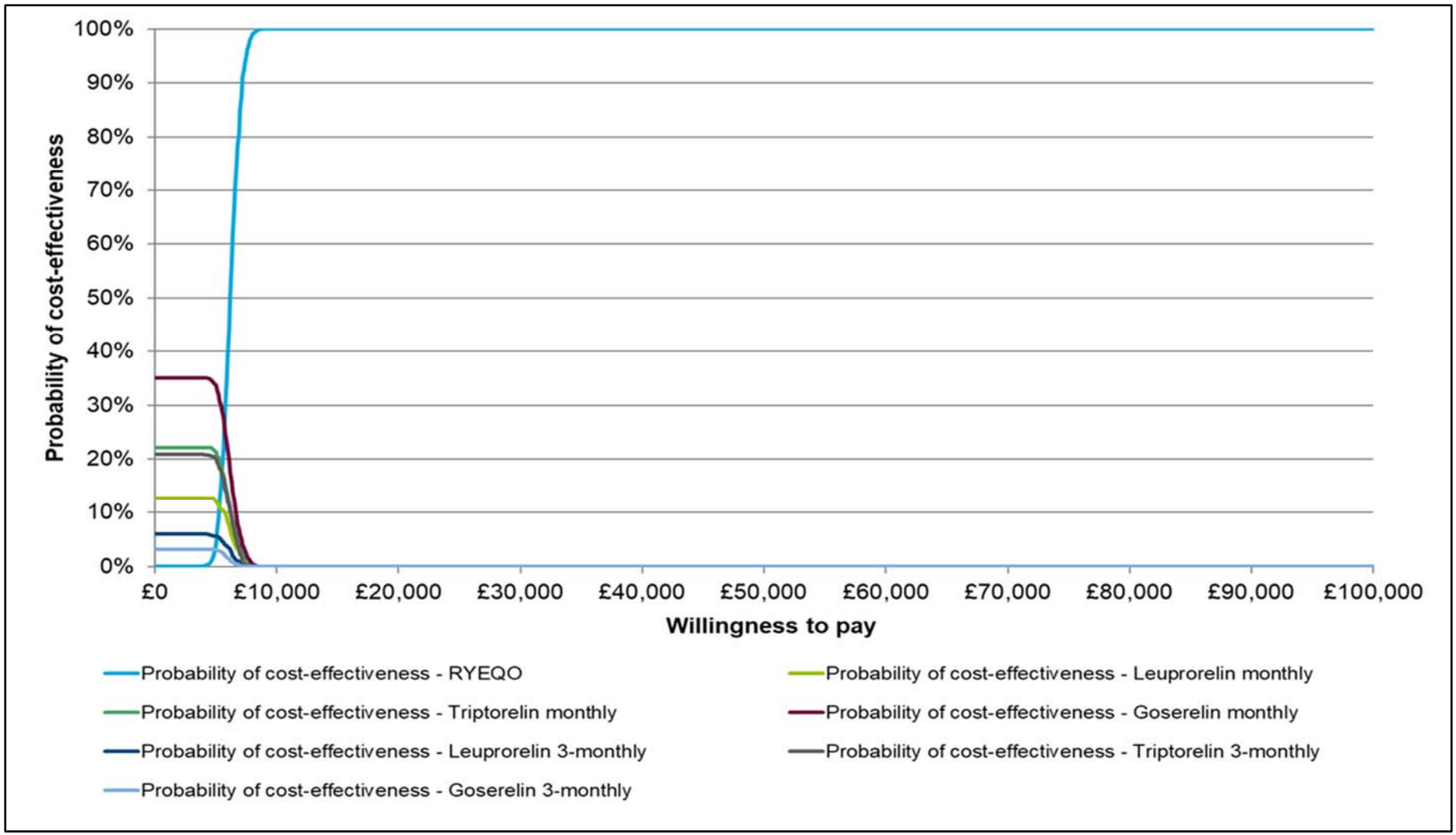


Figure 7 Company probabilistic analysis (CEAC) – all treatments [reproduced from Figure 2 of the company revised analysis following clarification queries]

The ERG has reviewed the company's approach to sampling from distributions for the PSA. The ERG agrees that the company has incorporated multiple parameters within their PSA, and that in general these included parameters are sampled from appropriate distributions (e.g., gamma distributions for costs). However, the ERG has several concerns around the importance of parameters that were not included in the company's PSA.

- *The most important excluded parameters from the PSA are the estimated differences in MBL between relugolix CT and best supportive care (from the LIBERTY trials) and the estimated differences between relugolix CT and GnRHa (from the ITC). The company failed to provide any estimates of uncertainty surrounding these effect sizes for use in the economic model, the ERG was able to recreate the company's ITC, including standard errors around the treatment effect. The ERG also approximates the standard error around the treatment effect from the LIBERTY studies for relugolix CT vs. BSC.*

- *Uncertainty surrounding the regression coefficients used to predict the impact of MBL on EQ-5D (mapped from UFS-QoL) was not incorporated in the original PSA. The ERG notes the company's concern that standard errors from their chosen OLS utility function may be biased because MBL is a repeated measures outcome. Following an ERG request, the company provided the results of a repeated measures model, including standard errors on estimated coefficients for both the OLS and repeated measures utility functions.*

- *Uncertainty surrounding KOL estimates of GnRHa discontinuation beyond six months of treatment was also excluded in the company base case probabilistic analysis. Despite some attempts to integrate this after clarification queries, the ERG still considers the magnitude of uncertainty assumed by the company (SE = 10% of mean) to be underestimated. The ERG prefers to calculate standard errors from available data provided in Table 44 of the CS across 7 KOLs.*

The impact of all these uncertainties on both the company and ERG preferred base case ICERs is illustrated in Section 6.

5.2 Company's sensitivity analyses

The company also provide a tornado diagram illustrating the impact of varying the most important model parameters by +/- 20% of their base case values on the ICER. The results are reproduced in Figure 8 below.

However, as described above, the ERG is of the view that the most important parameter drivers of cost-effectiveness have been excluded from the deterministic scenario analyses also. Therefore, the ERG is of the view that the deterministic scenario analyses and tornado plots substantially under-estimate the overall uncertainty surrounding cost-effectiveness in the company's economic model.

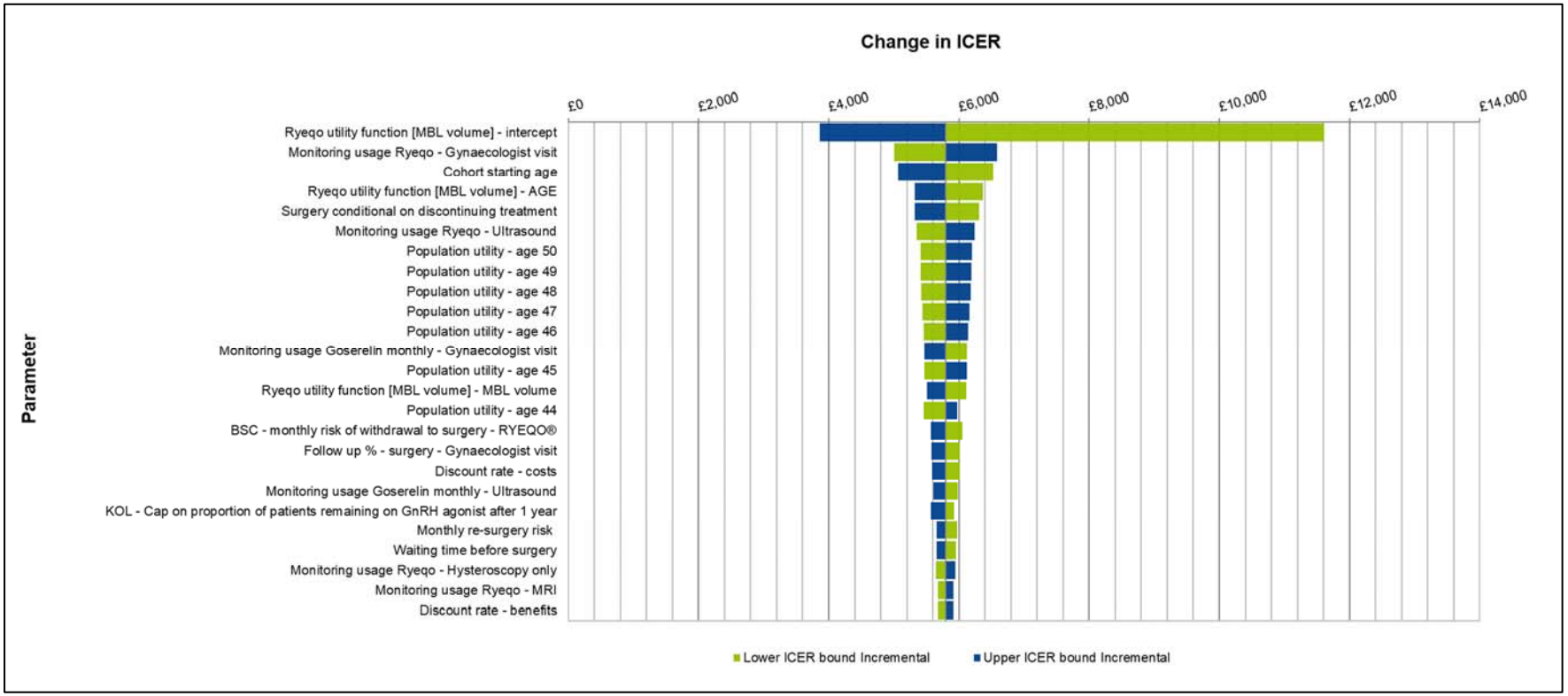


Figure 8 Tornado diagram of one-way sensitivity analyses [reproduced from Figure 3 of the company's clarification response]

The company conducted a total of 14 scenario analyses, varying assumptions around inclusion / exclusion of model states (surgery and waiting time), treatment discontinuation, utilities, and costs. The results of these scenario analyses are re-produced from the company's clarification response in Table 33.

The ERG notes that there is considerable uncertainty surrounding the base case ICER, with the company's one-way scenario analyses generating ICERs up to £15,978 per QALY gained when surgery states are removed from the model. Whilst the ICER under these one-way scenario analyses remains under £20,000 per QALY gained, the ERG notes that plausible optimistic and pessimistic combinations of assumptions and data inputs for relugolix CT would likely demonstrate much wider ICER ranges. The ERG conducts several additional scenario analyses in Chapter 6 to further illustrate the impact of uncertainty surrounding modelling assumptions and data inputs on the base case ICER.

Table 33 Company scenario analyses [reproduced from Table 5 of the company updated analyses following clarification queries]

Structural assumption	Base case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER (relugolix CT vs GnRHa)
Base case			**Goserelin monthly**	**£2,112**	**0.364**	**£5,796**
			Triptorelin 3-monthly	**£2,057**	**0.364**	**£5,645**
Modelling of treatment withdrawal in GnRH agonist arm	Withdrawal rates estimated from GnRH agonist arm of PEARL II for the first 6 months and from KOL expert opinion after the first 6 months	Withdrawal for GnRH agonist assumed equal to the modelled withdrawal rates for relugolix CT for the first 6 months of treatment and from KOL expert opinion after the first 6 months	Goserelin monthly	£2,067	0.362	£5,706
			Triptorelin 3-monthly	£2,013	0.362	£5,556
Modelling of adverse events	Adverse events for relugolix CT informed by LIBERTY studies. Adverse events for GnRH agonist informed by PEARL II	Assume identical adverse event profile for relugolix CT and GnRH agonists	Goserelin monthly	£2,116	0.354	£5,982
			Triptorelin 3-monthly	£2,061	0.354	£5,827
MBL volume input for utility algorithm	MBL volume for GnRH agonists derived from ITC	Mean MBL in the GnRH agonist arms assumed the same as relugolix CT for the utility algorithm	Goserelin monthly	£2,112	0.340	£6,212
			Triptorelin 3-monthly	£2,057	0.340	£6,050
			Goserelin monthly	£2,052	0.364	£5,632

Structural assumption	Base case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER (relugolix CT vs GnRHa)
Concomitant medication usage	Informed by proportions in LIBERTY 3 for relugolix CT arm and PEARL II for GnRH agonist arm	Assumed equal for relugolix CT and GnRH agonist arms	Triptorelin 3-monthly	£1,995	0.364	£5,475
Induction period of short-acting GnRH agonist required before receiving long-acting GnRH agonist	Yes	No	Goserelin monthly	£2,112	0.364	£5,796
			Triptorelin 3-monthly	£2,177	0.364	£5,974
Duration of short-acting GnRH agonist required before receiving long-acting GnRH agonist	3 months	1 month	Goserelin monthly	£2,112	0.364	£5,796
			Triptorelin 3-monthly	£2,062	0.364	£5,659
Inclusion of surgery health states	Included	Excluded	Goserelin monthly	£3,070	0.194	£15,798
			Triptorelin 3-monthly	£3,016	0.194	£15,516
Referral to surgery upon discontinuation of treatment	No referrals within 5 years of menopause	Referrals possible up until menopause (51 years of age)	Goserelin monthly	£2,203	0.344	£6,403
			Triptorelin 3-monthly	£2,148	0.344	£6,243
Waiting time before surgery	15 months	6 months	Goserelin monthly	£1,993	0.223	£8,947
			Triptorelin 3-monthly	£1,938	0.223	£8,700
Waiting time before surgery	15 months	12 months	Goserelin monthly	£2,099	0.353	£5,954
			Triptorelin 3-monthly	£2,044	0.353	£5,798

Structural assumption	Base case scenario	Other scenarios considered	Comparator	Incremental costs	Incremental QALYs	ICER (relugolix CT vs GnRHa)
GnRH agonist and HRT dose intensity	100%	50%	Goserelin monthly	£3,064	0.364	£8,409
			Triptorelin 3-monthly	£3,036	0.364	£8,331
Add-back therapy costs and effect on AEs for GnRH agonist	Included	Excluded	Goserelin monthly	£2,288	0.380	£6,019
			Triptorelin 3-monthly	£2,233	0.380	£5,875
GnRH agonist treatment duration and inclusion of add-back therapy	Cap on % remaining on treatment at multiple periods based on KOL opinion; add-back therapy included	Fixed maximum duration of 6 months as per SmPC, add-back therapy costs and effect on AEs excluded	Goserelin monthly	£3,362	0.497	£6,766
			Triptorelin 3-monthly	£3,354	0.497	£6,749
GnRH agonist treatment duration (including add-back)	Cap on % remaining on treatment at multiple periods based on KOL opinion	Fixed maximum duration of 12 months; PEARL II withdrawal rates applied throughout	Goserelin monthly	£2,960	0.488	£6,070
			Triptorelin 3-monthly	£2,949	0.488	£6,047

Abbreviations: AE: Adverse events; GnRHa: Gonadotropin-releasing hormone analogue HRT: Hormone replacement therapy; ICER: Incremental cost-effectiveness ratio; ITC: Indirect treatment comparison; KOL: Key opinion leader; QALY: quality adjusted life year

5.3 Model validation and face validity check

The ERG has quality assessed the model against the black-box checklist described by Tappenden and Chilcott 2014[42] and through additional face validity and a random selection of formulae checks in cells on the model trace. The findings of the ERG checks are provided in Table 34. Checks were applied to the company's updated economic model supplied in response to clarification queries, which corrected errors identified in the ERG's initial face validity checks. Those initial errors have been corrected by the company in response to clarification queries and are not discussed further here. The following issues were identified after completion of the updated model face validity check:

Table 34 'Black box' verification checks conducted on the company base case model

Model component	Model test	Unequivocal criterion for verification	Issues identified / ERG comment
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks, or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	No issues
	Sum expected health state populations at any model time-point (state transition models)	Total probability equals 1.0	No issues
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	No issues
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	No issues
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	No issues
Cost estimation	Set intervention costs to 0	ICER is reduced*	No issues
	Increase intervention cost	ICER is increased*	No issues

Model component	Model test	Unequivocal criterion for verification	Issues identified / ERG comment
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	The undiscounted total admin costs for GnRHa was picking up the adverse event costs and not the admin costs as it should (cell Q6 onwards in the 'Totals GnRH1-6' sheets). Correcting this error resulted in the discounted and undiscounted costs to equalize when discount rate is set at 0%. This does not affect any analyses conducted because the discounted values are calculated separately and are the ones used for the calculation of the ICERs.
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	No issues
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter (e.g., samples from beta distribution lie in range 0\x \1, samples from lognormal distribution lie in range x [0, etc.)	No issues
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	A minor issue was identified during FAC stage where the model traces did not completely capture all input parameters. This did not affect company analyses but impacted on subsequent ERG scenario analyses (Chapter 6)

Model component	Model test	Unequivocal criterion for verification	Issues identified / ERG comment
	Amend value of each individual model parameter*	ICER is changed	A selection of parameters was amended, and no issues identified. However, because the model parameters (live values in the 'Parameters' sheet of the model file) are not always active, it was cumbersome to identify which cell, for each model parameter, was being used in the model.
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	Partly attempted. ERG managed to get close to a full switch in treatment-specific parameters. Because the model file is not always flexible enough to switch the parameters, e.g. for the different cost inputs for relugolix and GnRHa, it is difficult to switch the parameters when e.g. the cost items are not the same.
ICER incremental cost-effectiveness ratio, LYG life-years gained, QALY quality-adjusted life-year * Note this assumes that the parameter is part of the total cost function and/or total QALY function			

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG has undertaken several further exploratory and sensitivity analyses to illustrate the impact of variation in different plausible assumptions on the ICER. Table 35 describes each of the analyses undertaken, together with a justification for each.

Table 35 ERG justification for additional exploratory and sensitivity analysis

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
	Model structure				
1 & 2	Appropriateness of the model 'waiting time' state	Company assumes that listing for surgery is conditional on treatment discontinuation. The proportion of the cohort that discontinue who are listed for surgery therefore enter a waiting time state of average duration 15 months following treatment discontinuation, prior to receiving surgery	**ERG preferred scenario:** Remove waiting time health state. **ERG exploratory scenario:** Reduce duration of waiting time state to 5 months	ERG clinical expert opinion is that patients will remain on treatment whilst waiting for surgery because pre-operative treatment is desirable to ensure optimal surgical outcomes. Exploratory analysis reducing waiting time is intended to reflect likely target waiting times post covid-19 pandemic.	4.2.2
3	Number of potential surgeries in the treatment pathway	Company assumes a maximum of two surgical procedures (one for hysterectomy)	**ERG exploratory analysis:** Assume only one round of surgery would be undertaken.	The ERG analysis explores the impact on the ICER of assuming multiple surgeries would not be conducted close to menopause in UK clinical practice.	4.2.2

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
	Clinical effectiveness & transition probabilities				
4	Treatment discontinuation assumptions on relugolix CT	Applies a modification of treatment discontinuation data from the LIBERTY studies based on clinical expert opinion that the trial over-estimates discontinuation that might be observed in UK clinical practice	**ERG preferred scenario:** Apply unmodified treatment discontinuation rates from the LIBERTY studies	The company's approach is subjective, inconsistent with GnRHa data from the PEARL II comparator, and reduces the costs required to deliver the MBL treatment benefit	4.2.6
5, 6 & 7	Treatment discontinuation for GnRHa	Proportion remaining on treatment based on the <u>average</u> response from N=7 KOLs: 43.2%, 13.6% and 0.7% would remain on treatment at 1, 5 and 10 years respectively	**ERG exploratory analyses:** Varying the proportion on treatment between the minimum and maximum estimates provided by KOLs: range: 5% to 80% at 1 year; 0% to 55% at 5	To explore the impact of this highly uncertain parameter on the ICER	4.2.6

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
			years and 0 to 5% at 10 years. Stopping all GnRHa treatment at 6 months reflecting its use within licence.		
8	Source for surgery rates	Based on the PEARL II study	**ERG exploratory analysis:** Using data from Strong et al.	To illustrate the impact of varying the rate of surgery on the ICER using alternative published sources.	4.2.6
	Utilities				
9	Utility function used to describe the impact of MBL on utility	Company base case uses a linear additive OLS regression model	**ERG preferred scenario:** The ERG prefers to use the repeated measures model provided by the company post – clarification (version corrected post FAC)	Whilst a complete assessment of the advantages and disadvantages of alternative utility functions has not been provided by the company, the ERG view is that the repeated measrues model more closely approximates general population	4.2.7

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
				utility for low MBL and allows estimation of unbiased standard errors for the probabilistic analysis.	
10	Disutility associated with anxiety from waiting for surgery	The company applies a disutility of -0.01 for each month the cohort is in the 'waiting' state to reflect potential anxiety whilst on the waiting list for surgery	**ERG preferred scenario:** To exclude waiting state completely, but even if waiting state is included, the ERG prefers to remove the disutility.	The ERG does not consider the utility source to be generalisable to a population on the waiting list for surgery. Furthermore, there may be positive utility associated with anticipation of a resolution of symptoms.	4.2.7
11	UK general population utility norms	The company apply age-adjusted general population norms for the whole population	**ERG preferred scenario:** General population age and sex-adjusted norms (female)	The ERG considers female-specific general population norms to be more appropriate in the context of the decision problem for this assessment	4.2.7
12	Relugolix CT, GnRHa and BSC utilities	Calculated directly from utility function	**ERG exploratory scenario:** Applied as a decrement to general population	To improve consistency between the application of utilities in treatment states and surgery states	4.2.7

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
	Resource use and costs				
12	Routine monitoring in clinical practice	In addition to dexa-scans, the company include the following routine monitoring resource use: Relugolix CT & GnRHa receive six-monthly gynaecologist consultations and annual scans BSC: receive no gynaecologist consultations, but the same annual scans as the on treatment cohort.	**ERG preferred scenario:** The ERG agrees with the company's modelled use of dexa scans (once only for relugolix CT and annual for GnRHa). The ERG prefers a one-off consultation and scan every time treatment is changed (i.e. 3-4 months after starting relugolix CT / GnRHa and again after treatment discontinuation)	The ERG's preferred assumptions are more likely to reflect patient monitoring in UK clinical practice, where consultations and scans are triggered by patient's symptom control rather than the treatment they receive.	4.2.8
	Scenarios to explore the impact of methodological uncertainty				
13 & 14	Discount rates	Costs: 3.5% per annum QALYs: 3.5% per annum	**ERG exploratory analyses** Discount rate for	Scenario analyses to comply with the NICE reference case[28]	4.2.5

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
			costs and QALYs varied between 0%-6%		
15	Time horizon	Lifetime horizon	**ERG exploratory analysis** Setting maximum time horizon of 9 years (from age 43 to 51).	The justification for this scenario is that all relevant costs and QALYs will most likely have been incurred by menopause (average age of 51).	4.2.5
	Scenarios to explore the impact of treating different subgroups				
16 & 17	Modelled population	Model cohort appears to be structured around the LIBERTY study population, with the intention of using medical treatment to avoid surgery among those who do not wish to have surgery	**Two ERG exploratory analyses:** Removing surgery states from the model to reflect approximate cost-effectiveness of long-term medical management when surgery is not an option.	The ERG provides scenario analyses to help understand the potential drivers of cost-effectiveness in different subgroups. The analyses also seek to illustrate the potential magnitude of bias associated with using surgery rates from the PEARL II study (where surgery was a trial inclusion criterion) to estimate transitions to surgery for relugolix	4.2.3

Analysis number	Parameter/ Analysis	Company base case assumptions	ERG preferred / exploratory analysis	Justification for ERG's assumption	ERG report section
			Apply a 3 month course of treatment for all in preparation for surgery to reflect approximate cost-effectiveness of short term medical management pre-surgery to optimize surgical outcomes (assumes equal effectiveness as per the limited available ITC data).	CT (where being listed for surgery was an exclusion criterion for the LIBERTY studies)	

Abbreviations: ITC: Indirect treatment comparison; MBL: Menstrual blood loss; QALY: Quality adjusted life year;

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

As noted in Section 5.1.3, the ERG considers the company's probabilistic analysis (see Figure 6 for the scatter plot of uncertainty around incremental costs and QALYs on the cost-effectiveness plane) to substantially under-estimate uncertainty surrounding the ICER. The ERG has therefore re-run the PSA, incorporating uncertainty surrounding the MBL (obtained from the LIBERTY studies and ITC), uncertainty surrounding the utility function parameters, and incorporation of broader uncertainty surrounding the elicitation of KOL inputs on GnRHa treatment discontinuation. The results of the ERG's preferred probabilistic analysis applied to the company's base case are illustrated in Figure 9 below. Table 36 then provides the results of all the ERG's exploratory analyses applied to the company base case ICER following clarification queries.

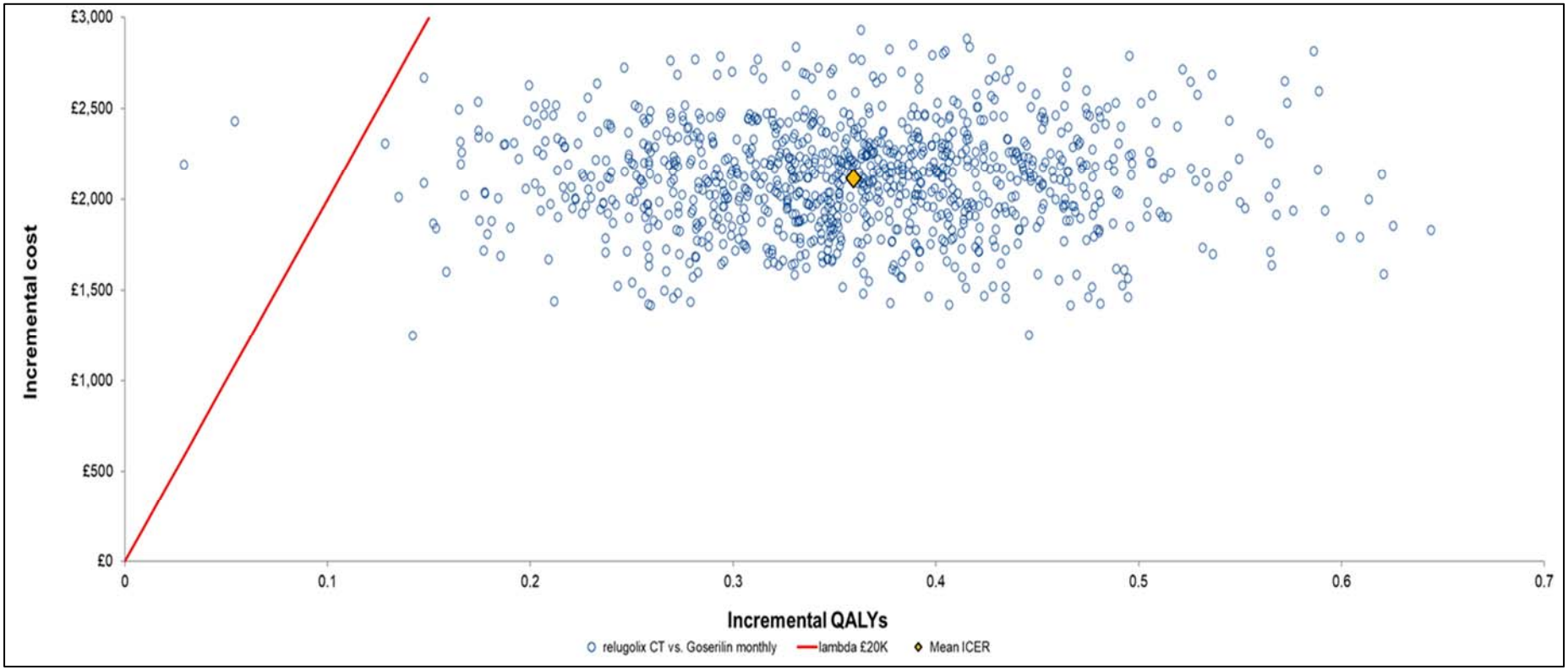


Figure 9 ERG preferred probabilistic analysis of the company's base case model configuration (relugolix CT versus goserelin monthly)

Table 36 ERG scenario analyses applied to the company base case analysis

Analysis number	Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Co BC	**Company preferred base case ICER**							
	Goserelin monthly	7,742	21.525	16.530				
	Relugolix CT	9,854	21.525	16.894	2,112	0.000	0.364	5,796
1	**Remove waiting time state prior to surgery (assumes transition directly to surgery following treatment discontinuation)**							
	Goserelin monthly	8,210	21.525	17.013				
	Relugolix CT	10,111	21.525	17.116	1,901	0.000	0.103	18,470
2	**Reduce waiting time to five months**							
	Goserelin monthly	8,037	21.525	16.831				
	Relugolix CT	10,013	21.525	17.031	1,975	0.000	0.200	9,859
3	**Assume one round of surgery only**							
	Goserelin monthly	7,339	21.525	16.712				
	Relugolix CT	9,686	21.525	16.970	2,347	0.000	0.258	9,102
4	**Apply unmodified withdrawal rates for relugolix CT as per the LIBERTY studies**							
	Goserelin monthly	7,742	21.525	16.530				
	Relugolix CT	8,185	21.525	16.633	444	0.000	0.103	4,311
5	**Proportion on GnRHa treatment set to minimum of KOL input**							
	Goserelin monthly	6,775	21.525	16.414				
	Relugolix CT	9,854	21.525	16.894	3,078	0.000	0.480	6,416

Analysis number	Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
6	**Proportion on GnRHa treatment set to maximum of KOL input**							
	Goserelin monthly	8,781	21.525	16.650				
	Relugolix CT	9,854	21.525	16.894	1,073	0.000	0.244	4,399
7	**GnRHa treatment discontinued at 6-months in line with marketing authorisation**							
	Goserelin monthly	6,491	21.525	16.401				
	Relugolix CT	9,854	21.525	16.894	3,362	0.000	0.493	6,816
8	**Source of surgery risk from Strong et al.**							
	Goserelin monthly	7,808	21.525	16.424				
	Relugolix CT	9,870	21.525	16.851	2,061	0.000	0.426	4,836
9	**Use a utility function based on a repeated measures model to predict the impact of MBL on utilities in the 'on' and 'off' treatment states**							
	Goserelin monthly	7,742	21.525	16.441				
	Relugolix CT	9,854	21.525	16.867	2,112	0.000	0.426	4,953*
10	**Exclude disutility associated with anxiety from the waiting time for surgery state**							
	Goserelin monthly	7,742	21.525	16.536				
	Relugolix CT	9,854	21.525	16.897	2,112	0.000	0.361	5,848
11	**Use female specific UK general population utility norms**							
	Goserelin monthly	7,742	21.525	16.576				
	Relugolix CT	9,854	21.525	16.939	2,112	0.000	0.363	5,818

Analysis number	Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
12	**Utilities for Relugolix CT, GnRHa and BSC applied as decrements from general population norms.**							
	Goserelin monthly	7,742	21.525	17.506				
	Relugolix CT	9,854	21.525	17.022	1,982	0.000	0.484	4,098
13	**Apply one-off scan and gynaecologist consultation across all treatment states (relugolix CT, GnRHa and BSC)**							
	Goserelin monthly	5,886	21.525	16.530				
	Relugolix CT	6,935	21.525	16.894	1,048	0.000	0.364	2,877
14	**Discount rate 0%**							
	Goserelin monthly	8,752	42.086	32.268				
	Relugolix CT	11,298	42.086	32.672	2,546	0.001	0.404	6,297
15	**Discount rate 6%**							
	Goserelin monthly	7,141	15.113	11.570				
	Relugolix CT	9,001	15.113	11.910	1,861	0.000	0.340	5,469
16	**Time horizon: up to menopause (Age 51)**							
	Goserelin monthly	7,742	7.600	5.525				
	Relugolix CT	9,854	7.600	5.889	2,112	0.000	0.364	5,805
17	**Subgroup: long term use in a group who will not transition to surgery**							
	Goserelin monthly	5,927	21.525	17.061				
	Relugolix CT	8,997	21.525	16.866	3,070	0.000	0.194	15,798
18	**Subgroup: short term use in preparation for surgery**							

Analysis number	Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
	Goserelin monthly	8,336	21.524	17.242				
	Relugolix CT	8,406	21.524	17.243	70	0.000	0.005	261,701

Abbreviations: ICER: Incremental cost-effectiveness ratio; LYG: Life year gains, QALY: Quality-adjusted life years

* Note: the ERG was not able to reproduce the results in the company scenario analysis with utility parameters estimated from repeated measures model (Table 17 in the clarification response document). The company estimated an ICER of £4,977 while the ERG estimated an ICER of £4953. The discrepancy is likely due to rounding differences in the utility input parameters, but it was not possible to replicate the company's exact analysis as this scenario analysis was not included within the company's submitted Excel model.

6.3 ERG's preferred assumptions

The key differences between the company's and ERG's preferred base case analyses are:

- The company prefers an economic model structure based on 'treatment' states whereas the ERG prefers an economic model structure based on 'health' states, defined according to symptom control. However, the ERG couldn't construct such a model given the available data.

- The company prefers a modelling assumption where women can only be listed for surgery after treatment discontinuation, when they enter a 'waiting time' state of duration 15 months. The ERG considers it more appropriate to remove the waiting time state because, in clinical practice, most women listed for surgery would continue to receive the primary medical treatment in preparation for surgery.

- The company prefers to modify treatment discontinuation data from the LIBERTY study, based on the assumptions of clinical expert opinion that discontinuation in the trial over-estimates discontinuation in real-world clinical practice. The ERG prefers the use of relugolix CT treatment discontinuation data sourced directly from the LIBERTY study because it is more consistent with the costs required to deliver the modelled treatment benefit and also ensures consistency with the data collected in the PEARL II study for GnRH agonists.

- The company uses a mapping algorithm to transform disease-specific quality of life (UFS-QoL) to generic EQ-5D and uses a linear (OLS) utility function to model the impact of MBL on mapped EQ-5D values. The ERG would prefer more details in support of the chosen model structure and how it was derived. Based on the currently available information, the ERG considers data from the repeated measures model provided by the company in response to clarification queries (with reporting error corrected post FAC) to be more appropriate to allow estimation of appropriate standard errors for inclusion in the probabilistic analysis

- The company assumes that all patients (whether on active treatment or BSC) will receive annual examination scans, but only patients on active treatment will receive gynaecologist appointments (6-monthly). The ERG would ideally prefer a model structure that allows follow-up resource use to be linked to the patient's symptom control ('health' states) rather than their 'treatment' received (other than for Dexa- scans). In a 'treatment' state model, the ERG prefers lower resource use: a one-off gynaecologist appointment and scan to make a treatment plan whenever treatment is started or discontinued.

- The company has included the key clinical outcome from the ITC (MBL) as a fixed-point estimate in the economic model, but the ERG prefers full incorporation of uncertainty surrounding the treatment effects for relugolix CT vs. GnRH agonists and relugolix CT vs. BSC into the probabilistic analyses.

The individual impact of all the ERG's preferred scenarios has been described in Table 36 above. The cumulative impact of the ERG's preferred assumptions on the base case ICER is illustrated in Table 37 below.

Table 37 ERG's preferred model assumptions

	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Company preferred base case ICER							
Goserelin monthly	7,742	21.525	16.530				
Relugolix CT	9,854	21.525	16.894	2112	0.000	0.364	5,796
+ Apply GnRHa trace correction							
Goserelin monthly	7,742	21.525	16.530				
Relugolix CT	9,854	21.525	16.894	2112	0.000	0.364	5,796
+ Apply unmodified withdrawal rates							
Goserelin monthly	7,742	21.525	16.530				
Relugolix CT	8,185	21.525	16.633	444	0.000	0.103	4,311
+ Exclude disutility from waiting time							
Goserelin monthly	7,742	21.525	16.536				
Relugolix CT	8,185	21.525	16.638	444	0.000	0.102	4,339
+ Remove waiting time before surgery							
Goserelin monthly	8,210	21.525	17.013				
Relugolix CT	8,617	21.525	17.059	407	0.000	0.046	8,784

	Total costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
+ Apply utility parameters from repeated measures model							
Goserelin monthly	8,210	21.525	16.922				
Relugolix CT	8,617	21.525	16.992	407	0.000	0.070	5,846
+ Source for general population utilities: female							
Goserelin monthly	8,210	21.525	16.968				
Relugolix CT	8,617	21.525	17.037	407	0.000	0.069	5,866
+ Alternative resource use assumptions assuming one-off/routine admin/monitoring/examination costs							
Goserelin monthly	6,379	21.525	16.968				
Relugolix CT	6,573	21.525	17.037	194	0.000	0.069	2,795
ERG preferred base case analysis (deterministic)							
Goserelin monthly	6,379	21.525	16.968				
Relugolix CT	6,573	21.525	17.037	194	0.000	0.069	2,795
ERG preferred base case analysis (probabilistic)							
Goserelin monthly	6 376	--	16.957				
Relugolix CT	6 573	--	17.026	197	--	0.069	2 833

Abbreviations: ICER: Incremental cost-effectiveness ratio; LYG: Life year gains, QALY: Quality adjusted life years

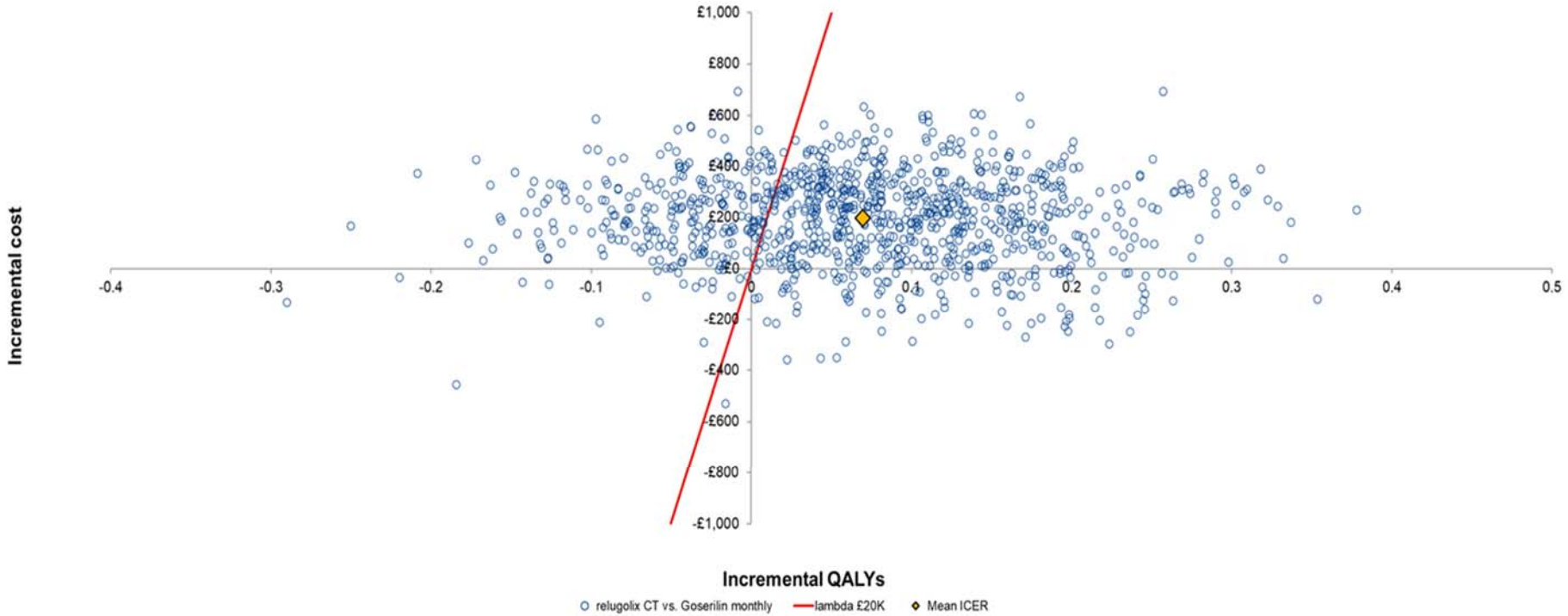


Figure 10 Scatter plot of the cost-effectiveness plane for the ERG's preferred base case probabilistic analysis (relugolix CT versus goserelin monthly)

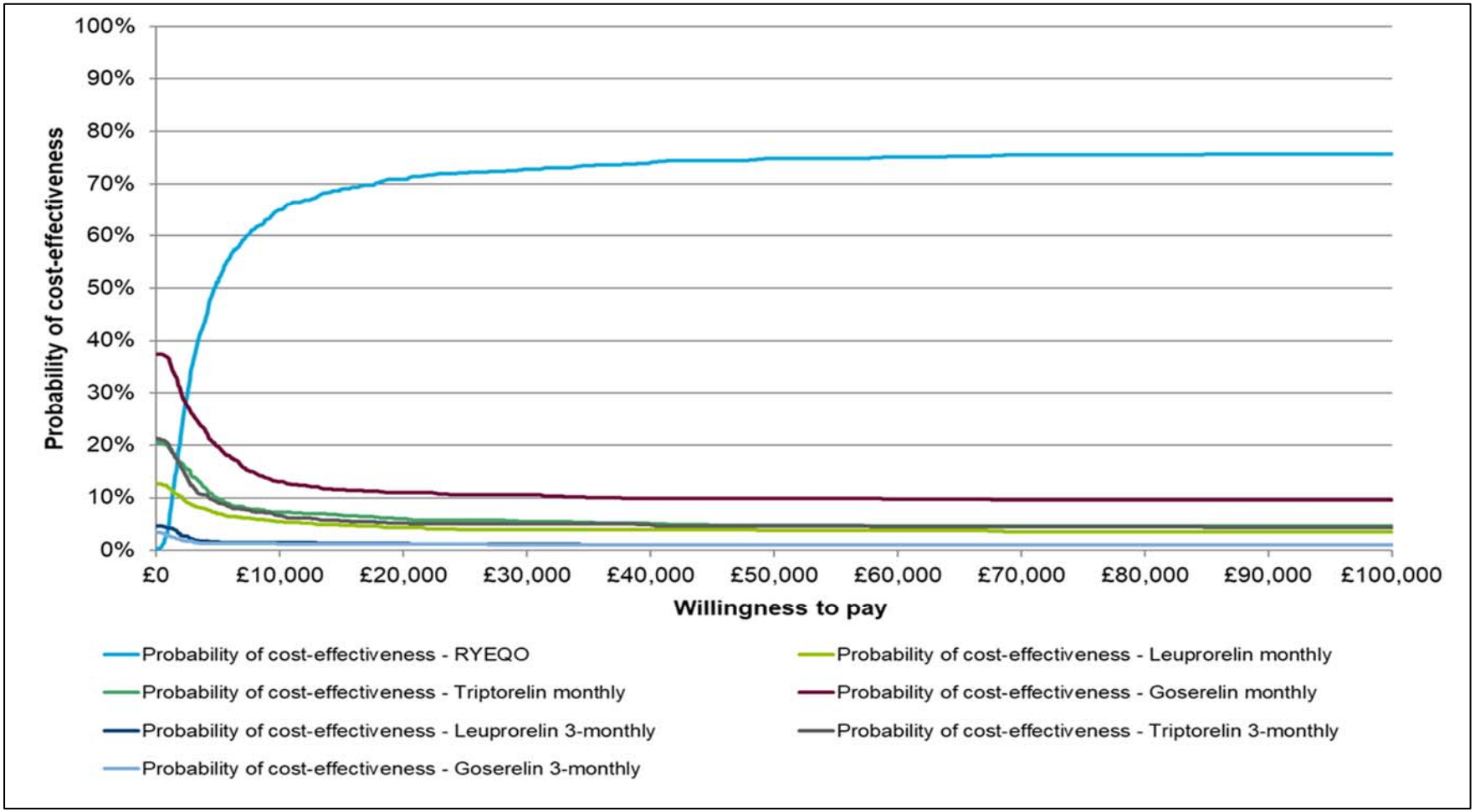


Figure 11 Cost-effectiveness acceptability curves for the ERG's preferred base case probabilistic analysis

Table 38 Scenario and exploratory analyses applied to the ERG preferred base case

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
ERG preferred base case analysis							
Goserelin monthly	6,379	21.525	16.968				
Relugolix CT	6,573	21.525	17.037	194	0.000	0.069	2,795
One round of surgery (i.e. no one needs repeat surgery - cure rate = 100%)							
Goserelin monthly	5,787	21.525	17.082				
Relugolix CT	6,054	21.525	17.136	267	0.000	0.054	4,983
Apply the minimum KOL max cap on the proportion on GnRHa treatment							
Goserelin monthly	5,928	21.525	16.966				
Relugolix CT	6,573	21.525	17.037	645	0.000	0.072	9,014
Apply the maximum KOL max cap on the proportion on GnRHa treatment							
Goserelin monthly	6,891	21.525	17.370				
Relugolix CT	6,573	21.525	17.037	-318	0.000	0.059	Dominant
Use GnRHa within its licence (6 months)							
Goserelin monthly	5,768	21.524	16.970				
Relugolix CT	6,573	21.525	17.037	805	0.000	0.068	11,901
Source for surgery rates (Strong et al.)							
Goserelin monthly	6,559	21.525	16.912				
Relugolix CT	6,727	21.525	16.989	167	0.000	0.077	2,163

	Total Costs (£)	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Utilities for Relugolix CT, GnRHa, and BSC applied as decrements from general population norms							
Goserelin monthly	6 379	21.525	17.405				
Relugolix CT	6 573	21.525	17.498	194	0.000	0.093	2,082
0% discount rate							
Goserelin monthly	7,086	42.085	32.699				
Relugolix CT	7,335	42.086	32.775	249	0.000	0.075	3,302
6% discount rate							
Goserelin monthly	5,957	15.113	11.977				
Relugolix CT	6,118	15.113	12.042	161	0.000	0.066	2,454
Time horizon: until menopause (aged 51)							
Goserelin monthly	6,379	5.920	6.330				
Relugolix CT	6,573	5.990	6.341	194	0.000	0.069	2,797
Subgroup analysis: long-term treatment = 0% transition to surgery							
Goserelin monthly	2,856	21.525	16.868				
Relugolix CT	3,452	21.525	16.768	596	0.000	0.100	5,967
Subgroup analysis: short-term treatment = 100% transitions to surgery							
Goserelin monthly	8,519	21.524	17.241				
Relugolix CT	8,536	21.524	17.245	17	0.000	0.004	4,563

6.4 Conclusions of the cost-effectiveness section

The company preferred base case analysis and associated scenario analyses generate ICERs well below £20,000 per QALY gained. The ERG's suggested alternative base case also generates a similar ICER, but with substantially lower incremental costs and incremental QALY gains compared to the company base case. As noted in the critique throughout this report, the ERG's main conclusion is that it is very difficult to draw a clear conclusion on the most appropriate base case set of assumptions as data are often sparse and assumptions unclear. Plausible combinations of different scenario analyses would lead to wide variation in the ICER, and results are highly uncertain. The revised ERG probabilistic analyses illustrate substantial uncertainty that is not apparent when examining deterministic analyses alone. The ERG view is that it is essential that decision-makers are aware of this uncertainty and consider it in their judgments.

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National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 5 January 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Instances of a capital R being used in 'relugolix CT'. As 'relugolix' is a generic name, lower-case 'r' should be used. The capital R is erroneously used on pages xiii, xiv and xxiii of the document.	We suggest the ERG replaces the upper case 'R' to lower case so that it reads: 'relugolix CT'	Use of lower case 'r' for relugolix since this not the brand name	Text amended as suggested

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page xviii, section 1.3, Issue 1 table the ERG states: *"It is unclear whether the company intend to use relugolix CT for different patient populations: a) for women who wish to have symptoms relief but not surgery which is similar to the LIBERTY trials (relugolix CT) and /or b) those who have already been listed for surgery (pre-surgical use), which is more consistent with the PEARL trials (GnRH agonists)."* (row 2) "*The ERG would welcome further details from the company regarding whether they intend to*	We would suggest that the ERG either: (1) removes the statements referring to potential pre-surgical use and subgrouping, OR (2) prefaces these comments with the statement that the company considers that relugolix CT is positioned in women who wish to avoid or delay surgery. For the benefit of stakeholders reading the ERG report distinction should be made between the relugolix CT label, which does not specify pre-surgical use, versus the GnRHa labels, which specify use pre-surgery. Use of GnRHa for UF outside these settings, can be considered off-label.	The CS at no point has suggested use of relugolix CT prior to surgery, but numerous times refers to use in women wishing to avoid or delay surgery, including: Submission page 38: "***Proposed place of relugolix CT*** *As described above, there is an 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****."*	We agree that 'pre-surgical' use is not specified within the relugolix CT marketing authorisation and accept the company clarification that they wish to seek a recommendation for relugolix CT as a treatment for women who wish to avoid or delay surgery. However, this would not necessarily exclude the usage of relugolix CT as a 'pre surgery' treatment in clinical practice. We have revised the text in sections 1.3 and 1.6 to

position relugolix CT as a longer-term treatment for women not wishing to have surgery, as a pre-treatment for surgery, or both."(row 5) The ERG further suggests that subgroup analyses of use of relugolix CT pre-surgery are carried out in Issue 1 and Issue 6. However, the intended positioning for relugolix CT with respect to this point has already been stated in the company submission (CS), and pre-surgical use is not indicated in the relugolix CT label while being specifically indicated in the GnRH labels.		Submission Table 80, row 4: "*Relugolix CT is positioned as a treatment for patients who wish to avoid having surgery and is* ***not a pre-surgical treatment***." Furthermore, the relugolix CT indication is for "*treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age*." Whereas for goserelin it is: "*In conjunction with iron therapy in the haematological improvement of anaemic patients with fibroids* ***prior to surgery****."* And for leuprorelin: "***Preoperative*** *management of uterine fibroids to reduce their size and associated bleeding*". These amendments will make it clear to stakeholders what the company position is and how relugolix CT is differentiated from GnRHa in terms of its labelling.	improve clarity about the company's positioning of relugolix CT. However, we have retained the subgroup analyses in Chapter 6 as we believe they may be of interest to the NICE Committee.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On pages xv and 129, regarding assumptions, the ERG states:	We suggest that the ERG specifies here which medicinal treatments patients would receive in	Key reasons for which patients would wish to discontinue to	This is not a factual inaccuracy. Nevertheless, we

"The company prefers a modelling assumption where women can only be listed for surgery after treatment discontinuation, when they enter a 'waiting time' state of duration 15 months. The ERG considers it more appropriate to remove the waiting time state because, in clinical practice, most women listed for surgery would receive ***medical treatment*** *in preparation for surgery."* Also page xxiv, Issue 5, first row of table: *"The ERG's clinical expert advice is that, in clinical practice, patients remain* ***on treatment*** *whilst waiting for surgery"*	preparation for surgery – the primary treatment or others.	surgery would be either poor tolerability or lack of efficacy. It is unclear, therefore, whether the suggestion is that the patients would nevertheless be kept on the primary treatment (relugolix CT or GnRHa) or whether an alternative treatment would be provided.	have amended the text on pages xv, xxiv, and 129 to provide further clarity that we refer to 'primary' medical treatment (i.e. relugolix CT or GnRHa). For clarity, the implicit assumption behind the ERG's preferred scenario (removing the 'waiting time' state from the model) is that patients who discontinue from 'treated' states to 'surgery' would remain on the primary treatment until their surgery. This assumption is supported by the ERG's clinical expert opinion. We note that the cohort may also enter the surgery state after discontinuing to BSC in the model, in which case they would receive BSC treatment before surgery.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Issue 3 (page xxii), Description of issue and why the ERG has identified it as important? The ERG notes that "*i.e., avoiding the application of MBL data from the trial's ITT analysis directly to an 'on treatment' cohort.…*" The mITT cohort was analysed for the ITC and model.	Where the ITT cohort is referred to with respect to source of MBL data for the ITC, change to mITT [defined as randomised patients who received any amount of study drug (relugolix, oestradiol, norethisterone acetate or placebo)].	Clarifies what cohort was used in the ITC and model.	Text amended as suggested.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Issue 3 (page xxii), what is the expected effect on the cost-effectiveness estimates? The ERG notes that "*The direction and magnitude of any biases are unclear, but it is likely that MBL data used in the company base case ~~post clarification~~, based on an intention to treat analysis of the LIBERTY trial data, would* ***under***-	We suggest the ERG elaborates on any differences between the MBL data used in the company base case pre- vs. post- clarification, or changes the wording to	Implies to the reader that the MBL data used in the company base case changed following clarification, which was not the case.	Text amended as requested.

estimate the MBL in an on-treatment cohort." It is unclear what the ERG means by "*the MBL data used in the company base-case post clarification*" as these did not change from the original submission.			

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Issue 3 (page xxii), what is the expected effect on the cost-effectiveness estimates? The ERG notes that "*The direction and magnitude of any biases are unclear, but it is likely that MBL data used in the company base case post clarification, based on an intention to treat analysis of the LIBERTY trial data, would* ***under****-estimate the MBL in an on-treatment cohort*." We believe use of "under-estimate" may have been an error. The same inaccuracy applies to bullet number 1 on page 86.	The ITC utilises data from the mITT population, which includes patients that have discontinued. This would be expected to increase the MBL of the mITT cohort vs. MBL in a purely on-treatment cohort. We therefore believe that the wording "**over**-estimate" should be used instead of "under-estimate".	We believe this was an oversight by the ERG but should be corrected for clarity.	This was an oversight. The typographical error has been amended on page xxii. Please note that we do not consider the use of 'under-estimate' on page 86 to be a typographical error as it relates to a different issue.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG Issue 7 (page xxvi), what is the expected effect on the cost-effectiveness estimates? The ERG states "*The repeated measures model generates a smaller reduction in utility for every unit increase in MBL compared to the company preferred OLS model. The implication is higher QALYs in both arms of the model, lower incremental QALY gains for relugolix CT and hence a higher ICER compared to the company preferred base case model."* We believe that the repeated measures model, which has a coefficient of larger magnitude than the OLS, produces a larger reduction in utility for every unit increase in MBL.	The text should, be changed to: "*The repeated measures model generates a larger reduction in utility for every unit increase in MBL compared to the company preferred OLS model*". The ERG may wish to revise the sentence regarding implication, especially considering that the intercept has also changed slightly, which is the largest driver of ICER.	The coefficient for MBL is -0.00039 for OLS and -0.00059 for repeated measures. As there is an inverse relationship between MBL and QoL (higher MBL values lead to poorer QoL), this means that one unit decrease in MBL increases QoL more in the repeated measures model compared to the OLS. This should be updated for accuracy, given that this algorithm underpins QALY gain.	Not a factual inaccuracy. The text correctly reflects the data provided by the company in their response to the ERG's clarification points. However, in response to an additional ERG's request following the company's FAC, it has transpired that the utility co-efficient from the repeated measures model provided by the company relates to **ml** and not **dL** as suggested in the company's clarification response. We have now reviewed the full report, including all instances where the repeated measures model is referred to, updating the appropriate text and tables, as well as re-running all analyses in Chapter 6 where the incorrect data were used. Upon further review, we have identified two further minor errors on the company's model trace that were not identified in

			the ERG's main report (one-off costs of routine monitoring for post-treatment BSC were not picked up on the model trace). We have now corrected these issues and updated all relevant analyses. We have updated the excel model file configured to the ERG's preferred base case accordingly and implemented all changes with switches to enable reproducibility.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Four instances of "relugolix" instead of "relugolix CT" in the treatment pathway section (pages 4-5). This use also appears on page 26 within the "Change in haemoglobin levels" bullet: *"30 and 23 women in the relugolix group"*	We suggest consistent use of "relugolix CT" instead of "relugolix" throughout the ERG report when referring to relugolix in combination with oestradiol and norethisterone.	Correct use of "relugolix CT" will provide clarity and distinguish between relugolix combination therapy and relugolix monotherapy.	We have checked and corrected when necessary the use of "relugolix CT" throughout the report.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 7, page 22, Surgery for UF row: Error in the LIBERTY 1, relugolix CT arm data: bracketed value of "8.4" is incorrect	Please amend the error in value for Surgery for UF, No, so that it reads "108 (84.4)"	Incorrect value	Text amended as suggested

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 7, page 22, UFS-QoL (BPD subscale), mean (SD) row: Error in the LIBERTY 2 data for all 3 arms. It appears that the LIBERTY 1 results have been accidentally duplicated for LIBERTY 2.	Please remove the current incorrect values for LIBERTY 2, which appear to be duplicates of the LIBERTY 1 results, and replace with: • Relugolix CT: 70.66 (20.811) • Relugolix-delayed CT: 72.00 (22.905) • Placebo: 70.01 (20.259)	Incorrect values	Text amended as suggested

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 9, page 29, second row for "proportion of patients who achieved amenorrhoea at Week 52"	Please amend the value for the proportion of patients who achieved amenorrhoea in the placebo arm to 95 (not 9).	Incorrect value	Text amended as suggested

Incorrect value n=9 for the Placebo arm			

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 9, page 29, fourth row for "change in **USF**-QoL BPD scale score from parent study baseline to Week 52" Typo: should be UFS-QoL, not USF-QoL	Please correct the typo, change from USF-QoL to UFS-QoL	Typographical error	Text amended as suggested

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 11, page 33, placebo cumulative column values: Nervous system disorders [redacted] Syncope [redacted] Zeros (highlighted as red font) to be removed after the brackets	Please remove the zeros that appear after the brackets as described.	Correction	Text amended as suggested

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 14, page 38, baseline disease-specific characteristics, third row "Total UF volume, cm^3, median (IQR)" For PEARL I, this is the correct disease specific characteristic; however, for PEARL II, this characteristic was slightly altered to "Total UF volume of the three largest myomas"	We suggest the ERG adds a table footnote for PEARL II to indicate the slightly altered disease specific characteristic for total UF volume which is based on the total UF volume of the three largest myomas.	Accuracy of reporting	Not a factual inaccuracy. The ERG report correctly reports "uterine volume-cm^3" from Table 1 of Donnez 2012b.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Top of page 55 reporting on the model structure, third line down: *"The proportion of the cohort modelled to receive surgery enter a tunnel state for 12 cycles (maximum duration 12 months), after which they are either assumed to have full resolution of symptoms or non-hysterectomy surgeries can progress to further revision surgery if required after a second waiting time."*	Suggest using the text from the company submission: "*The surgery state is a tunnel state that patients remain in for one cycle. This state includes different types of surgery which are each explicitly modelled to describe the distribution of patients currently undergoing surgery by surgery type and to allow correct application of surgery related mortality risks and adverse events. Following surgery, patients move to a post-surgery state that is divided in two – reflecting patients who received hysterectomies and those who did not. Patients who did not receive hysterectomies can then transition to a*	Patients enter a surgery state that runs for one model cycle, after which they enter the post-surgery state. Surgery specific disutility is applied over 12 months as well as disutility from any adverse events. This would provide a more accurate description of the model structure.	Text amended as suggested.

This implies that patients remain in the surgery state for 12 months, which is not the case.	*second surgery state following the completion of further waiting time*."		

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Bottom of page 58, surgery model states: The ERG states that "*To illustrate the impact of these uncertainties on the modelled ICERs, the ERG has conducted scenario analyses removing the surgery states in the model."* The report implies that this analysis was a *de novo* analysis undertaken by the ERG, whereas this scenario analysis was already carried out by the company (CS Document B, Table 84. Scenario entitled "**Inclusion of surgery health states**").	We suggest the ERG updates the report to comment on the provision of this scenario by Gedeon Richter.	Incorrectly implies that the company had not already undertaken this scenario analysis.	Text amended as suggested.

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Bottom of page 60, Intervention: relugolix CT: "A Dexa-scan is **required before treatment** to assess bone mineral density and osteoporosis risk."	Please amend "required before treatment" to	Correction of clinical information to align with product SmPC.	Text amended as suggested.

The Ryeqo® summary of product characteristics (SmPC) states that "*a DXA scan is recommended after the first 52 weeks of treatment to verify that the patient does not have an unwanted degree of BMD loss, that exceeds the benefit of treatment with Ryeqo*." Therefore the use of '**required before treatment**' in the ERG report is incorrect. [https://www.ema.europa.eu/en/documents/product-information/ryeqo-epar-product-information_en.pdf]	"recommended after 52 weeks of treatment".		

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Bottom of page 63, Summary of model transition probabilities: "*The company has not directly reported transition matrices used in the model to describe the progression of the cohort through the model*." This statement is not relevant, as the model does not use transition matrices given that probabilities change over time, with almost all subsequent transitions conditional on rates of treatment discontinuation. These discontinuation rates were reported within the original CS in tables 41-43 of Document B. The CS states that the discontinuation to BSC and surgery is applied as conditional on discontinuation each month.	We propose that wording relating to transition matrices be removed and that charts of the Markov traces would be more informative than the approximated transition matrices in ERG Tables 24 and 25 (which we believe may be inaccurate given the time-changing nature of treatment discontinuation and the presence of tunnel states.	The text implies that the model employs fixed transition matrices, which is not the case and may over-simplify how the model works.	Not a factual inaccuracy. We do not suggest that the transition matrices are used directly in the model. However, we believe that the approximated transition matrices may help the Committee to understand how the cohort moves through the model states and the key differences between treatment arms. Therefore, we have retained the approximated transition matrices but amended the text slightly to ensure it is clear we are not suggesting the model makes

			direct use of transition matrices.

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73, second paragraph: "*The ERG is concerned that the long-term transitions into the surgery state are not evidence-based and that the use of data from PEARL II is inappropriate. The data from the PEARL II study reflect the proportion of patients (45.1%) in that study who did not have a planned surgery cancelled by week 13 of follow-up. The ERG does not consider these data to be transferrable to the modelled cohort, who did not wish to or were unable to have surgery at the point of medical treatment initiation.* ***To ensure some face validity of the model output, the company assumed that this proportion would apply at year 10, rather than month 3****. However, this decision appears to be arbitrarily chosen without any appropriate justification. The ERG considers that the company's approach may therefore substantially over-estimate the proportion of the*	We suggest using the text similar to that in CS document B page 141, **Surgery rates upon pharmacological treatment discontinuation,** but clarifying the rate per cycle as below. "*The proportion of patients discontinuing treatment and subsequently going on to have surgery was not available from the LIBERTY studies of relugolix CT. The rate of surgery in those women who discontinue pharmacological treatment was thus informed by the proportion of patients who went on to have surgery at the end of the 13-week treatment period in PEARL II (patients could not have surgery before the end of the study). The study reported that 45.1% of patients went on to have surgery. This proportion was therefore applied to the proportion of patients discontinuing pharmacological treatment at each cycle."*	Accuracy in reporting model assumptions.	We have revised the 2nd paragraph on page 73 to reflect, more accurately, what the company have done in the economic model.

modelled cohort that enters the surgery states after treatment discontinuation." The assumption at year 10 is incorrect. Gedeon Richter assumes that the surgery proportion from PEARL II (45.1%) is applied to all patients withdrawing from treatment at each model cycle (1 month).			

Issue 20

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 31, page 97, Treatment-related adverse events" The rates for all the treatment-related adverse events appear to be incorrectly copied over from the CS data provided.	Please can the ERG refer to Table 50 in the CS Document B for the AE rates and update the rates for each AE individually (one row at a time) to match the correct rates for the relevant AE.	Correct to provide accuracy in the data used.	We accept the proposed amendment. We have revised Table 31 to match the rates for all the treatment-related adverse events in Table 50 of the CS.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page xv (bullet point at the bottom of the page) and on page 129 states: "*The ERG considers a repeated measures model to be more appropriate to allow estimation of appropriate standard errors for inclusion in the probabilistic analysis."*	We would suggest that the ERG adds a point to state that a repeated measures model and results were provided at Clarification, e.g.: "*The ERG considers **the** repeated measures model **provided by the company at clarification** to be more appropriate to allow estimation of appropriate standard errors for inclusion in the probabilistic analysis*."	As it currently reads, it gives the impression to the reader that this was not provided and is still outstanding when this work has, in fact, been carried out and provided by the company.	Text amended as suggested (see also our response to issue 7 above).

Please note that a repeated measures model and results, were provided by the company at Clarification.			

Issue 22

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 44, Section 3.4 Critique of the indirect comparison and/or multiple treatment comparison: The ERG states that they are *"unsure why and how the ITC shown in Table 20 has been performed*". The company feels it is important to clarify that no ITC is performed for UPA and leuprorelin (apart from setting the UPA arms in PEARL I and II equal). The ITC is performed between relugolix CT and UPA and then an extension is used based on the assumption that UPA arms in the PEARL trials are very similar (as described in CS Appendix D1.4).	Add a comment in this section to state that "*the ITC is performed between relugolix CT and UPA and then and then an extension is used based on the assumption that the UPA arms in the PEARL trials are very similar."* Further information from CS Appendix D1.4 could also be added: "*To calculate mean difference in MBL percentage change from baseline (CFB) for relugolix CT vs UPA, mean difference in percentage CFB of relugolix CT vs. placebo and UPA vs. placebo were used in a Bucher ITC. The formula below describes the calculation of ITC mean difference, where MD=mean difference.* $$ITC\ MD\ (Ryeqo\ vs.UPA) = MD_{Ryeqo\ vs.placebo} - MD_{UPA\ vs.placebo}$$ ***Mean difference in percentage CFB in MBL of UPA vs. GnRH agonist from PEARL II was calculated in the same way as for UPA vs. placebo from PEARL I. Mean MBL values for***	Further clarity regarding the method of indirect comparison employed by the company.	We understand how the ITC was performed between relugolix CT and UPA. Please note that it was the incorrect heading used in the submisson (acknowledged in issue 23), which has caused the confusion. We have now removed *"unsure why and how the ITC shown in Table 20 has been performed*".

	***Placebo were retrieved directly from the LIBERTY studies**."*		

Issue 23

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 44, Table 20, Table heading "ITC results: leuprorelin versus UPA" The results here represent the direct comparison of leuprorelin vs. UPA from head-to-head comparison based on PEARL II. Thus, the table heading should be re-worded to "*Results from the direct comparison of leuprorelin vs. UPA*" Apologies, as this was an incorrect table heading in the original CS Document B.	Pleas,e amend the heading for Table 20 to read: "*Results from the direct comparison of leuprorelin vs. UPA*"	Accuracy in table heading description of results in Table 20	Table heading amended as suggested.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday 11 February 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	David Jordan
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Gedeon Richter UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: trial populations and UK clinical practice	No	**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** Relugolix CT is licensed as a treatment for moderate to severe symptoms of UF in adult women of reproductive age. The label and positioning is broad and is, thus, not restricted to pre-surgical use but rather as a longer-term treatment option for women who wish to delay or avoid surgery. 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. This positioning differs to that of gonadotrophin-releasing hormone agonist (GnRHa) for UF which specify pre-surgical use in their label. The use of GnRHa for UF outside of these settings can be considered off label, however, with the current COVID-19 pandemic causing long surgical waiting times, GnRHa are being used outside of their label. The LIBERTY trials and PEARL II comprised similar study populations, with key baseline characteristics such as age aligned between the studies. Furthermore, only 45.1% of patients in PEARL II went on to have surgery at the end of the 13-week treatment period, with the rest transferring to BSC. GnRHa was therefore not used solely as a pre-operative treatment, thus making outcomes for this treatment arm more comparable to the LIBERTY populations.

<table>
<tr>
<td>Issue 2: lack of formal comparison between treatments</td>
<td>Yes</td>
<td>
1) Relative efficacy is not a key determinant of cost-effectiveness
The key relative efficacy parameter used in the model is menstrual blood loss (MBL), which is utilised in an algorithm to calculate utility and hence QALYs. However, while relative efficacy is a large driver of value in the model, so is the fact that the patient is able to remain on an effective treatment and control symptoms for longer on relugolix CT than they are able to on an unlicensed therapy such as GnRHa. Thus, while relative efficacy impacts results, the base case ICER is so low that relugolix CT remains cost effective even under more pessimistic efficacy assumptions.
For example, assuming that efficacy of relugolix CT is equal to that of GnRHa (by assuming the same utility as GnRHa) produces a highly cost-effective ICER of £10,014 (Table 1).

Table 1: Scenario assuming equal efficacy to GnRHa
<table>
<tr><th>Technology</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th></th></tr>
<tr><td colspan="6">ERG base case</td></tr>
<tr><td>Goserelin monthly</td><td>£6,379</td><td>16.968</td><td></td><td></td><td></td></tr>
<tr><td>Relugolix CT</td><td>£6,573</td><td>17.037</td><td>£194</td><td>0.069</td><td>£2,795</td></tr>
<tr><td colspan="6">Equal efficacy (same utility)</td></tr>
<tr><td>Goserelin monthly</td><td>£6,379</td><td>16.968</td><td></td><td></td><td></td></tr>
<tr><td>Relugolix CT</td><td>£6,573</td><td>16.987</td><td>£194</td><td>0.019</td><td>£10,014</td></tr>
</table>
2) A full network meta-analysis (NMA) would not have been more informative than the method used
The model uses MBL at 14 different timepoints and converts the values to utility. Therefore, a NMA of these timepoints would be required to provide inputs in the model. Furthermore, when running sensitivity analysis, correlation between the MBL value sampled at each timepoint would need to be maintained.
</td>
</tr>
</table>

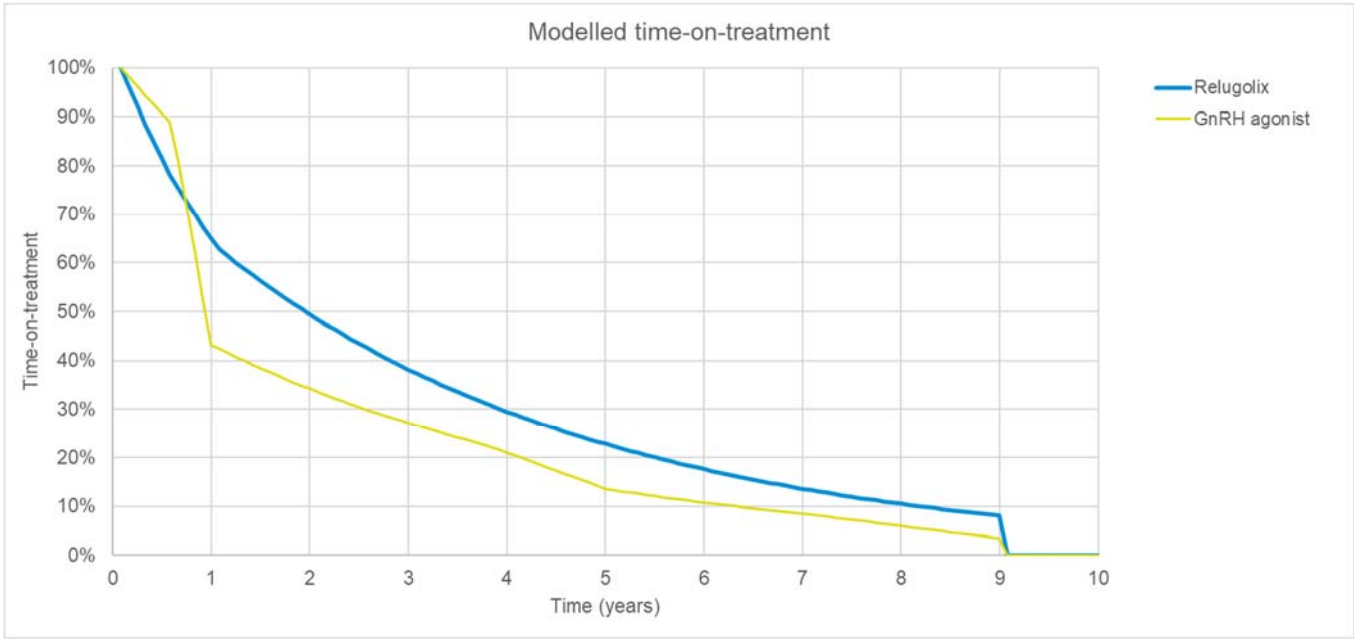
		This would have required complex analysis and modelling, layering further uncertainty on top of an evidence synthesis already rendered challenging by the use of different MBL measurement methods across studies (alkaline haematin [AH] in the LIBERTY studies and the pictorial blood assessment chart [PBAC] in the PEARL studies. Gedeon Richter felt that the method used, which assumed transitivity between changes in MBL from baseline between studies, was more transparent. Furthermore, given the only way the indirect treatment comparison (ITC) is used is to derive utility, the method did not preclude exploratory sensitivity analyses being carried out by varying the utility gains directly (which we have done in a number of scenarios in this response). **3) ITC of other outcomes was not feasible** Below we reiterate the issues with other outcomes that precluded indirect comparison, as stated in our clarification response: Time to MBL response • Time to MBL response was not included as a defined outcome in the LIBERTY or PEARL trials and timepoints of measurement were not exactly aligned between the studies. During the LIBERTY studies the MBL was measured via the AH method which only reports values on a 4-weekly basis, whereas during the PEARL studies the MBL was reported on a daily basis via the PBAC scoring system. Therefore, a direct comparison of exact time to response cannot be measured. Moreover, the actual classification of a responder was defined differently in the studies. Pain • The effect on pain was only measured for a subgroup of patients with high baseline pain scores i.e. NRS ≥4 (moderate/severe pain) in the LIBERTY trials and was therefore not included. Uterine fibroid volume (UFV) / uterine volume (UV) • The method of measurement of UFV was different in the LIBERTY and PEARL trials and thus are not directly comparable. Haemoglobin (Hb) levels

		• Hb levels are interesting to detect potential anaemia. However, they are a consequence of HMB; therefore if HMB is controlled then Hb levels should be within normal ranges. Therefore, it is more relevant to focus on MBL than Hb levels • Also, in the LIBERTY studies again a sub-group of patients were actually assessed i.e. those with Hb ≤ 10.5 g/dL at baseline who subsequently had an increase of > 2 g/dl. This was a defined endpoint rather than the actual raw change in Hb levels Change in bone mineral density (BMD) • The trial data used in the ITC covered a period of 3 months which is too short to measure changes in BMD Rates and route of surgery • This was not collected in the LIBERTY trials Impact on fertility and pregnancy and teratogenic effects • This was not collected in the LIBERTY trials Mortality • Mortality was not included as no deaths were reported during the LIBERTY trials Adverse effects of treatment, including but not limited to vasomotor symptoms, incontinence and pelvic organ prolapse • Safety outcomes were not assessed in the ITC. The trial data used in the ITC covered a period of 3 months and no relevant safety events were observed in the LIBERTY or PEARL studies during this time period Health-related quality of life • QoL in PEARL I was measured using a subset of UFS-QoL questions and was answered only by a subset of patients. Therefore, comparison of HRQoL was not included.
Issue 3: economic model structure	No	**Consistent response criteria were not available to allocate patients to health states** A health state-based model requires a consistent definition of a responder between studies. This was not the case between the LIBERTY and PEARL studies, which had different definitions of responder. Nor was it possible for Gedeon Richter to re-analyse the data using a consistent response definition, as

		we did not have access to individual patient data to be able to do so. Only the mean MBL value (whether measured on the PBAC or AH) could be used for the model. In light of the above, use of a treatment states model (by Gedeon Richter) provides 3 main advantages: **1. The best use of limited available data** • MBL volume is measured on a continuous scale and its effect on QoL in the model is an important driver of the results • The use of continuous treatment effect in the way presented in the company model, allows the utility function to work as a form of infinite health state • The current model structure allows for the direct use of granular trial data – in order to reach a similar granularity using health states, very many health states would be needed o The patients' complex situation is measured in terms of QoL without the need to define if improvements are linked to reduced bleeding only or other, non-observed symptoms. This allows for maximum flexibility in calculating the QoL and it better reflects how QoL is actually generated in the patient cohort, leaving the generated QoL more transparent o Challenge to model by bleeding-related health states: if a health states model was used, valuable information would be lost from reducing the available data into a small number of health states (namely 'responder' [defined as MBL volume of <80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment] and 'non-responder', which would not differentiate between patients experiencing no reduction in bleeding and those with a 49% reduction from baseline, even though the latter would most likely have significant symptom relief) • Challenge to model by symptom-related health states: no relevant data is available from the full trial populations and trial period to inform health states based on symptom control. **2. Enables comparability to other treatments** • The trial endpoints in the LIBERTY and PEARL trials were not identical, resulting in difficulty in comparing what dictates response to treatment

		o LIBERTY endpoint: MBL volume of <80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment o PEARL endpoint: control of uterine bleeding (PBAC score <75 at week 13) • Thus, defining health states based on trial endpoints which were relevant for all included treatments was not considered feasible. **3. Allows modelling of treatment discontinuation based on trial data** • The ERG suggests that *"[...] a proportion of the cohort in those states could be modelled to be 'on' or 'off' treatment, according to available treatment discontinuation data from LIBERTY for relugolix CT and from PEARL II / clinical expert opinion for GnRHa"* o However, no treatment discontinuation data would have been available by health states relevant for the health-economic model o As noted by the ERG, treatment discontinuation cannot be defined along the lines of health-states (e.g. "treatment is discontinued for all non-responders") but would affect proportions of patients within each health state. This type of data was not available • Related to treatment discontinuation the ERG criticizes that *the "company's approach [...] applies intention to treat effectiveness (i.e., MBL) data to an 'on treatment' cohort";* however, the current model implicitly considers non-responders via withdrawal rates to BSC and surgery. Withdrawal rates in the model are derived from withdrawal observed in the clinical trial. The present model structure is based on the same approach as used by a relevant and peer-reviewed publication by Geale et al., 2017(1) for ulipristal acetate. Furthermore, the QoL algorithm mentioned in this publication was used as part of the health economic evaluation of UPA in the 2016 update of the HMB guidelines.
Issue 4: treatment	Yes	**No published data are available for treatment discontinuation rates on GnRHa** Use of GnRHa as a long-term treatment for UFs is off-license. This is articulated for example in the goserelin SmPC:

discontinuation assumptions		*"Endometriosis should be treated for a period of six months only, since at present there are no clinical data for longer treatment periods. Repeat courses should not be given due to concern about loss of bone mineral density…* *For use in endometrial thinning: four or eight weeks treatment. The second depot may be required for the patient with a large uterus or to allow flexible surgical timing….* *For women who are anaemic as a result of uterine fibroids: Zoladex 3.6 mg depot with supplementary iron may be administered for up to three months before surgery."* Gedeon Richter has been unable to identify any published literature indicating the average length of treatment for patients receiving longer-term GnRHa. Instead, seven UK gynaecologists provided estimates to the question *"How long do patients wishing to avoid surgery stay on GnRHa plus add-back therapy in clinical practice? Roughly what % would remain on treatment after 6 months, 1 year, 5 years and 10 years?"* Gedeon Richter considers that, in the absence of published evidence, these provided robust evidence for treatment discontinuation of GnRHa. **The relugolix CT discontinuation rates in the model demonstrate good face validity** As can be seen from Figure 1, the existing ERG base case model predicts discontinuation rates with high face validity. In the initial 6 months of the model, discontinuation is 20%. This compares with 34% by week 24 in the pooled LIBERTY 1 and 2 studies (MVT-601-3001 and MVT-601-3002 CSR Tables 7.1.7.1, see standalone presentation Appendix 3). However, 45% of discontinuations in LIBERTY 1 and 2 were indicated as being due to patient choice (as opposed to lack of efficacy, which was a separate reason). Notably, the LIBERTY studies utilised the AH method for measuring MBL, which is confined to the research setting due to its practical limitations. In a systematic review of MBL collection methods (2), a key disadvantage was stated as being that "*Patients in the clinical setting may be deterred by having to collect, store, and send sanitary products for analysis*." It is therefore likely that a good proportion of discontinuations in LIBERTY 1 and 2 may have been due to the inconvenience of the AH collection method. 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 (20% in the next 6 months in the model vs. [redacted] for relugolix CT rollover patients in LIBERTY 3 (MVT-601-3003 CSR Table 8.1.7.1, see Appendix 3). Annual discontinuation thereafter in the model is 23-24% per year vs. [redacted] in the randomised withdrawal study (RWS) (MVT-601-035 CSR Table 8.1.7.1, see Appendix 3). Once more, it should be noted that the AH method continued to be used in the LIBERTY 3 and RWS, which can be expected to reduce compliance. **Figure 1: Model discontinuation - ERG base case** 
Issue 5: waiting time health state	No	**Relugolix CT remains cost-effective if no waiting time is assumed** Gedeon Richter notes that the ERG base case assumes no waiting time, yet relugolix CT remains cost-effective under this assumption.

		The Waiting Time state was included based on clinical input and is representative of the pathway of care As part of the model development, clinical expert validation was sought with respect to the waiting time for surgery. While the waiting time may have been shorter pre-Covid-19, it is likely to take many years before pre-pandemic waiting times are once again achieved. Even then, some waiting time for surgery is to be expected. Given the average patient age at baseline in the model is 42 years old, surgery is unlikely after age 45 and menopause occurs at age 51, the wait for surgery comprises a significant proportion of the time during which changes in cost and quality of life in the model are captured. Furthermore, it is unrealistic for patients to be kept on their primary treatment while waiting for surgery if they have discontinued due to lack of efficacy and AEs. In the LIBERTY 1 and 2 studies, of the 51 patients who terminated treatment in the CT arm, 15 (29%) did so due to lack of efficacy or AEs (3). As Gedeon Richter believes that a significant proportion of patients discontinued due to the inconvenience of the AH method of MBL measurement (see response to Issue 4), in clinical practice the proportion of patients discontinuing due to lack of efficacy or safety issues would be even higher. These patients are more likely to receive alternative, less effective treatments if some type of treatment is continued while awaiting surgery, which the ERG's approach does not account for.
Issue 6: role of surgery and data on surgery health state	Yes	**The model surgery estimate lies well within the bounds of available evidence sources** 1) The national Heavy Menstrual Bleeding audit (4) We have only been able to identify one published source of surgery rates in the UK. The heavy menstrual bleeding (HMB) audit published in 2014 lists the proportion of patients who received different types of treatment one year after their first outpatient visit in secondary care (Table 2). If missing data and 'no treatment' are excluded, then of the patients receiving active treatments, 45% received surgery. However, relugolix CT is positioned for patients in the UF treatment pathway who are unsuitable for conventional hormonal treatments and the IUS, thus the category "Oral medication/IUS" should be excluded from the count (Esmya was not available at the time of the audit). If we exclude the latter treatments to focus on the relugolix CT target population, then 79% of women referred to secondary care subsequently received surgery. This is much higher than the proportion assumed to be referred for surgery upon discontinuation in our model (45.1%).

Table 2: Distribution of treatments in secondary care

Treatment reported	N	Distribution by active treatments	Distribution excluding oral medication/IUS
No treatment	1431	NA	NA
Oral medication/IUS	2796	42%	NA
Surgical treatment[1]	**2973**	**45%**	**79%**
Other treatment	809	12%	21%
Missing	313	NA	NA

Source HMB audit 2014 (Table 5.1). Surgery included endometrial ablation, hysterectomy, myomectomy or uterine artery embolisation. NA, not applicable.

2) Gynaecologist survey

As part of our gynaecologist survey, Gedeon Richter asked 4 participants what proportion of patients who discontinued active treatment would be referred for surgery. The question wording and responses are summarised in Table 3 below. It can be seen that responses ranged from 25% to nearly all patients. Thus, the model estimate of 45% is a reasonable one that lies within the clinician estimates.

Table 3: Clinician responses regarding % having surgery

KOL 1	KOL 2	KOL 3	KOL 4
Once patients have been taken off pharmacological treatment, what % are likely to require surgery?	Once patients have been taken off pharmacological treatment, what % are likely to require surgery?	Once patients wishing to delay or avoid surgery discontinue GnRHa, what % are likely to be referred for surgery?	Once patients wishing to delay or avoid surgery discontinue GnRHa, what % are likely to be referred for surgery?
50%	25%	About 75%	Unless they have gone through the menopause - perhaps all those initiated

		treatment before age 48 would end up with a hysterectomy.

Note: question wording changed slightly due to different representative contacting the gynaecologists.

The lowest estimate of surgery rate still produces a cost effective ICER

The lowest clinician estimate of surgery rate was 25%. When this is applied in the model instead of the current ERG base case rate of 45.1%, relugolix CT delivers a highly cost-effective ICER of £3,625 (Table 4). Even removing surgery altogether from the ERG's preferred base case leads to a cost-effective ICER of £5,967.

Table 4: Scenario analysis with lowest estimate of surgery rate

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	
ERG base case (45.1% have surgery upon discontinuation of medical therapy					
Goserelin monthly	£6,379	16.968			
Relugolix CT	£6,573	17.037	£194	0.069	£2,795
25% have surgery upon discontinuation of medical therapy					
Goserelin monthly	£5,567	16.903			
Relugolix CT	£5,853	16.982	£287	0.079	£3,625

Issue 7: uncertainty surrounding	Yes	**Alternative model specifications for the utility algorithm are unlikely to have a significant impact upon the cost-effectiveness results**

the utility function		Symptom-based utility functions were previously applied in a cost-effectiveness model of uterine fibroids presented by Geale et al., 2015 (5,6) using data from PEARL II and PEARL III, where an ordinary least squares (OLS) regression model was used. Both linear and non-linear (quadratic) specifications of the OLS model were explored with the EQ-5D as the dependent variable and PBAC and visual analogue scale (VAS) scores from the trials as the independent variables. The analyses did not find the non-linear components to be clinically or statistically relevant as the quadratic coefficient estimates were very small, positive, and not statistically significant.(5,6) Therefore, adding non-linear terms would likely not significantly contribute to the predictions of the utility algorithm, and we thus used the most parsimonious model and avoided the risk for overspecification of the model. Given the minimal impact of applying quadratic terms in the OLS model, it is unlikely that this would improve specification of the repeated measures model. [Note: the Geale et al. poster presentation (5) is provided as Appendix 2]. **Utility gains similar to that in the model have been observed in UK HMB cohorts.** EQ-5D was measured pre- and post- treatment in the HMB audit (4). The baseline EQ-5D in the cohort of women who received surgical treatment and 'other treatment' in Table 4.1 of the audit was 0.666 and 0.682 respectively, which are close to the utility of 0.694 at baseline in the economic model. The increase in EQ-5D one year after the first outpatient visit for women who received surgery in the audit was 0.141 unadjusted for baseline characteristics and 0.06 (CI 0.044, 0.076) after adjustment. This compares with a maximum utility gain in the model of 0.122 in the relugolix CT arm and 0.117 in the GnRHa arm. The utility gain in the model thus lies between the unadjusted and adjusted gain following surgery in the audit. However, it is unclear how soon after surgery the EQ-5D was captured in the audit and whether some post-surgical discomfort was still being experienced, nor for what proportion the surgery was considered successful. **A scenario assuming lower utility gain in the model still produces a cost-effective ICER** In order to see the impact of reducing the utility gain predicted in the model, Gedeon Richter has conducted a scenario whereby the maximum utility gain in the model was reduced from 0.122 in the relugolix CT arm to 0.06, the utility gain observed in the surgery group of the HMB audit. This comprises a reduction of 51% of the existing gain in utility vs. baseline in the relugolix CT arm. The same % reduction was applied to the utility gain from baseline in the GnRHa and best supportive care (BSC) arms of the model and was applied to all utility gains post-baseline. The rescaled utility values applied

<table>
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<td>in the model are shown in Table 6 in Appendix 1 and the results of this scenario are shown below in Table 5. Even assuming this significant reduction in utility gains, but in line with EQ-5D increase observed following surgery in the UK, relugolix CT delivers a cost effective ICER of £10,230.

Table 5: Scenario assuming utility gain capped at gain observed in HMB audit

<table>
<tr><th>Technology</th><th>Total costs (£)</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental QALYs</th><th></th></tr>
<tr><td colspan="6">ERG base case</td></tr>
<tr><td>Goserelin monthly</td><td>£6,379</td><td>16.968</td><td></td><td></td><td></td></tr>
<tr><td>Relugolix CT</td><td>£6,573</td><td>17.037</td><td>£194</td><td>0.069</td><td>£2,795</td></tr>
<tr><td colspan="6">Utility gain in model reduced to a maximum of 0.06</td></tr>
<tr><td>Goserelin monthly</td><td>£6,379</td><td>16.798</td><td></td><td></td><td></td></tr>
<tr><td>Relugolix CT</td><td>£6,573</td><td>16.817</td><td>£194</td><td>0.019</td><td>£10,230</td></tr>
</table>
</td>
</tr>
<tr>
<td>Issue 8: resource use in UK clinical practice</td>
<td>No</td>
<td>Gedeon Richter engaged with a total of 8 clinical experts, all of whom are experienced consultant gynaecologists that regularly treat patients with uterine fibroids, in order to seek opinions on the management of patients and healthcare resource use within the evidence submission. Gedeon Richter had not asked experts to comment specifically on HRU at the point of stopping treatment and going onto BSC.

Therefore, as advised by the ERG, Gedeon Richter explored further engagement with clinical experts, to gain a better understand of any heterogeneity in resource use in UK clinical practice and HRU at the point of stopping treatment and going onto BSC. A range of experts were approached, however, unfortunately we were unable to gather input in the time available.</td>
</tr>
</table>

		Of interest, we acknowledge that since FAC, the draft ERG report has been updated to show that any impact on the ICER is modest related to this issue. Table 2 of the final ERG report shows that the impact of changing the HRU assumption from the company base case to the ERG's preferred assumption causes a small reduction in the ICER from £5,796/QALY to £2,795/QALY.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Gedeon Richter has no further issues from the ERG report to comment on.

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

N/A - Gedeon Richter does not have any strong objections to the ERG's preferred base case.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)

Sensitivity analyses around revised base case
N/A

References

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5. Geale K, Hultberg M, Henriksson M. Applying Symptom-Based Utility Functions in Health Economic Modelling: A Case Study of Uterine Fibroids [Poster]. ISPOR Eur 2015 Conf Milan, Italy [Internet]. 2015;PRM258. Available from: https://www.ispor.org/heor-resources/presentations-database/presentation/ispor-18th-annual-european-congress/applying-symptom-based-utility-functions-in-health-economic-modelling-a-case-study-of-uterine-fibroids

6. Geale K, Hultberg M, Henriksson M. Applying Symptom-Based Utility Functions in Health Economic Modelling: A Case Study of Uterine Fibroids [ABSTRACT]. Value Heal [Internet]. 2015;18(7):A728. Available from: https://doi.org/10.1016/j.jval.2015.09.2772

Appendix 1

The rescaled utility scenario can be applied using *Settings* sheet cell I104 in the updated model "*ID3842 relugolix CE model GR Tech Eng response.xlsm*". The rescaled utility calculations are to be found in that version in sheet *Utilities* cells I48:N65.

Table 6: Rescaled utility values for scenario analysis capping at HMB audit gain

	Rescaled change from baseline			**Rescaled utility value**		
Cycle	**Relugolix CT**	**GnRHa**	**BSC**	**Relugolix CT**	**GnRHa**	**BSC**
Baseline	0	0	0	0.694	0.694	0.694
1	0.033	-0.001	0.014	0.727	0.693	0.708
2	0.052	0.057	0.012	0.745	0.751	0.706
3	0.056	0.049	0.013	0.749	0.743	0.707
4	0.055	0.049	0.019	0.749	0.743	0.713
5	0.055	0.049	0.017	0.749	0.743	0.711
6	0.054	0.049	0.020	0.748	0.743	0.714
7	0.055	0.049		0.749	0.743	
8	0.058	0.049		0.752	0.743	
9	0.059	0.049		0.752	0.743	

	Rescaled change from baseline			Rescaled utility value		
10	0.059	0.049		0.752	0.743	
11	0.060	0.049		0.754	0.743	
12	0.059	0.049		0.753	0.743	

Note: Rescaled values are applied in the Tools sheet, activated via a new dropdown in the Controls sheet cell I105:L105.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

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

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Friday 11 February 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating uterine fibroids and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Mr. Alexander E. Oboh
2. Name of organisation	The Mid Yorkshire Hospitals NHS Trust
3. Job title or position	Consultant Gynaecologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with uterine fibroids? ☐ A specialist in the clinical evidence base for uterine fibroids or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for uterine fibroids? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The aim of treatment of uterine fibroids varies from prevention of disability due to anaemia or pressure effect or impact on fertility. In my clinical practice, the aim for treatment of women with uterine fibroids is determined by the patients clinical presentations, impact on quality of life, fertility desires and most important, the preferred treatment by the patient
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	In my patients (women) with heavy menstrual bleeding due to fibroids, a clinically significant response to medical treatment of uterine fibroids will be to control of heavy menstrual bleeding which reduces risk of anaemia and improve quality of life. In women with large uterine fibroids and heavy menstrual bleeding, a 50% reduction in size of fibroid would be a clinical benefit to reduce pressure effect if the fibroid size is<12cm. In women with larger fibroids a reduction will only be helpful as a pre-surgical treatment to facilitate ease at myomectomy or hysterectomy surgery.
10. In your view, is there an unmet need for patients and healthcare professionals in uterine fibroids?	Yes, there are still unmet needs for treatment of women uterine fibroids. The current treatment options are skewed toward surgery which is unacceptable in some patients, especially of black and ethnic minority (BAME) group. In my practice, the use of hormonal pills including Mirena IUS is reduced due to associated irregular menstrual bleeding, weight gain and mood changes. The GnRH agonist injections require healthcare specialist to administer and also its side effects on the vasomotor menopause symptoms, bone density and mood. There is still a reluctance to offer this treatment for >6months to patients. We currently have an established nurse-led clinic for monthly injections and our patients treatments were disrupted during the covid-19 pandemic with reduce hospital visits and staff availability

11. How is uterine fibroids currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There are two options of treatment for women with symptomatic uterine fibroids and these are in line with the NICE guidelines – medical or/and surgical treatments and uterine fibroid embolization. Medical treatment is aimed at reducing the blood loss during menstruation to prevent anaemia at its impact of health and wellbeing. These vary between non-hormonal drugs such as tranexamic acid and hormonal drugs such as the contraceptive pills, Depo-provera or Mirena IUS. All of these drugs can be offered in primary and secondary care setting in UK. The use of Esmya and GnRH agonists are initiated in secondary care and in some CCGs, follow up treatment occurs in primary care. The surgical treatment offered in my hospital includes endometrial ablation, hysteroscopy resection of submucosal fibroids, myomectomy and hysterectomy. We would refer women who wish to have fibroid embolization to interventional radiology team for treatment. The current NICE pathway in my opinion is well defined. Unfortunately I still see women in my clinic who have not been offered any treatment in primary care. The technology under review offers patient a self-administered oral drug for the treatment of uterine fibroids causing heavy menstrual bleeding. The technology would fit into both primary care and secondary care treatment in the current pathway for treatment of uterine fibroids. This in my opinion could offer patients more choices on treatment options, reduce the need and stress to attend GP surgery or Hospitals, reduce cost of travel for treatment as well as carbon foot prints from monthly hospital visits.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology will be used in the same way as current care for women with heavy menstrual bleeding due to uterine fibroids who desire medical treatment, and want to avoid surgery or waiting for surgery. The technology would fit into both primary care and secondary care treatment in the current pathway for treatment of uterine fibroids. However, in patients that need treatment for the long term, there should be safeguards to assess effects on bone density as currently in practice for women on long term use of Depo-provera or Leuprolide acetate. The investment required for the introduction of this technology will be best spent on education of women (patients) and healthcare providers on the availability of new drug and treatment outcomes. This is important to ensure women are empowered to demand more options for their healthcare providers.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, I do expect the technology to provide meaningful benefit to patients. The published research work suggests a significant reduction in menstrual blood loss which will reduce risk of anaemia inpatients and improve quality of life. It is difficult to say with all certainty that the technology will increase health related quality of life more than current care as there are no direct comparable studies with current care. The LIBERTY 1 and LIBERTY 2 studies were placebo-controlled studies. However the results show very significant reduction in blood loss which will reduce risk of anaemia and improve quality of life.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology will be suitable for all women with heavy menstrual bleeding except women with allergies to any of the drug constituents. In my opinion, it should be used with caution in women with hypertension, migraine headaches or past deep vein thrombosis due to its oestrogen component
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	In my opinion, the technology will not pose any difficulty with patients or healthcare professional more than the current care. It offers less demand on staff and patients compared to the administration of GnRH analogue injections.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The technology contains a GnRH antagonist with potential impact on bone density. As with my current practice for women on GnRH agonist who have a DEXA scan every two years, I will consider same practice of testing for women on long term use.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The trial results from LIBERTY 1, 2 and 3 studies suggest a significant improvement in menstrual blood loss and haemoglobin levels which is the desire of most of my patients with heavy menstrual bleeding due to fibroids. The technology will offer women, who do not have any significant side effects a treatment regime that is solely within their control as compared to GnRH agonist. In addition, it offers a longer period of use with minimal supervision by GPs or gynaecologists.

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, I consider this technology a step change in the care and treatment of women with heavy menstrual bleeding due to uterine fibroids. It addresses the many unmet needs and benefits in the care of patients with heavy menstrual bleeding due to uterine fibroids. This is an oral, patient control of treatment with >50% reduction in menstrual blood loss, fewer side effects than Esmya or GnRH agonist. It also offers the benefits of 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.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects as reported from the LIBERTY 1, 2 and 3 studies are not in excess of published side effects in the literature on leuprolide acetate. However the side effects are potentially going to be a reason for patients to continue with the treatment long term.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The LIBERTY 1, 2 and 3 trials for this technology were designed to match the clinical practice in UK. These trials have included more women of colour (BAME) with heavy menstrual period as compared to other studies in the last decade. The ethnic background of the study patients relate with my clinic patient population, which is significantly women of BAME background and desire non-surgical treatment.

	In my view, the two most important outcomes in my clinical practice are the menstrual blood loss and improvement in haemoglobin status which were measured in the studies. The clinical trial results have not reported any issues with effect of mental health of patients, as in my practice many women stop hormonal drugs on GnRH agonist due the impact on their mental health
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I am not aware of any relevant evidence that is not available by the systematic review
22. How do data on real-world experience compare with the trial data?	The results from the LIBERTY 1, 2 and 3 studies on menstrual blood loss and improvement in haemoglobin levels are as good as real-world experience with use of hormonal contraceptives. It has the added benefit of long term use compared to Leuprolide acetate. However it will be better to have a direct comparative study for non-subjective opinions. The results have been reported for all groups of women and there are no secondary analyses on outcome for women of colour in the trials. It will be important to review the data on black women who in my practice have larger uterine fibroids and more likely to demand medical treatment compared to surgery
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	In my opinion the LIBERTY 1 and 2 studies have recruited a substantial number of women of ethnic minority background with heavy menstrual bleeding. This reflects my clinic population of women who have larger uterine fibroids and more likely to demand medical treatment compared to surgery.

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	The treatment offers a benefit that will reduce time and expenditure for BAME women in attending hospitals as compared to use of leuprolide 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 DNA rate to clinics. .

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1 (ERG report section 2.3 [Table 3] and 4.2.3): 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	I do agree it is a challenge to compare the outcome of two randomised trials on different patient population, with different inclusion criteria and follow up regime. The Liberty trials had a different starting MBL as well as review time period during the trial compared to PEARL studies. It would have been preferable like the PEARL 2 study to have a direct comparative RCT between the technology and leuprolide acetate. However, the Liberty studies do show consistently over all three studies a reduction in MBL and improvement in haemoglobin levels which is of key importance to patients and clinicians. In my opinion, the technology could be used in clinical practice for women who wish long term medical treatment instead of surgery as well as women who are waiting for definitive surgery; to reduce menstrual blood loss, improve haemoglobin levels prior to surgery as I would do with GnRH agonist for women with anaemia.

Key Issue 2 (ERG report section 3.4, 3.5, 4.2.6 and 5.1): Lack of formal comparison between relugolix CT and GnRH agonists	I do agree there is no formal comparison between the technology and GnRH agonist which make it difficult to compare outcomes in patients. However, the new technology aims to reduce menstrual blood loss which improve haemoglobin levels and reduce the risk of anaemia which impacts on the quality of lives of women with HMB due to fibroids. The LIBERTY studies show a significant reduction in MBL and improvement of haemoglobin levels. These in my clinical opinion are relevant to patients care. I do believe the technology and GnRH agonist will offer more medical options to different patients and not necessarily one or the other.
Key Issue 3 (ERG report section 4.2.2): The appropriateness of using "treatment" rather than "health" states in the economic model structure	In clinical practice, I would use the health status to ascertain the response to treatment and not treatment status as used in the trial. We do not measure MBL or use PBAC in clinical practice, more of the patient's subjective health status.
Key Issue 4 (ERG report section 4.2.6): The most appropriate assumptions about treatment discontinuation in UK clinical practice for both relugolix CT and GnRH agonists	The discontinuation rate for GnRH agonist has changed in the last two years and likely to stay the same, a change driven by the covid-19 pandemic. As prior to the covid-19 pandemic, majority of my patients would be having surgery after a three months treatment with GnRH agonist which reduces anaemia and the size of fibroids to facilitate keyhole surgery. However significant proportions have stayed on the off-label use for more than 6 months with HRT addback therapy due to delays in surgery. The new technology offers the benefit of a licence for long term use and satisfactory improvement in haemoglobin levels for women who chose to or not to have surgery. The most appropriate method to ascertain discontinuation rate would be to do a comparative study between the new technology and GnRH agonist.

Key Issue 5 (ERG report section 4.2.3 and 4.2.6): The appropriateness of a 'waiting time' health state post-treatment discontinuation	I do agree with the ERG that in clinical practice, patients will be kept on medical treatment while awaiting surgery except if they chose not to be on treatment or have side effects of the treatment.
Key Issue 5 (ERG report section 4.2.2 and 4.2.6): The role of surgery in the treatment pathway and the lack of data to inform transitions to the surgery health state	In my clinical practice, some women strongly do not want surgery especially women from the black and ethnic minority groups (BAME). Many feels forced to have surgery due to poor response or side effects of current treatment options. However surgery is still any important and dominant choice for women who have completed their families and had failed treatment with current treatment armamentarium.
Key Issue 7 (ERG report section 4.2.7): Uncertainty surrounding the utility function	No Comment.
Key Issue 8 (ERG report section 4.2.8): Monitoring and follow up resource use in UK clinical practice	In my clinical practice, women with heavy menstrual bleeding due to uterine fibroids do not have annual follow up in clinic or by ultrasound scan. I would request an ultrasound scan as a base line test for diagnosis on size, number and position of fibroids to help with counselling for decision on treatment. If a patient chooses medical treatment, the outcome will be assessed by patient's subjective health outcome. The new technology if adopted into clinical practice would require DEXA scan every two years for women on long term treatment. I would only request a scan examination if there are changes in the clinical

	symptoms in my patients such as sensation by patient of increase size of fibroids or pressure effect on bladder or bowel.
Are there any important issues that have been missed in ERG report?	The covid-9 pandemic and current drive to reduced human activity impact on the environment has revealed significant gaps in our current clinical practice and care for patients and need to adopt different and new ways for care of our patient. In my opinion, there has been no assessment on the impact of this technology on the environment. The technology assessment has compared clinical outcome and cost effectiveness against GnRH agonist and no mention of the impact on environment such as disposal of plastics, bottle and needles or travel carbon footprints.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is a need for an oral drug for treatment of heavy menstrual bleeding due to uterine fibroids in women who do not desire surgery as treatment.

The new technology (drug) under review offers patients the option of an oral drug to reduce menstrual blood loss and improve haemoglobin levels in patients which will improve their quality of life.

The new technology (drug) offers patients more options for treatment of HMB due to fibroids with a licence for long term use and requires fewer hospital review visits for treatment.

The new technology (drug) offers patients an oral drug with reduced side effect profile compared to GnRH agonist for treatment of heavy menstrual bleeding that is not controlled by non-hormonal treatment or contraceptives.

The use of the new technology (drug) will offer significant benefits to patients, NHS and the environment as compared to use of GnRH agonist, with savings on time and money for monthly visit to healthcare facilities for treatment, staff cost and cost of disposable of injections.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday 11 February 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	FEmISA – Fibroid Embolisation: Information, Support & Advice an independent, voluntary patient group supporting women with fibroids
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Summary of FEmISA's response		If it can be demonstrated that Relugolix has fewer and more acceptable side effects than other GNRH agonists and a fully evidenced longer-term safety and efficacy profile then it would be a very useful short to medium term treatment for fibroid symptoms, particularly with NHS waiting list at an all-time high due to the COVID-91 pandemic. However, the evidence, information and data presented to this Technology Appraisal is insufficient and much more clinical evidence is required. It is very surprising that Gedeon Richter has applied for a Technology Appraisal with such a paucity of data and evidence. A direct comparative trial of Relugolix versus other commonly used GNRH agonists is required to demonstrate superiority. The data used for economics modelling is not credible, poorly researched and old. The comprehensive and extensively researched data submitted in FEmISA's earlier submission has not been duplicated here as it is already available and the NICE review committee is urged to use it. There is insufficient safety and efficacy data for Relugolix to be used for 'long-term' use. (text in blue is from the company submission documents)

Issue 1: trial populations and UK clinical practice	Yes/~~No~~	The most important issues that are not addressed in the clinical evidence or UK clinical practice are – 1. **The safety of patients** – there is a complete lack of any safety, efficacy or other data for use of Relugolix 'on a longer-term' basis. The company is trying to position the medicine for longer-term use. Most GNRH agonists are licensed for use for only 6 months i.e., before in-patient treatment. The clinical evidence published has a maximum duration of 52 weeks and apparently there is unpublished data for 2 years. **This medicine should not be used for longer than 1 year while there is no evidence to show safety or efficacy for longer**. **In addition, Esyma has been associated with liver failure requiring transplantation and was withdrawn for some time**. **There is no reported evidence in the submission of liver safety or toxicity for Relugolix** **2**. **Duration Requirements for Fibroid Treatments** – The average age for in-patient treatment for fibroids is 42, [NHS HES data] while the average age for the menopause is 51, when symptoms should diminish if HRT is not required. However, fibroid symptoms will start much earlier than 42 and women will have suffered, tried drug treatments and had to wait for in-patient treatment sometimes for many years. An Inquiry conducted by the All Party Parliamentary Group for Women's Health in which FEmISA was involved reported that diagnosis of fibroids alone can take 1-2 years - https://static1.squarespace.com/static/5757c9a92eeb8124fc5b9077/t/5d41adfc49a80d0001f41b82/1564585493903/Informed+Choice+Report+Final.pdf So, if treatment by medicines alone for symptomatic fibroids is to be contemplated it would be needed for **at least 10 years and would need evidence to show it was safe and effective to use for this period of time**. **This has not been demonstrated in the case of Relugolix.** **3. Fibroids in black, Afro-Caribbean and women with darker skins** – while the evidence is correct that this group of women have a higher incidence of fibroids what is not mentioned is that fibroid symptoms also start much early, sometimes in the women's 20s. This gives rise to additional challenges for fibroid treatment, including required duration.

		4. Fertility i) Black, Afro-Caribbean and women with darker skins require treatment for symptomatic fibroids for much longer possibly 30 years if they do not receive in-patient treatment. ii) Fertility is a significant issue. Any treatment must maintain fertility, particularly for younger women and the age for first pregnancy is increasing. This has not been demonstrated in any of the clinical evidence for Relugolix iii) Fibroids can have a detrimental effect on fertility, so treatment for women wishing to become pregnant at any later stage must treat the fibroids and not just the symptoms, as Relugolix does. The only treatments that treat fibroids and retain/enhance fertility are myomectomy and UAE/UFE. [Uterine-Artery Embolization or Myomectomy for Uterine Fibroids -Isaac Manyonda, Ph.D., Anna-Maria Belli, F.R.C.R., Mary-Ann Lumsden, M.D.,- July 30, 2020 N Engl J Med 2020; 383:440-451] *"impact on fertility and pregnancy and teratogenic effects"* – were not considered. **They should have been as these medicines are used in women of reproductive age and contraception is required.** **5. Libido and Sexual Function** The enjoyment of sex is not confined to men. Women need and enjoy sex too, although this fact is often ignored in clinical trials and assessment of treatments for women's conditions e.g., hysterectomy. GNRH agonist are known to reduce libido and lubrication, so sex can become painful. The fact that the effect on libido and sexual function from Relugolix has not been studied measured or considered must be condemned, as this is unlikely to have been ignored in medicines for men**. An acceptable 'long-term' treatment for a benign condition cannot have a detrimental effect on libido or sexual function and no evidence has been submitted on this for Relugolix.**

		6. Efficacy to Supress/Reduce Fibroid Symptoms There is a large number of symptoms from uterine fibroids, depending on the number, position and size of the fibroids. Common symptoms include – Symptoms Approximately 25% or more of women with fibroids have symptoms. These vary with the position, type of fibroid and size. Common symptoms are: - • Menorrhagia • Iron deficiency anaemia • Dysmenorrhea • Bladder incontinence/urgency • Infertility or miscarriage • Pressure symptoms on the bowel leading to constipation • Pressure symptoms on the ureters, bladder and/or kidneys • Back pain and sciatica • Abdominal swelling, as in pregnancy • Indigestion, discomfort sitting, etc., as in pregnancy • Dyspareunia • Dyspnoea • Varicose veins and haemorrhoids • Infertility or miscarriage • Painful intercourse and dryness in the vagina [http://www.femisa.org.uk/index.php/about-uterine-leiomyomata]

		Not all women with symptomatic fibroids would have HMB and amenorrhea is not necessarily the desired outcome of women with HMB. Some would prefer the return to normal periods and bleeding. The clinical evidence submitted on Relugolix is confined to menstrual bleeding and amenorrhea, fibroid size and size of uterus, but does not include the other symptoms, nor are the subjects in the trials asked if their symptoms have been controlled adequately**. An acceptable long-term treatment for symptomatic fibroids would need to show efficacy to reduce most common symptoms. The evidence submitted for Relugolix does not show this.** **7. Adverse Events, Undesirable effects and Side Effects** If Relugolix is to be acceptable as a treatment for women with fibroids it must have few and mild side effects. As FEmISA has mentioned in our previous submission many gynaecologists do not use GNRH agonists as their severe menopausal side effects are unacceptable to many women. Side effects reported for a commonly used a GNRH agonist goserelin acetate from the SmPC are – • Pituitary tumour • Degeneration of uterine fibroid • Pituitary haemorrhage • Hypercalcaemia • Libido decreased • Mood changes, depression • Psychotic disorder • Paraesthesia • Headache • QT prolongation – cardiac disorder • Hot flush

		• Blood pressure abnormal • Hyperhidrosis, acne, rash, alopecia • Arthralgia • Vulvovaginal dryness • Breast enlargement • Ovarian cyst • Ovarian hyperstimulation syndrome (if concomitantly used with gonadotrophins) • Withdrawal bleeding • Tumour flare, tumour pain • Bone density decreased weight increased Other commonly reported menopausal symptoms – • Sleep disturbance • Night sweats • Memory loss • Loss of intellect – brain fog Side effects in the SmPC for Relugolix are - • Hot flush (8.3%) • Uterine bleeding (4.7%) • Irritability • Dyspepsia • Alopecia • Hyperhidrosis • Night sweats

		• Breast cyst • Libido decreased • Uterine myoma expulsion While there are fewer undesirable effects for Relugolix listed in the SmPC there is little evidence in the submission on 'undesirable effects' and these for Relugolix have not been shown to be acceptable to the women in the trials, particularly over a longer period. "*Bone Mineral Density (BDM) is not an outcome in the economic model as it is assumed that BMD may resolve once treatment with GnRH agonist therapy (the comparator for relugolix) ceases*" *"it would appear that relugolix CT has the potential benefit to preserve BMD even when used without interruption for extended periods of time*" – **There is no evidence upon which to make the assumption that BMD returns to normal after 52 weeks and this is a significant safety issue for women which must be fully investigated.**
Issue 2: lack of formal comparison between treatments	Yes/~~No~~	There is no comparative study of Relugolix versus other commonly used GNRH, **so no evidence that Relugolix is superior with fewer side effects than other GNRH agonist or that it is more acceptable to women**. The list of undesirable effects from the respective SmPCs is listed in 7 above. EQ-5D may be a useful health economics tool for modelling, but it is inadequate as a measurement of patient acceptability. Many parameters are missing or inadequately expressed in EQ5D e.g. • Urinary incontinence or urgency • Loss of libido • Sexual dysfunction • Fertility etc In fact, most of the symptoms from fibroids and the side effects of treatment with GNRH agonists listed above in Issue 1 6 and 7 are not adequately represented in EQ-5D.

		As with statins if the side effects of medicines are unacceptable to patients there will be greatly reduced compliance and use. **The clinical evidence submitted does not demonstrate that Relugolix is superior or acceptable safe and efficacious for longer-term use. A direct comparative trial is required.**
Issue 3: economic model structure	Yes/~~No~~	No costs to patients or wider society are included. 78% of the NHS workforce are women and the impact of fibroids and their treatment both directly and indirectly needs to be assessed. Are QALY'S sufficiently sensitive to capture the quality of life of someone with symptomatic fibroids? The symptoms from fibroids and side effects from treatment are not adequately captured. Detailed concerns have been voiced in other Issue sections but here is a summary – 1. There is no comparative study and no evidence on the superiority of Relugolix. 2. Comparative economic data is derived and not evidence based. 3. The Use of KOL estimates is not accurate or acceptable, especially as gynaecologists they will lack sufficient knowledge of UAE and MRgFUS, both interventional radiology procedures, not performed by gynaecologist 4. The data used for 'surgery' inpatient fibroid treatments is poorly researched in many cases out of date and inaccurate
Issue 4: treatment discontinuation assumptions	~~Yes/No~~	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 5: waiting time health state	Yes/~~No~~	The average age for in-patient treatment for fibroids is 42, [NHS HES data] while the average age for the menopause is 51, when symptoms should diminish, if HRT is not required. However, fibroid symptoms will start much earlier than 42 and women will have suffered, tried drug treatments and had to wait for in-patient treatment sometimes for many years. Women will typically wait many years suffering HMB and other symptoms from fibroids before first going to their GP to seek treatment. An Inquiry conducted by the All Party Parliamentary Group for Women's Health, in which FEmISA was involved, reported that diagnosis of fibroids alone can

		take 1-2 years - https://static1.squarespace.com/static/5757c9a92eeb8124fc5b9077/t/5d41adfc49a80d0001f41b82/1564585493903/Informed+Choice+Report+Final.pdf Women's health has always had a lower priority in the NHS. Pre-pandemic RCOG reported lengthening waiting list for non-life-threatening women's conditions. This has worsened during the pandemic. The December '21 national waiting time data shows – Gynaecology Services having the 4th highest numbers of patients waiting - 447,339 with 23,582 waiting more than 52 weeks – a year. **There is a need for treatments that reduced side effects while women are waiting for treatment.** [waiting list data - https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.england.nhs.uk%2Fstatistics%2Fwp-content%2Fuploads%2Fsites%2F2%2F2022%2F02%2FIncomplete-Commissioner-Dec21-XLS-7184K.xls&wdOrigin=BROWSELINK
Issue 6: role of surgery and data on surgery health state	Yes/~~No~~	The information and data on 'surgical treatments' for fibroids is exceedingly poor using very old out of date references which is unacceptable and could result in misleading conclusions. FEmISA has researched, compiled and supplied evidence based and fully referenced information on all in-patient treatments for symptomatic fibroids. We refer to our information in our earlier submission which was published with the company's submission and is more accurate and recent. Outlined here are some of the incorrect and missing information on each in-patient – 'surgical' treatment – **Hysterectomy** – This has never been formally reviewed for safety and efficacy. It causes early menopause and there is little and insufficient knowledge and study of the effect on libido and sexual function after this treatment. Pelvic prolapse is a common longer-term complication and it has until recently been treated with surgical mesh, with severe and sometimes irreversible consequences, including death -[First Do No Harm]. Large fibroids are highly vascularised and there is a serious risk of severe haemorrhage with both hysterectomy and myomectomy. Women become infertile and menopause is earlier.

		Hysterectomy has a high morbidity and mortality which are shown in FEmISA's earlier submission – mortality at 3 months approximately 180 women p.a. in the NHS in England alone. This figure does not include deaths in the private sector or other UK countries. Hysterectomy is the second commonest operation in the private sector after joint replacement. **Endometrial ablation** – This has only been assessed for safety and efficacy for small fibroids <3cm. There is a risk of perforation of uterus, and the effect on fertility is unknown. Women have complained that there is inadequate analgesia and it can be excruciatingly painful. **Myomectomy** – This has never been formally reviewed for safety and efficacy. Of even greater concern, the risk to women is unknown. There is very little data on morbidity and mortality. Women retain fertility, it may even improve fertility if fibroids are a cause of infertility. There have been a number of successful pregnancies following myomectomy. **There is a high incidence of fibroid regrowth and many women require a subsequent additional treatment with another myomectomy or UAE. Most women eventually go on to have a hysterectomy**. There is a very high incidence of adhesions requiring further surgical intervention. **These high readmission and retreatment rates are completely missing from the economic analysis** Uterine rupture has been reported with pregnancy. As with hysterectomy there is a high risk of severe haemorrhage with large fibroids. **UFE/UAE** – There is a completely incorrect definition of appropriate population. Embolisation can be used to treat all types of fibroids, of all sizes. There is no limit to the type of fibroid - pedunculated subserosal fibroids can be treated if the stalk is short and fibroid unlikely to break off or with removal of the pedunculated fibroid by myomectomy immediately post-UAE. UAE is much safer for women with very large fibroids than hysterectomy and myomectomy as there is little risk of haemorrhage. Fertility is retained with peer reviewed evidence of many successful pregnancies. Recent paper FEMME study - *Uterine-Artery Embolization or Myomectomy for Uterine Fibroids* *Isaac Manyonda, Ph.D., Anna-Maria Belli, F.R.C.R., Mary-Ann Lumsden, July 30, 2020*

N Engl J Med 2020; 383:440-451, UAE is considerably less expensive than myomectomy or hysterectomy and the women being treated, as hospital stay is shorter, procedural costs lower and return to work is quicker. There is a possibility of fibroid regrowth requiring further intervention either another UAE procedure or myomectomy. **There is a low incidence of fibroid expulsion, but the assumption in the economic model that this will require hospital intervention on each occasion is false, as FEmISA can attest from personal experience. If fibroids are expelled some may require assistance under anaesthetic, others, if smaller can fall out at home with no intervention.**

UAE has been formally, positively reviewed by NICE for safety and efficacy under the Interventional Procedures Review.

MRfUS – There are few centres offering this treatment in the UK. Like UAE it has been **formally, positively reviewed by NICE for safety and efficacy under the Interventional Procedures Review.** It is better for small fibroids.

Table 51 Risk of short-term adverse events related to surgery p145 – these figures are incorrect and out of date. Please see the adverse event data in FEmISA's earlier submission.

Table 53 Surgery-specific risk of mortality Surgery	**Risk of mortality**	**Source**
Abdominal hysterectomy	0.0028%	Settnes et al., 2020 (98)
Laparoscopic hysterectomy	0.0020%	Settnes et al., 2020 (98)
Vaginal hysterectomy	0.0031%	Settnes et al., 2020 (98)
Abdominal myomectomy	0.0028%	Assumed same as abdominal hysterectomy
Laparoscopic myomectomy	0.0000%	Assumption
Vaginal myomectomy	0.0000%	Assumption
Uterine artery embolisation	0.0200%	Zowall et al., 2008 (99)
MR-guided focused ultrasound	0.0000%	Gorny et al., 2011 (71)

		The real life data mortality figures – HES ONS 2014 for hysterectomy are considerably higher at 0.6% The mortality figures for UAE are out of date and completely incorrect. There have been no deaths from UAE in the past decade. Please also see the HES/ONS 2014 real time data mortality figures supplied by FEmISA in the earlier submission.
Issue 7: uncertainty surrounding the utility function	Yes/~~No~~	"*Surgery related utilities are calculated as a utility decrement applied to the population baseline utility or to the BSC utility, based on the proportion of patients assumed to be cured on uncured after surgery. An annual EQ-5D utility decrement per year for each surgery was sourced from a cost-effectiveness study of UPA in the treatment of UF* (87). " Table 58 Surgery-related disutilities reported in the literature Surgery EQ-5D QoL decrement/year " This is completely unrealistic. Following 'surgery'/in-patient treatment for fibroids a typical pattern of recovery will be severe pain immediately post-procedure and gradual recovery. The recovery rate will vary greatly. Invasive surgery such as abdominal hysterectomy and myomectomy will take longer while less invasive treatments like UAE may have very quick recovery indeed – one FEmISA member reported back to normal the next day. Symptoms should disappear immediately with surgery – hysterectomy and myomectomy, but take longer with UAE. So, a measurement assigning a 'decrement/year' is completely unrepresentative of the patient experience. Side effects or complications may persist for years, or be treated and resolved. They are unlikely to be constant. *"Loss of uterus* *The loss of the uterus may be associated with negative feelings and perceived loss of for example, femininity. According to the World Health Organisation (WHO) the loss of the uterus is associated with an annual disutility of -0.18, (104) thus the model applies one twelfth of this each month to patients in the post-hysterectomy state. The resultant disutility of -0.015 is applied per model cycle up until patients reach menopause."*

This only considers psychological effects. The loss of the uterus also causes physical effects – early menopause, loss of libido, sexual dysfunction, urinary incontinence and in the longer-term pelvic prolapse.

Table 61 Disutilities for surgery-related short-term adverse events

Pneumonia	-0.008	Assumption that same disutility as reported for influenza in Lloyd et al., 2006 (105)
Post embolisation syndrome	-0.012	Assumption that same as sum of pain and nausea

Table 62 Disutilities for long-term adverse events for hysterectomies

Death? Very very old papers

Housework problems	-0.005	(-0.004, -0.007)	Dolan, 1997 (115) (Disutilities associated with surgery, Page 145)

Table 61 - It is realistic to compare pneumonia with flu.

FEmISA members have personal experience of post-embolisation syndrome. It is similar to mild flu not associated with pain or nausea.

Table 62 Why hasn't death, mortality and morbidity been included, particularly for hysterectomy – mortality rate 0.6% and morbidity - serious 4.6% for abdominal hysterectomy and 7.10% for vaginal hysterectomy [Maresh et al VALUE Study]?

Housework problems? Has gynaecology not caught up with the fact that women have careers? There are certainly disulilities associated with trying to juggle a career and family responsibilities

both when suffering from symptomatic fibroids and recovering from 'surgical' in-patient treatment.

KOLS – these were all gynaecologists. Gynaecologists do not perform UAE or MRgFUS, have little or no training or education about them and lack the knowledge to advise about these procedures. FEmISA's report shows that gynaecologists have little or no education or training in UAE - http://www.femisa.org.uk/images/femisa%20report%20on%20patient%20choice%20and%20nice%20compliance%209.17%20-%20final.pdf

NHS HES data can provide detailed reports and data on diagnoses and follow through treatment and subsequent readmission rates and can some registries and the VALUE study. **There are many better measures of readmission and retreatment rates that estimates from KOLs which are not credible without backing data.**

Table 70 Examinations and test frequency for each treatment, KOL responses	**Frequency - relugolix CT**	**Frequency – GnRH agonist**	**Frequency - BSC**
Resource use			
DEXA scan	Once after the first year	Once a year	None
Ultrasound	Once a year	Once a year	Once a year
Full blood count	Once a year	Once a year	Once a year
Hysteroscopy	Required once a year in only 25% of patients	Required once a year in only 25% of patients	Required once a year in only 25% of patients
MRI	Required once a year in only 20% of patients	Required once a year in only 20% of patients	Required once a year in only 20% of patients

		The figures above are completely unrealistic of what happens in the NHS. A woman undergoing any 'surgical'/in-patient treatment for fibroids would normally get no follow-up unless they suffered symptoms that needed investigation. These follow up scans would only happen routinely in a clinical trial.
Issue 8: resource use in UK clinical practice	Yes/~~No~~	At a meeting of the APPG on Women's Health the funding of Esmya, which is also sold and promoted by Gedeon Richter was highlighted as an issue. Primary care cannot fund prescriptions for GNRH agonists, as they are above acceptable thresholds for GP prescribing. These need to be prescribed in hospital, where there is a funding mechanism for medicines at this level. **While oral administration is greatly preferable to women compared with injections, and also represents a cost saving to the NHS and patients, the funding mechanism or Relugolix in primary must be changed to allow it to be prescribed in primary care.**

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

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Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
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Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday 11 February 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Bayer Plc: Stakeholder
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Current Situation** • Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. • Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. • It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. **Past Situation** In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: trial populations and UK clinical practice	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 2: lack of formal comparison between treatments	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 3: economic model structure	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 4: treatment discontinuation assumptions	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 5: waiting time health state	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 6: role of surgery and data on surgery health state	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 7: uncertainty surrounding the utility function	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 8: resource use in UK clinical practice	No	Bayer agree with the view taken by the ERG in their report, that the anticipated positioning of relugolix CT is within its licensed indication and that the proposed care pathway is representative of current practice, as outlined in NG 88 (1).

		Likewise, intended as a means to avoid or delay surgery, after the failure of first-line treatment strategies, Bayer agree that the most appropriate comparator to relugolix CT are GnRHa. Notwithstanding, Bayer recognise the likely underestimation of best supportive care costs and benefits for those patients who discontinue treatment, as identified by the ERG's clinical expert. It is very clear from NG 88 (1) that a primary objective of the treatment of uterine fibroids is to allow informed treatment decisions guided by patient preference. The recommendations of NG 88 (1) illustrate that, for the majority of pre-menopausal women, the treatment intention is to preserve fertility and manage symptom burden. The submitted economic model assumes that after discontinuation of GnRHa/relugolix CT, patients (now in the BSC state) receive no active treatment and instead receive NSAIDs for pain and iron supplements for blood loss. The proportion of those patients that are scheduled for surgery then immediately enter a waiting time state of 15 months duration. As stated in B 1.3. of the CS, two "ideal" characteristics of treatments for UF are the "ability to preserve fertility" and the ability to "offer quick relief from symptoms". Mineral supplementation with iron and the pain management offered by NSAIDs (200mg ibuprofen) do not meet the above stated criteria. In table 3 of the CS, the manufacturer presents perceived advantages/disadvantages of different treatment options. The main disadvantage listed for NSAIDs is "Do not address the multifactorial symptoms associated with fibroids" and the main advantage is "may reduce pain".

		When inadequate symptom management drives a desire to lose or risk fertility with surgical intervention, it is not logically consistent that the desire or requirement to manage these symptoms whilst waiting 15 months for surgery would be lessened. Further, it does not follow that the importance of patient guided treatment decisions should end upon discontinuation of GnRHa/relugolix CT. Given the importance of patient preference in the treatment of uterine fibroids, it is likely that patients may not exhaust all first-line treatment options before progressing to GnRHa/relugolix CT. Therefore, a substantial proportion of patients who value long-term symptomatic management (e.g., menstrual blood loss) may benefit from hormonal contraceptives in the BSC state. In summary, Bayer agree with the ERG's clinical expert that hormonal treatments would play an important role in symptom management for patients in the BSC state, regardless of whether they have yet been scheduled for surgery. Bayer agree that this omission has likely resulted in an underestimation of costs and benefits associated with the BSC state. References: (1) National Institute for Health and Care Excellence (NICE). Assessment and management of heavy menstrual bleeding (NG88) [Internet]. NICE Clinical Guidelines. 2018. Available from: www.nice.org.uk/guidance/ng88

Additional issues

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NICE National Institute for Health and Care Excellence

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Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

CONFIDENTIAL UNTIL PUBLISHED

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

ERG critique of the company's response to Technical Engagement

Produced by Aberdeen HTA Group

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Date completed: **24 February 2022**

Contains: **AIC**

Version: **1**

This report presents a commentary and critique of the response document to the company's (Gedeon Richter UK Ltd) response to technical engagement (TE) in advance of the first committee meeting. Please read the report in conjunction with the company's response document. The 8 issues raised in the ERG report are addressed in this document. A confidential appendix to this report replicates the impact of additional ERG scenario analyses following TE, applying a confidential patient access scheme (PAS) discount for comparator (GnRHa) treatments.

Issue 1: LIBERTY and PEARL trial populations and use of relugolix/GnRH agonists in UK clinical practice

The economic model is informed by data derived from the LIBERTY trials (relugolix CT) and PEARL II trial (control arm for GnRHa). However, the goal of treatment is different in these studies. In the PEARL II study, women were scheduled for surgery after 13 weeks, with GnRHa used in the pre-surgery setting, whereas surgery was an exclusion criterion in the LIBERTY studies.

The ERG report queried how relugolix CT would be used in UK clinical practice and noted that it may be used by some clinicians as a pre-treatment prior to surgery to reduce fibroid volume with the goal of improving surgical outcomes. The company seem to position relugolix CT for a population of women who do not wish or cannot have surgery, consistent with its use in the LIBERTY studies. The ERG notes that the marketing authorisation for relugolix CT does not preclude its use in the pre-surgical setting, in a manner like how GnRHa is currently licensed for use (and similar to how it was used in the PEARL II study control arm).

If the committee are interested in the use of relugolix CT in the pre-surgical setting (possibly out with the company's positioning, but within the license), it may be useful to consider the ERG's exploratory scenario analysis for the pre-surgical setting. Within the existing model framework, assuming 12 weeks treatment duration with everyone transitioning to surgery post-treatment, relugolix CT remains cost-effective compared to GnRHa when all treatments are modelled at their list prices. As the company conducted meta-analyses show no evidence of a difference in clinical effectiveness, the ERG considers that in the case of short-term treatment in a pre-surgical setting, a cost-minimisation analyses may be appropriate. The ERG provides an additional analysis assuming equal efficacy between the treatments in the pre-surgical setting for the committee's consideration.

Furthermore, the ERG is concerned that differing goals of treatment in the LIBERTY and PEARL II studies adds substantial uncertainty to the most appropriate parameters to populate the model, particularly in relation to how data from PEARL II are used to populate transition to surgery. This point is further addressed in Issue 6 below.

Table 1 compares key study characteristics and summarises the data from LIBERTY and PEARL II studies used in the economic model.

Table 1: Comparison of LIBERTY (relugolix CT) and PEARL II (GnRHa) trial data used in the economic model

	LIBERTY trials (relugolix CT)	**PEARL II trial (GnRHa)**
Intended use of treatment	Long-term use for women who wish to avoid surgery	Short-term use, in the pre-surgical setting
Treatment discontinuation data available for	24 months	13 weeks
% women discontinuing treatment in the trials	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)
% women having surgery in the trials	No data as not included as an outcome in the LIBERTY studies	45.1% after 13 weeks (54.9% had their surgery cancelled due to symptom resolution)

Issue 2: Lack of formal comparison between relugolix CT and GnRH agonists

The company explains that they only conducted an ITC of menstrual blood loss (MBL) as MBL is the only outcome used in the economic model and that an ITC of the other outcomes was not considered feasible. The ERG would highlight that both the NICE final scope and the company decision problem include not only change in MBL volume but also "time to MBL response, pain, uterine fibroid volume (UFV) / uterine volume (UV), hemoglobin levels, adverse effects of treatment - including but not limited to vasomotor symptoms, incontinence and pelvic organ prolapse - and health-related quality of life." The ERG is of the opinion that

to provide a comprehensive assessment of the effects and safety of relugolix CT an indirect comparison of these outcomes should be considered the minimum requirement.

The ERG notes the various reasons stated by the company in their TE and clarification responses for not making indirect comparisons. In the clarification response the company state that the UFS-QoL will capture many of the symptoms associated with UF such as pain and pelvic discomfort. While an outcome such as this will reflect differences in the components, the ERG believes that considering that these outcomes were included in the NICE final scope, they should have been compared separately and not as part of a composite outcome. The ERG also notes that an indirect comparison of UFS-QoL, or UFS-QoL mapped to EQ-5D utilities, that could have been used in the economic model was not reported. The TE response indicates that outcomes were only measured for a subgroup of participants or using different methods in the respective trials. The ERG believes that the company - by having access to all data collected by the LIBERTY and PEARL studies - could have overcome some of these problems; however, if it was not possible to use these data for indirect comparisons then appropriate data should have been obtained.

Furthermore, as noted in the ERG's report, the ITCs presented by the company for MBL are for relugolix CT versus UPA and UPA versus leuprolide acetate GnRHa but not of relugolix CT versus GnRHa. Whilst the ERG is satisfied that the correct mean MBL data are used within the economic model, the lack of provision of a complete set of ITCs for MBL meant the ERG needed to re-produce the company's ITC to obtain SEs for use in the model probabilistic analysis.

Issue 3: The appropriateness of using "treatment" rather than "health" states in the economic model structure.

The company model structure is based on treatment (relugolix / GnRHa, BSC) states rather than health states (control of symptoms). The ERG noted that a model based on health states would have been more appropriate because it would allow application of monitoring and follow-up resource use that is more consistent with UK clinical practice (i.e., based on patient symptom control rather than treatment status). A consultant gynecologist, in response to technical engagement, agreed that health status rather than treatment status would be more consistent with clinical practice. In response to technical engagement, the company stated

that a range of experts were consulted but due to limited time constraints they were unable to gather the expert opinions in time for the submission. The ERG is unclear as to whether this information will be available for the first committee meeting.

The ERG also believes that a health state model would allow a more accurate modelling of the trial effectiveness data (MBL) which is likely to currently be under-estimated for both relugolix and GnRHa on-treatment cohorts, because the MBL on treatment includes data for all those randomised to a treatment in the trial arms, including those who discontinued to BSC. The ERG accepts that the magnitude of any bias would be small in analyses where the model replicates trial discontinuation rates, where discontinuation rates are similar for relugolix CT and GnRHa, and where the intensity of medical management in BSC is aligned with that in the LIBERTY studies. However, under alternative scenarios, the magnitude of bias may be greater, and the direction of any bias becomes less clear. The company provide several arguments as to why it would not be feasible or desirable to use a health state model:

1. To restructure the model from a treatment to a health state model, a re-analysis of the response data would be required. In response to technical engagement the company argued that this would not be appropriate because the definition of response is not consistent between the LIBERTY and PEARL studies. The definition of a responder in the LIBERTY studies is women who achieved a MBL volume of <80 and at least a 50% reduction from baseline MBL volume over the past 35 days of treatment. The definition of a responder in the PEARL trials is a pictorial bleeding assessment chart (PBAC) score <75 (in the normal range), summed over the preceding 28-day period. The ERG believe that it could have been possible to convert from PBAC score to MBL volume, using the approach adopted in Magnay et al. 2020, whilst noting any limitations of the methods used (such as differences in measurement time frames). Such data could have been used to populate a health state model.

2. The company further stated that they do not have access to patient level data for a reanalysis of the response data from the PEARL II study. The ERG would appreciate further clarification as to why this is the case, because it is our understanding that the same company ran both clinical trials.

3. The company suggested that to define health states based on 'responder' and 'non-responder' based on the trial data would lose valuable important information, with those with no reduction in bleeding up to 49% reduction being categorised as non-responders. The ERG accepts that the current structure captures a linear effect of MBL on utility, via the utility algorithm, but note that this too is associated with substantial uncertainty (see Issue 7). Furthermore, additional categories of MBL change (low, moderate, high improvement) could have been derived if the IPD data from both studies was available, and this would address the company's concern to some extent. Indeed, other studies have attempted something similar before, e.g., including health states such as controlled bleeding/uncontrolled bleeding, and mild/moderate/severe bleeding (see Table 22 in the ERG report).

4. The company argue that treatment discontinuation data would not be available to populate a health state model. However, the ERG believes that, with access to patient level data, the company could obtain the proportion discontinuing in each health state.

Despite the concerns noted above, the ERG appreciates that restructuring the model would require a substantial volume of work. However, it remains unclear what the impact on the ICER would be without seeing that level of data that is required for a health state model.

Issue 4: The most appropriate assumptions about treatment discontinuation in UK clinical practice for both relugolix CT and GnRH agonists

Treatment discontinuation is based on the LIBERTY studies (for relugolix CT) and PEARL II (for GnRHa). The LIBERTY studies have 24 months of follow-up whilst PEARL II has a 13-week follow-up (short-term/pre-surgical use of GnRHa).

Relugolix CT treatment discontinuation:

The original company submission used modified treatment discontinuation data for relugolix CT. However, the ERG maintains the view that the treatment discontinuation data from the trials should be used in the model because it is the best available data and ensures consistency with the limited available data for GnRHa discontinuation. Treatment discontinuation for relugolix CT was extrapolated from the LIBERTY withdrawal study for the remainder of the model time horizon up until the age of menopause (age 51). At the technical engagement

call, the company indicated that they would explore using Kaplan Meier data and time to treatment discontinuation modelling as a robustness check of their base case assumptions. However, such data has not been provided in the company's technical engagement response.

GnRHa treatment discontinuation:

Treatment discontinuation for GnRHa was extrapolated using trial data up to 6 months and thereafter KOL opinion was sought to inform the long-term use of GnRHa given there is no published evidence on the long-term off license use of GnRHa (beyond 6 months). The ERG understand that the evidence base is very limited and therefore the use of KOL opinion to inform treatment discontinuation for GnRHa in the longer term is acceptable.

Validation of treatment discontinuation

The ERG report noted that it would like to see further data that could provide some face validity of the modelled projections of treatment discontinuation over time (for both relugolix CT and GnRHa). Whilst the company has not provided any further information to validate treatment discontinuation data for GnRHa, they do provide additional relugolix CT data, provided as appendix 3 to their technical engagement response document. The data show that, at 24 weeks, [redacted] discontinue relugolix CT treatment in LIBERTY 1 and 2. This is substantially higher than the [redacted] reported in the company submission (Table 39, document B). The company explain the discrepancy because in [redacted] of cases, the reason for discontinuing treatment was patient choice, the actual discontinuation at 24 weeks is lower ([redacted]). The company note that the model predicts that at 6 months around 20% have discontinued treatment which is similar to the [redacted] calculated from data provided in appendix 3. The ERG is concerned that the company's latest documentation may imply that the treatment discontinuation data reported in the company submission may exclude patients who discontinued due to patient choice. If this was correct, it would imply that discontinuation of relugolix CT may be substantially higher than reported in the company submission and included in the economic model. Limited information is provided in the company response to technical engagement to explain whether this is the case, and the ERG believe that this should be clarified for the committee meeting.

Given the uncertainty as to what the additional data provided by the company measures, the ERG tentatively retains its preference to use unmodified treatment discontinuation data provided in the original CS (Table 39 in the CS, Document B). The ERG stress however that

this preference is subject to receipt of further clarification from the company regarding what the new data are measuring.

Issue 5A: The appropriateness of a 'waiting time' health state post-treatment discontinuation

Patients who discontinue relugolix CT or GnRHa treatment to have surgery are assumed to first enter a 'waiting time' health state for a 15-month duration in the company's preferred model. Whilst in this state, patients are assumed to receive best supportive care (BSC) and receive a disutility associated with the anxiety of waiting for surgery. Patients in the waiting time state are assumed to receive treatment with NSAIDs (ibuprofen) and iron supplements. As noted in the ERG report, the ERG prefers removal of the waiting time state because in clinical practice, a decision to schedule for surgery would be made prior to treatment discontinuation in most cases (unless there were concerns about adverse events). The ERG's clinical expert considered it inappropriate to only treat women with NSAIDs and iron (i.e., BSC) prior to surgery, and noted that GnRHa, and potentially relugolix CT may be used by clinicians as a pre-treatment for surgery. It is highly unlikely that treatment would be withdrawn for those who had decided to have surgery due to the risk of fibroids increasing in size prior to the surgical procedure.

Issue 5B: What constitutes best supportive care (BSC) in UK clinical practice for patients who discontinue relugolix CT / GnRHa and do not wish to have surgery.

The ERG's clinical expert considered it unethical to assume that BSC would only consist of iron tablets and ibuprofen. Such minimal intervention would be unlikely to deliver adequate symptom relief at this stage of the pathway, and more intensive medical management, such as hormonal treatments, would be appropriate. This is further emphasized by a consultant gynaecologist who provided clinical input in response to technical engagement, who noted that, due to patient preference for treatment of uterine fibroids in the care pathway, not all first-line treatment may have been exhausted before progressing to GnRHa or relugolix CT. Therefore, it may be that a large proportion of patients in the BSC state could benefit from hormonal treatments. The issue of the appropriateness of the definition of BSC was raised by the ERG as an issue in the report but has not been addressed by the company in response to technical engagement. The ERG considers this a remaining area of uncertainty, and therefore conducts several additional analyses to explore the potential impact of more intensive (more

costly and more effective) treatments in the BSC state. Given limited information on the distribution of treatments that might be used as BSC in UK clinical practice following relugolix CT or GnRHa for women who do not wish to have surgery, we provide a scenario analysis assuming hormonal treatments (Mirena, 33%), contraceptive injection (Depo-Provera, 33%), combined pill (33%) are used in addition to iron supplementation and NSAIDs whilst in the BSC state. Table 2 details the ERG's approach to costing each of these treatments. Adding more intensive medical management, incurring additional cost in the BSC state, reduces the ICER slightly due to longer time on treatment for relugolix CT in the base case analysis. This scenario alone ignores the fact that more intensive medical management in the BSC state would likely also have an impact on treatment effectiveness, reducing MBL compared to the less intensive BSC used in the control arm of the LIBERTY studies. The magnitude of such an effect on MBL is unclear, with MBL data for hormonal treatments likely to lie somewhere between the control and intervention arms of the LIBERTY study. Further work is required to determine plausible MBL estimates if the committee considered a more intensive medical management to be an appropriate definition of BSC in UK clinical practice.

Table 2 Cost of contraceptives

Name of drug	Units per pack	Frequency per month	Price	Proportion on each treatment	Usage per month	Cost per month	Source
Mirena*	1	N/A	£88	1/3	one-off	N/A	BNF 2022
Depo-Provera (Depo-Provera 150mg/1ml suspension for injection pre-filled syringes (Pfizer Ltd))	1	Every 3 months	£6.01	1/3	0.11	0.67	BNF 2022
Combined pill (Levest tablets, Ethinylestradiol 30 microgram/ Levonorgestrel 150 microgram, Morningside Healthcare Ltd	63	28	£1.80	1/3	9.33	0.27	BNF 2022

*Assume a one-off use of Mirena. Based on a 5-year lifespan, this would be mostly sufficient to last up to menopause

Issue 6: The role of surgery in the treatment pathway and the lack of data to inform transitions to the surgery health state

The economic model assumes that the proportion transitioning to surgery every month is 45.1%, calculated from the PEARL II study for GnRHa and applied to both model arms. There is no data available on the proportion transitioning to surgery following relugolix CT discontinuation, or for the setting where women explicitly do not wish to have surgery as a treatment option. The issue of generalisability of PEARL II (a cohort listed for surgery) to the modelled cohort (a cohort who wish to delay or avoid surgery) was discussed in Issue 1.

Given the very limited data on surgery rates for people with uterine fibroids, the ERG queried whether the model predictions regarding transition to surgery over time can be validated. In response to this issue, the company brought our attention to the HMB audit on UK surgery rates in 2014. This is a cohort of patients one year after their first outpatient visit in secondary care. For the data to be more comparable to the modelled cohort of patients who have failed first line treatments, the company excluded those patients from the published source that had 'no treatment', in addition to any missing data. This resulted in 45% having surgery by end of follow-up. It also excluded those receiving 'oral medications/IUS', resulting in 79% having surgery by end of follow-up. The ERG appreciates that the HMB audit is a useful data source, but the data as currently presented are not directly comparable to the modelled cohort for this assessment, or in line with the intended recipients of relugolix CT, who may be less willing to have surgery. The company also provided information obtained from a survey of four UK gynecologists, suggesting varying rates of transition to surgery from 25% to 100%, illustrating the substantial uncertainty surrounding this parameter. The ERG still considers the rate of progression to surgery to remain highly uncertain. To explore the uncertainty around the surgery rates in the modelled population further, the ERG provides scenario analyses varying the proportion transitioning to surgery from 0% to 100%, to illustrate the impact of uncertainty around the base case value (45.1%) on the ICER.

Additional comment on surgical mortality rates included in the model

In response to technical engagement, the Fibroid Embolisation: Information, Support & Advice an independent, voluntary patient group supporting women with fibroids (FEmISA) suggested that some of the surgery related mortality data applied in the model was out of

date. The ERG has therefore conducted an additional scenario analysis assuming 0.06% mortality rate for hysterectomies and 0% mortality for UAE.

Issue 7: Uncertainty surrounding the utility function

The ERG report raised a concern that the chosen utility function for predicting the impact of MBL on utility (mapped from UFS-QoL to EQ-5D) was poorly reported and validity of the prediction function had not been validated or different specifications explored in scenario analyses. In response to technical engagement, the company refers to Geale et al., 2015, who use an OLS regression to demonstrate that non-linearities are unlikely to have an impact on the predicted utilities. However, the ERG would have considered it reasonable to conduct further exploratory analyses around the utility function as it is a key driver of cost-effectiveness in the model, and small changes in the prediction model parameters, especially the constant, could have important implications for utilities and cost-effectiveness. The ERG does not consider the information provided by the company to be sufficient to make a judgement on the appropriateness of the utility function. For example, the ERG does not consider it sufficient to refer to the Geale et al. poster as the sole basis for justifying the exclusion of non-linear effects of MBL on mapped utility. The ERG would have preferred if the company provided a range of alternative model specifications for predicting utilities, with clear justification for the preferred utility function. This should have been done using the available data UFS-QoL, mapped utilities and MBL data obtained directly from the LIBERTY trials. Different model specifications should have been explored in scenario analyses.

The ERG notes the additional scenario analyses capping utility gains according to data included in the HMB audit. This helps to assess the uncertainty surrounding utility values, and the ERG acknowledges that the impact of applying these capped utilities does not increase the ICER above £20,000. However, when combined with other scenarios, such an analysis would likely have a bigger effect.

The ERG also notes the comment from FEmISA that it is unrealistic to apply an annual surgery utility decrement in the model. The ERG can clarify that the annual utility decrement following surgery is not a major driver of cost-effectiveness in the model and the more

important issue for magnitude of effect on the ICER is the most appropriate combination of assumptions about effectiveness and utilities in the relugolix / GnRHa vs. BSC states.

Issue 8: Monitoring and follow up resource use in UK clinical practice

In the absence of any additional information provided by the company in response to technical engagement, the ERG retains its preference for monitoring and follow-up resource use assumptions as per Table 30 of the ERG report. The ERG report assumed DEXA scans would be conducted annually for GnRHa patients and once only for relugolix CT patients. However, in response to technical engagement, a consultant gynaecologist suggested that, in clinical practice, all patients on longer term treatment would receive regular Dexa Scans (both relugolix CT and GnRHa). In addition to the annual DEXA scan already modelled for GnRHa, the ERG provides scenarios assuming 2-yearly or annual DEXA scans for relugolix CT patients as well.

Summary

The ERG has raised several concerns in this document regarding points of technical engagement that have not been fully addressed or resolved in the company's response. Whilst many of the scenario analyses suggest ICERs well below the typically accepted £20,000 / QALY threshold, all scenarios, including the ERG's tentative preferred assumptions from the ERG report should be interpreted cautiously. The preferred assumptions represent the ERG's preferences, conditional on the information available, but those preferred assumptions remain uncertain. This means that the ERG therefore has low confidence that the ICERs currently presented give the most robust estimate of cost-effectiveness possible, and that further data would likely be required to improve confidence in these estimates. The magnitude of impact on the ICER of remaining uncertainties is unclear. The results of scenario analyses that were feasible for the ERG to conduct, given the data available, are provided in Table 3 below.

Table 3: ERGs additional scenario analyses

Analysis No.	Description	Incremental Cost	Incremental QALY	ICER (relugolix CT vs. Goserelin monthly)
1	Tentative ERG preferred base case	£194	0.069	£2,795
2	Subgroup: short term use in preparation for surgery and assuming equal efficacy (utilities) between the treatments*	£23	0.002*	£13,397
3	Additional BSC costs: hormonal contraceptives (33%), contraceptive injection (33%) and the combined pill (33%)	£189	0.069	£2,724
4	Relugolix DEXA scan (every 2 years)	£278	0.069	£4,017
5	Relugolix DEXA scan (annual)	£363	0.069	£5,238
6	Proportion transitioning from relugolix CT/GnRHa to surgery (0%)	£402	0.091	£4,409
7	Proportion transitioning from relugolix CT/GnRHa to surgery (100%)	-£60	0.043	Dominant
8	Alternative mortality risk (based on HES/ONS 2014 real time data mortality figures supplied by FEmISA)	£194	0.070	£2,780

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

These results are reproduced in a confidential appendix to this report, considering the confidential comparator PAS prices.

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