Single Technology Appraisal

Linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Theramex:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **External Assessment Report** prepared by Southampton Health Technology Assessments Centre
   a. EAR report erratum

4. **External Assessment Report – factual accuracy check response**

5. **Statements from experts:**
   a. Funlayo Odejinmi, Consultant gynaecologist and obstetrician - clinical expert, nominated by Theramex

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

Linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190]

Document B

Company evidence submission

September 2023

File name	Version	Contains confidential information	Date
ID6190_Linzagolix_UF_Document-B_[redacted]_v2.0	2.0	No	26-Sep-23

Contents

List of figures

List of tables

Abbreviations

ABT/AB	Add-back therapy
AE	Adverse event
AH	Alkaline haematin
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
BSC	Best supportive care
CA	California
CAN	Canadian
CEAC	Cost-effectiveness acceptability curve
CFB	Change from baseline
CI	Confidence interval
CMA	Cost-minimisation analysis
CMH	Cochran-Mantel-Haenszel
COC	Combined oral contraceptive
CPK	Creatine phosphokinase
CRD	Common risk difference
CrI	Credible interval
CSR	Clinical study report
DIC	Deviance information criteria
DXA	Dual-energy x-ray absorptiometry
E2	Estradiol
EA	Endometrial ablation
eCRF	Electronic case report form
eDiary	Electronic diary
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions-3 level
EQ-5D-5L	EuroQol-5 Dimensions-5 level
ERG	Evidence Review Group
EUR	Euro
FAS	Full analysis set
FE	Fixed effects
FIGO	Federation of Gynaecology and Obstetrics
FSH	Follicle-stimulating hormone
GBP	Great British Pounds
GGT	Gamma-glutamyl transpeptidase
GLM	Generalised linear model
GnRH	Gonadotropin-releasing hormone
Hb	Haemoglobin
HCRU	Healthcare-resource utilisation
HMB	Heavy menstrual bleeding
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL/HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ICH GCP	International Council for Harmonisation Good Clinical Practice

IDA	Iron-deficiency anaemia
IPG	Interventional Procedure Guidance
IQR	Inter-quartile range
ITC	Indirect treatment comparison
IU	International units
IUD	Intrauterine device
IWRS	Interactive Web Response System
KOL	Key opinion leader
LASH	Laparoscopic supracervical hysterectomy
LGX	Linzagolix
LMM	Linear mixed model
LH	Luteinising hormone
LNG-IUS	Levonorgestrel-releasing intrauterine system
LS	Least squares
LY	Life-year
LYG	Life-years gained
MAA	Marketing Authorisation Application
MAIC	Matching-adjusted indirect treatment comparison
MBL	Menstrual blood loss
MCMC	Monte Carlo Markov Chain
MCS	Mental component summary
MRgFUS	Magnetic resonance-guided focused ultrasound
NCT	National Clinical Trials
NEL	Non-elective long stay
NES	Non-elective short stay
NETA	Norethisterone acetate
NG	NICE Guideline
NHB	Net-health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analyses
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drugs
OBE	Linzagolix
OC	Oral contraceptive
OLS	Ordinary least squares
ONS	Office for National Statistics
OP	Oral progestogen
OR	Odds ratio
OWSA	One-way sensitivity analysis
PAR	Public Assessment Report
PAS	Patient access scheme
PBAC	Pictorial blood assessment chart
PCS	Physical component summary
PGI-I	Patient Global Impression of Improvement scale
PICOS	Population, intervention, comparators, outcomes, and study
PK	Pharmacokinetics
PLD	Patient-level data
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal social services

PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised clinical trial
RE	Random effects
Relugolix CT	Relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate
RHMB	Reduced heavy menstrual bleeding
RMBL	Reduced menstrual blood loss
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SERM	Selective estrogen receptor modulator
SF-12v2	Short Form-12 version 2
SF-36	Short Form-36
SLR	Systematic literature review
SmPC	Summary of product characteristics
SPRM	Selective progesterone receptor modulator
STA	Single Technology Appraisal
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TTD	Time to treatment discontinuation
UAE	Uterine artery embolisation
UF(s)	Uterine fibroid(s)
UFS-QoL	Uterine Fibroid Symptom-quality of life
UK	United Kingdom
UPA	Ulipristal acetate
US	United States
UTI	Urinary tract infection
VAS	Visual analogue scale
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

SUMMARY

- Uterine fibroids (UFs) are non-cancerous smooth muscle tumours of the uterus, that develop during a woman's reproductive years;[1,2] the typical age range for patients with UFs is from 16 to 50 years (average of diagnosis ~40 years)[2,3]
- Major risk factors for UFs include age up to menopause (with risk typically reaching a peak in women aged 45 to 49 years),[3] and Black race (Black women have a two–threefold increased risk of UFs)[4–6]
- UFs are common; nearly 70% of White women and more than 80% of Black women will have had at least one UF by the age of 50[4]
- Approximately 25% to 30% of women with UFs experience symptoms, including heavy menstrual bleeding (HMB), pelvic pain, bloating, leg or back pain, increased urinary frequency, constipation and infertility[7–9]
- The substantial symptom burden of UFs causes significant morbidity and distress for women, impairing their physical activities, social activities, intimate relationships, work productivity, emotional well-being, and health-related quality of life (HRQoL)[3,8–12]
- UFs impose a substantial economic burden (primarily driven by surgical and non-surgical procedures to remove or treat UFs, but also due to need for pain relief and impact on fertility) and societal burden, as UF-related symptoms impact absenteeism and work productivity[13–16]
- Iron-deficiency anaemia (IDA) is a common comorbidity experienced by approximately two-thirds of women who experience HMB with UFs, and it can be life-threatening; mild cases can be managed with iron tablets, while more serious cases require blood transfusions and intravenous iron, increasing healthcare costs[2,17]
- The aim of treatment is to improve HRQoL[18] by reducing or eliminating UF-related symptoms, removing UFs with surgery, or reducing uterine and UF volume prior to surgery (which may also have the benefit of simplifying surgery)
- Management options include pharmacological treatment (non-hormonal and hormonal therapy), surgical management (e.g. hysterectomy or myomectomy), and interventional procedures (e.g. uterine artery embolisation [UAE])[18,19]
    - The complexity of surgery varies, depending on the size, number and location of UFs, patient preferences and desire to preserve fertility and/or the uterus[18]
    - Treatment options change if UFs grow, which may result in more invasive and time-consuming medical, hormonal and surgical interventions for a larger proportion of people with this condition[20]
    - Less invasive and less complex surgeries may be possible if uterine volume and UF size are reduced[21]
- Hormonal therapy includes gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists and ulipristal acetate[18]
    - Injectable GnRH agonists are mainly used for short-term use (<6 months) before surgery and require patients to attend outpatient clinics for administration. If they are given as longer-term therapy (off label) they can

be co-prescribed with hormone replacement therapy (hormonal add-back therapy [ABT]) to reduce menopausal side-effects.
    - Relugolix CT (Ryeqo®; a GnRH antagonist) can be used over the long-term.[22] As it is formulated as a fixed-dose combination with hormonal ABT, it is not suitable for people with UFs who are contraindicated to ABT, are at an elevated risk of estrogen- and progestogen-related side-effects, or prefer not to take ABT
    - Ulipristal acetate is a selective progesterone receptor modulator that is rarely used in clinical practice – following rare side-effects of liver toxicity
- Treatment decisions are tailored according to the individual needs of women. Treatment considerations include patient age, whether there is a desire to preserve fertility and/or the uterus, whether hormonal ABT is appropriate, patient wish to avoid surgery/interventional procedures, size and location of UFs and UF-related symptoms.
- In particular, hormonal ABT may not be appropriate for some patients for reasons including contraindications, elevated risk of side effects associated with hormone replacement therapy (HRT) (e.g. in women who smoke or are obese), personal preference and in those who prefer not to take hormonal treatments for other reasons (e.g. transgender men)
- Current pharmacological treatment options are limited and a high unmet need remains for effective, well tolerated pharmacological treatments that meet the individualised treatment needs of people with UFs. In particular, current options do not address the specific needs of:
    - People requiring short-term full estrogen suppression to reduce UF or uterus size to simplify surgery, for when surgery is delayed or when surgery needs to be avoided (e.g. when UFs are impacting fertility)
    - People requiring flexible dosing options for long-term use, because of a wish to delay or prevent the need for surgery or as a bridge to the menopause
    - People who wish to avoid or delay surgical or interventional procedures and are at higher risk or contraindicated to ABT, or prefer not to take hormone treatments.
- Addressing this unmet need is important in the overall context of the UK Government's prioritisation of menstrual health and gynaecological conditions, as well as the increasing size of waiting lists for gynaecology surgery in the UK[20,23,24]
- Linzagolix (Yselty®) is a new oral, once daily GnRH antagonist and is the first and only GnRH antagonist providing flexible dosing options for short- or long-term use with or without ABT.[25,26] It is being appraised in three subgroups of people with UFs:
    - People having short-term treatment of 6 months or less
    - People having longer-term treatment, with hormone-based therapy
    - People having longer-term treatment, without hormone-based therapy.

B.1.1 Decision problem

This submission focuses on linzagolix (Yselty®) as a treatment for moderate to severe symptoms of UFs in adults of reproductive age, in accordance with the final scope issued by the National Institute for Health and Care Excellence (NICE).

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

A summary of the decision problem is shown in Table 1.

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
Intervention	Linzagolix (with or without hormone-based therapy)	Linzagolix (with or without hormone-based therapy)	Not applicable
Population	People of reproductive age with moderate to severe symptoms associated with UFs	People of reproductive age with moderate to severe symptoms associated with UFs	Not applicable
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • People having short-term treatment of 6 months or less • People having longer-term treatment, with hormone-based therapy • People having longer-term treatment, without hormone-based therapy	• 1: People having short-term treatment of 6 months or less • 2: People having longer-term treatment, with hormone-based therapy • 3: People having longer-term treatment, without hormone-based therapy	Not applicable
Comparator(s)	GnRH agonists (off-label for some GnRH agonists) Relugolix-estradiol-norethisterone acetate Where hormone-based therapy is not suitable: established clinical management without linzagolix	GnRH agonists (off-label for some GnRH agonists) Relugolix CT (relugolix-estradiol-norethisterone acetate) Where hormone-based therapy is not suitable: established clinical management without linzagolix (NSAIDs and iron supplements)	The company considers NSAIDs and iron supplements to be established clinical management for patients who cannot receive hormone-based therapy, based on guidelines and discussion with clinical experts
Outcomes	The outcome measures to be considered include: • change in MBL volume • time to MBL response • pain • UF volume • haemoglobin levels	• Change in MBL volume • Time to MBL response • Pain • UF volume • Haemoglobin levels	Rates and route of surgery, impact on fertility, or pelvic organ prolapse were not specified endpoints in PRIMROSE 1 and PRIMROSE 2

	• change in BMD • rates and route of surgery • impact on fertility and pregnancy and teratogenic effects • mortality • AEs of treatment, including but not limited to vasomotor symptoms, incontinence and pelvic organ prolapse • HRQoL	• Change in BMD • Impact on pregnancy and teratogenic effects • Mortality • AEs of treatment, including but not limited to vasomotor symptoms and incontinence • HRQoL	
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. The availability and cost of biosimilar and generic products should be taken into account	• The most suitable type of economic evaluation varies between subgroups • For people having short-term treatment of 6 months or less and people having longer-term treatment with hormone-based therapy, where relugolix CT is the primary comparator of interest, cost-comparison methodology is used. This is based on population overlap between linzagolix and relugolix CT, findings from an indirect treatment comparison, clinical expert opinion, and guidance from NICE at the decision problem stage • For people having longer-term treatment without hormone-based therapy, where existing treatment options are limited, cost-effectiveness analysis is used, and expressed in terms of incremental cost per quality-adjusted life year	The blended approach to addressing the decision problem (an STA with cost-comparison methodology for a portion of the marketing authorisation population) was suggested by NICE and explored at the decision problem stage, and was considered appropriate by the company

Abbreviations: BMD, bone mineral density; CT, combination therapy; GnRH, gonadotropin-releasing hormone; HRQoL, health-related quality of life; MBL, menstrual blood loss; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NSAIDs, non-steroidal anti-inflammatory drugs; STA, single technology appraisal; UF, uterine fibroids

B.1.2 Description of the technology being appraised

A description of linzagolix is presented in Table 2 . The Summary of product characteristics (SmPC) and the UK Public Assessment Report (PAR) are provided in Appendix C.

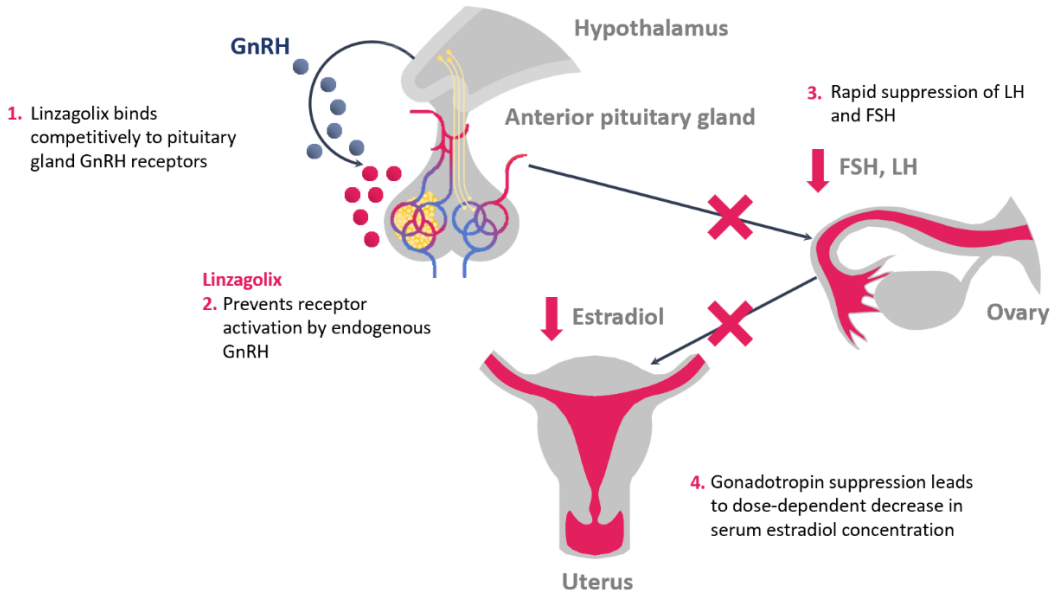
Table 2: Technology being appraised

UK approved name and brand name	Linzagolix (Yselty®)
Mechanism of action	Linzagolix is a selective, non-peptide small molecule GnRH receptor antagonist, that inhibits endogenous GnRH signalling by binding competitively to GnRH receptors in the pituitary gland. The onset of action is immediate and leads to dose-dependent suppression of serum luteinising hormone and follicle-stimulating hormone, which then leads to a dose-dependent reduction in serum estradiol (E2) and progesterone, without the initial stimulation (flare effect) of the receptors that occurs with GnRH agonists (Figure 1).[25–27] The mechanism of action of linzagolix allows for flexible dosing options (100 mg or 200 mg with or without the use of hormonal ABT; estradiol 1 mg/norethisterone acetate 0.5 mg) to support the individualised treatment needs of women with UF: • Partial suppression of E2 (≥20 and <60 pg/mL) with linzagolix 100 mg and linzagolix 100 mg + ABT reduces E2 into an optimal zone, controlling uterine fibroid symptoms while minimising BMD loss, suitable for short- (<6 months) or long-term (>6 months) treatment • Full suppression of E2 (<20 pg/mL) with linzagolix 200 mg requires the addition of ABT (linzagolix 200 mg + ABT) to return to an optimal zone (≥20 and <60 pg/mL) to control UF symptoms while minimising BMD loss, suitable for short- (<6 months) or long-term (>6 months) treatment • Full suppression of E2 (<20 pg/mL) with linzagolix 200 mg without ABT for short-term treatment (<6 months) when reduction of uterine and fibroid volume is desired e.g. prior to surgery
Marketing authorisation/CE mark status	Linzagolix received UK marketing authorisation on 14th June 2022
Indications and any restriction(s) as described in the SmPC	Treatment of moderate to severe symptoms of UFs in adult women of reproductive age
Method of administration and dosage	Linzagolix is administered as an oral tablet (100 mg or 200 mg), once daily with or without food. The 200 mg dose can be taken as either 1 x 200 mg tablet or 2 x 100 mg tablets. The recommended dose of linzagolix is: • 100 mg, or if needed, 200 mg once daily with concomitant hormonal ABT (estradiol 1 mg and norethisterone acetate 0.5 mg tablet once daily) • 100 mg once daily for women in whom ABT therapy is not recommended, or who prefer to avoid hormonal therapy • 200 mg once daily, for short-term use (<6 months) in clinical situations when reduction of uterine and fibroid volume is desired. Fibroid size may increase when the treatment is stopped. Due to the risk of BMD decrease with prolonged use,

	the 200 mg dose without concomitant ABT should not be prescribed for longer than 6 months
Additional tests or investigations	• In patients with risk factors for osteoporosis or bone loss, a DXA scan is recommended before starting linzagolix treatment • A DXA scan is recommended after 1-year treatment for all women, and there is a need for continued BMD monitoring thereafter, depending on the prescribed dose of linzagolix • BMD assessment is recommended annually (linzagolix 100 mg) or at a frequency determined by the treating physician based on the woman's individual risk and previous BMD assessment (linzagolix 100 mg with concomitant ABT linzagolix 200 mg with concomitant ABT)
List price and average cost of a course of treatment	Linzagolix list price: • Cost per 28-pack of 100 mg tablets: [redacted] • Cost per 28-pack of 200 mg tablets: [redacted] Hormonal ABT (estradiol/norethisterone) list price: • Cost per 84-pack of 1 mg/0.5 mg tablets: £13.20 (£15.84 with VAT) There is no set time duration (specified course) for this treatment, except for short-term use (<6 months) in clinical situations when reduction of uterine and fibroid volume is desired
Patient access scheme (if applicable)	A confidential simple discount PAS of [redacted] has been submitted to NHS England for linzagolix Linzagolix PAS price: • Cost per 28-pack of 100 mg tablets: [redacted] • Cost per 28-pack of 200 mg tablets: [redacted]

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; E2, estradiol; GnRH, gonadotropin-releasing hormone; PAS, patient access scheme; UF, uterine fibroids

Figure 1: Linzagolix mechanism of action



Abbreviations: GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone
Source: Adapted from Donnez et al. (2021)[28]

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Description

UFs – also known as myomas or leiomyomas – are non-cancerous smooth muscle tumours of the uterus and are the most common type of non-cancerous tumour in women.[1,2] Fibroids are common, with around two in three women developing at least one UF at some point in their life.[29]

Growing in clusters or alone, UFs vary in size from a few millimetres to larger growths of ≥20 cm diameter.[2] The exact aetiology of UFs is unknown, however, they are estrogen- and progesterone-dependent and as such, develop during a woman's reproductive years (age range 16 to 50 years), average age of diagnosis is approximately 40 years.[2,3] UFs are rare before puberty and the risk of developing a UF declines after menopause.[6]

B.1.3.1.2 Diagnosis and classification

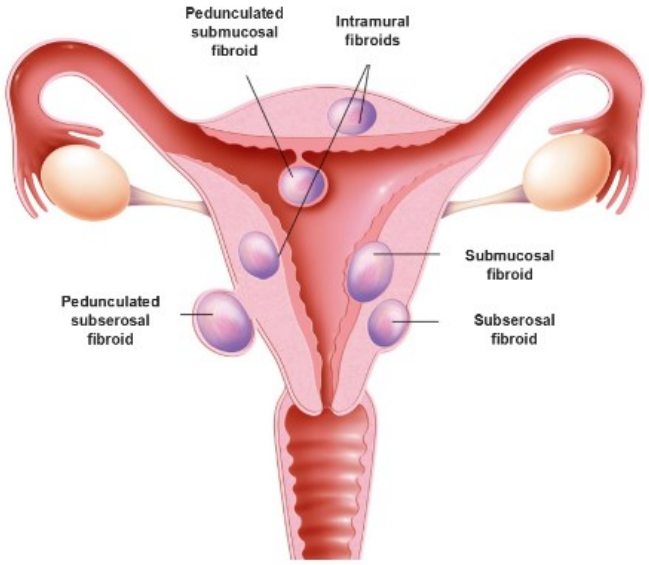
While UFs are common, many women do not know they have them as they are too small to cause symptoms and are often incidentally discovered during routine (vaginal) examinations and tests for other problems.[30,31] In symptomatic women, diagnosis of UFs is most often confirmed by ultrasound scan (abdominal or transvaginal), hysteroscopy or laparoscopy in secondary care.[31] In some cases, a biopsy may be performed during hysteroscopy or laparoscopy for closer investigation.[31]

There are three main types of UFs (Figure 2), classified depending on their location in the uterus[29,32]:

1. Intramural fibroids – develop within the uterine wall and are the most common type.
2. Subserosal fibroids – develop on the outside of the uterus into the pelvis and can become very large.
3. Submucosal fibroids – develop under the inner lining of the uterus protruding into the uterine cavity.

Subserosal and submucosal UFs can also be connected to the uterus by a stalk of tissue. These are known as pedunculated fibroids.

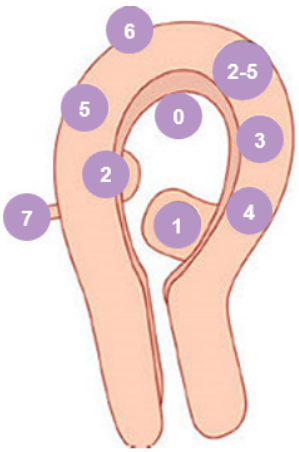
Figure 2: Types of uterine fibroids



Source: NHS: Fibroids[29]

Many UFs have more than one localisation in the uterus compartments. The number, size, and position of UFs may change the treatment options. The International Federation of Gynaecology and Obstetrics (FIGO) classification system for UFs can help clinicians to evaluate the optimal treatment option(s) for women (Figure 3).[33]

Figure 3: FIGO classification system for uterine fibroids



Type	Description
0	Pedunculated intracavitary
1	<50% intramural
2	≥50% intramural
3	Contacts endometrium 100% intramural
4	Intramural
5	Subserosal ≥50% intramural
6	Subserosal <50% intramural
7	Subserosal pedunculated
8	Other

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics
Source: Adapted from Munro et al. (2011)[33]

B.1.3.1.3 Epidemiology

The true incidence and prevalence of UFs are unknown, as the condition can be asymptomatic and women may remain undiagnosed.[9,31] However, UFs are common, with around 2 in 3 women developing at least one UF at some point in their life.[29] The UK incidence of UFs has been estimated at 5.8 per 1,000 woman-years among women aged 15–54 years.[34] In a large online study of 21,479 women across eight countries (including 2,500 from the UK), the self-reported prevalence of UFs in the UK was 4.5% for those aged 15 to 49 years, and 9.4% in those aged 40 to 49 years.[3] Despite being common, the life cycle of UFs is poorly understood with their growth being highly variable and unpredictable, and ranging from 18% to 120% per year.[35]

Major risk factors for UFs include age up to menopause – with average age at diagnosis being around 40 years[3] – and Black race. Black women have a two–threefold increased risk of UFs.[4–6] Moreover, Black women are more likely to have multiple and larger fibroids five to six years earlier and have higher rates of hospitalisations and surgical intervention compared to White women.[17,36] Other risk factors for UFs include family history of UFs, obesity, nulliparity (women who have not given birth to a child), early menarche (first menstrual period), time since last birth ≥5 years, hypertension, exposure to food additives and use of soybean milk.[9,6,19]

B.1.3.2 Burden of uterine fibroids

B.1.3.2.1 Clinical burden

Approximately 25% to 30% of women with UFs experience symptoms; the type and severity of symptoms depends on the size, location and number of UFs.[7,8] For example, as submucosal fibroids develop under the inner lining of the uterus, they can crowd the uterine space leading to HMB and fertility problems. Disease burden is higher for Black women, who typically present with more severe symptoms compared with their White counterparts.[10] In a large online study, 18% (95% CI: 16%, 20%) of the women with diagnosed UF reported a moderate negative impact of their symptoms in the last 12 months on their daily life and 15%

(95% CI: 13%, 17%) reported a severe negative impact.[3] In an online cross-sectional survey of women in the US with UFs (n=955), at least 43% of respondents rated the most common symptoms experienced in the past 4 weeks, as being 'moderate' or 'severe', and at least 16% of the women rated the four most frequent symptoms (lower back pain, fatigue/ weariness/anaemia, anxiety/stress, and bloating) as 'severe'.[38] Responses from market research (n=50 UK gynaecologists) indicates that [redacted] of women diagnosed with UF have moderate symptoms and [redacted] have severe symptoms.[39]

Approximately one-third of women with UFs have chronic HMB, the most common symptom of UFs.[9] Other menstrual bleeding-related symptoms include prolonged menstrual bleeding, spotting between menstrual cycles, frequent menstrual cycles, and menstrual pain or cramping.

IDA is a common comorbidity experienced by approximately two-thirds of women who experience HMB with UFs.[18,17] It causes weakness, severe fatigue, poor concentration and reduced work productivity and can be life-threatening in some situations.[2,17,40] Furthermore, even mild pre-operative anaemia is associated with increased morbidity and mortality following surgery.[41] Some cases of IDA can be treated with oral iron tablets, however these do not manage the underlying cause of the anaemia and are associated with gastrointestinal side-effects including nausea, flatulence, abdominal pain, diarrhoea and constipation, which may decrease compliance and long-term efficacy.[42,43] More complex cases of IDA require more expensive therapies such as blood transfusions and intravenous iron, requiring hospital visits. Non-elective expenditure in England due to IDA increased by 21% from £35.1 million in 2012/13 to £42.4 million in 2017/18.[44]

Other UF symptoms include pain (e.g. pelvic pain, menstrual pain and discomfort, or pain during sexual intercourse). Larger fibroids can lead to 'bulk symptoms' due to the impact of the fibroid on the uterus causing pelvic pressure, bloating, leg or back pain, increased urinary frequency, and constipation.[3,8,19]

In addition to the symptoms, UFs can impair fertility depending on their location; up to 10% of infertility cases are associated with UFs, and UFs are the only cause of infertility in 1% to 3% of women.[9] UFs are also associated with pregnancy-related complications occurring in 10% to 40% of pregnancies in women with UFs, including miscarriage (which is up to two–fold higher in women with symptomatic UFs), pre-term and caesarean delivery.[45]

B.1.3.2.2 Patient burden

The substantial symptom burden of UFs causes significant morbidity and distress for women, negatively impacting their daily lives and impairing their physical activities, social activities, intimate relationships, work productivity and emotional well-being.[3,9,10]

Several published studies have reported the patient burden of UFs.[3,46]

In a large cross-sectional online survey of women (n=21,000) experiencing uterine bleeding and pain across eight countries (including 2,500 women from the UK), 1,533 respondents had a diagnosis of UFs and reported mild to severe impact of symptoms; of these, 43% stated that their sexual life was negatively affected, 28% reported impaired performance at work, 27% said UFs had negatively affected relationships and family and 26% that it had impaired their ability to carry out activities of daily living.[3]

Another internet-based survey of women in five European countries (France, Germany, Netherlands, Spain, and Switzerland) with HMB (n=330) reported HMB to have a major negative impact on sexual life (62%), followed by physical activities (53%), productivity at

work (39%), sleep and ability to travel (both 35%), productivity at home (31%), relationship with spouse/and or children (28%) and social life (23%).[46]

In addition to the direct impact of symptoms, the emotional and psychological burden of UFs is high. Women experience concerns about their health, body image, sense of femininity and sexuality, feelings of sadness, hopelessness and 'not being in control of their lives making it difficult for women to maintain their emotional well-being'.[9,11]

In a cross-sectional survey of women with UFs in the US (n=968), most women reported fears due to their UF diagnosis including fears around the growth of their UFs (79%), future health complications (63%), and needing a hysterectomy (55%).[11] In the same survey, 19% of women reported feeling sad, discouraged, hopeless, 37% felt conscious about the size and appearance of their stomach, 34% were concerned about soiling clothes or bedding, 20% felt not in control of life and 21% reported that their UFs negatively affected their sense of femininity or sexuality, all or most of the time.[11]

Example quotes from women taking part in an open-ended interview study in women in the US with HMB and UFs (n=30) further highlight the negative impacts of UFs symptoms on women's daily living and emotional well-being.[8] (Table 3).

Surgery also imposes a burden on people with UFs, which rises as the complexity of surgery increases. Treatment options change if UFs grow and uterine size increases, which may result in more invasive and time-consuming surgical interventions for a larger proportion of people with this condition.[20] If UF growth is not suppressed while waiting for surgery, more severe HMB symptoms can cause higher rates of anaemia resulting in emergency hospital admissions.[20] Less invasive and less complex surgeries may be possible if UF volume and UF size is reduced,[21] and these are associated with fewer complications, reducing time spent away from family and work, the emotional burden of surgery, and saving healthcare costs. The mortality risk is reduced with less invasive surgeries; 0.013% for myomectomies (data from Republic of Korea), compared with 0.36% for abdominal hysterectomies (US data).[47]

Table 3: Example quotes regarding the impact of UF symptoms reported by ≥20% of women with HMB

Impact	Example patient quotes
Pain	"It would be like a stabbing pain. like something literally is trying to rip out of me—or it's a sharp, stabbing pain. And it would be crippling." "I feel a lot of pain, a lot of pain…When it comes, I sweat a lot [and] am cold…and it causes too much pain. And the cramps? It feels like I am having a baby! It causes strong contractions for a week."
Excessive bleeding	"No matter how many sanitary towels you put in, when the blood comes out, it drains down to your feet because it pours." ''I used to have clots as big as a jellyfish, where I could just stand up at work, like I said, and they would just fall out.'' "I spent one month and 20 days having nonstop menses". "I sleep every night with that baby diaper on me… I cannot go out because blood falls under my panties, it goes out and spills a lot, you know…Because tampons cannot control it." "I couldn't walk properly at home, so I went to the hospital and they told me that I should go to a blood bank because I was too anaemic for surgery. I turned on the shower, and I saw those large blood clots going down the

	drain and the drain got stuck. So I called my husband, and he called an ambulance, because it seemed that I was fainting."
Bloating	''I didn't want to look pregnant, and would always be asked when is the baby due, because of my uterus and the pressure and the bloated feeling.''
Financial	''I pretty much paid rent with the amount of money I was [spending on] buying for pads and tampons.''
Work/school	"I mean before when I would go into work, I certainly wasn't as efficient. I like to think I'm good at my job. When I'm on my period, it gets in the way of me being able to do my job."
Activities of daily living	"When I'm on my period or when I know I'm going to have my period I have to shift my whole life around. I definitely don't plan any events during my week of hell." ''As it got worse and worse, I just stopped doing things.''
Physical	"Yeah, because of the bleeding, I cannot exercise during my period, because then the flow ends up being heavier, and I practically have to break and change…the time I'm on my period, I'm not doing any exercise, I'm not doing any heavy lifting, I'm not doing any of those things." ''I was really anaemic, so I was just tired all the time. All the time. My hair was falling out a lot, my nails were kind of gross and brittle.'' ''Well, the first day I used to be in bed all the time. I couldn't stand up'' and ''I was just tired all the time. . Just exhausted and worn out.''
Sleep	"But I would have to get up in the middle of the night and change my pad because I messed up my bed...So, my sleep is interrupted, because I'm not sleeping through the whole night, you know, because I got to go change and—change sheets, change bed, you know, all that kind of stuff."
Relationships	"Yes. I would have to say I'm not in a relationship because of my uterine fibroids because I don't care to have sex because it's painful."
Social	"Like if I wanted to go out with family or friends, I wouldn't go, because you would be scared if you would mess up your clothes."
Emotional	"I think the biggest thing is the embarrassment surrounding it. It's really embarrassing to bleed through your clothes in public." "I would get depressed because I couldn't really do anything. I didn't understand what was going on in my body." "I am starting to bleed again, and I am scared!"

Abbreviations: HMB, heavy menstrual bleeding, UFs, uterine fibroids
Sources: Hunsche et al. (2022)[8]; Brito et al. (2014)[48]

B.1.3.2.3 Health-related quality of life burden

The high symptom and psychological burden of UFs cause significant morbidity and distress, negatively impacting women's HRQoL.[8,11,12]

A literature review identifying 40 studies reporting HRQoL, measured by EuroQol-5 Dimensions (EQ-5D), Short Form (SF)-36 and the validated disease-specific Uterine Fibroid Symptom-Quality of Life questionnaire (UFS-QoL), reported significantly lower HRQoL scores across all instruments for women with UFs compared to women without UFs.[49]

In an online cross-sectional survey of women (n=955) with UFs, mean UFS-QoL subscale scores were significantly ($p<0.05$) worse among women with symptoms (HMB, lower back pain, fatigue, bloating and pelvic pain/cramping) compared to women without symptoms.[38]

A community-based survey by Downes et al. across five European countries showed that UF causes impairment in disease-specific HRQoL, generic QoL, and productivity.[16] They

conducted an analysis of women (n=1,756) diagnosed with or experiencing UF-related symptoms in Germany, France, Italy, Spain, and the UK. The impact of UFs on HRQoL was assessed using UFS-QoL and the physical component summary (PCS), and the mental component summary (MCS) scores of SF-12v2 (with higher scores indicating better HRQoL for both UFS-QoL and SF-12v2). Mean UFS-QoL scores across all countries indicated moderate impairment of HRQoL and mean SF-12v2 PCS and MCS scores across all counties indicated considerable impairment of HRQoL in women with UF-related symptoms.[16] The authors concluded that the impairment of generic QoL appeared to be greater than that of other chronic conditions, such as asthma, irritable bowel syndrome, and gastro-oesophageal reflux disease.[16]

Table 4: Mean UFS-QoL, PCS and MCS scores of women with UFs

Measure	Mean range all countries
UFS-QoL, HRQL score, mean range, SD (95% CI)	59.2 ± 27.0 (54.2, 64.2) to 69.7 ± 22.0 (66.5, 73.0)
SF-12, PCS score, mean range, SD (95% CI)	43.8 ± 11.8 (41.6, 46.0) to 49.6 ± 9.0 (48.0, 51.1)
SF-12, MCS score, mean range, SD (95% CI)	38.5 ± 11.1 (36.4, 40.5) to 42.0 ± 9.3 (40.6, 43.4)

Abbreviations: CI, confidence interval; HRQL, health-related quality of life; MCS, mental component summary; PCS, physical component summary; SD, standard deviation; SF-12, Short Form-12; UFs, uterine fibroids; UFS-QoL, Uterine Fibroid Symptom-Quality Of Life Questionnaire
Source: Downes et al. (2010)[8,16]

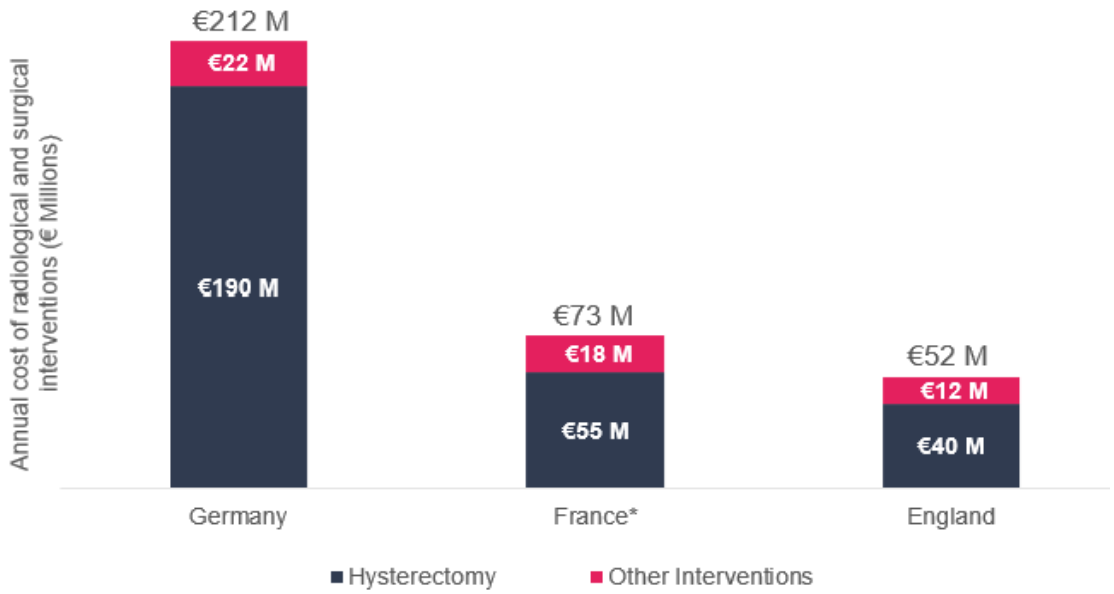
B.1.3.2.4 Economic and societal burden

Direct costs

UFs imposes a substantial financial burden on healthcare systems, primarily driven by surgical and non-surgical procedures to remove or treat UFs.[13–15] In the UK, of the 31,624 hysterectomies performed in England in 2017, 60% were for UFs, with total inpatient cost estimated at £103.5 million.[13] Hysterectomies can cause complications such as blood loss, adhesions, infection, post-operative pain, and damage to the vagina, bladder, ureters and rectum, and are associated with increased mortality.

An earlier cost study of UFs in England, France and Germany reported significant total costs of UFs interventions to payers from hospital admissions.[14] (Figure 4).

Figure 4: Total annual cost to payers from hospital admissions involving surgical or radiologic interventions for uterine fibroids (2009)



*Total cost in France excludes surgeon and anaesthetist fees in the private sector
Abbreviations: M, million
Source: Adapted from Fernandez et al. (2009)[14]

Data from an international systematic literature review (n=26 studies) reported total direct and indirect costs of UFs. Two studies reported total direct costs of $9,473 and $9,319 per patient during the year after UF diagnosis, with excess costs over controls (women without UFs) of $6,076 and $5,427, respectively.[15]

There are also financial implications for women due to the cost of sanitary products, which require frequent (often hourly) changes to address HMB. Period poverty (referring to a lack of access to menstrual products due to financial constraints) is a known issue in the UK for women without UFs. HMB associated with UFs will only exacerbate the financial constraints for some women.

In addition to the financial burden, UFs are associated with a societal burden as UF-related symptoms impact the absenteeism and work productivity of women. In a pooled analysis of women (n=1,756) diagnosed with or experiencing UF-related symptoms in five European countries (including the UK), absenteeism was reported by 33% of employed women with a diagnosis of UFs and overall work productivity was reduced by 36%.[16]

Data from an international systematic literature review (n=26 studies) reported total annual indirect costs of UFs ranging from $2,399 to $15,549, per patient per year, after diagnosis or surgery; with the excess indirect cost ranging from $323 to $4,824 compared with women without UFs.[15]

In a US study of women who had clinically significant symptomatic UFs (n=910) compared to matched women without UFs (n=910), mean 12-month indirect costs for women with UFs were $11,752 versus $8,083 for controls. Differences were statistically significant ($p<0.0001$).[50]

Obstetric complications due to UFs can also result in substantial costs, with 4% to 23% of total direct and indirect costs of UFs in the US (2010) being attributed to obstetric

outcomes.[51] These include surgical management of spontaneous abortions, care of pre-term infants and caesarean sections.

B.1.3.3 NHS Policy and national priority

The unmet needs of women with UFs in England occur within in the wider context of the Department of Health and Social Care's Women's Health Strategy for England (2022) which calls out menstrual health and gynaecological conditions as a key priority.[23,24]

During the call for evidence phase of strategy development, gynaecological conditions were the top topic selected for inclusion in the strategy (63% of respondents) and menstrual health was the fourth most selected topic (47%).[23,24] Researchers heard concerns that women had not been listened to in instances where pain is the main symptom, and women reported being told that heavy and painful periods are 'normal' or that they would 'grow out of them'. They also said they had to speak to doctors on multiple occasions over many months or years before receiving a diagnosis (e.g. for endometriosis). Only 8% of respondents felt that they had access to enough information on gynaecological conditions, such as fibroids.[23] Added to this, access to treatment for women with gynaecological conditions is particularly difficult. In April 2022, gynaecology waiting lists in England had grown the most in percentage terms of all elective specialties, increasing 60% since the start of the COVID pandemic, and representing one of the three highest specialties in terms of volume increase.[20] In England, the number of women waiting for over a year for gynaecological treatment had risen to more than one in 20 on the waiting list as of January 2022 (compared with less than one in a 1,000 women on the waiting list before the COVID pandemic).[20]

In response to these findings, the 10-year strategy sets out plans improving healthcare advice and support for menstrual health, gynaecological conditions, and urogynaecological conditions, as well as improving awareness and commissioning research and evidence collection.[23] As part of these plans, NHS England will roll out community diagnostic centres across the country to improve diagnosis and patient experience within gynaecology services, and update evidence-based guidelines and standardise clinical practice.[23] The aim is to optimise management and help women to make more informed choices around treatment decisions. Improving the support for women with UFs and increasing treatment options for UFs therefore fits well within NHS England's strategy framework.

B.1.3.4 Current treatment pathway and proposed linzagolix positioning

The aim of treatment is to improve HRQoL[18] by reducing or eliminating UF-related symptoms, removing UFs with surgery, or reducing uterine and UF volume prior to surgery (which may also have the benefit of simplifying surgery). Treatment options should take the patient's preferences into consideration.[18]

Management options for UFs treatment with non-hormonal and hormonal pharmacological therapies, surgical management (e.g. hysterectomy or myomectomy), and interventional procedures (e.g. UAE, second-generation endometrial ablation [EA], magnetic resonance-guided focused ultrasound [MRgFUS]).[19,18] The complexity of surgery varies, depending on the size of UFs, number and location of UFs, patient preferences and desire to preserve fertility and/or the uterus.[18] Treatment options change if UFs grow, which may result in more invasive and time-consuming medical, hormonal and surgical interventions for a larger proportion of people with this condition.[20]

Hormonal therapy includes GnRH agonists, GnRH antagonists and ulipristal acetate.[18] Injectable GnRH agonists are mainly used for short-term use (<6 months) before

hysterectomy or myomectomy if UFs are causing an enlarged or distorted uterus.[18] They usually require patients to attend outpatient clinics for administration. If they are given as longer-term therapy (off label) they may be co-prescribed with hormone replacement therapy (i.e. ABT) to reduce menopausal side-effects (such as hot flushes, headaches, insomnia, mood changes, depression and anxiety, vaginal dryness and irritation, weight changes, and decreased libido) and to minimise BMD loss.[19]

The National Institute for Health and Care Excellence (NICE) has recently recommended relugolix CT (Ryeqo®) (40 mg relugolix, 1 mg estradiol, 0.5 mg norethisterone acetate), a GnRH antagonist for the treatment of moderate to severe UFs in adult women of reproductive age.[22] Relugolix CT can be used over the long-term, but as it is formulated as a fixed-dose combination with ABT, it is not suitable for people with UFs who are at elevated risk of side effects associated with hormone HRT or who are contraindicated to, or prefer not to take ABT.

Ulipristal acetate is a selective progesterone receptor modulator that is rarely used in clinical practice following reports of rare side-effects of liver toxicity.[18] It was not considered to be a relevant comparator in the relugolix CT TA due to its low usage in clinical practice.[22]

Treatment decisions are guided by clinician assessment and tailored to the individual needs of women (e.g. women who desire to preserve fertility, who have contraindications to hormonal ABT, are at increased risk of estrogen- and progestogen-related side-effects or prefer not take hormonal ABT, or who wish to avoid surgery), together with the clinical scenario (e.g. patient age, number, size and location of UFs, severity of symptoms and contraindications to medications, such as ABT).

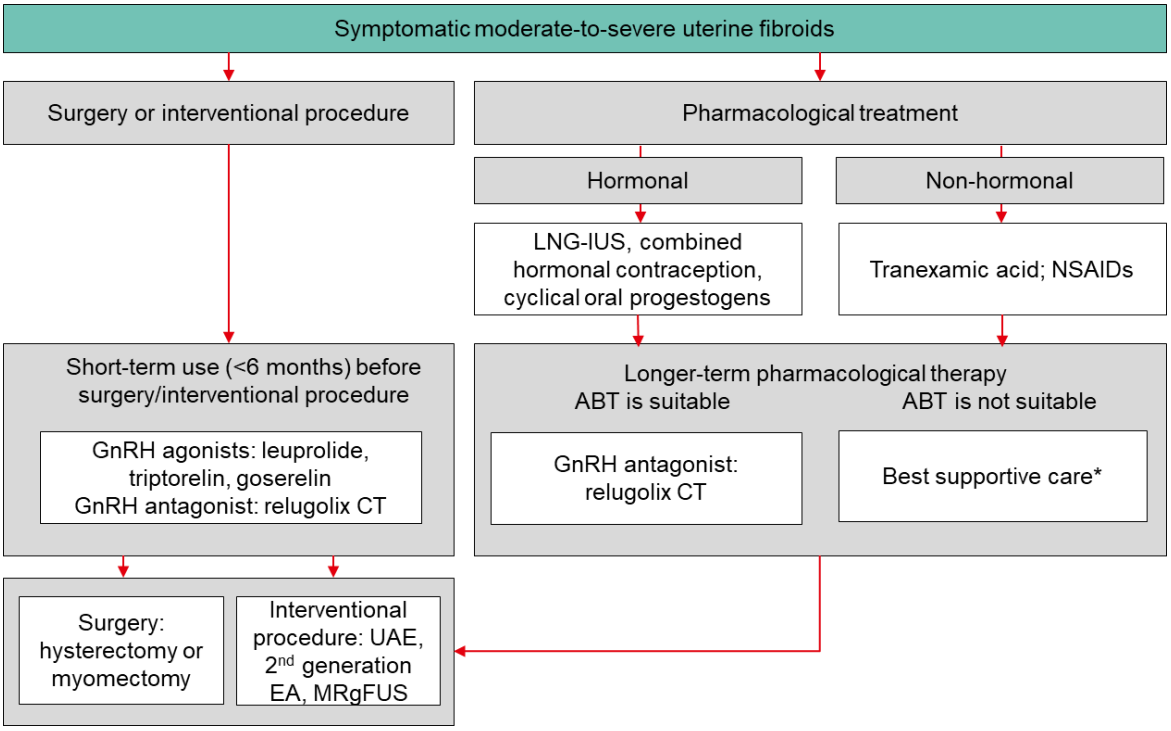
Current pharmacological treatment options therefore vary according to whether patients are likely to require short- or long-term therapy (either before or instead of surgery) and whether they are able to receive ABT. These populations align with those specified in the decision problem for this appraisal:

- Relugolix CT or GnRH agonists for people with UFs requiring short-term treatment for 6 months or less (prior to surgery, in the case of GnRH agonists, which are only licensed pre-operatively)
- Relugolix CT for people with UFs requiring long-term treatment who are able and willing to take hormonal ABT
- Options are limited for people with UFs who require long-term treatment and are unable or prefer not to take ABT.

B.1.3.4.1 Current treatment guidelines

The most relevant guideline for the treatment of UFs in England and Wales is NICE Guideline 88 (NG88) HMB: assessment and management, published in 2018.[18] Table 5outlines the current treatment pathway in England and Wales based on these guidelines and the NICE Technology Appraisal (TA) for relugolix CT in UFs (TA832).[22] Table 5 provides an overview of the treatment for UFs based on the NICE Guideline 88.

Figure 5: Current treatment pathway in England and Wales for moderate to severe based on NG88 and TA832



*Best supportive care includes NSAIDs for pain management and iron supplements for blood loss
Abbreviations: ABT, add-back therapy; CT, combination therapy; EA, endometrial ablation; GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; MRgFUS, magnetic resonance-guided focused ultrasound; NSAIDs, non-steroidal anti-inflammatory drugs; UAE, uterine artery embolisation

Table 5: Treatment of fibroids (NG88)

Treatments for women with no identified pathology, UFs less than 3 cm in diameter, or suspected or diagnosed adenomyosis	Treatments for women with UFs of 3 cm or more in diameter
• Consider an LNG-IUS as the first treatment in women with: o no identified pathology, or o UFs <3 cm in diameter, which are not causing distortion of the uterine cavity, or o suspected or diagnosed adenomyosis • If an LNG-IUS is declined or is not suitable consider: o non-hormonal: tranexamic acid, NSAIDS; hormonal: LNG-IUS, combined hormonal contraception, cyclical oral progestogens • If treatment unsuccessful, or treatment is declined, or symptoms are severe, consider referral to specialist care for alternative treatment options including: o pharmacological options not already tried o surgical options (second-generation endometrial ablation, hysterectomy)	• If pharmacological treatment is needed while investigations and definitive treatment are being organised, offer tranexamic acid and/or NSAIDs (off-label use for NSAIDs) • Advise women to continue using NSAIDs and/or tranexamic acid for as long as they are found to be beneficial • Take into account the size, location and number of fibroids, and the severity of the symptoms and consider the following treatments: o non-hormonal: tranexamic acid, NSAIDS (off-label use); hormonal: LNG-IUS (off-label use for some), combined hormonal contraception, cyclical oral progestogens, ulipristal acetate o surgical options (myomectomy and hysterectomy) o UAE and second-generation endometrial ablation, with the latter for women who meet the criteria specified in the manufacturers' instructions • Pre-treatment with a GnRH analogue (off-label use for some) before hysterectomy and myomectomy should be considered if UFs are causing an enlarged or distorted uterus o Only consider ulipristal acetate for the intermittent treatment of moderate to severe symptoms of UFs in premenopausal women if surgery and UAE for UFs are not suitable (e.g. because the risks to a woman outweigh the possible benefits), or surgery and UAE for UFs have failed, or the woman declines surgery and UAE for UFs

Abbreviations: GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; NSAIDs, non-steroidal anti-inflammatory drugs; UAE, uterine artery embolisation; UF, uterine fibroid
Source: NG88, HMB: assessment and management[18]

Other NICE TAs and interventional procedure guidance (IPG) for UFs are summarised in Table 6.

TA832 is the most relevant TA to this appraisal, as relugolix CT is the only GnRH antagonist recommended by NICE for the treatment of moderate to severe symptoms of UFs and as such, is the most relevant comparator for linzagolix in this appraisal. The linzagolix treatment pathway is essentially the same as that outlined in the relugolix CT NICE TA, although linzagolix is suitable for a wider patient population as it is not formulated with ABT and can be given without with or without ABT for short- or long-term use. Unlike linzagolix, relugolix

CT is formulated as a fixed-dose combination with ABT and is not suitable for people who have an elevated risk of estrogen- and progestogen-related side-effects, are contraindicated to, or prefer to avoid ABT.

Table 6: Summary of published NICE TAs and IPGs for UFs

Appraisal ID	Year	Intervention	Title
TA832	2022	Relugolix (formulated as a fixed-dose combination with ABT)	Relugolix-estradiol-norethisterone acetate for treating moderate to severe symptoms of uterine fibroids
IPG689	2021	Transcervical ultrasound-guided radiofrequency ablation	Transcervical ultrasound-guided radiofrequency ablation for symptomatic uterine fibroids
IPG704	2021	Hysteroscopic mechanical tissue removal (hysteroscopic morcellation)	Hysteroscopic mechanical tissue removal (hysteroscopic morcellation) for uterine fibroids
IPG657	2019	Ultrasound-guided high-intensity transcutaneous focused ultrasound	Ultrasound-guided high-intensity transcutaneous focused ultrasound for symptomatic uterine fibroids
IPG413	2011	Magnetic resonance image-guided transcutaneous focused ultrasound	Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids
IPG367	2010	Uterine artery embolisation	Uterine artery embolisation for fibroids
TA78	2004	Fluid-filled thermal balloon and microwave endometrial ablation	Fluid-filled thermal balloon and microwave endometrial ablation techniques for heavy menstrual bleeding
IPG30	2003	Magnetic resonance image-guided percutaneous laser ablation	Magnetic resonance image-guided percutaneous laser ablation of uterine fibroids

Abbreviations: ABT, add-back therapy; ID, identification; IPG, interventional procedure guidance; TA, technology appraisal; UF, uterine fibroid

B.1.3.4.2 First-line and second-line pharmacological therapy

For women who prefer to avoid surgery or interventional procedures (approximately 80% of women), non-hormonal therapies (tranexamic acid and non-steroidal anti-inflammatories ([NSAIDs]) or hormonal contraceptives (levonorgestrel-releasing intrauterine system [LNG-IUS] the Mirena® coil, combined oral contraceptives [COCs] and oral progestogen [OPs]) are first-line treatment options. For women who wish to conceive, tranexamic acid and NSAIDs are the only available pharmacological treatment options. However, tranexamic acid can only be used short-term during an acute bleeding period, and NSAIDs treat only pain symptoms and not bleeding. These options do not have a label in UFs.

Responses from market research (n=50 UK gynaecologists, conducted in 2022) confirm that the UK gynaecologists surveyed use LNG-IUS ([redacted]), tranexamic acid ([redacted]), NSAIDs/other

painkillers ([redacted]), COCs ([redacted]) and OPs ([redacted]) [redacted] as a first-line treatment for patients undergoing long-term pharmacological treatment.[39] Recurrence rate of symptoms following use of these treatments is estimated at around [redacted].[39]

For women with UFs progressing to second-line pharmacological therapy, the only available treatment options are GnRH analogues (and ulipristal acetate in restricted cases; see below). Injectable GnRH agonists (e.g. leuprorelin, triptorelin and goserelin) are used second-line but can only be used in the short-term for UF-symptom relief (<6 months) or to reduce uterine and fibroid volume before surgery. If they are given as longer-term therapy (off label) they can be co-prescribed with ABT, e.g. estradiol and norethisterone acetate, to reduce menopausal symptoms and minimise BMD loss.

NICE recently recommended a new-generation oral GnRH antagonist (relugolix CT) in a combined tablet with ABT, for treatment of moderate to severe UFs. Relugolix CT provides an alternative treatment option to injectable GnRH agonists with no restriction on treatment duration. However, this option is not suitable for women who have an elevated risk of estrogen- and progestogen-related side-effects, are contraindicated to, or prefer to avoid ABT.

Ulipristal acetate (UPA) is restricted to intermittent treatment of moderate to severe symptoms in premenopausal women if surgery and UAE are unsuitable, declined or unsuccessful. However, it is rarely used in practice given the potential risks of liver damage and the level of liver function monitoring needed. Due to the rare use of UPA in clinical practice it was not included in the relugolix CT manufacturer's submission as a comparator.

As a result, there are a lack of long-term effective and well tolerated pharmacological treatment options that are suitable for all women.

B.1.3.4.3 Surgical and interventional procedures

There are various options for women who wish to progress straight to surgery/interventional procedures, or for women in whom pharmacological therapy has failed, is not tolerated (i.e. have had side effects previously) or is contraindicated (e.g. have an allergy to the drug or a current or previous condition that prevents them taking a drug). Laparoscopic or open/abdominal hysterectomy (removal of the uterus) for women with no desire to maintain fertility, or myomectomy (removal of UFs without removing the uterus) which preserves fertility, are the conventional surgical options, with UFs being the main indication for hysterectomy.[19,30]

GnRH analogues can be used in the short-term (<6 months) to reduce uterine and UF volume prior to surgery. Reducing UF or uterus size may enable less invasive surgery, such that laparoscopic surgery or a vaginal procedure may be performed rather than a trans-abdominal procedure.[52] Surgery may be technically easier with reduced blood loss and lower rates of vertical abdominal incisions at surgery.[52]

Interventional procedures such as, UAE and second-generation EA are an alternative to surgery for women who meet the criteria.[30] Gynaecologists surveyed in the UK in 2022 (n=50) reported that on average, the recurrence rate of symptoms following myomectomy was [redacted] and following UAE was [redacted].[39]

B.1.3.4.4 Limitations of current treatments

Current treatments are associated with limitations and are not suitable for all women with UFs (Table 7). In particular, GnRH agonists have to be given by injection with the associated

resourcing needs, costs and inconvenience associated with clinic visits for injections. While relugolix CT is taken orally, it is formulated as fixed-dose combination with ABT so is unsuitable for people who have contraindications or prefer not to take ABT.

Table 7: Current limitations of treatments included in the linzagolix scope

Treatment	Limitations	Potential impact on fertility/pregnancy
NSAIDs	• Off-label • May relieve pain but do not address HMB or other symptoms of UF • Should be avoided in women with gastric ulcers or renal disease	• None
Tranexamic acid	• Off-label • Administered with care in women taking oral contraceptives due to risk of thrombosis • Contraindicated in women who had a thromboembolic event/family history • Contraindicated in women with gastric ulcers or renal disease	• None
GnRH agonist	• Exacerbate bleeding symptoms post administration due to initial 'flare effect' • Route of administration – injections (time constraints for patients, potential pain at injection site, administrative resource use and costs for NHS) • Short-term use only (<6 months) • Fibroid re-growth on cessation of treatment • Menopausal adverse events (hot flushes, BMD loss)	• Can take up to 3 months to restore menstruation on cessation of treatment
GnRH antagonist (relugolix CT)	• Formulated as a fixed-dose combination with ABT, as a result not suitable for women who have an elevated risk of estrogen- and progestogen-related side-effects, are contraindicated to, or prefer to avoid ABT • May reduce the ability to recognise the occurrence of	• After at least one month, inhibits ovulation

	pregnancy in a timely manner • Menopausal adverse events (hot flushes, BMD loss) • No significant impact on reduction of fibroid volume	
Hysterectomy	• Requires hospitalisation, lengthy recovery (~6 weeks) and costly to NHS • Surgical and post-surgical morbidity (blood loss, adhesions, tissue granulation, infection, post-operative pain, incontinence, constipation, sexual dysfunction, depression, and damage to the vagina, bladder, ureters, and rectum) • Early menopause • Increased mortality rate	• Permanent loss of fertility
Myomectomy	• Risk of UF recurrence and need for reintervention • Surgical and post-surgical morbidity (injury to bladder, bowel, and blood vessels, post-operative pain, infection, urinary complications, post-operative adhesions)	• Preserves fertility
UAE	• Morbidity (increased pain and HMB) • Risk of early menopause • Risk of reintervention	• Not generally indicated if maintenance of fertility is required
Second-generation endometrial ablation	• Post-surgical morbidity (infection, lower tract thermal injury, uterine trauma, distention fluid overload) • Risk of reintervention	• Not indicated if maintenance of fertility is required (can result in pregnancy complications e.g. premature birth)

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; GnRH, gonadotropin-releasing hormone; HMB, heavy menstrual bleeding; NHS, National Health Service; NSAIDs, non-steroidal anti-inflammatory drugs; UAE, uterine artery embolisation; UF, uterine fibroid

B.1.3.4.5 Unmet need

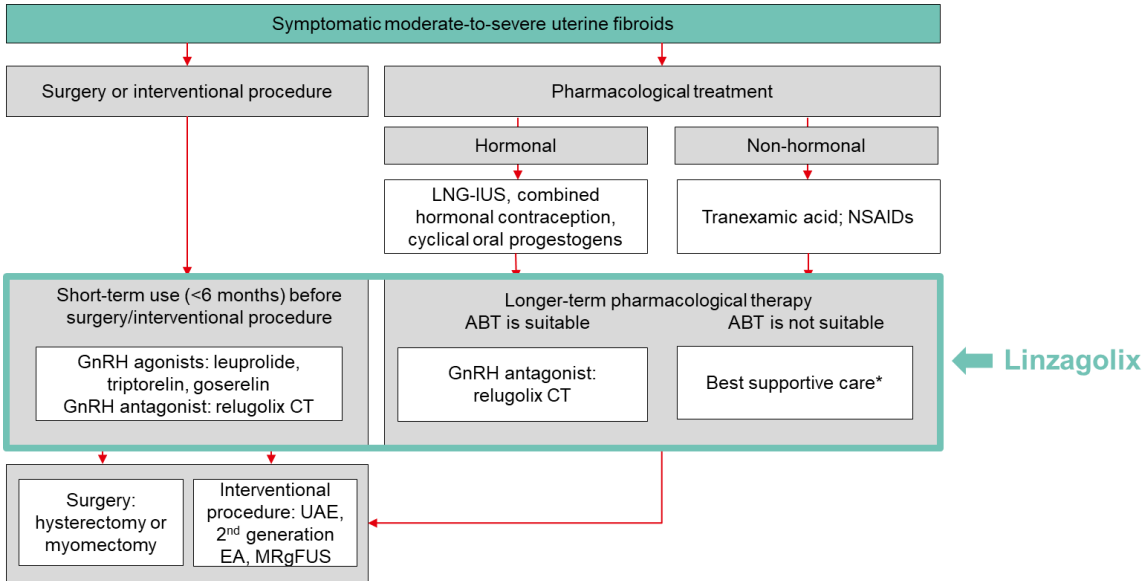
Given the limitations of existing treatment options, for people with UFs who wish to avoid surgery or interventional procedures, there remains a high unmet need for licensed safe and well tolerated pharmacological treatment options that are easy to administer and provide rapid relief of HMB and other UF-related symptoms, thereby improving HRQoL. There is a specific unmet need for treatments that reduce uterine and UF volume, can be used short- or long-term (not time restricted) and offer flexible dosing options with or without ABT that

would enable clinicians to tailor treatment to the individualised needs of women with UFs. A treatment option without ABT would fulfil an unmet need for people with moderate to severe UFs who 1) prefer not to take hormonal therapy; 2) are contraindicated to ABT — obesity, hypertension, and dyslipidaemia are ABT contraindications associated with higher risks of thrombosis, stroke and cardiac events, which disproportionately affect Black women, and 3) women with an elevated risk of estrogen- and progestogen-related side-effects. By avoiding surgery, a new effective pharmacological option would also meet a desire to preserve the uterus and preserve fertility.

B.1.3.4.6 Proposed place of linzagolix in the current treatment pathway

Linzagolix is a new oral, once daily GnRH antagonist. It is the first and only GnRH antagonist that provides flexible dosing options for use with or without ABT for short- (<6 months) or long-term use (>6 months) and provides an alternative treatment option to injectable GnRH agonists and the GnRH antagonist, relugolix CT. The proposed place of linzagolix in the current treatment pathway is provided in Figure 6.

Figure 6: Place of linzagolix in the current treatment pathway



*Best supportive care includes NSAIDs for pain management and iron supplements for blood loss
Abbreviations: ABT, add-back therapy; CT, combination therapy; EA, endometrial ablation; GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; MRgFUS, magnetic resonance-guided focused ultrasound; NSAIDs, non-steroidal anti-inflammatory drugs; UAE, uterine artery embolisation

B.1.4 Equality considerations

Recommending linzagolix would adequately address equality concerns that were highlighted in the relugolix CT NICE TA:

1. Should be available to everyone with UFs who is eligible; this may include people who are trans or non-binary (although no clinical data are available in this population).
2. Black women are two or three times more likely to develop UFs than White women and may be more opposed to surgery because of cultural beliefs.

3. The clinical experts highlighted that clinic visits for treatment with GnRH agonists can result in significant financial and time costs – this could be a particular problem for people from lower socioeconomic groups and may increase the 'did not attend' rate at clinics.

4. Clinical experts highlighted the need for a more effective non-surgical treatment option for people not wanting to have a hysterectomy. Patient organisation submission for relugolix CT noted the need for ‘equality of esteem’ with ‘men’s’ conditions. For example, prostatectomies are rare unless there is progressive cancer. But removal of the uterus and other reproductive organs is common and often the only option because of a lack of other treatment choices.

B.2 Clinical effectiveness

SUMMARY

- Results from two Phase 3, multicentre, 52-week, randomised, parallel, double-blind, placebo-controlled trials (PRIMROSE 1 [full analysis set (FAS) N=511] and PRIMROSE 2 [FAS N=501]) demonstrated consistent efficacy of linzagolix (100 mg or 200 mg with or without ABT)[25]
- A pooled analysis of efficacy data (individual patient data) up to Week 24 from PRIMROSE 1 and 2, and a pooled analysis of safety data up to Week 52 (plus a supplemental post-hoc analysis for select BMD assessments up to Week 76) were performed in accordance with Statistical Analysis Plans.[53,54] Pooled efficacy results at Week 24 and safety results up to Week 52 reflected the results of the individual trials (Appendix M)
- In the pooled analysis at Week 24, linzagolix (100 mg or 200 mg) with or without ABT:[55,56]
    - Reduced HMB at Week 24 compared with the placebo group (nominal p≤0·001 for all comparisons). Reductions in HMB were observed within 4 to 8 weeks
    - Reduced the number of days of uterine bleeding, increased in the rates of amenorrhoea, and shortened the time to amenorrhoea compared with placebo
    - Provided improvements in Hb levels in patients who were anaemic (Hb <12g/dL) at baseline (nominal p≤0.002 versus placebo)
- Improvements versus placebo also occurred in UF-related pain scores, and in HRQoL assessed using the UFS-QoL symptom severity and HRQL total scores[55,56]
- Linzagolix 200 mg without ABT resulted in substantial and clinically meaningful mean reductions in fibroid volumes (48% reduction) and uterine volumes (39% reduction) at Week 24 (nominal p<0.001 versus placebo)[55,56]
- In the pooled analysis, linzagolix was safe and well tolerated up to Week 52, compatible with long-term treatment[55,56]
- Incidence of any treatment-emergent adverse event (TEAE) was slightly higher across the linzagolix treatment groups compared to the placebo group at Week 24. Most TEAEs were mild or moderate in severity. Hot flushes were the most common TEAE (14.6% overall), followed by headache (7.7% overall) and anaemia (6.0% overall)
- Overall fewer TEAEs were reported from Week 24 up to Week 52 than from baseline up to Week 24, despite the fact that most patients were on active therapy after Week 24. Similarly, incidence of severe TEAEs and serious adverse events (SAEs) up to Week 24 was low, and lower from Week 24 up to Week 52. Incidence of TEAEs leading to permanent treatment discontinuation was low up to Week 24, and incidence was lower from Week 24 up to Week 52[55,56]
- Small changes in BMD were observed in the lumbar spine, femoral neck, and total hip at Week 24 and Week 52[55,56]
    - Reductions in BMD were most prominent in the spine, which is known to be most sensitive to BMD change in the context of E2 reductions
    - At Week 76 (off treatment) a trend to reversibility of BMD loss was seen, with recovery of BMD loss lower in patients who did not receive ABT
    - The results from the long-term, follow-up trial, PRIMROSE 3, indicate that there may be no long-term consequences on BMD following linzagolix treatment[57]

- The pooled analysis results at Week 24, demonstrate the robust efficacy of linzagolix, the only GnRH antagonist providing flexible dosing options (100 mg or 200 mg with or without ABT), to meet the individualised treatment needs of people with moderate to severe symptoms of UFs

B.2.1 Identification and selection of relevant trials

A systematic literature review (SLR) was conducted to identify randomised clinical trials (RCTs) for linzagolix and comparator treatments for the management of symptomatic uterine fibroids (UFs). Full details of the methodology and results of the SLR are provided in Appendix D.1.

B.2.2 List of clinical effectiveness evidence

The SLR identified six publications relating to two Phase 3, placebo-controlled trials (PRIMROSE 1 and PRIMROSE 2; see Table 8 for details) that provide evidence on the efficacy and safety of linzagolix at full estradiol (E2) suppression (200 mg) and partial E2 suppression (100 mg) doses with or without hormonal ABT; 1 mg E2 and 0.5 mg norethisterone acetate [NETA]) for the treatment of symptomatic UFs.[25]

Unpublished data were also identified for PRIMROSE 3, a long-term (up to 24 months) follow-up of patients completing PRIMROSE 1 or 2 exploring data on the dynamics and recovery of BMD following linzagolix treatment (see Section B.2.11.1).[57]

The goal of ABT is to minimise or prevent hypoestrogenic side-effects, including BMD loss associated with gonadotropin-releasing hormone (GnRH) analogues while preserving efficacy. However, ABT is not a suitable option for some patients including those who have a contraindication to, are at increased risk for complications with, or prefer not to take ABT.[25,58] Linzagolix is the only available GnRH antagonist that has the flexibility to be taken without ABT.[25]

Fourteen studies (19 publications) were identified for the indirect treatment comparison (ITC) for four therapies; relugolix CT (n=5 studies; n=10 publications), goserelin (n=1 study; n=1 publication), leuprolide (n=1 study; n=1 publication), ulipristal acetate (n=7 studies; n=7 publications). These studies were assessed for feasibility to support ITC (see Section B.2.9).

Table 8: Clinical effectiveness evidence | PRIMROSE 1 and 2

Trial	PRIMROSE 1 (NCT03070899)	PRIMROSE 2 (NCT03070951)
Trial design	Phase 3, multicentre, 52-week, randomised, parallel-group, double-blind, placebo-controlled	
Trial geography	US	Europe (8 countries) and the US
Population	Women aged ≥18 years with ultrasound-confirmed UFs and HMB defined as ≥80 mL of MBL per cycle for at least two cycles	
Intervention(s)	Patients in the trials received one of the following four treatment regimens, taken orally once daily for up to 52 weeks: • Linzagolix 100 mg (linzagolix 100 mg + placebo 1 mg E2/0.5 mg NETA) • Linzagolix 100 mg + ABT (linzagolix 100 mg + 1 mg E2/0.5 mg NETA) • Linzagolix 200 mg (linzagolix 200 mg + placebo 1 mg E2/0.5 mg NETA) • Linzagolix 200 mg + ABT (linzagolix 200 mg + 1 mg E2/0.5 mg NETA)	
Comparator(s)	Placebo (placebo linzagolix + placebo 1 mg E2/0.5 mg NETA)	
Indicate if trial supports application for marketing authorisation	Yes	Yes
Indicate if trial used in the economic model	Yes	Yes
Rationale for use/non-use in the model	Pivotal trials in relevant patient population; provided data for the MAA and represent the primary evidence base in the submission	
Reported outcomes specified in the decision problem	• **Change in MBL volume** • Time to MBL response • Pain • UF volume • Haemoglobin levels • Change in BMD • Impact on pregnancy and teratogenic effects • Mortality • **AEs of treatment,** including but not limited to vasomotor symptoms and incontinence • **HRQoL**	
All other reported outcomes	• Not applicable	
Key publication	Donnez et al, 2022[25]	Donnez et al, 2022[25]
Secondary sources	• PRIMROSE 1 CSR Week 24[59] • PRIMROSE 1 CSR Week 52[60] • PRIMROSE 1 CSR Week 76[61] • Al-Hendy et al, 2022 Obstetrics & Gynecology A107[62]	• PRIMROSE 2 CSR Week 52[64] • PRIMROSE 2 CSR Week 76[65] • Al-Hendy et al, 2022 Obstetrics & Gynecology A107[62] • Taylor et al, 2022 Obstetrics & Gynecology A108[63]

	• Taylor et al, 2022 Obstetrics & Gynecology A108[63] • PRIMROSE 1 and 2 pooled analyses[55]	• PRIMROSE 1 and 2 pooled analyses[55]

Abbreviations: ABT, add-back therapy; CSR, clinical study report; E2, estradiol; HMB, heavy menstrual bleeding; MAA, marketing authorisation application; MBL, menstrual blood loss; NCT, National Clinical Trials; NETA, norethisterone acetate; UFs, uterine fibroids; US, United States of America

The PRIMROSE 3 trial was not used to populate the economic model but is included in Section B.2.11.1. The results of this trial provide evidence on the long-term (up to 24 months) recovery of BMD following linzagolix treatment.[57]

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

B.2.3.1 Trial design

PRIMROSE 1 and 2 are completed Phase 3, multicentre, 52-week, randomised, parallel-group, double-blind, placebo-controlled trials.[25] The trials included two treatment periods and a follow-up period (in which patients were not on treatment):

- Treatment period 1: 24 weeks (Day 1 to Week 24)
- Treatment period 2: 28 weeks (Week 24 to Week 52)
- Follow-up period: 24 weeks (Week 52 to Week 76); the last Visit occurred at Week 76, however efficacy endpoints analysed beyond Week 52 (i.e. those not derived from menstrual blood loss [MBL] by the alkaline haematin [AH] method) were assessed 12 weeks after the end of treatment, at Week 64.

Eligible patients with UF-HMB, defined as MBL >80 mL per cycle for at least two cycles, were randomly assigned in a 1:1:1:1:1 ratio, using an interactive web response system to the treatment groups outlined in Table 8.[25]

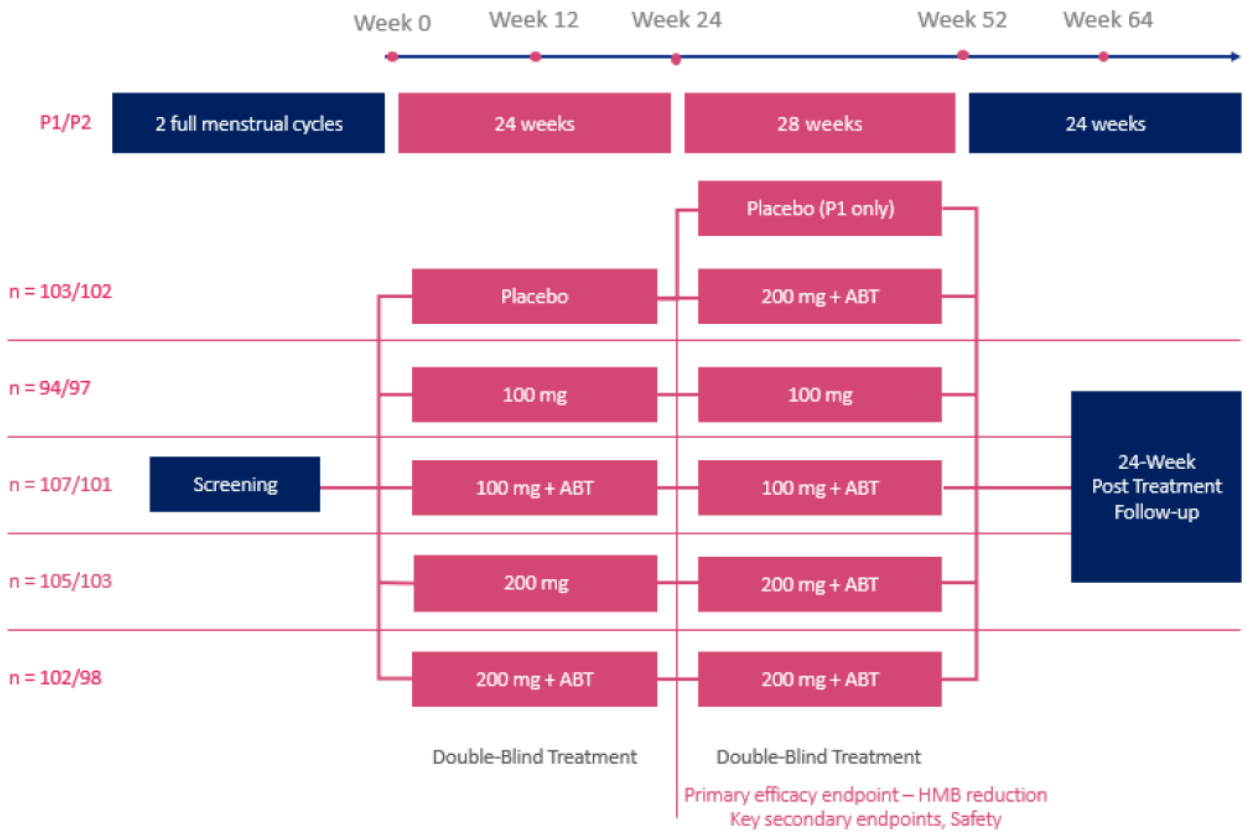
Randomisation was stratified by race (Black/non-Black) in order to ensure an equal representation of Black patients across treatment groups.[25] Blinding was achieved by using tablets with an identical appearance between the linzagolix treatments and corresponding placebo and over-encapsulation of the 1 mg E2 and 0.5 mg NETA and corresponding placebo.[25] The sponsor was masked to group allocation until after all the patients had completed the Week 24 visit in PRIMROSE 1 and the Week 52 visit in PRIMROSE 2.[25] Patients and investigation teams remained blinded until the end of the trials.

PRIMROSE 1 and 2 were very similar in design with the only difference being the treatment switch from the placebo groups at Week 24:

- In PRIMROSE 1, 50% of patients allocated to the placebo group at baseline remained in the placebo group and 50% of patients allocated to the placebo group at baseline switched to 200 mg linzagolix + ABT (selected at random assignment) to Week 52
- In PRIMROSE 2, all patients allocated to the placebo group at baseline switched to 200 mg linzagolix + ABT to Week 52.

A summary of the trial designs is shown in Figure 7 and the trial methodology in Table 9. A more detailed overview over the inclusion and exclusion criteria for PRIMROSE 1 and 2 is provided in Appendix M.1.

Figure 7: PRIMROSE 1 and 2 | Trial design



Abbreviations: ABT, add-back therapy (1 mg estradiol and 0.5 mg norethisterone acetate); HMB, heavy menstrual bleeding; n, number; P1, PRIMROSE 1; P2, PRIMROSE 2; Source: Donnez et al. (2022)[25]

Table 9: PRIMROSE 1 and 2 | Summary of methodology

	PRIMROSE 1	PRIMROSE 2
Trial design	Phase 3, multicentre, randomised, parallel-group, double-blind, placebo-controlled patients	
Duration of trial	6- to-17-week screening, 52 weeks treatment, 24 weeks untreated follow-up	
Settings and locations where data were collected	94 sites (hospitals, clinics and private research facilities) in the US	95 sites (hospitals, clinics and private research facilities) in the US and eight European countries (Bulgaria, Czech Republic, Hungary, Latvia, Lithuania, Poland, Romania and Ukraine)
Patient eligibility criteria	**Key inclusion criteria** • Premenopausal women aged ≥18 years with ultrasound-confirmed UFs, and HMB defined as ≥80 mL of MBL per cycle for at least two cycles as assessed by the AH method • ≥1 fibroid of ≥2 cm diameter (or multiple small fibroids with a calculated uterus volume of >200 cm^3) and no fibroid with a diameter >12 cm. (uterine size <20 weeks or <20 cm from cervix to fundus) • Menstrual cycles ≥21 days and ≤40 days prior to starting screening • Experienced abnormal HMB (heavy or lasting >5 days) in most menstrual periods over the last 6 months • Willing to use and collect sanitary protection (pads or tampons) provided by the Sponsor and compatible with the AH method • If of childbearing potential, agreed to use non-hormonal contraception until the end of the trial	
	Key exclusion criteria • Pregnant, breast-feeding or planning a pregnancy within the duration of the trial • Women with only subserosal, pedunculated fibroids (FIGO classification type 7) • History of uterine surgery that could interfere with the trial (e.g. myomectomy or endometrial ablation within the last 6 months) • Undiagnosed uterine bleeding (assessed by endometrial biopsy at screening) • History of or were at the time taking systemic glucocorticoid therapy • At substantial risk of osteoporosis, or history of osteoporosis or other metabolic bone disease • Not willing to stop oral contraceptives or other sex hormones during the trial • Contraindication to ABT	

Trial drugs, up to 24 weeks	Randomised in ratio 1:1:1:1:1, stratified by race **Interventions (administered orally):** • Linzagolix 100 mg (linzagolix 100 mg + placebo linzagolix + placebo 1 mg E2/0.5 mg NETA) • Linzagolix 100 mg + ABT (linzagolix 100 mg + placebo linzagolix + 1 mg E2/0.5 mg NETA) • Linzagolix 200 mg (2x linzagolix 100 mg + placebo 1 mg E2/0.5 mg NETA) • Linzagolix 200 mg + ABT (2x linzagolix 100 mg + 1 mg E2/0.5 mg NETA) **Comparator (administered orally):** • Placebo (2x placebo linzagolix + placebo 1 mg E2/0.5 mg NETA)	
Treatment switch, at Week 24	At Week 24, 50% of patients allocated to the placebo group at baseline remained in the placebo group and 50% of patients allocated to the placebo group at baseline switched to linzagolix 200 mg + ABT (selected at random assignment) to Week 52 At Week 24, all patients allocated to linzagolix 200 mg at baseline switched to linzagolix 200 mg + ABT to Week 52	At Week 24, all patients allocated to the placebo group or linzagolix 200 mg group at baseline switched to linzagolix 200 mg + ABT to Week 52
Concomitant medication	**Permitted concomitant medication**: any medications apart from those excluded by the protocol that were considered necessary for the patient's welfare and/or would not interfere with the trial medication could be given at the discretion of the Investigator. Non-hormonal contraception was required for women of childbearing age. Iron supplements were permitted and provided if the Hb level was below 10 g/dl (taken at least four hours apart from trial medication) **Prohibited concomitant medication:** IUD or hormonal IUD, GnRH, antagonists, GnRH agonist injections/depot injections, combined contraceptives, progestins, depot contraceptives, SPRMs, SERMs, systemic glucocorticoid treatments, acetylsalicylic acid, mefenamic acid, anticoagulants, strong CYP 3A4 inducers or inhibitors	
Primary endpoint	A **reduction in HMB** at Week 24, defined as MBL ≤80 mL and ≥50% reduction in MBL from baseline in the last 28 days before Week 24 visit	
Other endpoints used in the model/specified in scope	• Time to MBL response • Pain • UF volume • Haemoglobin levels • Change in BMD • Rates and route of surgery • Impact on fertility and pregnancy and teratogenic effects • **Mortality**	

	• **AEs of treatment**, including but not limited to vasomotor symptoms, incontinence and pelvic organ prolapse • **HRQoL**
Pre-planned subgroups	• Race (Black or African American; other) • Cycle length (≤28 days; >28 days) • Excessively HMB (defined by Q3 for baseline MBL in the FAS) • Baseline FIGO classification of 0, 1, or 2 in at least one fibroid • Fibroid size (≥1 fibroid with the longest diameter of ≥2 cm; multiple small fibroids and a calculated uterine volume ≥200 cm^3)

Note: Outcomes listed in **bold** are included in the economic model
Abbreviations: ABT, add-back therapy (1 mg estradiol and 0.5 mg norethisterone acetate); AE, adverse event; AH, alkaline haematin; BMD, bone mineral density; CYP 3A4, cytochrome P450 3A4; E2, estradiol; FAS: full analysis set; FIGO, International Federation of Gynaecology and Obstetrics; GnRH, gonadotropin-releasing hormone; Hb, haemoglobin; HMB, heavy menstrual bleeding, HRQoL, health-related quality of life; IUD, intrauterine device; MBL, menstrual blood loss; NETA, norethisterone acetate, Q3, third quartile; SERM, selective estrogen receptor modulator; SPRM, selective progesterone receptor modulator; UF, uterine fibroid; US, United States of America
Sources: Donnez et al. (2022)[25]; NICE Final Scope (2023)[66]

B.2.3.1.1 Trial endpoints

Trial endpoints and their definitions are provided in Table 10.

Table 10: PRIMROSE 1 and 2 | Summary of key endpoints

Endpoint/assessment	Definition/measurement
A reduction in HMB at Week 24	Defined as MBL of ≤80 mL and a ≥50% reduction in MBL from baseline in the 28 days before Week 24 MBL was measured using the AH method: this involved collection of all used sanitary products, which were shipped to a central laboratory masked to the trial treatment for analysis and assessment of daily MBL using a validated method Also assessed at Week 52
Time to reduced HMB up to Week 24	Defined as the number of days from Day 1 of treatment to the first day the woman reached the definition of HMB (MBL of ≤80 mL and a ≥50% reduction in MBL from baseline in the 28 days before Week 24) and MBL was maintained up to Week 24 Determined using the AH method Also assessed up to Week 52
Amenorrhoea (absence of bleeding) at Week 24	Defined as having no sanitary material returned or volume < lower limit of quantification within at least a 35-day interval maintained up to Week 24 Determined using the AH method Also assessed at Week 52
Time to amenorrhoea up to Week 24	Defined as the number of days from Day 1 to the first day the woman reached the definition of amenorrhoea and without having bleeding after this time up to Week 24 Also assessed up to Week 52
Number of days of uterine bleeding in the last 28-day interval before Week 24	Assessed via the AH method Also assessed up to Week 52
Hb concentrations in a prespecified subgroup of patients who were anaemic at baseline	Anaemia defined as Hb <12 g/dL Assessed at Weeks 12, 24, 36, 52 and 64
Pain related to UFs	Assessed by patient self-reporting using an eDiary at site with a NRS from 0 (no pain) to 10 (worst possible pain) over the preceding 28-day interval before the questionnaire was completed. Categorised as: none, 0; mild, 1 to 3; moderate, 4 to 6; and severe, 7 to 10 Assessed at Weeks 12, 24, 36, 52 and 64
Uterine volume	Uterine dimensions were estimated using ultrasonography† and volumes were calculated by the prolate ellipsoid formula: length × height × width × 0·523 Assessed at Weeks 12, 24, 36, 52 and 64
Fibroid volume	Fibroid dimensions were estimated using ultrasonography† and volumes were calculated by the prolate ellipsoid formula: length × height × width × 0·523 Up to the three largest fibroids were included in the volume calculation Assessed at Weeks 12, 24, 36, 52 and 64

Quality of life endpoints (patient reported outcomes): • Symptom severity score (UFS-QoL) • HRQL questionnaire score (UFS-QoL) • EQ-5D-5L questionnaire scores • PGI-I scale scores	Symptom severity and HRQoL were assessed using the 3-month recall version of the UFS-QoL questionnaire Questionnaires completed at site in the eDiary Assessed at Weeks 12, 24, 36, 52 and 64
Serum estradiol	Measured in a central laboratory using a highly sensitive validated high-performance liquid chromatography tandem mass spectrometry assay (Esoterix Endocrinology, Calabasas Hills, CA, US)
Bone mineral density loss (percentage change from baseline)	Assessments using dual-energy x-ray absorptiometry (each site required to use the machine for the duration of the trial) All dual-energy x-ray absorptiometry scans were reviewed by a central imaging laboratory (Canfield Scientific, Parsippany, NJ, US) for scan quality including prequalification and cross-calibration phantom scans and a monthly phantom scan and review of quality data at each site
Endometrial ultrasound and histology	Ultrasound examination† to measure endometrium thickness, assess ovaries and report any abnormality (e.g. adenomyosis, polyp) Endometrial biopsies were done at screening and Weeks 24 and 52 using a Pipelle de Cornier or equivalent, and were assessed by pathologists in a central laboratory (Klimopath, Hamburg, Germany)
Clinical laboratory tests	Haematology, blood chemistry, coagulation parameters, lipids, urinalysis, hormones, bone biomarkers and PK measurements
Incidence of adverse events	An AE was defined as any untoward medical occurrence in a clinical trial patient who received an investigational trial treatment, but which did not necessarily have a causal relationship with this treatment. It could therefore be any unfavourable sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a trial treatment, whether or not considered related to the treatment

*Key secondary endpoints were analysed sequentially in ranked order (see Table 11) within each linzagolix treatment group, thus continuing to protect against an overall type 1 error. An endpoint was only claimed to be statistically significant if the resulting p-value for that endpoint and all endpoints higher up in the testing order (for a given treatment group) were <0.0125. The additional efficacy endpoints were tested using a p-value of <0.0125 with no further adjustments for having multiple endpoints; †Transvaginal ultrasound done by the same operator at each visit if possible; abdominal ultrasound if transvaginal ultrasound not possible
Abbreviations: AEs, adverse events; AH, alkaline haematin; CA, California; eDiary, electronic diary; EQ-5D-5L, Euroqol-5 Dimension-5-Level; Hb, haemoglobin; HMB, heavy menstrual bleeding; HRQoL, health-related quality of life; MBL, menstrual blood loss; NJ, New Jersey; NRS, Numeric Rating Scale; PGI-I, Patient Global Impression Of Improvement Scale; PK, pharmacokinetic; UFs, uterine fibroids; UFS-QoL, Uterine Fibroid Symptom-Quality Of Life Questionnaire; US, United States of America
Source: Donnez et al. (2022)[25]; PRIMROSE 1 CSR Week 24[59]; PRIMROSE 2 CSR Week 52[64]

Screening period assessments

The screening period lasted between 6 and 17 weeks (excluding washout) and generally covered two full menstrual cycles, ending on the first day of menstruation for the third cycle.[25] Assessments included demographic data, medical history, physical and gynaecological examination, transvaginal ultrasound of uterus and ovaries, endometrium biopsy, cervical smear, and blood and urine tests.[25]

Assessment timepoints and follow-up

Trial visits occurred at the following timepoints: Trial Day 1 (Baseline visit), Week 4 (Day 29 ± 3 days), Week 8 (Day 57 ± 3 days), Week 12 (Day 85 ± 3 days), Week 24 (Day 169 ± 3 days), Week 28 ± 7 days, Week 32 ± 7 days, Week 36 ± 7 days, Week 52 (End of treatment visit), Week 64 ± 7 days Week 76 ± 7 days (End of follow-up visit).[25]

Phone calls occurred between the Week 36 and Week 52 visits.[25] eDiary recordings throughout trial period until Week 64 occurred off-site daily, at approximately the same time each evening, to record trial medication intake and uterine bleeding. At site, at visits on Day 1, Week 12, Week 24, Week 36, Week 52 and Week 64, eDiaries were used to capture Uterine Fibroid Symptom-Quality of Life questionnaire (UFS-QoL), EuroQol-5 Dimension-5 (EQ-5D) and pain Numeric Rating Scale (NRS) questionnaire scores; and at visits at Week 12, Week 24, Week 36, Week 52 and Week 64 for Patient Global Impression of Improvement scale (PGI-I) questionnaire scores.[25]

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

B.2.4.1 Statistical analyses

Statistical methods used in PRIMROSE 1 and 2 are summarised in Table 11.

Table 11: PRIMROSE 1 and 2 | Summary of statistical analyses

	PRIMROSE 1	PRIMROSE 2
Hypothesis objective	The trial hypothesis was that linzagolix at full E2 suppression (200 mg) and partial E2 suppression (100 mg) without or + ABT (1 mg E2 and 0·5 mg NETA) is superior to placebo in reducing HMB (defined as MBL of ≤80 mL and a ≥50% reduction in MBL from baseline in the 28 days before Week 24) in premenopausal patients with symptomatic UFs characterised by HMB The primary analysis of the primary endpoint tested the null hypothesis of no difference in the percentage of patients meeting the primary endpoint for each linzagolix group vs. placebo	
Statistical analysis	Carried out using Statistical Analysis System version 9.4 (Statistical Analysis System Institute, Cary, NC, US) Individual active-versus-placebo efficacy comparisons were carried out at Week 24 using a Bonferroni type 1 error of 0·0125 to account for the multiplicity of the four active treatment groups **Primary endpoint (reduction in HMB at Week 24):** analysed as a categorical variable (yes/no response). A CMH test with adjustment for the stratification factor race was used to test the null hypothesis of no treatment effect for each linzagolix group versus placebo with regards to the proportion of patients with reduced MBL. ORs were estimated from the CMH test together with the associated 95% CIs and corresponding p-values. The proportion per treatment group was displayed together with exact Clopper-Pearson 95% CIs. In addition, the CRD between each linzagolix group and	

	placebo was provided, along with 95% CI (stratified Newcombe confidence limits). The homogeneity of the ORs was explored using the Breslow-Day test. A logistic regression model with terms for treatment, the stratification factor race, and the interaction between treatment and race was fitted. OR statements provided separate tests for each linzagolix group versus placebo for each stratum. The primary efficacy analysis used AH data only. Two sensitivity analyses on the primary endpoint were done to assess the robustness of the primary efficacy analysis results under alternative assumptions for days on which there were no data from the AH method. The first was done by imputing daily bleeding data based on the eDiary responses for days when no sanitary products were returned but bleeding had been reported in the eDiary. The second was done by assigning patients who discontinued early or who did not return any sanitary protection tools and had missing bleeding information in the eDiary as non-responders **Ranked secondary efficacy endpoints:** analysed sequentially in ranked order within each linzagolix treatment group, thus continuing to protect against an overall type 1 error. An endpoint was only claimed to be statistically significant if the resulting p-value for that endpoint and all endpoints higher up in the testing order (for a given treatment group) were less than 0·0125. Between group comparisons for continuous endpoints were analysed via repeated measures analysis of covariance, including the baseline and stratification factor race as a covariate, with each treatment group compared versus placebo using contrasts. Ranked secondary efficacy endpoints: • Time to reduced MBL up to Week 24 analysed using KM methodology and each linzagolix group vs. placebo was compared using a two-sided log-rank test stratified by race. In addition, the treatment difference as measured by the HR and its corresponding 95% CI was estimated using a stratified Cox regression model with race as stratification factor • Amenorrhoea at Week 24 analysis used the same methods as for the primary endpoint • Time to amenorrhoea up to Week 24 analysed in the same way as for time to reduced MBL • Number of days of uterine bleeding for the last 28 days prior to Week 24 analysed using a negative binomial model and a zero-inflated negative binomial model using maximum likelihood estimations with the baseline value and race as covariate. The estimated LS means and treatment differences were presented together with the 95% CI and p-value • Hb levels at Week 24 in a prespecified subgroup of patients with anaemia was assessed by using the actual Hb values to compare each treatment group to placebo for the set of FAS patients with baseline Hb <12 g/dL via mixed model repeated measures, including baseline as a covariate and the stratification factor race, treatment and visit as fixed effects. Terms for interactions between the time (visit) and baseline, treatment, and race were included in the model. Visit was considered as a repeated variable within a patient. Each treatment group was compared versus placebo at Weeks 12 and 24. The estimated LS means and treatment differences were presented together with the 95% CIs and p-value **Additional efficacy endpoints:** tested using a p-value of less than 0·0125 with no further adjustments for having multiple endpoints. Only descriptive statistics presented for the additional secondary endpoints of time to reduced MBL, amenorrhoea, time to amenorrhoea, number of days of uterine bleeding, and Hb levels in a prespecified group of patients with anaemia using data after Week 24, as there was no comparative placebo group for which to conduct hypothesis tests. For pain (NRS), change from baseline was compared between each active treatment group and placebo via mixed model repeated measures, including baseline as a covariate and the stratification factor race, treatment, and visit as fixed effects. Terms for

	interactions between the time (visit) and baseline, treatment, and race were included in the model. Visit was considered as a repeated variable within a patient. Each treatment group was compared with the placebo group using the OR statement. For UF volume and uterine volume endpoints, the change from baseline was used to compare each treatment group with the placebo group via mixed model repeated measures **HRQoL endpoints** • Symptom Severity Score and HRQL Questionnaire Score (UFS-QoL questionnaire) were analysed via mixed model repeated measures • QoL with EQ-5D-5L Questionnaire index score and VAS were analysed via mixed model repeated measures analysis • PGI-I analysed using Mantel-Haenszel methodology **Safety endpoint:** analyses were based on the safety analysis set and were assessed versus baseline conditions and differences between treatment groups. Descriptive statistics were produced, where applicable**.** BMD loss compared between the linzagolix treatment groups and placebo in terms of % change from baseline
Sample size, power calculation	Assuming response rates for the primary endpoint of 30% for placebo and 70% for linzagolix, based on results from a previous trial of elagolix (another oral GnRH antagonist), 64 patients per treatment group were required to assess the primary endpoint for 90% power
Data management, patient withdrawals	In general, missing data were not imputed. Patients who had less than 28 days of data were counted as non-responders. Patients who discontinued prematurely due to lack of efficacy or AEs or who underwent operative or radiological interventions for UFs were considered as non-responders for the primary analysis and in a similar way for the secondary endpoints of amenorrhea and reduced MBL. If the timing of a patient's withdrawal corresponded to a blank visit Week 12, Week 24, Week 36, or Week 52 (± 14 days) and the patient took the double-blind trial drug up to the withdrawal visit (± 3 days up to Week 24 and ± 7 days up to Week 52), then the withdrawal data was to be allocated to that visit for analysis For the primary endpoint, a sensitivity analysis was done to check the robustness of the analysis results under alternative assumptions with regards to missing data by imputing data when missing AH data was indicated by a record of uterine bleeding in the daily eDiary on a day when no lab data was reported
Statistical analysis timepoints	Analysis of Week 24 data, including the primary endpoint, the ranked secondary endpoints and BMD assessments, was done once all randomised patients had completed Week 24 or had withdrawn from the trial. A further analysis was done after all patients had completed Week 52 and a follow-up analysis was done after the final Week 76 database lock

Abbreviations: ABT, add-back therapy; AE, adverse event; AH, alkaline haematin; BMD, bone mineral density; CMH, Cochran-Mantel-Haenszel; CI, confidence interval; CRD, common risk difference; E2, estradiol; eDiary, electronic diary; EQ-5D-5L, EuroQol-5 Dimension-5-Level; FAS, full analysis set; GnRH, gonadotropin-releasing hormone; Hb, haemoglobin; HMB, heavy menstrual bleeding; HR, hazard ratio; HRQoL, health-related quality of life; KM, Kaplan–Meier; LS means, least squares means; MBL, menstrual blood loss; NETA, norethisterone acetate; NRS, Numeric Rating Scale; OR, odds ratio; PGI-I, Patient Global Impression Of Improvement Scale; QoL, quality of life; UFs, uterine fibroids; UFS-QoL, Uterine Fibroid Symptom-Quality of Life questionnaire; US, United States of America; VAS, Visual Analogue Scale
Source: Donnez et al. (2022)[25]; PRIMROSE 1 CSR Week 24[59]; PRIMROSE 2 CSR Week 52[64]; Linzagolix EPAR[56]

B.2.4.1.1 Pooled PRIMROSE 1 and 2 results

A pooled analysis (efficacy and safety) of PRIMROSE 1 and 2 at Week 24 was performed in accordance with Statistical Analysis Plans.[53,54]

Pooling of efficacy data (individual patient data) up to Week 24 from both trials is appropriate as both studies have the same design up to Week 24, the same inclusion/exclusion criteria, no difference in study conduct, and efficacy results were generally similar. Pooling of efficacy data up to Week 52 was not conducted as only one trial (PRIMROSE 1) had a placebo arm after Week 24. The aim of the 24-week pooled efficacy analysis was to improve the precision of the treatment effect estimates for the efficacy outcomes and to evaluate whether overall positive results are also seen in specific subgroups. As the aim of the pooled efficacy analysis is to improve precision, statistical results are to be regarded from an exploratory perspective. No adjustment was made for multiplicity within the pooled analysis.[53]

A pooled analysis of safety data was performed up to Week 52 (see Section 0) in the primary analysis.[54] A supplemental post-hoc analysis includes pooled data up to Week 76 for select BMD assessments.[54] The aim of the pooled safety analysis was to provide a comprehensive overview and more precise estimates for the rates of AEs and for potential bone BMD loss with linzagolix treatment.

Efficacy results from the individual trials are provided in Appendix M.

B.2.4.2 Analysis sets

B.2.4.2.1 Pooled analysis sets

The pooled randomised set included all randomised patients in PRIMROSE 1 and PRIMROSE 2.[53] The pooled full analysis set (Pooled FAS) included all randomised patients in PRIMROSE 1 and PRIMROSE 2, and who received at least one dose of double-blind study drug irrespective of the treatment received and who did not violate the following exclusion criteria prior to first administration of double-blind study drug:

- The patient is at significant risk of osteoporosis or has a history of, or known osteoporosis or other metabolic bone disease.
- The patient has alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) or total bilirubin ≥2 times the upper limit of normal at screening.

All efficacy analyses on the pooled efficacy Week 24 datasets were performed using the Pooled FAS. Subjects were analysed according to randomised treatment (Table 12).[53]

The Pooled Safety Analysis Set (Pooled SAS) included all randomised patients in PRIMROSE 1 and 2 who received at least one dose of double-blind study drug irrespective of the treatment received. Subjects were analysed according to treatment received.[54]

The Pooled Week 52 SAS included all patients from the Pooled SAS who received at least one dose of double-blind study drug after Week 24 irrespective of the treatment received during the second treatment period. Subjects were analysed according to treatment received. All safety analyses were conducted using the Pooled SAS (Table 12) and the Pooled Week 52 SAS (Table 13).[54]

Table 12: PRIMROSE 1 and 2 | Pooled efficacy and safety analysis sets Week 24

	Number of patients					
	Placebo	**LGX 100 mg**	**LGX 100 mg + ABT**	**LGX 200 mg**	**LGX 200 mg + ABT**	**Total**
Pooled FAS	205	191	208	208	200	1,012
Pooled SAS	209	199	211	210	208	1,037

Abbreviations: ABT, add-back therapy; FAS, full analysis set; LGX, linzagolix; SAS, safety analysis set
Source: Linzagolix EPAR[56]

Table 13: PRIMROSE 1 and 2 | Pooled SAS Week 52

	Number of patients						
	Placebo	**Placebo/ LGX 200 mg + ABT**	**LGX 100 mg**	**LGX 100 mg + ABT**	**LGX 200 mg/ LGX 200 mg + ABT**	**LGX 200 mg + ABT**	**Total**
Pooled Week 52 SAS	31	123	141	146	162	154	757

Abbreviations: ABT, add-back therapy; LGX, linzagolix; SAS, safety analysis set
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.4.3 Patient flow

In PRIMROSE 1 and 2, at total of 1,109 patients were randomised to treatment, 485 (44%) patients in Europe and 624 (56%) patients in the US.[25] Of these, 72 patients discontinued before Day 1 (i.e. never received the trial drug) and 25 patients started the trial drug but were excluded based on baseline assessments. Thus, 1,012 patients were included in the Pooled FAS. A total of 770 patients completed treatment up to Week 24.[25] (See Appendix M.2 for individual trial consort diagrams for up to Weeks 24 and 52).

B.2.4.4 Patient baseline characteristics

The baseline characteristics for the pooled analysis of the PRIMROSE 1 and 2 trials are shown in Table 14. In the Pooled FAS, overall there were 349 (34.5%) Black/African American patients and 643 (63.5%) White patients, with a mean (±standard deviation [SD]) age of 42.3 (±5.6) years, weight of 81.3 (±19.2) kg, and body mass index (BMI) of 29.9 (±6·9) kg/m².[55,56] Baseline demographic and clinical characteristics were generally comparable across the FAS treatment groups. In the US PRIMROSE 1 trial, patients had a higher mean BMI, a higher number of Black patients and a higher percentage of patients who were anaemic at baseline (Hb <12 g/dL) compared with the US and Europe PRIMROSE 2 trial.[25]

The baseline characteristics for the individual trials are shown in Appendix M.

Table 14: PRIMROSE 1 and 2 | Pooled patient baseline demographic characteristics (Pooled FAS*)

Characteristic	Placebo n=205	LGX 100 mg n=191	LGX 100 mg + ABT n=208	LGX 200 mg n=208	LGX 200 mg + ABT n=200	Total N=1,012
Age, years; mean (SD)	42.5 (5.5)	42.3 (5.7)	42.1 (5.6)	42.0 (6.0)	42.4 (5.4)	42.3 (5.6)
Race, Black or African American; n (%)	70 (34.1)	64 (33.5)	75 (36.1)	74 (35.6)	66 (33.0)	349 (34.5)
Race, White; n (%)	134 (65.4)	121 (63.4)	127 (61.1)	131 (63.0)	130 (65.0)	643 (63.5)
BMI (kg/m^2); mean (SD)	29.51 (6.70)	30.30 (7.19)	30.05 (6.80)	29.66 (6.63)	29.95 (7.14)	29.89 (6.88)
Haemoglobin (g/dL); mean (SD)	11.33 (1.61)	10.89 (1.74)	10.93 (1.85)	11.15 (1.84)	11.06 (1.73)	11.07 (1.76)
MBL (mL); median (Q1 to Q3)	171.70 (126.15 to 239.10)	178.65 (128.90 to 269.00)	160.53 (119.65 to 260.58)	157.23 (124.33 to 262.20)	164.68 (122.45 to 228.65)	164.40 (122.98 to 250.48)
Total fibroid volume (cm^3); median (Q1 to Q3)	52.0 (22.8 to 129.0)	65.1 (25.7 to 141.2)	49.8 (20.9 to 134.9)	43.4 (18.7 to 115.9)	58.4 (24.0 to 121.2)	53.1 (22.2 to 127.4)
Uterine volume (cm^3); median (Q1 to Q3)	234.6 (161.0 to 419.4)	253.6 (168.2 to 408.3)	240.5 (166.2 to 406.5)	239.0 (147.3 to 390.0)	243.9 (163.1 to 375.2)	240.6 (160.3 to 395.9)
Pain score; mean (SD)	5.3 (2.8)	5.8 (2.7)	5.7 (2.8)	6.0 (2.9)	5.4 (2.9)	5.6 (2.8)
UFS-QoL symptom severity score; mean (SD)	55.59 (19.08)	58.03 (19.80)	59.70 (20.04)	59.34 (19.28)	55.92 (19.57)	57.72 (19.59)
UFS-QoL HRQL total score; mean (SD)	42.21 (21.16)	39.44 (21.55)	38.76 (21.41)	37.45 (21.44)	43.74 (22.66)	40.32 (21.73)
BMD by DXA (g/cm^2); mean (SD)*	n=209	n=199	n=211	n=210	n=208	n=1,037
Lumbar spine	1.103 (0.133)	1.095 (0.124)	1.101 (0.134)	1.093 (0.124)	1.092 (0.121)	1.097 (0.127)
Total hip	0.990 (0.143)	0.994 (0.139)	0.998 (0.130)	0.986 (0.135)	0.995 (0.139)	0.992 (0.137)
Femoral neck	0.917 (0.138)	0.910 (0.134)	0.905 (0.124)	0.905 (0.124)	0.907 (0.126)	0.909 (0.129)

Note: The BMD by DXA values are based on the Pooled SAS, whereas all other variables are based on the Pooled FAS

Abbreviations: ABT, add-back therapy (1 mg estradiol and 0.5 mg norethisterone acetate); BMI, body mass index; DXA, dual-energy x-ray absorptiometry; FAS, full analysis set; LGX, linzagolix; MBL, menstrual blood loss; Q: quartile; SAS, safety analysis set; SD, standard deviation; UFS-QoL HRQL, Uterine Fibroid Symptom-Quality of Life and Health-Related Quality of Life questionnaire; UFS-QoL, Uterine Fibroid Symptom-Quality of Life questionnaire

Source: PRIMROSE 1 and 2 pooled analyses[55]; Linzagolix EPAR[56]

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

The included studies were critically appraised using the National Institute for Health and Care Excellence (NICE) checklist for RCTs.

Table 15: PRIMROSE 1 and 2 | Quality assessment results using Donnez et al, 2022[25]

Questions	PRIMROSE 1	PRIMROSE 2
Was randomisation carried out appropriately?	Yes. Patients were randomised using a computer-generated randomisation list using the random allocation of treatment according to a permuted block randomisation stratified by race (Black or African American vs. other)	
Was the concealment of treatment allocation adequate?	Yes. Patients were randomised to treatment groups by IWRS	
Were the groups similar at the outset of the trial in terms of prognostic factors?	Yes. As the prevalence of fibroids is higher and symptoms are more severe in Black women, randomisation was stratified to ensure equal distribution of Black patients among treatment groups In the PRIMROSE 1 trial, patients had a higher mean BMI, a higher number of Black patients and a higher percentage of patients who were anaemic at baseline (Hb <12 g/dL) compared the PRIMROSE 2 trial	
Were the care providers, patients and outcome assessors blind to treatment allocation?	Yes. Masked treatment kits were sent to each site and kept in controlled conditions. Masking was achieved by using tablets with an identical appearance between the linzagolix treatments and corresponding placebo and over-encapsulation of the ABT and corresponding placebo. All patients took two tablets and one capsule daily. The operational teams were masked to group allocation until unmasking after the database was locked; patients and investigation teams at each site remained blinded	
Were there any unexpected imbalances in dropouts between groups?	No. In order to consider all randomised and treated patients in the analysis, the assessment of the primary endpoint for patients who discontinued prior to Week 24 for a reason other than lack of efficacy, AEs, or operative or radiological interventions for UF was based on the results from the 28 days prior to the last eDiary entry in order to use as many data as possible up to Week 24 after the start of treatment, irrespective of actual treatment taken. Patients who had less than 28 days of data were considered as non-responders. The secondary endpoint of amenorrhea was assessed in a similar way	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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. A sensitivity analysis was conducted on the primary efficacy endpoint to check the robustness of the analysis results under alternative assumptions with regards to missing data. Results of sensitivity analyses imputing missing data and results in the PP Set were consistent with those of the main analysis. Missing values for continuous efficacy endpoints were handled within the analysis itself via mixed model repeated measures, with the assumption that the model specification was correct, and that the data were missing at random. All data recorded in the eCRF were included in data listings.	
Was there good quality assurance for this trial?	Yes, the trial was conducted in accordance with ICH GCP guidelines and regulatory requirements. The study monitor reviewed eCRFs and other study documents, and conducted source data verification, to verify that these and the trial protocol were followed	

Abbreviations: ABT, add-back therapy; AE, adverse event; eCRF, electronic case report form; eDiary; electronic diary; ICH GCP; International Council for Harmonisation Good Clinical Practice; IWRS, Interactive Web Response System; PP per protocol, UF, uterine fibroid

B.2.6 Clinical effectiveness results of the relevant trials

Pooled efficacy data from the PRIMROSE 1 and 2 trials up to Week 24 (first treatment period; Day 1 to Week 24), are presented in this section. The 24-week pooled efficacy data are the primary source for the clinical data in the economic model. Efficacy data from the individual PRIMROSE 1 and 2 trials, including Week 52 and Week 64 results are presented in Appendix M. Pooled efficacy data are not available beyond Week 24, as only PRIMROSE 1 had a placebo arm after Week 24.

Efficacy results from the individual PRIMROSE 1 and 2 trials, at Week 24, Week 52 and Week 76 (off treatment) are presented in Appendix M.

B.2.6.1 Primary efficacy endpoint | Reduction in HMB

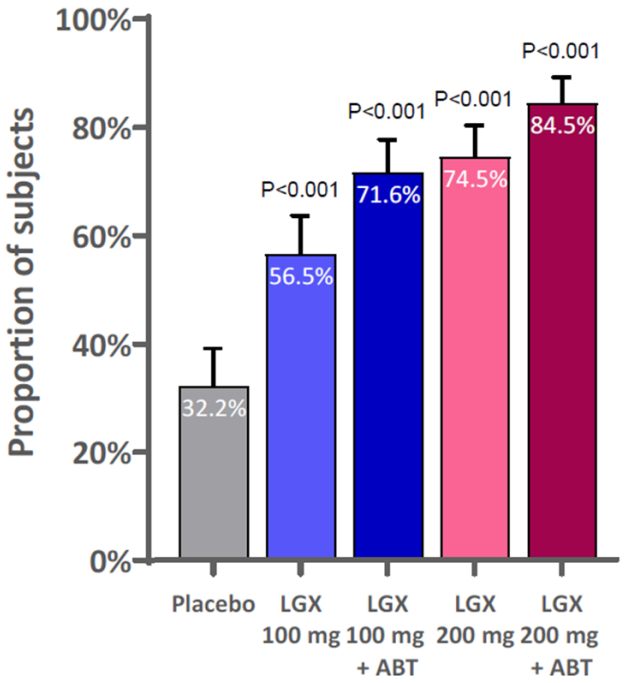
In the pooled analysis, all linzagolix treatment groups demonstrated a clinically meaningful reduction in HMB at Week 24 (the primary efficacy endpoint; defined as MBL ≤80 mL and ≥50% reduction in MBL from baseline in the last 28 days before Week 24 visit) compared with the placebo group (nominal p≤0·001 all comparisons) (Figure 8 and Table 16).[56] HMB is the most common symptom of UFs.[9] Attaining this endpoint is considered to be clinically meaningful because 80 mL/cycle of MBL is widely accepted as the threshold for defining HMB,[67,68] and the addition of reducing MBL by at least a half makes the threshold more meaningful. This primary endpoint has been used for drug approval for other drugs, including relugolix CT[22] and elagolix.[69]

Responses across treatment groups were generally consistent for pre-defined subgroups, including race (Black or African American; other), weight categories, BMI and age categories (see Figure in Appendix E.1).[55]

The reduction in HMB (the most common symptom of UFs) with linzagolix treatment is likely to be particularly meaningful for patients in clinical practice given its prevalence and associated burden.

The trends observed in the pooled analysis reflected those observed in the individual studies (Appendix M).

Figure 8: PRIMROSE 1 and 2 pooled data | Proportion of patients with a reduction in HMB† at Week 24 (error bars are 95% CI; Pooled FAS)



†MBL ≤80 mL and ≥50% reduction in MBL from baseline in the last 28 days before Week 24 visit
Nominally significant p-values (not controlled for multiplicity)
Abbreviations: ABT, add-back therapy (1 mg estradiol and 0.5 mg norethisterone acetate); CI, confidence interval; FAS, full analysis set; HMB, heavy menstrual bleeding; LGX, linzagolix; MBL, menstrual blood loss
Source: Linzagolix EPAR[56]

Table 16: PRIMROSE 1 and 2 pooled data | Proportion of patients with a reduction in HMB† at Week 24 (Pooled FAS)

	Number of patients				
	Placebo n=205	LGX 100 mg n=191	LGX 100 mg + ABT n=208	LGX 200 mg n=208	LGX 200 mg + ABT n=200
Reduced HMB†					
Yes; n (%)	66 (32.2)	108 (56.5)	149 (71.6)	155 (74.5)	169 (84.5)
No; n (%)	139 (67.8)	83 (43.5)	59 (28.4)	53 (25.5)	31 (15.5)
Proportion	32.2	56.5	71.6	74.5	84.5
95% CI[1]	25.9; 39.1	49.2; 63.7	65.0; 77.7	68.0; 80.3	78.7; 89.2
Common risk difference[2]	-	24.3	39.7	42.3	52.3
95% CI[2]	-	14.5; 33.4	30.4; 48.0	33.1; 50.4	43.5; 59.8
CMH[3]					
OR	-	2.75	5.54	5.99	10.77
95% CI	-	1.82; 4.16	3.61; 8.50	3.92; 9.15	6.66; 17.42
p-value	-	<0.001	<0.001	<0.001	<0.001
Breslow-Day test p-value[4]	-	0.622	0.128	0.121	0.002

†MBL ≤80 mL and ≥50% reduction in MBL from baseline in the last 28 days before Week 24 visit; [1]Clopper-Pearson 95% CI; [2]Common risk (proportion) difference between each linzagolix group and placebo, with race and study as stratification factors, along with stratified Newcombe confidence limits; [3]Cochran-Mantel-Haenszel test with race and study as stratification factors; [4]Breslow-Day test to explore homogeneity of odds ratios
Nominally significant p-values
Abbreviations: ABT, add-back therapy (1 mg estradiol and 0.5 mg norethisterone acetate); CI, confidence interval; FAS, full analysis set; HMB, heavy menstrual bleeding; LGX, linzagolix; MBL, menstrual blood loss
Source: PRIMROSE 1 and 2 pooled analyses[55]; Linzagolix EPAR[56]

B.2.6.2 Secondary efficacy endpoints

B.2.6.2.1 Reduction in fibroid volume and uterine volume

Dose-dependent reductions in fibroid and uterine volume from baseline were observed in all linzagolix treatment groups at Week 24 (Table 17).[56] Substantial reductions in fibroid and uterine volumes were observed with linzagolix 200 mg (nominal p<0.001), with a 48% and 39% reduction in fibroid and uterine volume, respectively.[55] The linzagolix 200 mg dose resulted in the greatest reduction of serum E2 concentrations (Section B.2.10.5.1), showing that full suppression of E2 to less than 20 pg/mL is needed to achieve this effect.[25] Reductions in fibroid volume of approximately 25%, 15% and 22% were observed in the linzagolix 100 mg, 100 mg + ABT, and 200 mg + ABT groups. Reductions in uterine volume of approximately 15% were seen in the linzagolix 200 mg + ABT and 100 mg groups, with no meaningful change in the 100 mg + ABT group.[55]

The uterine and fibroid volume changes observed demonstrate that linzagolix 200 mg results in substantial and clinically meaningful reductions in fibroid and uterine volume.[56] As well as reducing bulk-related symptoms, short-term use (<6 months) of linzagolix at this dose (as per the licensed indication) is likely to simplify surgery so that patients may be more likely to have a less invasive laparoscopic surgery rather than open/abdominal surgery.

The trends observed in the pooled analysis reflected those observed in the individual studies (Appendix M).

Table 17: PRIMROSE 1 and 2 pooled data | Fibroid and uterine volume changes at Week 12 and 24 (Pooled FAS)

	Placebo n=205	LGX 100 mg n=191	LGX 100 mg + ABT n=208	LGX 200 mg n=208	LGX 200 mg + ABT n=200
Week 12 Fibroid volume (mL)					
n (missing)	174 (31)	155 (36)	160 (48)	170 (38)	162 (38)
Change from baseline; mean (SD)	10.08 (70.31)	-18.09 (46.19)	-13.93 (51.14)	-32.48 (75.92)	-7.15 (47.65)
LS means of ratio to baseline (95% CI)	1.015 (0.910; 1.132)	0.796 (0.710; 0.893)	0.826 (0.738; 0.92)	0.572 (0.513; 0.637)	0.812 0.725; 0.908
LS means of ratio to placebo (95% CI)	-	0.785 (0.672; 0.915)	0.814 (0.698; 0.948)	0.563 (0.484; 0.655)	0.800 (0.687; 0.931)
p-value	-	0.002	0.008	<0.001	0.004
Week 24 Fibroid volume (mL)					
n (missing)	147 (58)	137 (54)	136 (72)	157 (51)	145 (55)
Change from baseline; mean (SD)	9.45 (77.71)	-14.13 (53.89)	-5.39 (64.52)	-44.22 (79.69)	-14.72 (114.59)
LS means of ratio to baseline (95% CI)	0.968 (0.840; 1.116)	0.749 (0.646; 0.868)	0.846 (0.731; 0.980)	0.519 (0.452; 0.595)	0.777 (0.672; 0.898)
LS means of ratio to placebo (95% CI)	-	0.774 (0.633; 0.945)	0.874 (0.716; 1.067)	0.536 (0.441; 0.650)	0.802 (0.659; 0.977)
p-value	-	0.012	0.186	<0.001	0.028
Week 12 Uterine volume (mL)					
n (missing)	177 (28)	162 (29)	167 (41)	174 (34)	164 (36)
Change from baseline; mean (SD)	1.10 (142.40)	-50.23 (155.34)	-20.85 (157.64)	-102.49 (176.43)	-25.50 (127.64)
LS means of ratio to baseline (95% CI)	0.984 (0.926; 1.047)	0.837 (0.785; 0.893)	0.876 (0.822; 0.932)	0.662 (0.623; 0.704)	0.869 (0.815; 0.926)
LS means of ratio to placebo (95% CI)	-	0.851 (0.780; 0.928)	0.889 (0.816; 0.969)	0.672 (0.618; 0.732)	0.883 (0.810; 0.962)
p-value	-	<0.001	0.008	<0.001	0.005
Week 24 Uterine volume (mL)					
n (missing)	150 (55)	140 (51)	141 (67)	160 (48)	148 (52)
Change from baseline; mean (SD)	9.10 (156.05)	-45.51 (163.27)	2.17 (257.40)	-124.25 (208.44)	-30.86 (168.09)
LS means of ratio to baseline (95% CI)	1.006 (0.935; 1.082)	0.839 (0.778; 0.904)	0.931 (0.864; 1.002)	0.612 (0.570; 0.657)	0.846 (0.786; 0.911)
LS means of ratio to placebo (95% CI)	-	0.834 (0.753; 0.923)	0.925 (0.836; 1.024)	0.609 (0.551; 0.672)	0.841 (0.761; 0.930)
p-value	-	<0.001	0.132	<0.001	<0.001

Fibroid and uterine volume values were log-transformed prior to analysis, with the subsequent results back-transformed and hence reported in terms of ratios. The change from baseline was calculated using log-transformed value; analysis using mixed model repeated measures with change from baseline as response variable, baseline value, treatment, visit, study and race as covariates and including treatment, baseline score and race by visit interactions
Nominally significant p-values
Abbreviations: ABT, add-back therapy; CI, confidence interval; LGX, linzagolix; LS means, least square means; SD, standard deviation
Source: PRIMROSE 1 and 2 pooled analyses[55]

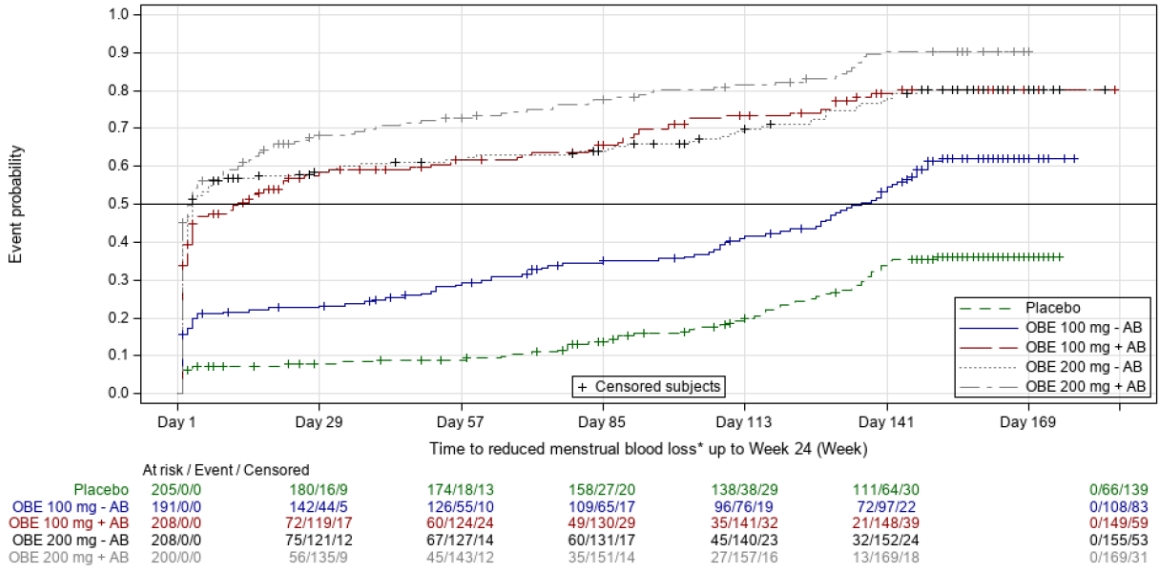
B.2.6.2.2 Bleeding-related endpoints

Time to reduced HMB

The impact of linzagolix on HMB is rapid (within days) and significant (see Figure 9). In the pooled analysis, time to reduced HMB at Week 24 (including maintaining the reduction in HMB to Week 24) was shorter in all linzagolix treatment groups compared with the placebo group (nominal p≤0.001 for all comparisons) (Table 18).[55,56]

The trends observed in the pooled analysis reflected those observed in the individual studies (Appendix M).

Figure 9: PRIMROSE 1 and 2 pooled data | Time to reduced HMB* up to Week 24: KM curves (Pooled FAS)



*Defined as the number of days from Day 1 of treatment to the first day the patient reached the definition of HMB (MBL of ≤80 mL and a ≥50% reduction in MBL from baseline in the 28 days before Week 24) and MBL was maintained up to Week 24
Abbreviations: AB, add-back therapy; FAS, full analysis set; HMB, heavy menstrual bleeding; KM, Kaplan–Meier; MBL, menstrual blood loss; OBE, linzagolix
Source: PRIMROSE 1 and 2 pooled analyses[55]

Table 18: PRIMROSE 1 and 2 pooled data | Time to reduced HMB* at Week 24 (Pooled FAS)

	Placebo n=205	LGX 100 mg n=191	LGX 100 mg + ABT n=208	LGX 200 mg n=208	LGX 200 mg + ABT n=200
Events, n (%)	66 (32.2)	108 (56.5)	149 (71.6)	155 (74.5)	169 (84.5)
HRs (95% CI)†	-	2.10 (1.54; 2.85)	4.33 (3.22; 5.81)	4.29 (3.20; 5.74)	5.73 (4.28; 7.67)
Stratified log-rank test p-value**	-	<0·001	<0·001	<0·001	<0·001
KM probability estimate at Week 4 (95% CI)	0.08 (0.05; 0.12)	0.23 (0.18; 0.30)	0.59 (0.52; 0.65)	0.58 (0.52; 0.65)	0.68 (0.62; 0.75)

*Defined as the number of days from Day 1 of treatment to the first day the patient reached the definition of HMB (MBL of ≤80 mL and a ≥50% reduction in MBL from baseline in the 28 days before Week 24) and MBL was maintained up to Week 24; †Estimated HRs and 95% CIs calculated using a stratified Cox model with treatment group and trial as main effect and race as stratification factor; **p-value obtained from a 2-sided stratified log-rank test for each linzagolix group versus placebo comparison using race and study for pooled analysis as stratification factor
Nominally significant p-values
Abbreviations: ABT, add-back therapy; CI, confidence interval; FAS, full analysis set; HMB, heavy menstrual bleeding; HR, hazard ratio; KM, Kaplan–Meier; LGX, linzagolix; MBL, menstrual blood loss
Source: Linzagolix EPAR[56]

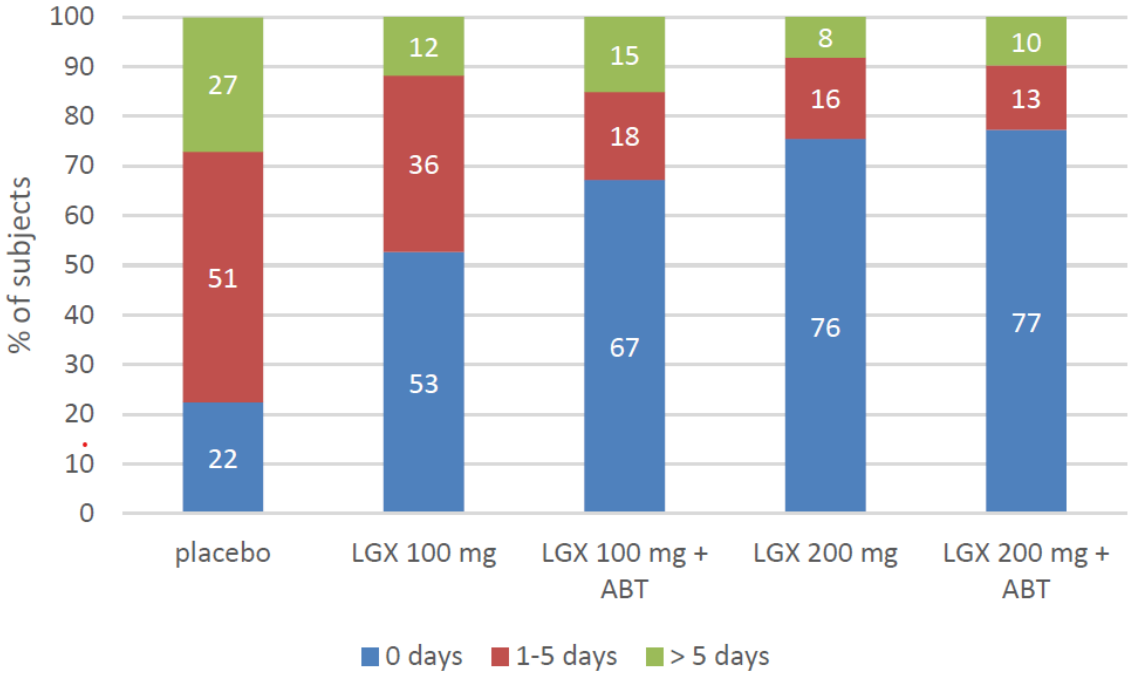
Number of days of uterine bleeding for the last 28-day interval

There was a reduction in the number of days of uterine bleeding in the last 28-day interval up to Week 24 in all linzagolix groups compared with the placebo group (nominal p≤0.001 for all comparisons) (Figure 10).[56]

More than half of patients had zero days of uterine bleeding in the last 28-day interval prior to Week 24 in all linzagolix treatment groups.[56] The percentage of patients with zero days of uterine bleeding was highest for the linzagolix 200 mg (76%) and linzagolix 200 mg + ABT (77%) groups in the Pooled FAS.[56] These results reinforce the clinically meaningful reduction in HMB with linzagolix treatment.

The trends observed in the pooled analysis reflected those observed in the individual studies (Appendix M).

Figure 10: PRIMROSE 1 and 2 pooled data | Number of days of uterine bleeding for the last 28-day interval prior to Week 24 (Pooled FAS)



Abbreviations: ABT, add-back therapy; FAS, full analysis set; LGX, linzagolix
Source: Linzagolix EPAR[56]

B.2.6.2.3 Amenorrhoea

Amenorrhoea (absence of menstrual bleeding) was determined using the AH method, and defined as having no sanitary material returned (or the menstrual blood volume was less than the lower limit of quantification) over at least a 35-day interval.[25] In the pooled analysis, the proportion of patients with amenorrhea was higher in all linzagolix treatment groups compared with the placebo group at Week 24 (nominal p<0.001 for all comparisons) (Table 19).[56] Highest proportions were observed in the linzagolix 200 mg (65.4%) and linzagolix 200 mg + ABT (69.0%) groups. These results reinforce the clinically meaningful reduction in HMB with linzagolix treatment.

The trends observed in the pooled analysis reflected those observed in the individual studies (Appendix M).

Table 19: PRIMROSE 1 and 2 pooled data | Proportion of patients with amenorrhoea* at Week 24 (Pooled FAS)

	Placebo n=205	LGX 100 mg n=191	LGX 100 mg + ABT n=208	LGX 200 mg n=208	LGX 200 mg + ABT n=200
n (%), (95% CI)†	34 (16.6%) (11.8; 22.4)	69 (36.1%) (29.3; 43.4),	109 (52.4%) (45.4; 59.4)	136 (65.4%) (58.5; 71.8)	138 (69.0%) (62.1; 75.3)
CRD from placebo (95% CI)**	-	19.6 (10.9; 27.9)	36.1 (27.2; 44.1)	48.8 (39.9; 56.4)	52.4 (43.5; 59.9)
OR (95% CI)‡	–	2.84 (1.77; 4.56)	5.40 (3.43; 8.49)	8.99 (5.68; 14.24)	10.25 (6.42; 16.35)
p-value	–	<0.001	<0.001	<0.001	<0.001

*Defined as having no data from the alkaline haematin method from the central laboratory or volume below the lower limit of quantification over at least a 35-day interval and without showing bleeding after this interval; †Clopper-Pearson 95% CI; **Common risk (proportion) difference between each linzagolix group and placebo, with race and study as stratification factors, along with stratified Newcombe confidence limits; ‡Cochran-Mantel-Haenszel test with race and study as stratification factors
Nominally significant p-values
Abbreviations: ABT, add-back therapy; CI, confidence interval; CRD, common risk difference; FAS, full analysis set; LGX, linzagolix; OR, odds ratio
Source: PRIMROSE 1 and 2 pooled analyses[55]; Linzagolix EPAR[56]

B.2.6.2.4 Time to amenorrhoea at Week 24

In the pooled analysis, time to amenorrhoea (including maintaining amenorrhea) at Week 24 was shorter in all linzagolix treatment groups compared with the placebo group (nominal p<0.001 for all comparisons) (Table 20).[55,56] In the pooled population, the probability of achieving amenorrhea by 4 weeks was higher in the linzagolix treatment groups compared with the placebo group (Table 20).[56]

The trends observed in the pooled analysis reflected those observed in the individual studies (Appendix M).

Table 20: PRIMROSE 1 and 2 pooled data | Time to amenorrhoea* at Week 24 (Pooled FAS)

	Placebo n=205	LGX 100 mg n=191	LGX 100 mg + ABT n=208	LGX 200 mg n=208	LGX 200 mg + ABT n=200
Events, n (%)	34 (16.6)	69 (36.1)	109 (52.4)	136 (65.4)	138 (69.0)
HRs (95% CI)†	-	2.50 (1.66; 3.78)	4.70 (3.19; 6.92)	7.01 (4.80; 10.22)	7.45 (5.11; 10.87)
Stratified log-rank test p-value‡	-	<0.001	<0.001	<0.001	<0.001
KM probability estimate at Week 4 (95% CI)	0.04 (0.02; 0.08)	0.15 (0.10; 0.21)	0.31 (0.25; 0.38)	0.49 (0.43; 0.56)	0.48 (0.41; 0.55)

*Defined as having no data from the alkaline haematin method from the central laboratory or volume below the lower limit of quantification over at least a 35-day interval and without showing bleeding after this interval; †Estimated HRs and 95% CIs obtained from stratified Cox model with treatment group and study as main effects and race as stratification factor; ‡p-value obtained from a 2-sided stratified log-rank test for each linzagolix group versus placebo comparison using race and study as stratification factor; each active treatment group is compared versus placebo at the 0.0125 level of significance
Nominally significant p-values
Abbreviations: ABT, add-back therapy; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; KM, Kaplan–Meier; LGX, linzagolix
Source: PRIMROSE 1 and 2 pooled analyses[55]; Linzagolix EPAR[56]

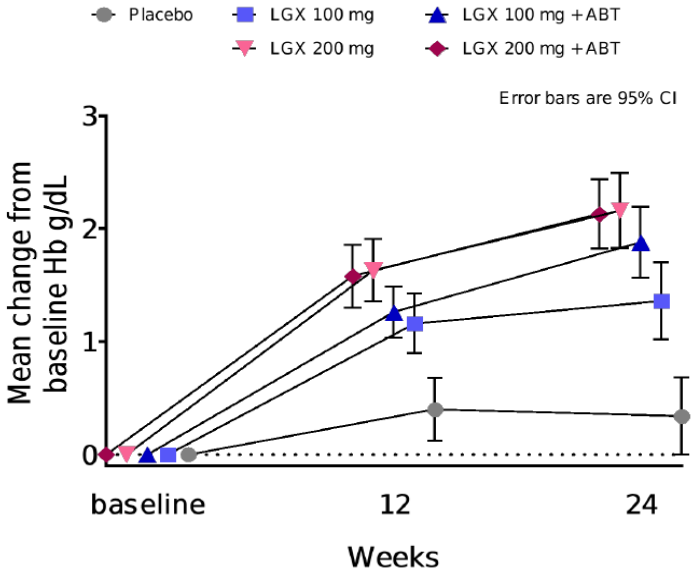
B.2.6.2.5 Haemoglobin concentrations in patients with anaemia at baseline

Anaemia (defined as Hb <12g/dL) was observed at baseline in 662 (65.4%) patients in the Pooled FAS.[55] At Week 24, improvements in Hb levels were observed in patients who were anaemic at baseline in all linzagolix treatment groups compared with the placebo group (nominal p≤0.002 for all comparisons).[56] The effect was more pronounced with linzagolix 200 mg with and without ABT (Figure 11 and Table 21).[56]

Anaemia secondary to HMB is a common comorbidity experienced by approximately two-thirds of women, causing weakness, severe fatigue, poor concentration and reduced work productivity and can be life-threatening in some situations.[2,17,40] These results demonstrate that linzagolix treatment successfully increases Hb levels in patients with anaemia, which may lead to improvements in HRQoL and work productivity, and may reduce post-operative morbidity for women undergoing surgery.

The trends observed in the pooled analysis reflected those observed in the individual studies (Appendix M).

Figure 11: PRIMROSE 1 and 2 pooled analysis | Change in Hb levels up to Week 24 in patients with anaemia (Hb <12 g/dL) at baseline (Pooled FAS patients with baseline Hb <12 g/dL)



Abbreviations: ABT, add-back therapy; CI, confidence interval; FAS, full analysis set; Hb, haemoglobin; LGX, linzagolix
Source: Linzagolix EPAR[56]

Table 21: PRIMROSE 1 and 2 pooled data | Hb concentration in patients with anaemia* at baseline (g/dL) at Week 24 (Pooled FAS patients with baseline Hb <12 g/dL)

	Placebo	LGX 100 mg	LGX 100 mg + ABT	LGX 200 mg	LGX 200 mg + ABT
Patients with anaemia* at baseline, n (missing)	127 (0)	129 (0)	145 (0)	133 (0)	128 (0)
Week 24 change from baseline					
n (missing)	88 (39)	91 (38)	97 (48)	99 (34)	97 (31)
Mean (SD)	0.34 (1.62)	1.36 (1.64)	1.88 (1.56)	2.16 (1.66)	2.13 (1.52)
Week 24 LS means (95% CI)	10.64 (10.35; 10.94)	11.29 (11.00; 11.58)	11.92 (11.63; 12.20)	12.20 (11.91; 12.48)	12.20 (11.91; 12.49)
Week 24 LS means difference from placebo (95% CI)	-	0.65 (0.24; 1.06)	1.27 (0.87; 1.68)	1.55 (1.15; 1.96)	1.56 (1.15; 1.96)
p-value	-	0.002	<0.001	<0.001	<0.001

*Defined as Hb <12g/dL
Analysis using mixed model repeated measures with actual value as response variable, baseline Hb value, treatment, visit, study and race as covariates and including treatment, baseline value and race by visit interactions
Nominally significant p-values
Abbreviations: ABT, add-back therapy; CI, confidence interval; FAS, full analysis set; Hb, haemoglobin; LGX, linzagolix; LS means, least squares means
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.6.2.6 UF-associated pain

In PRIMROSE 1 and 2, pain was measured using an NRS, with a score of 0 representing no pain and a score of 10 representing the worst possible pain. The overall mean ± SD baseline score in the Pooled FAS population was 5.6±2.8, and 761 (75.2%) patients reported moderate or severe pain (scores of ≥4) at baseline.[55]

In the pooled analysis, the mean reduction from baseline in pain score at Week 24 was greater in the linzagolix groups compared with the placebo group (nominal p≤0.001 all comparisons) (Table 22).[55,56] The proportions of patients with a baseline score of at least 4 who had a score of 0 or 1 (none to very mild pain) at Week 24 were higher in the linzagolix treatment groups compared with the placebo group (nominal p<0.001 all comparisons).[56]

Analysis of pain scores as categorical changes (categories: no pain=0, mild=1 to 3, moderate=4 to 6, severe=7 to 10) also showed similar results. In the pooled analysis, of patients with mild, moderate or severe pain at baseline in the Pooled FAS (n=923), 61.8% (95% CI 53.6; 69.6) of patients in the linzagolix 100 mg group, 62.3% (54.4; 69.8) in the 100 mg + ABT group, 77.5% (70.2; 83.7) in the 200 mg group, and 68.2% (60.1; 75.6) in the 200 mg + ABT group had decreased pain by one or more categories at Week 24, compared with 36.6% (29.2; 44.6) in the placebo group (nominal p<0.001 all comparisons).[55] Of patients with moderate or severe pain at baseline in the Pooled FAS (n=761), the proportions of patients with a decrease of two or more categories at Week 24 were 29.0% (21.4; 37.6) in the linzagolix 100 mg group, 36.4% (28.5; 45.0) in the 100 mg + ABT group, 53.0% (44.2; 61.8) in the 200 mg group, and 46.2% (37.0; 55.6) in the 200 mg + ABT group, compared with 11.9% (6.8; 18.9) in the placebo group (nominal p<0.001 all comparisons).[55] Of patients with severe pain at baseline in the Pooled FAS (n=434), the proportions of patients with a decrease of three or more categories at Week 24 were 14.7% (7.6; 24.7) in the linzagolix 100 mg group, 21.3% (12.7; 24.7) in the 100 mg + ABT group, 35.0% (24.7; 46.5) in the 200 mg group, and 32.3% (21.2; 45.1) in the 200 mg + ABT group, compared with 3.2% (0.4; 11.2) in the placebo group (nominal p≤0.026 all comparisons).[55]

Pain associated with UFs is a frequently reported symptom (e.g. pelvic pain, menstrual pain and discomfort, or pain during sexual intercourse).[3,8,19] Larger fibroids can lead to 'bulk symptoms' due to the impact of the fibroid on the uterus causing leg or back pain.[3,8,19]

Across PRIMROSE 1 and 2 at baseline, 68.0%, 50.0% and 28.0% of patients experienced abdominal pain, lower back pain and pain during sexual intercourse, respectively.[25] Reduction in pain with linzagolix treatment may be particularly meaningful for patients in clinical practice given its prevalence and associated burden.

The trends observed in the pooled analysis reflected those observed in the individual studies (Appendix M).

Table 22: PRIMROSE 1 and 2 pooled data | Change in pain scores from baseline at Week 24 (Pooled FAS)

	Placebo n=205	LGX 100 mg n=191	LGX 100 mg + ABT n=208	LGX 200 mg n=208	LGX 200 mg + ABT n=200
Baseline n (missing)	203 (2)	184 (7)	204 (4)	200 (8)	196 (4)
Mean (SD)	5.3 (2.8)	5.8 (2.7)	5.7 (2.8)	6.0 (2.9)	5.4 (2.9)
Week 24 change from baseline					
n (missing)	149 (56)	138 (53)	144 (64)	157 (51)	146 (54)
Mean (SD)	-0.6 (2.6)	-2.5 (3.2)	-2.7 (3.1)	-3.5 (3.4)	-2.8 (3.5)
Week 24 LS means (95% CI)	-0.87 (-1.29; -0.45)	-2.16 (-2.60; -1.72)	-2.51 (-2.94; -2.08)	-3.26 (-3.67; -2.84)	-2.99 (-3.42; -2.56)
LS means difference from placebo (95% CI)	-	-1.29 (-1.88; -0.69)	-1.64 (-2.23; -1.05)	-2.38 (-2.97; -1.80)	-2.12 (-2.71; -1.53)
p-value	-	<0.001	<0.001	<0.001	<0.001

Pain is measured with a Numeric Rating Scale from 0 (no pain) to 10 (worst possible pain); analysis using mixed model repeated measures with change from baseline as response variable, baseline pain score, treatment, visit, study and race as covariates and including treatment, baseline score and race by visit interactions
Nominally significant p-values
Abbreviations: ABT, add-back therapy; CI, confidence interval; LGX, linzagolix; LS means, least square means; SD, standard deviation
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.6.2.7 HRQoL

Symptom severity score and HRQL total score (UFS-QoL)

PRIMROSE 1 and 2 assessed HRQoL using the 3-month recall version of the uterine fibroid symptom and HRQL questionnaire (UFS-QoL), at baseline, Week 12 and Week 24.[25] The UFS-QoL is a disease-specific self-reported questionnaire for detecting differences in symptom severity and HRQoL among patients with UFs. It measures both a patient's objective pre-treatment and post-treatment symptoms (bleeding, cramping) and subjective experience (feeling 'blue' or less productive').

In the pooled analysis, there were marked decreases in the symptom severity scores (indicating improvement) and increases in the HRQL scores (indicating improvement) from baseline at Week 24 in the linzagolix groups compared with the placebo group (nominal $p<0.001$ all comparisons) (Table 23), demonstrating that all linzagolix dose groups reduced symptom severity and improved HRQoL in participants with UFs compared with the placebo group.[56]

Increases in HRQoL were observed across all six subdomains of the UFS-QoL (Concern, Activities, Energy/mood, Control, Self-consciousness, Sexual function) in the linzagolix groups compared with the placebo group. Increases were most pronounced in the concern and activities domains and tended to be higher in the linzagolix 200 mg and 200 mg + ABT groups (Table 23).[56]

The high symptom and psychological burden of UFs impose a substantial negative impact on HRQoL.[8,11,12] These results demonstrate that linzagolix treatment substantially and meaningfully reduces symptom severity and improves HRQoL in patients with UFs.

The trends observed in the pooled analysis reflected those observed in the individual studies (Appendix M).

Table 23: PRIMROSE 1 and 2 pooled data | UFS-QoL symptom severity, HRQL total score and subdomain scores at Week 24 (Pooled FAS)

	Placebo n=205	LGX 100 mg n=191	LGX 100 mg + ABT n=208	LGX 200 mg n=208	LGX 200 mg + ABT n=200
Baseline n (missing)	203 (2)	184 (7)	204 (4)	200 (8)	196 (4)
Symptom severity score					
Mean (SD) at baseline	55.59 (19.08)	58.03 (19.80)	59.70 (20.04)	59.34 (19.28)	55.92 (19.57)
Week 24 CFB, n (missing)	149 (56)	138 (53)	144 (64)	157 (51)	147 (53)
Week 24 CFB, mean (SD)	-10.28 (21.71)	-21.33 (22.29)	-29.73 (21.46)	-35.09 (23.89)	-31.80 (22.02)
Week 24 LS means	-11.75	-21.38	-28.43	-33.63	-32.94
95% CI	-14.80; -8.71	-24.55; -18.20	-31.52; -25.35	-36.62; -30.65	-36.04; -29.84
Week 24 LS means difference from placebo	-	-9.62	-16.68	-21.88	-21.18
95% CI	-	-13.92; -5.33	-20.92; -12.43	-26.06; -17.70	-25.42; -16.95
p-value	-	<0.001	<0.001	<0.001	<0.001
HRQL total score					
Mean (SD) at baseline	42.21 (21.16)	39.44 (21.55)	38.76 (21.41)	37.45 (21.44)	43.74 (22.66)
Week 24 CFB, mean (SD)	10.28 (19.99)	22.93 (25.24)	29.05 (27.31)	33.48 (29.54)	29.02 (26.65)
Week 24 LS means	12.65	21.83	28.15	32.06	31.51
95% CI	9.07; 16.24	18.09; 25.58	24.52; 31.78	28.50; 35.61	27.84; 35.18
Week 24 LS means difference from placebo	-	9.18	15.49	19.40	18.85
95% CI	-	4.11; 14.24	10.49; 20.50	14.45; 24.36	13.85; 23.86
p-value	-	<0.001	<0.001	<0.001	<0.001
HRQL subdomain scores					
Concern					
Week 24 CFB, mean (SD)	11.88 (23.09)	27.83 (31.83)	43.68 (34.31)	48.12 (37.23)	43.06 (32.44)
Activities					
Week 24 CFB, mean (SD)	11.22 (23.92)	26.50 (27.94)	35.04 (31.47)	38.97 (32.93)	34.21 (29.70)
Energy/mood					
Week 24 CFB, mean (SD)	9.52 (21.20)	21.89 (27.99)	25.22 (29.09)	28.07 (30.73)	25.15 (29.18)

Control					
Week 24 CFB, mean (SD)	11.01 (22.70)	22.46 (25.89)	24.48 (30.28)	29.30 (32.14)	23.84 (31.01)
Self-conscious					
Week 24 CFB, mean (SD)	9.62 (26.17)	14.61 (30.54)	19.62 (29.04)	23.94 (32.37)	20.35 (32.44)
Sexual function					
Week 24 CFB, mean (SD)	4.78 (31.32)	15.49 (30.90)	10.42 (36.18)	21.42 (36.00)	15.31 (34.34)

Higher symptom severity scores indicate increasing symptom severity and higher HRQL scores indicate better HRQL. Analysis using mixed model repeated measures with change from baseline as response variable, baseline HRQL total score, treatment, visit, study and race as covariates and including treatment, baseline score and race by visit interactions
Nominally significant p-values
Abbreviations: ABT, add-back therapy; CFB, change from baseline; CI, confidence interval; LGX, linzagolix; LS means, least square means; SD, standard deviation; UFS-QoL HRQL, Uterine Fibroid Symptom-Quality of Life and Health-Related Quality of Life questionnaire
Source: PRIMROSE 1 and 2 pooled analyses[55]

EQ-5D-5L

In the pooled analysis, there were small increases in the EQ-5D-5L index values and the visual analogue scale (VAS) score in all linzagolix groups and the placebo group at Week 24 (Table 24).[56] There were no noticeable differences between the linzagolix groups and the placebo group.[56] In the PRIMROSE trials, EQ-5D was captured at baseline, Week 12 and Week 24. As the effects of fibroids are complex, and patients may report differently depending on exactly which timepoint in their menstrual cycle they complete the EQ-5D assessment, a singular measurement on a single day may not truly reflect patients' overall HRQoL. These issues raise questions as to the degree of validity and reliability of the EQ-5D scores from the PRIMROSE trials. The disease-specific UFS-QoL is therefore likely to be a more reliable and appropriate measure to use in the assessment of HRQoL for patients with UFs.

Table 24: PRIMROSE 1 and 2 pooled data | EQ-5D-5L index values and VAS score changes from baseline at Week 24 – mixed model repeated measures (Pooled FAS)

	Placebo n=205	LGX 100 mg n=191	LGX 100 mg + ABT n=208	LGX 200 mg n=208	LGX 200 mg + ABT n=200
Index value					
LS means	0.054	0.075	0.045	0.051	0.074
95% CI	0.030; 0.078	0.050; 0.100	0.021; 0.069	0.028; 0.075	0.050; 0.098
LS means difference from placebo	-	0.021	-0.009	-0.003	0.020
95% CI	-	-0.013; 0.054	-0.042; 0.024	-0.035; 0.030	-0.013; 0.053
p-value		0.222	0.603	0.873	0.237
VAS					
LS means	3.83	7.02	3.55	5.89	6.78
95% CI	1.17; 6.49	4.25; 9.78	0.86; 6.24	3.29; 8.49	4.08; 9.49

LS means difference from placebo	-	3.18	-0.29	2.06	2.95
95% CI	-	-0.56; 6.93	-3.98; 3.41	-1.59; 5.71	-0.74; 6.65
	-	0.096	0.879	0.268	0.117

Higher index values indicate better quality of life**;** higher VAS scores indicate better health; analysis using mixed model repeated measures with change from baseline as response variable, baseline index value/VAS score, treatment, visit, study and race as covariates and including treatment, baseline score and race by visit interactions
Nominally significant p-values
Abbreviations: ABT, add-back therapy; CI, confidence interval; EQ-5D-5L, EuroQol-5 Dimension-5-Level; FAS, full analysis set; LGX, linzagolix; LS means, least square means; VAS, Visual Analogue Scale
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.6.3 Efficacy conclusions

The pooled analysis of PRIMROSE 1 and 2 confirmed the efficacy of all four linzagolix treatment options (100 mg or 200 mg once daily, with and without ABT) compared with placebo, across various clinically-relevant endpoints including reduced MBL and UF reduction. Pooled efficacy results at Week 24 reflected the results of the individual trials (Appendix M).

Linzagolix treatment (100 mg or 200 mg) with or without ABT resulted in clinically meaningful reductions in HMB at Week 24 (primary efficacy outcome) compared with the placebo group (nominal p≤0·001 for all comparisons). Responses across treatment groups were generally consistent for pre-defined subgroups defined by race (Black or African American; other), weight categories, BMI categories and age categories.

All linzagolix treatment groups demonstrated a reduction in the number of days of uterine bleeding (nominal p≤0.001 for all comparisons), increases in the rates of amenorrhoea (nominal p<0.001 for all comparisons) and shortening of the time to amenorrhoea (nominal p<0.001 for all comparisons) compared with the placebo group.

In patients who were anaemic (Hb <12g/dL) at baseline, improvements in Hb levels were observed in all linzagolix treatment groups at Week 24 compared with the placebo group (nominal p≤0.002 for all comparisons).

Improvements from baseline in mean UF-related pain scores at Week 24 were greater in the linzagolix groups compared with the placebo group (nominal p≤0.001 all comparisons). The proportions of patients with a baseline score of at least 4 (moderate to severe pain) who had a score of 0 or 1 (none to very mild pain) at Week 24 were higher in the linzagolix treatment groups compared with the placebo group (nominal p<0.001 all comparisons).

All linzagolix treatment groups resulted in fibroid volume and uterine volume reductions, linzagolix 200 mg without ABT resulted in substantial and clinically meaningful reductions in fibroid volumes (48% reduction) and uterine volumes (39% reduction) at Week 24 (nominal p<0.001 versus the placebo group). A reduction in the fibroid and uterine volume may help to reduce pressure effects (such as bloating, leg or back pain, increased urinary frequency, and constipation) and may prevent, delay or simplify surgery (patients may be more likely to have a less invasive laparoscopic surgery rather than a trans-abdominal surgery).

The pooled analysis results at Week 24, demonstrate the robust efficacy of linzagolix, the only GnRH antagonist providing flexible dosing options (100 mg or 200 mg with or without ABT), to meet the individualised treatment needs of people with moderate to severe symptoms of UFs.

B.2.7 Subgroup analyses

In the pooled analysis, subgroup analyses of the primary endpoint showed that responses across treatment groups were generally consistent for the pre-defined subgroups defined by race (Black or African American; other), weight, BMI and age.[55] See Figure in Appendix E.1.

Subgroup analyses for the individual PRIMROSE 1 and 2 trials are presented in Appendix E.2.

The final scope issued by NICE indicated that, if the evidence allows, the following subgroups will be considered:

- People having short-term treatment of 6 months or less
- People having longer-term treatment, with hormone-based therapy
- People having longer-term treatment, without hormone-based therapy.

Although these subgroups were considered in the economic analysis (Section B.3), specific subgroup analyses of clinical trial data were not required to inform the economic evaluations. As described in Section B.3.2, for the population of patients having short-term treatment of 6 months or less and the population of patients having longer-term treatment with hormone-based therapy, it is anticipated that linzagolix is likely to provide similar or great health benefits compared with existing treatment options, therefore cost-comparison methodology is used to address the decision problem for these subgroups, and clinical effectiveness data are not directly used in the modelling.

For the population of patients having longer-term treatment without hormone-based therapies, the linzagolix 100 mg, linzagolix 200 mg, and placebo arms from the pooled PRIMROSE 1 and 2 data are used to inform the cost-effectiveness analysis, as these groups of patients did not receive hormonal add-back therapy prior to 24-weeks.

B.2.8 Meta-analysis/pooled analysis

Data from PRIMROSE 1 and PRIMROSE 2 were pooled to maximise the sample sizes of the linzagolix and placebo arms (placebo, n=205; linzagolix 100 mg, n=191; linzagolix 100 mg + ABT, n=208; linzagolix 200 mg, n=208; linzagolix 200 mg + ABT, n=200) and provide more information on the treatment effect for linzagolix. As discussed in Section B.2.3.1, this was possible due to the near identical trial designs and the similarities between patient populations at baseline (see Appendix D.3.3.1), as well as the availability of patient-level data for both RCTs.

As shown in Table 14, within the pooled dataset, most of the key demographics and baseline characteristics (e.g. age, BMI, race, haemoglobin, the proportion of patients with a pain score ≥4, and BMD [lumbar spine and total hip]) were comparable between treatments arms. Table 14 also shows some slight differences in baseline menstrual blood loss (MBL), fibroid volume, and uterine volume; however, these were not statistically significant (i.e. one-way analysis of variance (ANOVA) p-values >0.05). The main difference to note is that there is a larger proportion of Black patients in PRIMROSE 1 than in PRIMROSE 2 (approximately 63% versus 5% across arms, respectively), although the proportion of Black patients, relative to other ethnicities, is comparable between the placebo and linzagolix treatment arms within the individual PRIMROSE trials as well as the pooled data set.

Outcome definitions were also aligned between the trials. See Appendix D.3.4.3 for additional details.

Due to the lack of head-to-head RCT data for linzagolix versus other active therapies for treating moderate to severe symptoms of UFs, an ITC (presented in Section B.2.9) was conducted.

B.2.9 Indirect and mixed treatment comparisons

In the absence of head-to-head data, an NMA was conducted to compare the efficacy of linzagolix to the comparator(s) of relevance to the decision problem in this evaluation, using published evidence identified from the clinical SLR (Appendix D). The efficacy outcomes considered in the NMA were based on the outcomes specified in the final scope issued by NICE, as well as the availability of data reported in the literature. The outcomes included in the NMA were response (reduced MBL, defined as a menstrual blood loss ≤80 mL and ≥50% reduction from baseline), percentage change in MBL, improvement in pain (defined as a NRS score ≤1 for participants with an NRS score ≥4 at baseline), percentage change in primary fibroid volume, percentage change in haemoglobin for participants with haemoglobin ≤10.5 g/dL at baseline, and improvement in HRQoL (defined as the change UFS-QoL total score).

B.2.9.1 Identification and selection of relevant studies from the clinical SLR

An SLR (Appendix D) was conducted in August 2021 and updated in March 2022 and again in February 2023 to identify and review clinical evidence of the efficacy, safety, and QoL outcomes for the treatment of UFs, and the pharmacological and surgical procedures available for the management of heavy menstrual bleeding and other symptoms relating to UFs.

A total of 3,746 publications were identified through electronic databases (PubMed, n=1,017; Embase, n=1,940; Cochrane, n=719 and DARE, n=70) and after duplicate publications were removed from the sample, 2,537 publications were screened for eligibility based on their title or abstract. Following this, a total of 242 selected citations were considered for full-text review, out of which 118 were finally selected. Multiple publications of the same study were linked based on NCT number or trial name to include a final set of 40 studies. One additional citation was identified from ad hoc searches hence 41 studies were included in the report. During the first update of the SLR (March 2022), which was performed for GnRH antagonists only, four new publications were identified (one was a newly added study, while three publications were linked to previous studies). During the second update of the SLR (February 2023), no new relevant publications were identified. After both updates, 42 studies (from 46 publications) were finally included and summarised; further details, including PRISMA diagrams, are provided in Appendix D.2. A full list of the included studies is provided in Appendix D.3.1, with a full list of all references excluded at the full-text stage of review, with reason for exclusion, provided in the reference pack (Appendix D.3.2).

B.2.9.2 Risk of bias

A risk of bias assessment was performed on all included clinical trials (as per NICE guidelines manual Appendix C: Methodology checklist: randomised controlled trials), which assessed four major categories: selection, performance, attrition, and detection.[70] Results of the quality assessment can be found in Appendix D.3.7.

B.2.9.3 Overview of the selected studies

The scope of the literature review was defined by the criteria for relevant population, intervention, comparators, outcomes, and study design (PICOS); these criteria are

presented in Appendix D.1.3. A wide scope in terms of the comparator choices was initially considered to ensure that all possible connections were captured before then restricting the inclusion criteria further to better align with the final scope for this submission. As discussed in Section B.1.3.4, the GnRH antagonist, relugolix CT, is considered to be the most relevant comparator of interest for the decision problem addressed within this appraisal, and for the cost-comparison analysis described in Section B.3. In the only prior NICE appraisal in moderate to severe symptoms of UFs (TA832), relugolix CT was recommended as a treatment option for adult patients of reproductive age with moderate to severe symptoms of UFs, and it was determined that relugolix CT and GnRH agonists are equally effective (TA832).[22] Furthermore, clinical expert opinion has indicated that linzagolix and relugolix CT, and relugolix CT and GnRH agonists are considered to be clinically comparable in NHS England practice with respect to reduced menstrual bleeding. As such, to ensure the most relevant and up to date studies were selected to inform an ITC, the following criteria were considered:

- Only studies where relugolix CT was a comparator were included
- Studies older than 20 years were excluded (i.e. dated prior to 2003)
- Studies where the patient populations were not US or EU based (e.g. four papers were excluded as the patient populations were from Japan only)

Of the 42 studies included in the SLR, four studies met these additional criteria and were required to appropriately connect the intervention (i.e. linzagolix) with the comparator of relevance to the decision problem in this evaluation (i.e. relugolix CT) via an ITC, as shown in Table 25.

Table 25: Trials considered for inclusion in the NMA

Trial name	Treatment
PRIMROSE 1 PRIMROSE 2	Placebo linzagolix + placebo ABT[1.] 100 mg linzagolix + placebo ABT 100 mg linzagolix + ABT 200 mg linzagolix + placebo ABT[1.] 200 mg linzagolix + ABT
LIBERTY 1 LIBERTY 2	Placebo relugolix + placebo ABT 40 mg relugolix + ABT 40 mg relugolix + placebo ABT[2]

Note: 1. Approximately three-quarters of patients (half from PRIMROSE 1 and all from PRIMROSE 2) that were treated with placebo linzagolix + placebo ABT were swapped onto 200 mg linzagolix + ABT at week 24, as well as all patients that were treated with 200 mg + placebo ABT. Only outcomes reported at 24 weeks are considered in the analyses; 2. Patients in LIBERTY 1 and LIBERTY 2 that were treated with 40 mg relugolix + placebo ABT were switched to 40 mg relugolix + ABT at week 12. This treatment arm is not considered in the analyses
Abbreviations: ABT, add-back therapy; mg, milligram

As detailed in Section B.2.8, data from PRIMROSE 1 and PRIMROSE 2 were pooled for use in the NMA to maximise the sample sizes of the linzagolix and placebo arms and provide more information on the treatment effect for linzagolix. Details of the studies included in the NMA are presented in Appendix D.3.

B.2.9.4 Heterogeneity assessment of trials included

Study similarity was assessed for heterogeneity according to the patient characteristics at baseline, outcome definitions, and study design for PRIMROSE 1, PRIMROSE 2, LIBERTY 1, and LIBERTY 2 (as detailed in Appendix D.3.4). In general, there was good alignment between the trials; the inclusion and exclusion criteria were identical between PRIMROSE 1 and 2, as well as between LIBERTY 1 and 2, with there also being substantial overlap of criteria between the PRIMROSE and LIBERTY studies. Some key examples include:

- Premenopausal women of adult age with an ultrasound-confirmed fibroids diagnosis
- Experiences HMB (defined as a MBL of 80 mL or more per cycle for at least two cycles, as assessed by the alkaline hematin method) associated with UFs, and has a menstrual cycle of at least 21 days
- Has at least one fibroid that is at least 2 cm in diameter, or multiple small fibroids with a large total uterus volume
- Has no history of uterus surgery that would interfere with the study, and does not need/expect to undergo surgery within 6 months of enrolment
- Has no history of clinically significant condition(s).

Additional inclusion and exclusion criteria for the four studies are presented in Appendix D.3.4.

There were also reported outcomes that were defined in the same way in the PRIMROSE and LIBERTY trials, such as response (defined as a volume of MBL <80 ml and a ≥50% reduction in volume from baseline) and the percentage change in MBL (assessed by the AH method). There were also other outcomes reported in the LIBERTY papers such as the improvement in pain (defined as a NRS score ≤1 for participants with an NRS score ≥4 at baseline), percentage change in primary fibroid volume, percentage change in haemoglobin for participants with haemoglobin ≤10.5 g/dL at baseline, and improvement in HRQoL (defined as the change in UFS-QoL total score) which could be replicated using the pooled PRIMROSE patient-level data (PLD) allowing for additional comparisons to be made.

The main difference between the PRIMROSE and LIBERTY studies was in the proportion of Black patients (approximately 35% across arms in the pooled PRIMROSE data [approximately 63% versus 5% across arms in PRIMROSE 1 and PRIMROSE 2, respectively] versus 47% and 42% across arms in LIBERTY 1 and LIBERTY 2, respectively). There were also some differences in other baseline characteristics, such as: the proportion of Hispanic or Latino patients (11.8% across arms in the pooled PRIMROSE data versus 20.7% across arms in LIBERTY 1 and 2; p-value <0.001), mean baseline MBL (207.6 across arms in the pooled PRIMROSE data versus 229.2 across arms in LIBERTY 1 and 2; p-value = 0.007), uterine volume (328.2 across arms in the pooled PRIMROSE data versus 393.2 across arms in LIBERTY 1 and 2; p-value <0.001), fibroid volume (98.9 across arms in the pooled PRIMROSE data versus 72.9 across arms in LIBERTY 1 and 2; p-value < 0.001), and the proportion of patients with a pain score ≥4 (77.1% across arms in the pooled PRIMROSE data versus 71.8% across arms in LIBERTY 1 and 2; p-value = 0.029).

Overall, the trials appeared to be broadly comparable and an NMA was chosen as the appropriate method of indirect comparison. A matching adjusted indirect comparison (MAIC) was also considered as a scenario analysis to explore whether differences in baseline

characteristics may have impacted comparative results from the NMA (see Section B.2.9.7 and Appendix D.3.8 for more details).

B.2.9.5 NMA methodology

The NMAs were conducted in a Bayesian framework using Monte Carlo Markov Chain (MCMC) and implemented using the *multinma* package in the statistical software R (version 4.2.2)[71]. Both fixed-effects (FE) and random-effects (RE) models were fitted and were compared based on the deviance information criteria (DIC) to determine which was the better fitting model. Residual deviance plots of the chosen model were also inspected to determine whether the chosen model appeared to provide a good fit.

Placebo was selected as the reference treatment for which all other treatments were compared to as placebo is a common comparator for all of the active treatment arms. For the individual comparisons of each linzagolix regimen to each comparator treatment, the relative effects (odds ratios [ORs] for binary outcomes and mean differences for continuous outcomes) are presented in tables alongside 95% credible intervals (CrIs).

For more details, see Appendix D.3.5.2.

B.2.9.6 NMA results

B.2.9.6.1 Response

Results were consistent between the fixed-effects and random-effects models (see Appendix D.3.5.3), with no meaningful difference in model fit between the two (fixed-effects DIC = 16.45; random-effects DIC = 17.53). The fixed-effects model, with smallest DIC, was therefore determined to be the most appropriate model and also appears to be a visually good fit, with residual deviance values being very small and close to 1 (see Figure 13).

Although the NMA estimated a high probability (≥95%) that linzagolix 100 mg is less likely to achieve a response than relugolix CT (OR = [redacted]; 95% CrI does not contain 1), for the remaining linzagolix regimens this is not the case (Table 26). For the comparisons of linzagolix 100 mg + ABT, linzagolix 200 mg, and linzagolix 200 mg + ABT the CrIs contain 1 within their bounds meaning that the available evidence does not indicate a difference in efficacy between these linzagolix regimens versus relugolix CT. Although a difference in efficacy could not be determined for the comparison of linzagolix 200mg + ABT versus relugolix CT (i.e., the CrI contains 1), it should be noted that the point estimate of the comparative results is in favour of linzagolix 200mg + ABT (OR = [redacted]).

The log odds ratios are presented in Figure 12, which visually demonstrates the results detailed above.

The estimated R-hat statistics reported by the NMA are 1.00, meaning there is little to no disagreement in the chain estimates suggesting that the NMA model converged successfully.

Table 26: Fixed-effects network meta-analysis for response

Median odds ratio (95% CrI)	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 100 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Model fit statistics: Residual deviance = 8.42; pD = 8.03; DIC = 16.45		

Abbreviations: ABT, add-back therapy; CrI, credible interval; DIC, deviance information criteria; mg, milligram; pD, the effective number of parameters; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

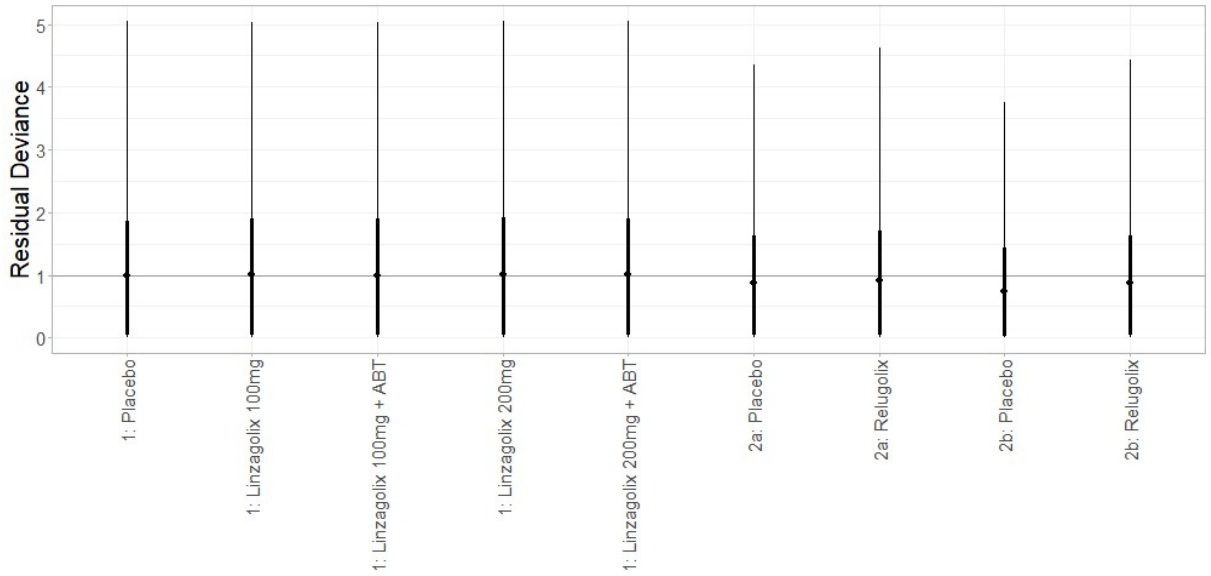
Figure 12: Forest plot for median Log ORs and 95% CrI from the fixed-effects network meta-analysis for response

Note: results presented in the figure demonstrate the log odds ratios as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines).

Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; OR, odds ratio; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

Figure 13: Residual deviance from the fixed-effects network meta-analysis for response



Note: results presented in the figure demonstrate the residual deviances as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

B.2.9.6.2 Menstrual blood loss (MBL), percentage change from baseline

It should be noted that there were differences between the PRIMROSE and LIBERTY trials in the methods used to collect sanitary products from patients, with product collection being more burdensome on patients in the PRIMROSE trials, as well as differences in how missing data were handled. This means that the results of the NMA presented below are likely conservative as the relative treatment effect of linzagolix versus relugolix CT may be underestimated. See Section B.2.9.7 for more details.

Results were consistent between the fixed-effects and random-effects models (see Appendix D.3.5.3), with no meaningful difference in model fit between the two (fixed-effects DIC = 16.69; random-effects DIC = 16.75). The fixed-effects model, with smallest DIC, was therefore determined to be the most appropriate model and also appears to be a visually good fit, with residual deviance values being very small and close to 1 (see Figure 15).

Although the NMA estimated a high probability (≥95%) that linzagolix 100 mg, 100 mg + ABT, and 200 mg achieve a smaller reduction in the percentage change in MBL than patients treated with relugolix CT (mean differences = [redacted], [redacted], and [redacted], respectively; 95% CrIs do not contain zero), this is not the case for all comparisons (Table 27). For the comparison of linzagolix 200 mg + ABT, the CrI contains zero within its bounds meaning that the available evidence does not indicate a difference in efficacy between this linzagolix regimen versus relugolix CT. It is notable too that the linzagolix 100 mg + ABT and linzagolix 200 mg regimens have CrIs that narrowly exclude zero. These results are shown visually in Figure 14.

The estimated R-hat statistics reported by the NMA are 1.00, meaning there is little to no disagreement in the chain estimates suggesting that the NMA model converged successfully.

Table 27: Fixed-effects network meta-analysis for percentage change in menstrual blood loss

Median relative effect (95% CrI)	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 100 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Model fit statistics: Residual deviance = 8.66; pD = 8.03; DIC = 16.69		

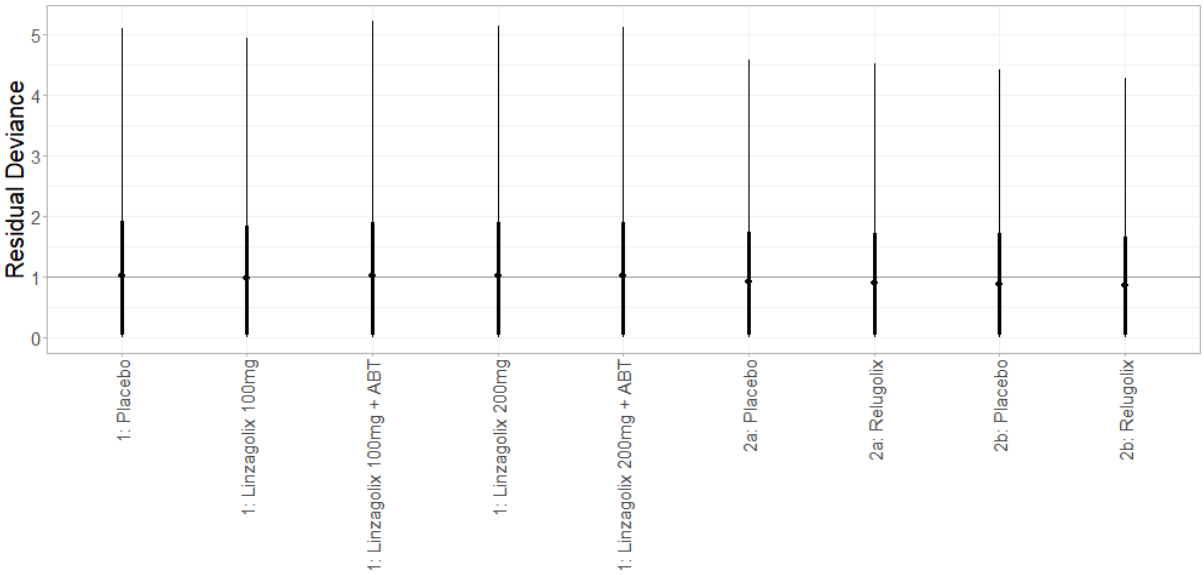
Abbreviations: ABT, add-back therapy; CrI, credible interval; DIC, deviance information criteria; mg, milligram; pD, the effective number of parameters; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

Figure 14: Forest plot for median mean differences and 95% CrI from the fixed-effects network meta-analysis for percentage change in menstrual blood loss

Note: results presented in the figure demonstrate the log odds ratios as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

Figure 15: Residual deviance from the fixed-effects network meta-analysis for percentage change in menstrual blood loss



Note: results presented in the figure demonstrate the residual deviances as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

B.2.9.6.3 Pain - numerical rating scale (NRS) score ≤ 1 for participants with an NRS score ≥ 4 at baseline

Results were consistent between the fixed-effects and random-effects models (see Appendix D.3.5.3), with no meaningful difference in model fit between the two (fixed-effects DIC = 16.58; random-effects DIC = 17.67). The fixed-effects model, with the smallest DIC value, was therefore determined to be the most appropriate model and also appears to be a visually good fit, with residual deviance values being very small and close to 1 (see Figure 17).

Based on the findings of the NMA (Table 28), the available evidence does not indicate a difference in efficacy between any linzagolix regimen versus relugolix CT as all 95% CrIs contain 1. The log odds ratios are presented in Figure 16, which visually demonstrates these results.

The estimated R-hat statistics reported by the NMA are 1.00, meaning there is little to no disagreement in the chain estimates suggesting that the NMA model converged successfully.

Table 28: Fixed-effects network meta-analysis for pain

Median odds ratio (95% CrI)	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 100 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Model fit statistics: Residual deviance = 8.56; pD = 8.02; DIC = 16.58		

Abbreviations: ABT, add-back therapy; CrI, credible interval; DIC, deviance information criteria; mg, milligram; pD, the effective number of parameters; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

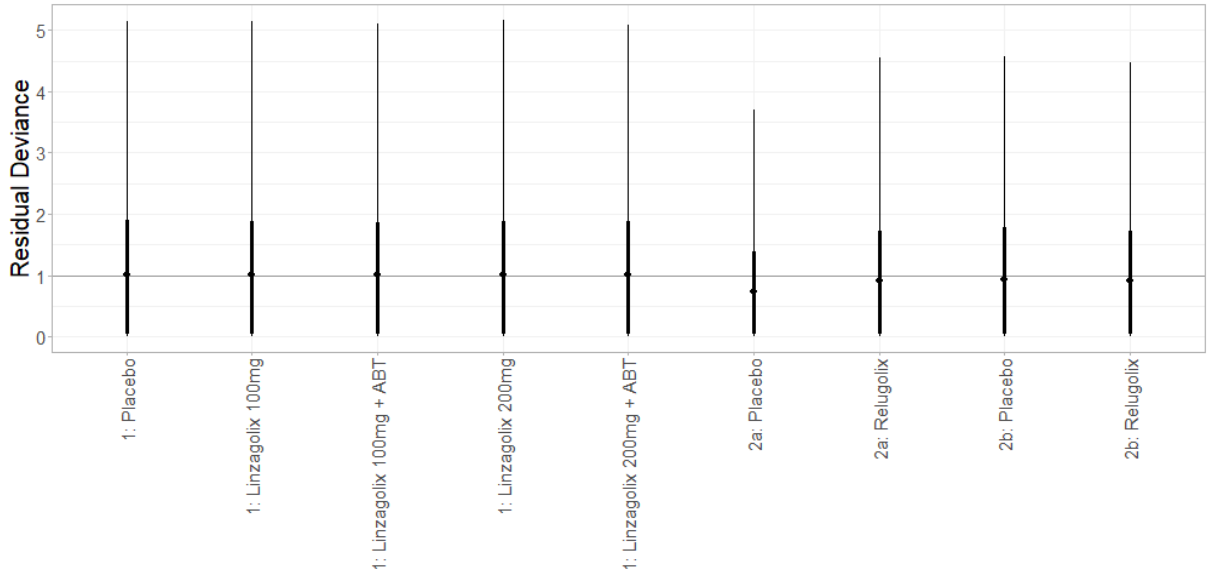
Figure 16: Forest plot for median Log ORs and 95% CrI from the fixed-effects network meta-analysis for pain

[redacted]

Note: results presented in the figure demonstrate the log odds ratios as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; OR, odds ratio; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

Figure 17: Residual deviance from the fixed-effects network meta-analysis for pain



Note: results presented in the figure demonstrate the residual deviances as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

B.2.9.6.4 Primary fibroid volume (largest fibroid at baseline) percentage change from baseline

It should be noted that inspection of the primary fibroid volume suggested that the data were not normally distributed, with some very small, and some very large values, and so the assumption of normality made in general linear model fitting was violated. As such, the percentage change in log-transformed primary fibroid volume was considered instead and then back-transformed onto the natural scale. The log-transformed primary fibroid volume data appeared consistent with an assumption of normality, resulting in a more appropriate estimate of the fibroid volume standard error. More details can be found in Appendix D.3.5.1.

Results were consistent between the fixed-effects and random-effects models (see Appendix D.3.5.3), with no meaningful difference in model fit between the two (fixed-effects DIC = 16.00; random-effects DIC = 16.48). The fixed-effects model, with smallest DIC, was therefore determined to be the most appropriate model and also appears to be a visually good fit, with residual deviance values being very small and close to 1 (see Figure 19).

Although it should be noted that the NMA estimated a high probability (≥95%) that linzagolix 200mg achieves a larger reduction in the percentage change in fibroid volume than patients treated with relugolix CT (mean difference = [redacted]; 95% CrI does not contain zero), for the remaining linzagolix regimens this is not the case (Table 29). For the comparison of linzagolix 100 mg, 100 mg + ABT, and 200 mg + ABT, the CrIs contain zero within their bounds meaning that the available evidence does not indicate a difference in efficacy

between these linzagolix regimens versus relugolix CT. These results are shown visually in Figure 18.

The estimated R-hat statistics reported by the NMA are 1.00, meaning there is little to no disagreement in the chain estimates suggesting that the NMA model converged successfully.

Table 29: Fixed-effects network meta-analysis for percentage change in primary fibroid volume

Median relative effect (95% CrI)	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 100 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Model fit statistics: Residual deviance = 8.01; pD = 7.98; DIC = 16.00		

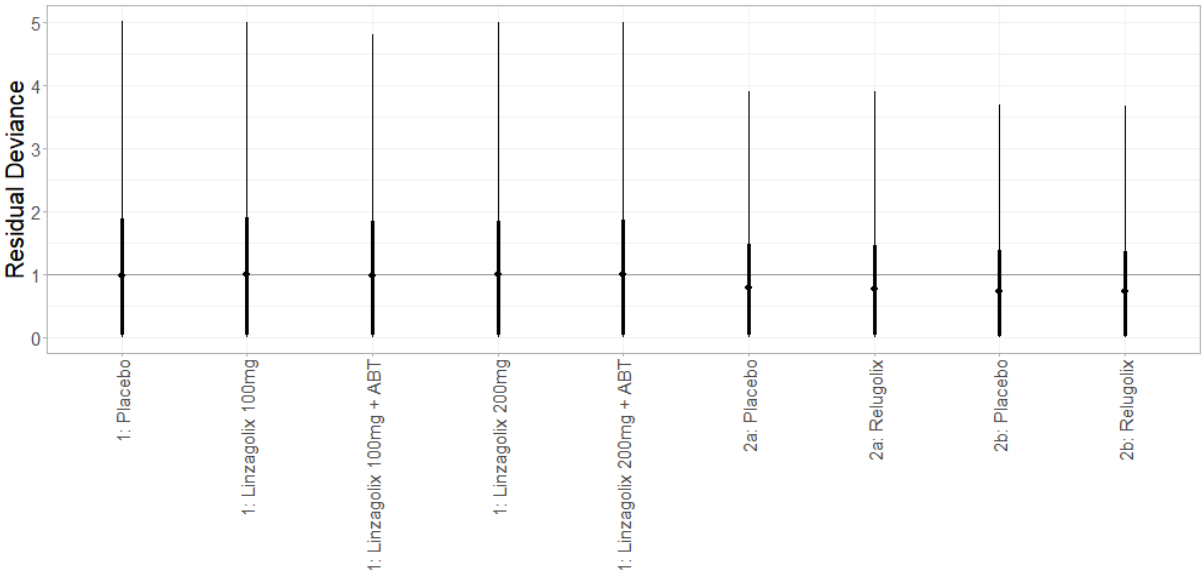
Abbreviations: ABT, add-back therapy; CrI, credible interval; DIC, deviance information criteria; mg, milligram; pD, the effective number of parameters; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

Figure 18: Forest plot for median mean differences and 95% CrI from the fixed-effects network meta-analysis for percentage change in primary fibroid volume

Note: results presented in the figure demonstrate the log odds ratios as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

Figure 19: Residual deviance from the fixed-effects network meta-analysis for percentage change in primary fibroid volume



Note: results presented in the figure demonstrate the residual deviances as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

B.2.9.6.5 Haemoglobin percentage change from baseline for participants with haemoglobin ≤10.5g/dL at baseline

Results were consistent between the fixed-effects and random-effects models (see Appendix D.3.5.3), with no meaningful difference in model fit between the two (fixed-effects DIC = 18.05; random-effects DIC = 18.09). The fixed-effects model, with smallest DIC, was therefore determined to be the most appropriate model and also appears to be a visually good fit, with residual deviance values being very small and close to 1 (see Figure 21).

Based on the findings of the NMA (Table 30), the available evidence does not indicate a difference in efficacy between any linzagolix regimen versus relugolix CT as all 95% CrIs contain zero. These results are shown visually in Figure 20.

The estimated R-hat statistics reported by the NMA are 1.00, meaning there is little to no disagreement in the chain estimates suggesting that the NMA model converged successfully.

Table 30: Fixed-effects network meta-analysis for percentage change in haemoglobin

Median relative effect (95% CrI)	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 100 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Model fit statistics: Residual deviance = 10.14; pD = 7.91; DIC = 18.05		

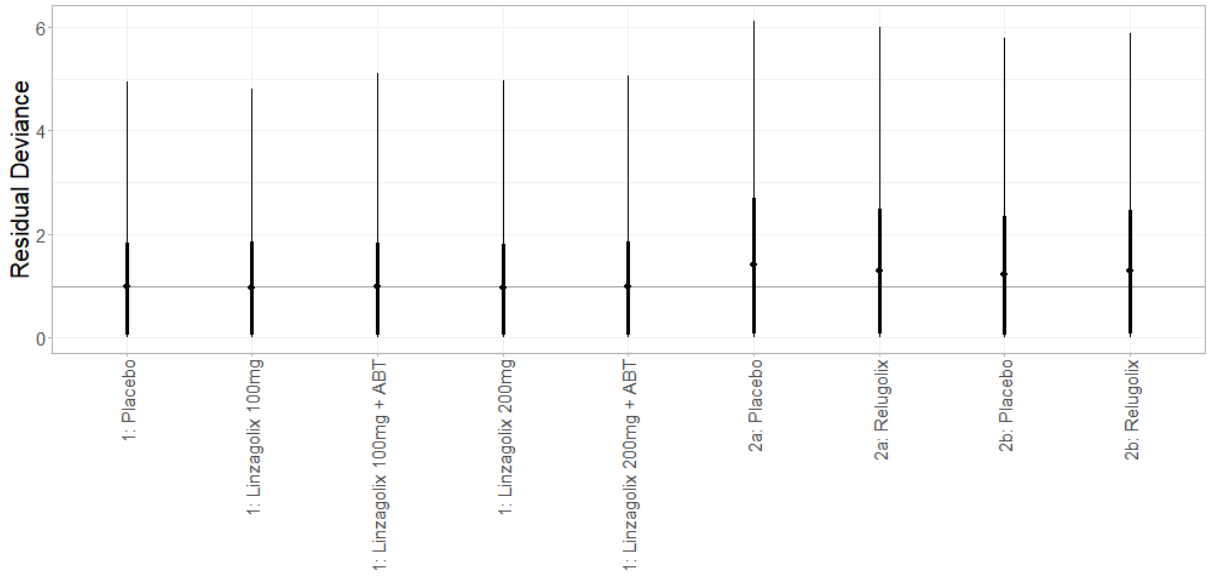
Abbreviations: ABT, add-back therapy; CrI, credible interval; DIC, deviance information criteria; mg, milligram; pD, the effective number of parameters; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

Figure 20: Forest plot for median mean differences and 95% CrI from the fixed-effects network meta-analysis for percentage change in haemoglobin

Note: results presented in the figure demonstrate the log odds ratios as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

Figure 21: Residual deviance from the fixed-effects network meta-analysis for percentage change in haemoglobin



Note: results presented in the figure demonstrate the residual deviances as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

B.2.9.6.6 Uterine fibroid symptom and quality of life (UFS-QoL) total score, change from baseline

Results were consistent between the fixed-effects and random-effects models (see Appendix D.3.5.3), with no meaningful difference in model fit between the two (fixed-effects DIC = 16.06; random-effects DIC = 16.77). The fixed-effects model, with smallest DIC, was therefore determined to be the most appropriate model and also appears to be a visually good fit, with residual deviance values being very small and close to 1 (see Figure 23).

Although the NMA estimated a high probability (≥95%) that linzagolix 100 mg and 100 mg + ABT achieve a smaller increase in UFS-QoL than patients treated with relugolix CT (mean differences = [redacted] and [redacted], respectively; 95% CrIs do not contain zero), this is not the case for all comparisons (Table 31). For the comparison of linzagolix 200 mg and 200 mg + ABT, the CrIs contain zero within their bounds meaning that the available evidence does not indicate a difference in efficacy between these linzagolix regimens versus relugolix CT. These results are shown visually in Figure 22.

The estimated R-hat statistics reported by the NMA are 1.00, meaning there is little to no disagreement in the chain estimates suggesting that the NMA model converged successfully.

Table 31: Fixed-effects network meta-analysis for change in uterine fibroid symptom and quality of life (UFS-QoL) total score

Median relative effect (95% CrI)	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 100 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Model fit statistics: Residual deviance = 8.06; pD = 8.00; DIC = 16.06		

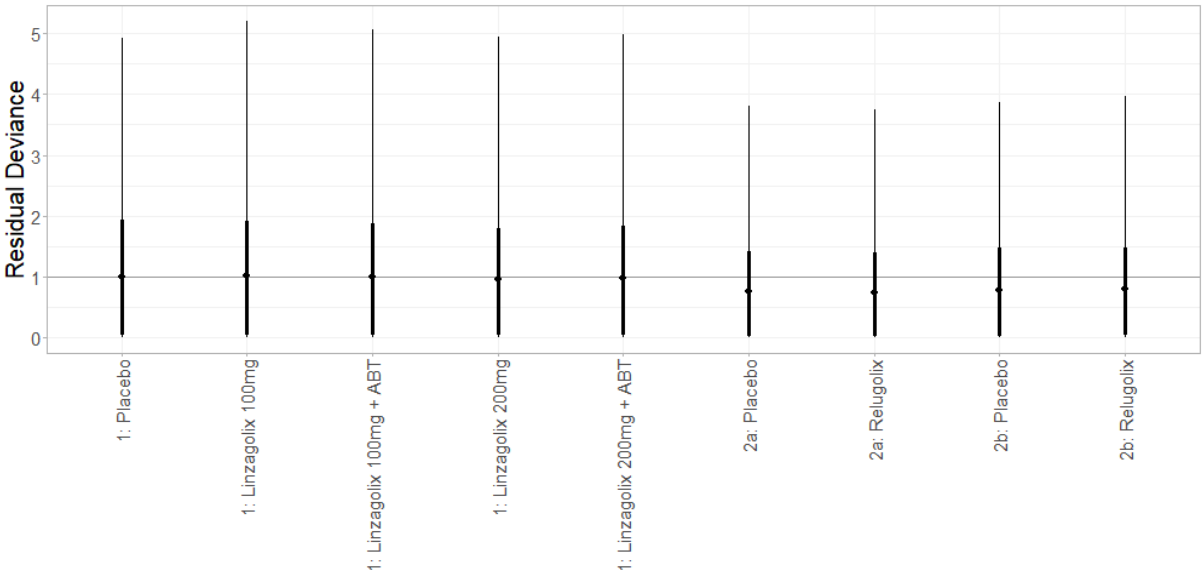
Abbreviations: ABT, add-back therapy; CrI, credible interval; DIC, deviance information criteria; mg, milligram; pD, the effective number of parameters; UFS-QoL, Uterine Fibroid Symptom-Quality of Life questionnaire; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

Figure 22: Forest plot for median relative effect and 95% CrI from the fixed-effects network meta-analysis for change in uterine fibroid symptom and quality of life (UFS-QoL) total score

Note: results presented in the figure demonstrate the log odds ratios as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; UFS-QoL, Uterine Fibroid Symptom-Quality of Life questionnaire; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

Figure 23: Residual deviance from the fixed-effects network meta-analysis for change in uterine fibroid symptom and quality of life (UFS-QoL) total score



Note: results presented in the figure demonstrate the residual deviances as point estimates, 66% CrIs (thick horizontal lines) and 95% CrIs (thin horizontal lines)
Note: 'relugolix' is referring to relugolix CT

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; UFS-QoL, Uterine Fibroid Symptom-Quality of Life questionnaire; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate)

B.2.9.7 Uncertainties in the indirect and mixed treatment comparisons

There are some limitations of the NMA that should be noted. Firstly, although there was generally good alignment between the trials, the proportion of Black patients differed between the PRIMROSE and LIBERTY studies (approximately 35% across arms in the pooled PRIMROSE data [approximately 63% versus 5% across arms in PRIMROSE 1 and PRIMROSE 2, respectively] versus 47% and 42% across arms in LIBERTY 1 and LIBERTY 2, respectively). There were also some more minor differences, including: the proportion of Hispanic or Latino patients, mean baseline MBL, uterine volume, fibroid volume, and the proportion of patients with a pain score ≥4 (see Appendix D.3.4.1). To address the uncertainty caused by these differences in the patient populations, an anchored matching-adjusted indirect treatment comparison (MAIC) was performed where the patients in the pooled PRIMROSE data were reweighted so that the baseline characteristics better aligned with the LIBERTY studies. This was done by matching on the proportion of Black patients, uterine volume, total fibroid volume, MBL, and haemoglobin. These matching variables were selected as possible treatment effect modifiers, based on clinical advice from Theramex medial colleagues. The adjusted results are presented in Appendix D.3.8 and demonstrate results that are broadly consistent with the findings of the NMA.

In addition to there being some small differences between the PRIMROSE and LIBERTY trials at baseline, there were also differences in the methods used to collect sanitary products from patients and the approach to analysing the data collected. These factors may mean that the NMA outcomes for MBL are a conservative estimate of the relative effectiveness of linzagolix versus relugolix CT.

Firstly, in the LIBERTY trials, patients were required to collect their used sanitary products and return them at each 4-weekly follow-up visit, whereas patients in the PRIMROSE trials

were required to return their used sanitary products more frequently (either once their collection box was full or within a maximum of 12-days after using the products). With patients on the placebo arm experiencing more blood loss than patients receiving the active treatment, there is greater burden to return all used products (as set out in the constraints of the PRIMROSE 1 and 2 trial protocol). Hence, there is a risk that some patients, particularly those on placebo, may not have returned all products for logistic reasons. This means that it is possible that patients in PRIMROSE 1 and 2 had higher levels of bleeding than captured (which will be more apparent in those on placebo), thus leading to the relative treatment effect of linzagolix versus placebo being an underestimation. Given the approach is less burdensome for patients in the LIBERTY trials, this risk of underestimation is lower, meaning the overall relative effect of linzagolix versus relugolix CT (with the placebo arm forming the treatment network) may be underestimated.

Secondly, missing values for MBL in the LIBERTY trials were imputed using a mixed-effects model to predict percent change in MBL volume from baseline. This is contrary to the approach taken in the PRIMROSE trials, which assumes that patients who had not returned any used products and thus had no MBL were considered as having experienced no bleeding. Again, this creates a conservative approach to understanding the relative effective of linzagolix versus placebo. This difference in MBL derivation further supports the argument that the results of the NMA for the bleeding-related endpoints are likely conservative in terms of the relative treatment effect of linzagolix versus relugolix CT.

Additionally, there were also differences in the timings used to determine a patients MBL and therefore response status; in the LIBERTY trials, MBL is calculated based on the 35-days prior to follow-up, whereas in the PRIMROSE trials MBL is calculated based on the prior 28-days. This minor difference in endpoint definitions may lead to differences in MBL and response rate between the studies, but the direction and magnitude of this potential bias is unclear. However, as the definitions are consistent for all treatment arms within the PRIMROSE and LIBERTY trials, it is reasonable to assume that there should be very little impact on the relative treatment effect of linzagolix or relugolix CT versus placebo (within each respective trial) and as such it is expected that this difference will have a minimal impact on the findings of the NMA.

Finally, the network in the analysis was also small, containing few studies which leads to relatively large uncertainty intervals, as can be seen in the analysis results. Also, as there were no head-to-head data available comparing relugolix CT and linzagolix directly in RCTs, the analysis relies solely upon indirect evidence, and as a result the innate limitations accompanying indirect comparison are present.

Despite the above limitations, the analysis used the available data to produce an indirect treatment comparison in line with NICE guidance and was based on data from high-quality randomised trials, to estimate the relative efficacy of linzagolix versus the relevant treatments for moderate to severe symptoms of UFs and so is appropriate to support decision making.

B.2.9.8 Conclusions of the NMA

Overall, linzagolix consistently demonstrated higher efficacy in treating moderate to severe symptoms of UFs than placebo, across all outcomes. Further to this, the outcomes of the NMA from the available evidence does not generally indicate any expected differences in treatment efficacy for linzagolix when compared with relugolix CT, with the majority of comparative results having shown no substantial differences between the treatment arms.

Although it should be noted that the NMA estimated linzagolix 200mg to have a high probability of achieving larger fibroid shrinkage compared to relugolix CT.

For example, in the comparison of response, those treated with linzagolix 100 mg, 100 mg + ABT, and 200 mg achieved a smaller response rate than those treated with relugolix CT, but those treated with linzagolix 200 mg + ABT achieved a larger response rate; however, the estimate of no effect was contained within the CrIs for the comparison of linzagolix 100 mg + ABT, 200 mg, and 200 mg + ABT versus relugolix CT, meaning the available evidence does not indicate a difference in efficacy between these linzagolix regimens versus relugolix CT in terms of achieving a response.

Additionally, in the comparison of fibroid volume, those treated with linzagolix 100 mg, 200 mg, and 200 mg + ABT achieved a larger decrease in fibroid volume than those treated with relugolix CT, but those treated with linzagolix 100 mg + ABT achieved a smaller decrease in fibroid volume; however the estimate of no effect was contained within the CrIs for linzagolix 100 mg, 100 mg + ABT, and 200 mg + ABT versus relugolix CT, meaning the available evidence does not indicate a difference in efficacy between these linzagolix regimens versus relugolix CT in terms of reducing fibroid volume.

Overall, the results across all NMAs, which considered six outcomes and compared four linzagolix regimens versus relugolix CT, suggested that any differences between linzagolix and relugolix CT are unlikely to be substantial, with the majority of comparisons not showing a high probability of there being a difference in efficacy between linzagolix versus relugolix CT.

B.2.10 Adverse reactions

Pooled safety data (PRIMROSE 1 and 2) are presented in this section. The safety data from the individual trials is provided in Appendix M. Week 24 results are for the first treatment period (Day 1 to Week 24), Week 52 results are for the second treatment period (Week 24 to Week 52).

B.2.10.1 Treatment period: Week 24 and Week 52

B.2.10.1.1 Treatment compliance and exposure

In the pooled analysis, mean overall compliance was high (98.7% and 99.3% at Week 24 and Week 52, respectively).[55] A summary of pooled treatment exposure at Week 24 and Week 52 is provided in Table 32 and Table 33, respectively.

Table 32: PRIMROSE 1 and 2 pooled | Summary of treatment exposure Week 24 (Pooled SAS)

Treatment duration (weeks) per eDiary	Pooled PRIMROSE 1 and 2				
	Placebo n=209	LGX 100 mg n=199	LGX 100 mg + ABT n=211	LGX 200 mg n=210	LGX 200 mg + ABT n=208
Mean (SD)	21.07 (6.71)	20.85 (7.11)	20.23 (7.43)	20.83 (7.38)	21.01 (7.28)
Median	24.00	24.14	24.00	24.14	24.14

Abbreviations: ABT, add-back therapy; eDiary, electronic diary; LGX, linzagolix; mg, milligram; SAS, safety analysis set; SD, standard deviation
Source: PRIMROSE 1 and 2 pooled analyses[55]

Table 33: PRIMROSE 1 and 2 pooled | Summary of treatment exposure Week 52 (Pooled Week 52 SAS)

Treatment duration (weeks) per eDiary	Pooled PRIMROSE 1 and 2					
	Placebo n=31	Placebo/LGX 200 mg + ABT n=123	LGX 100 mg n=141	LGX 100 mg + ABT n=146	LGX 200 mg/LGX 200 mg + ABT n=161	LGX 200 mg + ABT n=154
Mean (SD)	24.50 (6.48)	23.62 (8.10)	23.72 (7.88)	23.47 (7.80)	22.21 (8.10)	24.82 (6.75)
Median	27.43	27.57	27.29	27.07	26.86	27.71

Abbreviations: ABT, add-back therapy; eDiary, electronic diary; LGX, linzagolix; mg, milligram; SAS, safety analysis set; SD, standard deviation
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.10.1.2 Summary of treatment-emergent adverse events

A summary of TEAEs at Week 24 and Week 52 for the pooled analysis is provided in Table 34 and Table 35.

At Week 24:

- Incidence of TEAEs was slightly higher across the linzagolix treatment groups compared to the placebo group (Table 34)
- Most TEAEs were mild or moderate in severity
- Incidence of severe TEAEs and SAEs was low (Table 34)
- Incidence of TEAEs leading to permanent treatment discontinuation was low and similar in the linzagolix treatment groups and the placebo groups (Table 34)
- No fatal TEAEs occurred in any treatment group (Table 34).

Table 34: PRIMROSE 1 and 2 pooled | Summary of TEAEs Week 24 (Pooled SAS)

Event	Pooled PRIMROSE 1 and 2				
	Placebo n=209 n (%)	LGX 100 mg n=199 n (%)	LGX 100 mg + ABT n=211 n (%)	LGX 200 mg n=210 n (%)	LGX 200 mg + ABT n=208 n (%)
Any TEAE	103 (49.3)	115 (57.8)	107 (50.7)	133 (63.3)	115 (55.3)
TEAE leading to permanent treatment discontinuation	17 (8.1)	14 (7.0)	17 (8.1)	22 (10.5)	17 (8.2)
Serious TEAE	4 (1.9)	4 (2.0)	5 (2.4)	1 (0.5)	4 (1.9)
Severe TEAE	11 (5.3)	10 (5.0)	9 (4.3)	15 (7.1)	6 (2.9)
Fatal TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ABT, add-back therapy; LGX, linzagolix; mg, milligram; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: PRIMROSE 1 and 2 pooled analyses[55]

At Week 52:

- Overall, fewer TEAEs were reported than at Week 24, despite the fact that most patients were on active therapy after Week 24 (Table 35)
- Incidence of TEAEs was fairly consistent across the treatment groups and no apparent dose dependency in terms of TEAEs was observed (Table 35)
- Similar to Week 24, most of the TEAEs were mild to moderate in severity
- Incidence of severe TEAEs and SAEs was low, and incidence was lower than at Week 24 (Table 34 and Table 35)
- No fatal TEAEs occurred in any treatment group (Table 35).

Table 35: PRIMROSE 1 and 2 pooled | Summary of TEAEs Week 52 (Pooled Week 52 SAS)

Event	Pooled PRIMROSE 1 and 2					
	Placebo n=31 n (%)	Placebo/ LGX 200 mg + ABT n=123 n (%)	LGX 100 mg n=141 n (%)	LGX 100 mg + ABT n=146 n (%)	LGX 200 mg/LGX 200 mg + ABT n=161 n (%)	LGX 200 mg + ABT n=154 n (%)
Any TEAE	12 (38.7)	46 (37.4)	47 (33.3)	54 (37.0)	67 (41.6)	46 (29.9)
TEAE leading to permanent treatment discontinuation	1 (3.2)	8 (6.5)	9 (6.4)	9 (6.2)	13 (8.1)	2 (1.3)
Serious TEAE	0 (0.0)	3 (2.4)	2 (1.4)	5 (3.4)	5 (3.1)	2 (1.3)
Severe TEAE	0 (0.0)	4 (3.3)	5 (3.5)	8 (5.5)	4 (2.5)	3 (1.9)
Fatal TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: ABT, add-back therapy; LGX, linzagolix; mg, milligram; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.10.1.3 Most common treatment-emergent adverse events

The most common TEAEs in the pooled analysis across treatment groups at Week 24 are provided in Table 36. Hot flushes were the most common TEAE (14.6% overall), followed by headache (7.7% overall) and anaemia (6.0% overall) at Week 24.[55]

The incidence of hot flushes was dose-dependent and higher in the linzagolix without ABT groups compared with linzagolix with ABT, demonstrating that the use of ABT mitigates estrogen suppression-related TEAEs.[72] Headache was reported with a higher incidence in the 200 mg group (11.9%) compared with placebo (5.7%) and other linzagolix groups (≤7.7%), which could suggest a dose exposure response with respect to estradiol depletion.[55,72] Anaemia is an expected TEAE in this patient population.[56]

Table 36: PRIMROSE 1 and 2 pooled | Most common TEAEs (reported by >2% in at least one active treatment group) Week 24 (Pooled SAS)

TEAE	Pooled PRIMROSE 1 and 2				
	Placebo n=209 n (%)	LGX 100 mg n=199 n (%)	LGX 100 mg + ABT n=211 n (%)	LGX 200 mg n=210 n (%)	LGX 200 mg + ABT n=208 n (%)
Hot flush	11 (5.3)	20 (10.1)	11 (5.2)	70 (33.3)	20 (9.6)
Hypertension	4 (1.9)	5 (2.5)	9 (4.3)	6 (2.9)	5 (2.4)
Headache	12 (5.7)	12 (6.0)	11 (5.2)	25 (11.9)	16 (7.7)
Dizziness	3 (1.4)	4 (2.0)	4 (1.9)	1 (0.5)	2 (1.0)
Pelvic pain	5 (2.4)	6 (3.0)	5 (2.4)	6 (2.9)	5 (2.4)
Vaginal haemorrhage	3 (1.4)	2 (1.0)	7 (3.3)	3 (1.4)	5 (2.4)
Metrorrhagia	0 (0.0)	3 (1.5)	3 (1.4)	1 (0.5)	5 (2.4)
Vulvovaginal dryness	0 (0.0)	1 (0.5)	2 (0.9)	5 (2.4)	0 (0.0)
Anaemia	14 (6.7)	20 (10.1)	11 (5.2)	6 (2.9)	13 (6.3)
GGT increased	5 (2.4)	8 (4.0)	4 (1.9)	6 (2.9)	5 (2.4)
ALT increased	3 (1.4)	5 (2.5)	3 (1.4)	6 (2.9)	5 (2.4)
AST increased	2 (1.0)	4 (2.0)	1 (0.5)	3 (1.4)	5 (2.4)
Blood CPK increased	3 (1.4)	2 (1.0)	1 (0.5)	3 (1.4)	7 (3.4)
Nausea	2 (1.0)	3 (1.5)	7 (3.3)	11 (5.2)	4 (1.9)
Abdominal pain upper	3 (1.4)	1 (0.5)	7 (3.3)	1 (0.5)	0 (0.0)
Arthralgia	5 (2.4)	5 (2.5)	2 (0.9)	6 (2.9)	5 (2.4)
Back pain	3 (1.4)	3 (1.5)	3 (1.4)	6 (2.9)	2 (1.0)
Nasopharyngitis	5 (2.4)	6 (3.0)	3 (1.4)	3 (1.4)	8 (3.8)
Urinary tract infection	3 (1.4)	5 (2.5)	2 (0.9)	1 (0.5)	1 (0.5)
Fatigue	4 (1.9)	1 (0.5)	3 (1.4)	5 (2.4)	3 (1.4)
Mood swings	3 (1.4)	4 (2.0)	1 (0.5)	3 (1.4)	1 (0.5)
Hyperhidrosis	1 (0.5)	2 (1.0)	0 (0.0)	7 (3.3)	0 (0.0)

Abbreviations: ABT, add-back therapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; GGT, gamma-glutamyl transferase; LGX, linzagolix; mg, milligram; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: Linzagolix EPAR[56]

The most common TEAEs in the pooled analysis across treatment groups at Week 52 are provided in Table 37. The incidence of hot flushes was low across all treatment groups at Week 52. Incidence of headache and anaemia was lower at Week 52 than at Week 24, and there was no incidence of hyperhidrosis (Table 36 and Table 37). The most common TEAE at Week 52 was hypertension (2.8% overall), followed by vaginal haemorrhage and bone density decreased (both 2.0% overall).[55]

Table 37: PRIMROSE 1 and 2 pooled | Most common TEAEs (reported by >2% in at least one active treatment group) Week 52 (Pooled Week 52 SAS)

TEAE	Pooled PRIMROSE 1 and 2					
	Placebo n=31 n (%)	Placebo/LGX 200 mg + ABT n=123 n (%)	LGX 100 mg n=141 n (%)	LGX 100 mg + ABT n=146 n (%)	LGX 200 mg/LGX 200 mg + ABT n=161 n (%)	LGX 200 mg + ABT n=154 n (%)
Vaginal haemorrhage	0 (0.0)	1 (0.8)	3 (2.1)	1 (0.7)	7 (4.3)	1 (0.6)
Pelvic pain	0 (0.0)	2 (1.6)	2 (1.4)	2 (1.4)	5 (3.1)	0 (0.0)
Menorrhagia	0 (0.0)	3 (2.4)	2 (1.4)	1 (0.7)	4 (2.5)	1 (0.6)
Metrorrhagia	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	4 (2.5)	0 (0.0)
Dysmenorrhoea	0 (0.0)	2 (1.6)	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Uterine haemorrhage	0 (0.0)	4 (3.3)	0 (0.0)	1 (0.7)	1 (0.6)	0 (0.0)
Nasopharyngitis	3 (9.7)	3 (2.4)	3 (2.1)	3 (2.1)	2 (1.2)	3 (1.9)
Urinary tract infection	1 (3.2)	2 (1.6)	2 (1.4)	3 (2.1)	1 (0.6)	2 (1.3)
Bronchitis	0 (0.0)	0 (0.0)	1 (0.7)	3 (2.1)	1 (0.6)	0 (0.0)
Vaginal infection	1 (3.2)	0 (0.0)	3 (2.1)	0 (0.0)	2 (1.2)	0 (0.0)
Hypertension	0 (0.0)	1 (0.8)	4 (2.8)	7 (4.8)	3 (1.9)	3 (1.9)
Hot flush	0 (0.0)	3 (2.4)	3 (2.1)	2 (1.4)	1 (0.6)	3 (1.9)
Bone density decreased	1 (3.2)	2 (1.6)	4 (2.8)	2 (1.4)	5 (3.1)	1 (0.6)
Blood CPK increased	0 (0.0)	3 (2.4)	1 (0.7)	2 (1.4)	0 (0.0)	4 (2.6)
Weight increased	0 (0.0)	1 (0.8)	0 (0.0)	3 (2.1)	0 (0.0)	1 (0.6)
Anaemia	1 (3.2)	9 (7.3)	2 (1.4)	4 (2.7)	3 (1.9)	1 (0.6)
Headache	1 (3.2)	2 (1.6)	4 (2.8)	2 (1.4)	2 (1.2)	1 (0.6)
Arthralgia	2 (6.5)	0 (0.0)	0 (0.0)	3 (2.1)	3 (1.9)	1 (0.6)

Abbreviations: ABT, add-back therapy; CPK, creatine phosphokinase; LGX, linzagolix; mg, milligram; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.10.1.4 Linzagolix-related TEAEs

In the pooled analysis, TEAEs considered possibly related to linzagolix by investigators were reported in 269 patients (25.9%) at Week 24 (Table 38).[55] The most common linzagolix-related TEAEs were hot flushes, a known hypoestrogenic symptom, headache, vaginal haemorrhage and alanine aminotransferase (ALT) increased at Week 24 (Table 38).[55] The linzagolix 100 mg dose (with or without ABT) and the linzagolix 200 mg dose with ABT were associated with a low incidence of hot flushes, whereas >30.0% of patients on the linzagolix 200 mg dose had hot flushes (Table 38).[55]

Table 38: PRIMROSE 1 and 2 pooled | Linzagolix-related TEAEs Week 24 (Pooled SAS)

TEAE	Pooled PRIMROSE 1 and 2				
	Placebo n=209 n (%)	LGX 100 mg n=199 n (%)	LGX 100 mg + ABT n=211 n (%)	LGX 200 mg n=210 n (%)	LGX 200 mg + ABT n=208 n (%)
Patients with ≥1 linzagolix-related TEAE	30 (14.4)	48 (24.1)	46 (21.8)	88 (41.9)	57 (27.4)
Hot flush	8 (3.8)	21 (10.1)	11 (5.2)	65 (31.0)	20 (9.6)
Headache	5 (2.4)	8 (4.0)	3 (1.4)	13 (6.2)	5 (2.4)
Vaginal haemorrhage	1 (0.5)	2 (1.0)	5 (2.4)	2 (1.0)	4 (1.9)
ALT increased	2 (1.0)	3 (1.5)	1 (0.5)	4 (1.9)	2 (1.0)

Abbreviations: ABT, add-back therapy; ALT, alanine aminotransferase; LGX, linzagolix; mg, milligram; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: PRIMROSE 1 and 2 pooled analyses[55]

In the pooled analysis, TEAEs considered to be possibly related to linzagolix by investigators were reported in 83 patients (11.0%) at Week 52.[55] The most common linzagolix-related TEAEs were bone density decreased, vaginal haemorrhage and hot flushes at Week 52 (Table 39).[55] Hot flushes were reported much less frequently at Week 52 than at Week 24.

Table 39: PRIMROSE 1 and 2 pooled | Linzagolix-related TEAEs Week 52 (Pooled Week 52 SAS)

TEAE	Pooled PRIMROSE 1 and 2					
	Placebo n=31 n (%)	Placebo/LGX 200 mg + ABT n=123 n (%)	LGX 100 mg n=141 n (%)	LGX 100 mg + ABT n=146 n (%)	LGX 200 mg/LGX 200 mg + ABT n=161 n (%)	LGX 200 mg + ABT n=154 n (%)
Patients with ≥1 linzagolix-related TEAE	1 (3.2)	12 (9.8)	21 (14.9)	13 (8.9)	20 (12.4)	16 (10.4)
Bone density decreased	1 (3.2)	1 (0.8)	3 (2.1)	2 (1.4)	4 (2.5)	1 (0.6)
Vaginal haemorrhage	0 (0.0)	1 (0.8)	3 (2.1)	1 (0.7)	6 (3.7)	0 (0.0)
Hot flush	0 (0.0)	3 (2.4)	3 (2.1)	1 (0.7)	0 (0.0)	3 (1.9)

Abbreviations: ABT, add-back therapy; LGX, linzagolix; mg, milligram; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.10.2 Treatment discontinuation

In the pooled analysis, overall the incidence of TEAEs leading to permanent treatment discontinuation was low up to Week 24. Discontinuation rates were comparable to the placebo group (8.1%) for all linzagolix groups (7.0% to 10.5%) (Table 40).[55]

The most frequent TEAEs leading to permanent treatment discontinuation were headache (1.1%), hot flushes (1.1%), GGT increased (0.8%), nausea (0.7%), bone density decreased (0.5%), and migraine (0.5%) at Week 24.[72]

Table 40: Pooled PRIMROSE 1 and 2 | TEAEs leading to permanent treatment discontinuation Week 24 (Pooled SAS)

	Pooled PRIMROSE 1 and 2				
	Placebo n=209 n (%)	LGX 100 mg n=199 n (%)	LGX 100 mg + ABT n=211 n (%)	LGX 200 mg n=210 n (%)	LGX 200 mg + ABT n=208 n (%)
Patients with ≥1 TEAE leading to permanent discontinuation of trial drug	17 (8.1)	14 (7.0)	17 (8.1)	22 (10.5)	17 (8.2)

Abbreviations: ABT, add-back therapy; LGX, linzagolix; mg, milligram; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: PRIMROSE 1 and 2 pooled analyses[55]

The incidence of TEAEs leading to permanent discontinuation was lower for all linzagolix groups up to Week 52 than up to Week 24 (Table 41).

The most frequent TEAEs leading to permanent treatment discontinuation were related to BMD loss (i.e. preferred terms of bone density decreased) (1.3%) and vaginal haemorrhage (0.5%) up to Week 52.[56]

Table 41: Pooled PRIMROSE 1 and 2 | TEAEs leading to permanent treatment discontinuation Week 52 (Pooled Week 52 SAS)

TEAE	Pooled PRIMROSE 1 and 2					
	Placebo n=31 n (%)	Placebo/ LGX 200 mg + ABT n=123 n (%)	LGX 100 mg n=141 n (%)	LGX 100 mg + ABT n=146 n (%)	LGX 200 mg/LGX 200 mg + ABT n=161 n (%)	LGX 200 mg + ABT n=154 n (%)
Patients with ≥1 TEAE leading to permanent discontinuation of trial drug	1 (3.2)	8 (6.5)	9 (6.4)	9 (6.2)	13 (8.1)	2 (1.3)

Abbreviations: ABT, add-back therapy; LGX, linzagolix; mg, milligram; SAS, safety analysis set; TEAE, treatment-emergent adverse event
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.10.3 Serious adverse events

In the pooled analysis incidence of SAEs was low across the linzagolix and placebo treatment groups at Week 24 and Week 52.

At Week 24, 14 patients (1.7%) treated in the linzagolix groups reported 15 SAEs and four patients (1.9%), in the placebo group reported 5 SAEs.[55] Anaemia and uterine haemorrhage were the only SAEs reported by more than one patient: three patients (0.3% overall) and two patients (0.2% overall), for anaemia and uterine haemorrhage, respectively. All other SAEs

were reported by one patient each. There was one SAE related to linzagolix in the period up to Week 24 (hypertension in a subject in the 100 mg group).[72]

At Week 52, 17 patients (2.2%) reported 19 SAEs in the linzagolix groups with a similar frequency of SAEs across the linzagolix groups.[55] Of the 19 SAEs, two SAEs (0.9%) were considered related to linzagolix, one SAE of menorrhagia and one SAE of vaginal haemorrhage.[72]

B.2.10.4 Pregnancies

Women participating in PRIMROSE 1 and 2 could not be planning to become pregnant until the end of the trial and were required to use double non-hormonal barrier contraception from screening to 12 weeks after end of treatment if at risk of pregnancy.[25] Two pregnancies were reported during the trials: one woman became pregnant after completing 24 weeks of 200 mg linzagolix and voluntarily interrupted treatment (with no exposure to treatment when pregnant) and was lost to follow-up; the second became pregnant when taking 100 mg linzagolix (40 days of exposure when pregnant). She underwent an elective abortion because of foetal malformations consistent with chromosomal congenital anomalies, which were considered by the investigator as not related to the treatment.[25]

B.2.10.5 Clinical laboratory evaluation

B.2.10.5.1 Serum E2 levels

As described earlier, linzagolix reduces serum E2 in a dose-dependent manner (see Section B.1.2). These declines can result in dose-dependent BMD loss due to increased bone resorption, which is most pronounced with high doses when close to full E2 suppression is reached.[56] The aim of lower doses and the use of ABT with higher doses is to achieve E2 levels within a range that limits BMD loss (i.e. partial suppression of E2).[56]

As expected in the pooled analysis, serum E2 levels decreased promptly after the start of linzagolix treatment (Table 42). Median E2 levels for linzagolix 200 mg dose showed close to full suppression (<20 pg/mL) by Week 4 and was maintained at similar levels to Week 24. As expected, moderate reductions were observed with the linzagolix 100 mg, 100 mg + ABT and 200 mg + ABT groups (Table 42).

At Week 52, decreases below baseline levels were observed in the placebo/linzagolix 200 mg + ABT and linzagolix 200 mg groups. Increases in serum E2 levels towards baseline were seen in the linzagolix 100 mg + ABT and linzagolix 200 mg/200 mg + ABT groups. In the linzagolix 100 mg group serum E2 levels increased above baseline level (Table 43).

Table 42: Pooled PRIMROSE 1 and 2 | Serum E2 levels up to Week 24 (Pooled SAS)

E2 (pg/mL)	Pooled PRIMROSE 1 and 2				
	Placebo n=209 n (%)	LGX 100 mg n=199 n (%)	LGX 100 mg + ABT n=211 n (%)	LGX 200 mg n=210 n (%)	LGX 200 mg + ABT n=208 n (%)
Baseline					
Mean (SD)	86.6 (89.7)	66.5 (70.2)	75.2 (75.2)	75.4 (77.9)	79.0 (83.8)
Week 4					
Mean (SD)	104.7 (87.7)	56.5 (62.6)	59.0 (50.2)	21.2 (41.0)	59.8 (86.2)
Week 8					
Mean (SD)	126.2 (106.1)	55.6 (61.0)	58.4 (48.3)	25.2 (44.8)	52.8 (50.0)
Week 12					
Mean (SD)	112.7 (106.3)	57.5 (78.5)	57.7 (50.6)	25.8 (42.3)	51.3 (42.0)
Week 24					
Mean (SD)	125.9 (97.5)	64.0 (67.7)	59.6 (45.3)	27.8 (44.7)	48.5 (40.8)

Abbreviations: ABT, add-back therapy; E2, estradiol; LGX, linzagolix; mg, milligram; SAS, safety analysis set; SD, standard deviation
Source: PRIMROSE 1 and 2 pooled analyses[55]

Table 43: Pooled PRIMROSE 1 and 2 | Serum E2 levels up to Week 52 (Pooled Week 52 SAS)

E2 (pg/mL)	Pooled PRIMROSE 1 and 2					
	Placebo n=31 n (%)	Placebo/ LGX 200 mg + ABT n=123 n (%)	LGX 100 mg n=141 n (%)	LGX 100 mg + ABT n=146 n (%)	LGX 200 mg/ LGX 200 mg + ABT n=161 n (%)	LGX 200 mg + ABT n=154 n (%)
Baseline						
Mean (SD)	84.4 (72.5)	85.9 (94.3)	68.4 (73.2)	77.0 (78.7)	76.3 (74.7)	70.9 (63.9)
Week 24						
Mean (SD)	122.2 (108.6)	126.8 (95.5)	63.1 (67.8)	59.7 (45.6)	27.5 (44.7)	47.7 (38.7)
Week 52						
Mean (SD)	84.4 (69.5)	57.8 (64.8)	72.9 (83.7)	69.8 (61.7)	62.9 (71.9)	54.5 (56.2)

Abbreviations: ABT, add-back therapy; E2, estradiol; LGX, linzagolix; mg, milligram; SD, standard deviation; SAS, safety analysis set
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.10.6 Treatment-emergent adverse event of special interest

B.2.10.6.1 Bone mineral density

As expected, given the mechanism of action of linzagolix, changes in BMD were observed at all three anatomic sites (lumbar spine, femoral neck, and total hip). Overall, the observed changes in BMD were small, and were not considered to be clinically meaningful except in patients treated with linzagolix 200 mg. Furthermore, changes in BMD slowed after Week 24, were mitigated by the concomitant use of hormonal ABT, and showed evidence of recovery following treatment discontinuation.

Reductions in BMD were most prominent in the spine, which is known to be most sensitive to BMD change in the context of E2 decrease. At Week 24, there was a trend of dose-dependence, with the addition of ABT mitigating some of the BMD loss. The greatest reduction in BMD in the spine was in the linzagolix 200 mg group, followed by the linzagolix 100 mg group, with the smallest reduction in the linzagolix 200 mg + ABT, and linzagolix 100 mg + ABT groups (Table 44).

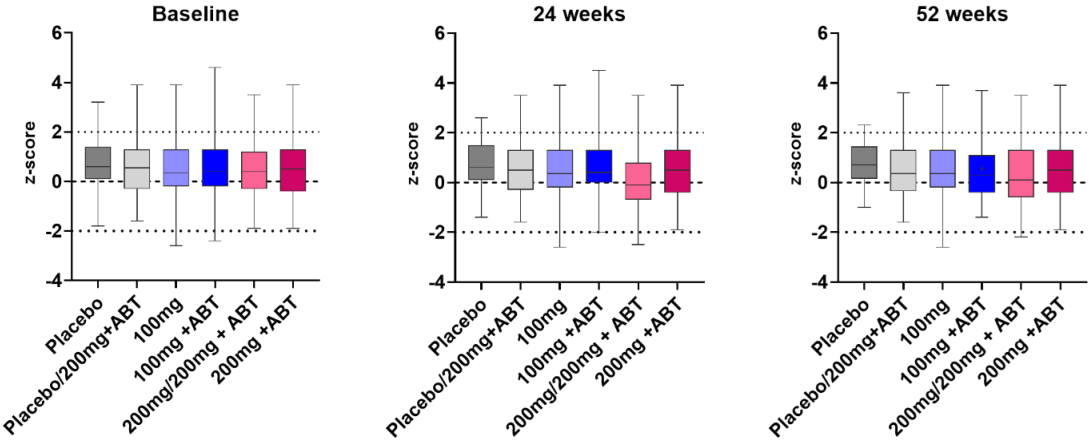
The linzagolix 200 mg dose was restricted to 6 months of treatment only due to the risk of BMD reduction. As expected, the addition of ABT limited the risk of BMD decrease. At Week 52, in general, the BMD decrease stabilised in the linzagolix groups compared with the first treatment period. The greatest reduction in BMD in the spine was in the linzagolix 200 mg/200 mg + ABT group, followed by the linzagolix 100 mg group, with the smallest reductions in the linzagolix 100 mg + ABT and placebo/linzagolix 200 mg + ABT groups (Table 45). While further decrease in BMD was seen in the groups that continued the same treatments after Week 24, the decrease was less rapid than that observed during the initial 24 weeks; this suggests that rates of BMD change may reach a plateau over time, as is seen during menopause.

Z-score data were assessed to provide important information on BMD of the study population compared to a reference group of women of the same age (z-score = number of standard deviations below or above BMD of a reference group of same age and gender. A woman with an average BMD has a z-score of zero and is at the 50th percentile). In the Pooled SAS, baseline z-scores for BMD were generally comparable across treatment groups. At Week 24, median absolute changes from baseline in z-scores for the lumbar spine were -0.20 for 100 mg, -0.15 for 100 mg + ABT, -0.40 for 200 mg, and -0.10 for 200 mg + ABT versus 0.00 for placebo.[55] For the total hip, median changes from baseline were -0.10 for 200 mg and 0.00 for all other groups, and for the femoral neck, median changes were -0.20 for 200 mg, -0.10 for 100 mg and 200 mg + ABT groups, and 0 for placebo and 100 mg + ABT groups.[55] Consistent with the small median BMD changes observed, median BMD z-scores at Week 24 remained ≥0, with the exception of a median of -0.10 in the 200 mg group for the lumbar spine: medians at Week 24 ranged from -0.10 to 0.55 for the lumbar spine (see Figure 24), from 0.50 to 0.60 for the total hip, and from 0.20 to 0.30 for the femoral neck.[55]

At Week 52, median absolute changes from baseline for the lumbar spine were -0.10 for placebo/200 mg + ABT, -0.20 for 100 mg, -0.1 for 100 mg + ABT, -0.3 for 200 mg/200 mg + ABT and -0.1 for 200 mg + ABT versus 0 for placebo.[55] Median z-scores at Week 52 were >0 for all groups (see Figure 24).[55] Similar patterns were observed for the femoral neck and the hip.[55]

See Appendix M for individual PRIMROSE 1 and 2 trial results.

Figure 24: Pooled PRIMROSE 1 and 2 | Lumbar spine BMD z-scores at baseline, Week 24 and Week 52 (Pooled Week 52 SAS)



Box plot shows median, 1st and 3rd quartiles, and the whiskers show minimum and maximum
Abbreviations: ABT, add-back therapy; BMD, bone mineral density; mg, milligram; SAS, safety analysis set
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.10.6.2 Off treatment period: Week 76

In the pooled analysis, at Week 76 (off treatment) a trend to reversibility of BMD loss was seen in patients with follow-up data. Recovery of BMD loss was slowest in patients who did not receive ABT.[56]

Table 44: Pooled PRIMROSE 1 and 2 | Percent change from baseline in BMD Week 24 (Pooled SAS)

	Pooled PRIMROSE 1 and 2				
	Placebo n=209	**LGX 100 mg n=199**	**LGX 100 mg + ABT n=211**	**LGX 200 mg n=210**	**LGX 200 mg + ABT n=208**
Lumbar spine (g/cm^2)					
Baseline					
Mean (SD)	1.103 (0.133)	1.095 (0.124)	1.101 (0.134)	1.093 (0.124)	1.092 (0.121)
% CFB at Week 24					
Mean (SD)	0.456 (2.285)	-1.985 (2.694)	-0.963 (2.696)	-3.697 (2.859)	-1.129 (2.690)
95% CI	0.060; 0.853	-2.470; -1.500	-1.446; -0.480	-4.178; -3.215	-1.601; -0.657
Total hip (g/cm^2)					
Baseline					
Mean (SD)	0.990 (0.143)	0.994 (0.139)	0.998 (0.130)	0.986 (0.135)	0.995 (0.139)
% CFB at Week 24					
Mean (SD)	0.437 (3.227)	-0.711 (2.864)	0.005 (2.471)	-1.564 (2.702)	-0.133 (2.924)
95% CI	-0.110; 0.985	-1,223; -0.200	-0.435; 0.444	-2.019; -1.110	-0.641; 0.374
Femoral neck (g/cm^2)					
Baseline					
Mean (SD)	0.917 (0.138)	0.910 (0.134)	0.905 (0.124)	0.905 (0.124)	0.907 (0.126)
% CFB at Week 24					
Mean (SD)	-0.139 (3.493)	-1.026 (3.599)	-0.440 (3.247)	-1.884 (3.627)	-0.631 (3.409)
95% CI	-0.732; 0.453	-1.668; -0.383	-1.018; 0.137	-2.494; -1.273	-1.222; -0.039

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; CFB, change from baseline; CI, confidence interval; cm^2, square centimetres; LGX, linzagolix; mg, milligram; SAS, safety analysis set; SD, standard deviation
Source: PRIMROSE 1 and 2 pooled analyses[55]

Table 45: Pooled PRIMROSE 1 and 2 | Percent change from baseline in BMD Week 52 (Pooled Week 52 SAS)

	Pooled PRIMROSE 1 and 2					
	Placebo n=31	**Placebo/ LGX 200 mg + ABT n=123**	**LGX 100 mg n=141**	**LGX 100 mg + ABT n=146**	**LGX 200 mg/ LGX 200 mg + ABT n=161**	**LGX 200 mg + ABT n=154**
Lumbar spine (g/cm^2)						
Baseline						
Mean (SD)	1.138 (0.131)	1.092 (0.130)	1.093 (0.120)	1.104 (0.132)	1.098 (0.119)	1.084 (0.120)
% CFB at Week 24						
Mean (SD)	0.184 (2.140)	0.571 (2.318)	-2.052 (2.708)	-0.900 (2.671)	-3.717 (2.879)	-1.103 (2.703)
95% CI	-0.699; 1.067	0.109; 1.034	-2.548; -1.556	-1.389; -0.411	-4.211; -3.223	-1.582; -0.625
% CFB at Week 52						
Mean (SD)	-0.851 (2.521)	-0.652 (2.906)	-2.310 (3.550)	-0.949 (2.127)	-2.676 (2.857)	-1.608 (3.052)
95% CI	-2.030; 0.329	-1.286; -0.017	-3.033; -1.587	-1.408; -0.490	-3.271; -2.081	-2.223; -0.993
Total hip (g/cm^2)						
Baseline						
Mean (SD)	1.029 (0.134)	0.969 (0.142)	0.994 (0.137)	0.999 (0.131)	0.991 (0.125)	0.986 (0.128)
% CFB at Week 24						
Mean (SD)	0.371 (4.264)	0.384 (2.974)	-0.737 (2.901)	-0.026 (2.505)	-1.582 (2.734)	-0.139 (2.946)
95% CI	-1.315; 2.058	-2.03; 0.971	-1.263; -0.210	-0.480; 0.429	-2.051; -1.113	-0.654; 0.376
% CFB at Week 52						
Mean (SD)	-0.613 (2.547)	0.279 (3.856)	-1.325 (3.385)	-0.078 (2.896)	-1.556 (2.980)	0.103 (2.736)
95% CI	-1.805; 0.579	-0.558; 1.115	-2.011; -0.639	-0.688; 0.531	-2.177; -0.936	-0.443; 0.649
Femoral neck (g/cm^2)						
Baseline						
Mean (SD)	0.948 (0.138)	0.908 (0.142)	0.905 (0.122)	0.906 (0.124)	0.910 (0.119)	0.895 (0.115)
% CFB at Week 24						
Mean (SD)	-0.548 (3.854)	0.026 (3.478)	-1.014 (3.649)	-0.426 (3.279)	-1.827 (3.665)	-0.580 (3.405)

95% CI	-2.073; 0.977	-0.661; 0.712	-1.677; -0.352	-1.022; 0.169	-2.455; -1.198	-1.175; 0.016
% CFB at Week 52						
Mean (SD)	-1.741 (3.529)	-0.488 (3.400)	-1.718 (4.709)	-0.551 (3.540)	-1.799 (4.111)	-0.317 (3.597)
95% CI	-3.393; -0.090	-1.226; 0.250	-2.672; -0.764	-1.297; 0.194	-2.655; -0.943	-1.034; 0.401

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; CFB, change from baseline; CI, confidence interval; cm^2, square centimetres; LGX, linzagolix; mg, milligram; SAS, safety analysis set; SD, standard deviation
Source: PRIMROSE 1 and 2 pooled analyses[55]

B.2.10.7 Safety conclusions

In the pooled analysis up to Week 52, linzagolix was well tolerated, compatible with long-term treatment. Pooled safety results at Week 24 and Week 52 reflected the safety results of the individual trials (Appendix M).

The majority of TEAEs in the linzagolix treatment groups were mild to moderate in severity. The most common TEAEs were hot flushes and headaches and incidence was increased with higher doses of linzagolix and mitigated by the addition of ABT. Incidence of hot flushes and headaches was lower at Week 52 than at Week 24, suggesting that these TEAEs mainly occur at start of treatment and do not increase with extended exposure.. Overall, fewer TEAEs were reported at Week 52, despite the fact that most patients were on active therapy.

Incidence of severe TEAE and SAEs was low at Week 24 and lower at Week 52. Incidence of TEAEs leading to treatment discontinuation was low at Week 24 and lower at Week 52.

As expected, given the mechanism of action of linzagolix, changes in BMD were observed at all three anatomic sites (lumbar spine, femoral neck, and total hip). Overall, the observed changes in BMD were small, and were not considered to be clinically meaningful except in patients treated with linzagolix 200 mg. Reductions in BMD were most prominent in the spine, which is known to be most sensitive to BMD change in the context of E2 decrease. The addition of ABT to linzagolix 200 mg from Week 24 onwards limited the risk of BMD decrease. In the pooled analysis, at Week 76 (off treatment) a trend to recovery of BMD loss was seen in patients with follow-up data.

B.2.11 Additional trials

B.2.11.1 PRIMROSE 3

PRIMROSE 3 was designed to collect long-term (up to 24 months) data on the dynamics and recovery of BMD in patients who completed at least 20 weeks of treatment with placebo or linzagolix within the PRIMROSE 1 or PRIMROSE 2 trials.[57] All patients who completed at least 20 weeks of treatment in PRIMROSE 1 or PRIMROSE 2 and had a DXA scan within 35 days from the last treatment administration (Week 24, early discontinuation or Week 52) were invited to enter the PRIMROSE 3 study.[57]

B.2.11.1.1 Trial description

The trial comprised an eligibility visit and up to three follow-up visits at 12, 18 and/or 24 months after the end of treatment in PRIMROSE 1 or PRIMROSE 2 (the number of subsequent visits depended on the date of enrolment).[57] Patients received no investigational study treatment during PRIMROSE 3 but could receive medications considered necessary for patient welfare at the discretion of the investigator and all patients were advised to take calcium 1,000 mg/day and vitamin D up to 600 IU/day.[57]

The primary endpoint was the change in lumbar spine (L1-L4), femoral neck, and total hip BMD at 12, 18 and 24 months from the end of treatment in PRIMROSE 1 and PRIMROSE 2.[57] The secondary endpoint was the change from baseline to each scheduled assessment in lumbar spine (L1-L4), femoral neck, and total hip.[57]

B.2.11.1.2 Trial patients

A total of 137 patients were screened, 134 (97.8%) were enrolled and 130 (94.9%) were included in the SAS (the number of patients in each treatment group ranged from 1 to 30).[57] In the SAS, 30 (21.9%) patients had a Month 12 Visit, 76 (55.5%) had a Month 18 Visit and 109 (79.6%) had a Month 24 visit. Most patients (110 subjects, 80.3%) completed the trial.[57]

At the eligibility visit for PRIMROSE 3, most subjects in all treatment groups were premenopausal (ranging from 69.2% to 87.0% of patients). The analyses were performed using the SAS BMD results.[57] The mean (SD) overall treatment duration in the PRIMROSE 1 and PRIMROSE 2 studies was 50.95 (3.89) weeks with a similar duration in all treatment groups.[57]

B.2.11.1.3 BMD results

Across all treatment arms, BMD in the spine was considered partially or completely recovered in 50% of subjects.[57] BMD in the femur was partially or completely recovered in at least 50% of patients in all treatment arms apart from linzagolix 200 mg + ABT group (38.5%). Total hip BMD was partially or completely recovered in at least 50% of patients in all treatment arms apart from linzagolix 100 mg + ABT group (40.0%). The observed small BMD changes from post-treatment baseline as well as from pre-treatment baseline to the Month 24 visit may not have any clinically-relevant impact on the overall bone health of the linzagolix treated subjects since the z-score of most subjects is within the expected range for age.[57]

B.2.11.1.4 Interpretation and summary

Overall, interpretation of the BMD data is limited due to the small number of patients in each treatment group and the resulting high data variability.[57] Patients could have been off treatment for a variable time before entering PRIMROSE 3, and this gap could have added

variability to the results if patients experienced events or took treatments that could have influenced BMD.

Small BMD changes from post-treatment baseline as well as from pre-treatment baseline to the Month 24 visit were observed, but these are not expected to have any clinically-relevant impact on the overall bone health of the linzagolix treated patients as the z-score of most patients was within the expected range for age.[57] Additionally, the observed changes in BMD values and z-scores in the linzagolix treatment groups were mostly within the same range as in the placebo group. In summary, results from PRIMROSE 3 indicate that there may be no long-term consequences on BMD following linzagolix treatment.[57]

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence base

Comparative efficacy and safety versus placebo

The linzagolix clinical trial programme in UF included two large, 52-week, Phase 3 RCTs with a pooled population of over 1,000 women, representative of patients with symptomatic, moderate to severe UFs in Europe and the US.[25] The pooled results of these pivotal trials, PRIMROSE 1 and 2, clearly demonstrated the efficacy and safety of linzagolix,[25,54,56,59,60,64] the only GnRH antagonist providing flexible dosing options (once daily oral dose of 100 mg or 200 mg with or without ABT), to meet the individualised treatment needs of people with moderate to severe symptoms of UFs. The trials showed that linzagolix provided rapid and sustained reductions in HMB and its accompanying endpoints, reduced UF-associated pain, improved HRQoL and increased Hb levels in patients who were anaemic at baseline, and was well tolerated, across both doses, with and without ABT. Linzagolix 200 mg without hormonal ABT also provided substantial reduction in uterine and fibroid volume, which has the benefits of simplifying, delaying or avoiding surgery. These linzagolix benefits were maintained during treatment for 52 weeks. Linzagolix was well tolerated with low discontinuation rates and high adherence rates.

Chronic HMB and UF-related pain are the most burdensome symptoms for women with UF, and secondary anaemia can be life-threatening.[2] In the pooled efficacy analysis, linzagolix (100 mg or 200 mg) with or without ABT showed a clinically meaningful reduction in HMB at Week 24 compared with the placebo group (nominal p≤0·001 for all comparisons).[56] Good efficacy was achieved with both 100 mg and 200 mg of linzagolix, and with and without ABT. The proportion of patients with a reduction in HMB at Week 24 was 56.5% for the linzagolix 100 mg group, 71.6% for the linzagolix 100 mg + ABT group, 74.5% for the linzagolix 200 mg group, and 84.5% for the linzagolix 200 mg + ABT group, compared with 32.2% for placebo.[56] Reductions in HMB were rapid (observed within 4 to 8 weeks) and were sustained throughout the 52-week treatment period. Reduction in HMB was reinforced by the positive results for the accompanying endpoints of number of days of uterine bleeding for the last 28-day interval, proportion of patients experiencing amenorrhoea, and time to amenorrhea at Week 24.[55,56]

Improvements in Hb levels were observed in patients who were anaemic at baseline in all linzagolix treatment groups at Week 24 compared with the placebo group (nominal p≤0.002 for all comparisons).[56] Anaemia secondary to HMB is common in women with UFs, and increasing Hb levels in patients with anaemia may lead to improvements in HRQoL and work productivity, and may reduce post-operative morbidity for people with UF subsequently undergoing surgery. Mean UF-related pain scores showed improvements at Week 24 in all

linzagolix treatment groups versus placebo (nominal p≤0.001 all comparisons). Reduction in pain with linzagolix treatment may be particularly meaningful for patients in clinical practice given its prevalence and associated burden. HRQoL assessed using the UFS-QoL symptom severity scores, HRQL total scores and scores across all six subdomains of the UFS-QoL showed improvements at Week 24 in all linzagolix treatment groups versus placebo.[55,56] Although there was some dose dependency, the efficacy results for all linzagolix treatment groups were consistently superior versus placebo across these endpoints, supporting dose flexibility. [25,55,56]

All linzagolix treatment groups reduced fibroid and uterine volume, the underlying problem for people with UFs, in a dose-dependent manner.[56] Linzagolix 200 mg without ABT resulted in substantial and clinically meaningful reductions in fibroid volumes (48% reduction) and uterine volumes (39% reduction) at Week 24 (nominal p<0.001 versus placebo).[56] Reductions in fibroid volume of approximately 35%, 15% and 22% were observed in the linzagolix 100 mg, 100 mg + ABT, and 200 mg + ABT groups.[56] The majority of shrinkage had occurred by 3 months of treatment (see second figure in Appendix M.3.3.3.5). Use of linzagolix 200 mg may therefore be beneficial for patients prior to surgery or in cases where avoidance or delaying of surgery is desired.

The results observed in the pooled efficacy analysis reflected those observed in the individual studies at Week 24; see Appendix M.[25,40,46,56] Moreover, results from the individual studies show that the results observed at Week 24 were generally maintained or increased during active treatment with once daily oral doses of linzagolix 100 and 200 mg for 6 months to Week 52 (with some differences due to the switch from placebo to active treatment at Week 24).[25,40,60,46,56] Linzagolix effects persisted 12 weeks after the end of treatment, although there was a partial return to baseline for all measured efficacy endpoints at Week 64 (i.e. endpoints other than those measured by the AH method).[61,65] The return to menstruation was rapid on treatment discontinuation, occurring within the first month for 43-49% of the patients and within 2 months for around 95% of the patients.[61,65]

In the pooled safety analysis up to Week 52, linzagolix was well tolerated and adherence was high, compatible with long-term treatment.[55,56] The majority of TEAEs in the linzagolix treatment groups were mild to moderate in severity.[55,56] The most common TEAEs, were hot flushes (14.6% overall) and headaches (7.7% overall), and incidence was increased with higher doses of linzagolix and mitigated by the addition of ABT.[55,72] Incidence of hot flushes and headaches was lower at Week 52 than at Week 24, suggesting that these TEAEs do not increase with extended exposure.[55,56] Overall, fewer TEAEs were reported at Week 52, despite the fact that most patients were on active therapy.[55,56] Incidence of severe TEAE and SAEs was low at Week 24 and lower at Week 52.[55,56] Incidence of TEAEs leading to treatment discontinuation was low at Week 24 and lower at Week 52.[55]

Small changes in BMD were observed at all three anatomic sites (lumbar spine, femoral neck, and total hip). Overall, the observed changes in BMD were small, and were not considered to be clinically meaningful except in patients treated with linzagolix 200 mg. Across both trials, the median and interquartile range (IQR) of the z-scores did not meaningfully change over time.[25] Reductions in BMD were most prominent in the spine, which is known to be most sensitive to BMD change in the context of E2. In the pooled analysis, at Week 76 (off treatment) a trend to recovery of BMD loss was seen in patients with follow-up data. Recovery of BMD loss was slowest in patients who did not receive ABT.[56] Results from the long-term, follow-up trial (PRIMROSE 3) indicate that there may be no long-term consequences on BMD following linzagolix treatment.[57]

Pooled safety results at Week 24 and Week 52 reflected the safety results of the individual trials (Appendix M).[25,40,60,55,46,56]

Efficacy and safety versus other pharmacological options

The relevant comparators for linzagolix as a second-line treatment option for people of reproductive age with moderate to severe symptoms of UFs are GnRH agonists and relugolix CT. There are no head-to-head trials to directly compare the efficacy of linzagolix with these therapies, or between GnRH agonists and relugolix CT. Based on an ITC conducted by the manufacturer, the Committee for TA832 concluded that relugolix CT is likely to be as equally effective as GnRH agonists.[22] Although the Committee noted uncertainty in the ITCs, and differences between the trials included in the ITC, they agreed with the conclusions of the manufacturer.

There is evidence to suggest that the GnRH agonists generally used to treat UFs have equivalent efficacy and are used interchangeably in clinical practice. The NICE HMB management guidelines (NG88; 2018) do not differentiate between the different GnRH analogues in the recommendation for their consideration as pre-treatment before surgery, but do note that this is an off-label use for some GnRH analogues.[18] A Cochrane review of 21 RCTs, cited in TA832, regarding pre-operative GnRH agonist therapy before hysterectomy or myomectomy for UFs, concluded that all GnRH agonists are equivalent when it comes to treatment of UFs.[21] Clinical expert opinion cited in TA832 confirms that the choice of GnRH agonists in clinical practice varies between NHS Trusts, with some clinicians preferring leuprorelin because of the smaller needle size while others preferred goserelin.[22] In August 2023, Theramex conducted interviews of UK key opinion leaders (KOLs). When asked, “Are all GnRH agonists considered clinically comparable”, respondents (n=2) stated that all IV GnRH agonists can be used interchangeably depending on formulary stocks, and no differences had been noted.[73]

In the absence of direct head-to-head trials, Theramex have conducted an NMA and MAIC to aid comparison of linzagolix with other pharmacological options (see Section B.2.9). As expected, given the known challenges in adequately matching patient populations for indirect comparison in this therapy area, the results from these analyses do not consistently favour any single therapy. There is some heterogeneity in the direction of treatment effects, partly due to heterogeneity between published studies included in the ITC that cannot be controlled for, but overall there is no strong indication that one treatment option is better than another.

Together, this evidence suggests that there is similar efficacy between linzagolix, relugolix CT and the GnRH agonists.

Conclusions

One of the strengths of linzagolix is that it is not formulated in combination with hormonal ABT. The trial results showed that linzagolix 100 mg without ABT is effective and well tolerated for long-term use (≥6 months), and linzagolix 200 mg without ABT for short-term use (<6 months).[25,40,60,46,56] ABT is an important issue for many people with UFs, and linzagolix provides a flexible treatment option that can be used with and without ABT.

Overall, the PRIMROSE 1 and 2 trial results confirm the efficacy and safety of linzagolix 200 mg and 100 mg with or without ABT for patients with moderate to severe UFs, providing clinically meaningful, rapid, and consistent control of HMB at doses of 100 mg and 200 mg.[25] Additional benefits include a reduction in pelvic pain, improvements in Hb levels in people with anaemia, and improvements in HRQoL. Linzagolix 200 mg without hormonal ABT

reduces uterine and UF volume, and could be particularly beneficial to simplify, delay or avoid surgery. This is particularly relevant in the context of increased NHS surgical waiting times of up to 18 months for gynaecology and the need for more invasive and time-consuming surgical interventions if treatment is delayed.[20]

While relugolix CT can be used over the long-term, it is formulated as a fixed-dose combination with ABT and as such cannot be taken without ABT. The availability of an effective GnRH antagonist that can be taken without hormonal ABT for short-term (i.e. 200 mg) or for longer term (i.e. 100 mg) is thus an important option for people who have a contraindication to, are at increased risk for complications with, or prefer not to use exogenous estrogen and progestogen (e.g. due problems of pelvic pain, endometriosis recurrence).

B.2.12.2 Strengths and limitations of the clinical evidence base

B.2.12.2.1 Strengths of the evidence base

The PRIMROSE 1 and 2 Phase 3, multicentre, 52-week, randomised, parallel-group, double-blind, placebo-controlled trials – provide robust efficacy and safety data supporting the four linzagolix treatment options (100 mg, 100 mg +ABT, 200 mg, 200mg + ABT, once daily by mouth).[25] The trials included 1,012 (FAS) adult premenopausal women with ultrasound-confirmed UFs and HMB defined as ≥80 mL of MBL per cycle for at least two cycles from clinical sites in Europe (8 countries) and the US.[25] The pooled population represented a large population of patients, generally representative of people with symptomatic, moderate to severe UFs, and generalisable to UK practice. Compliance with trial medication was high in both trials, as was compliance with eDiary completion.[59,60,64] The trials demonstrated robust, clinically meaningful and statistically significant (individual trial data) and rapid (4 to 8 weeks) treatment effects of linzagolix on the study's primary efficacy endpoint – the proportion of women who had a reduction in HMB at 24 Weeks.[25] The response rates observed across treatment groups were independent of BMI and race, and the results were generally consistent between the two trials.[25]

The primary endpoint was supported by several secondary endpoints, including time to reduced HMB, number of days of HMB, rates of amenorrhoea, time to amenorrhoea, UF-associated pain, Hb levels in patients who were anaemic at baseline, and reduction in fibroid and uterine volume (most markedly at the 200 mg without ABT dose).[25] These efficacy assessments are widely used and generally recognised as reliable, accurate, and relevant. The AH method is a recognised method for quantitative measurement of the blood content of used sanitary products (tampons and pads). Its use for measurement of MBL in clinical trials is recommended/required by regulatory authorities. The UFS-QoL is a disease-specific self-reported questionnaire for detecting differences in symptom severity and HRQoL among patients with UFs that is perceived to be a reliable and appropriate scale for use in the assessment of QoL for patients with UFs.[74] DXA scanning is the standard for quantitative measurement of BMD, with the z-score for BMD comparing a person’s bone density to the average values for a person of the same age and gender. Throughout both trials, key efficacy and safety assessments were performed and/or read centrally wherever possible to minimise interobserver variability.

The similarity of the two PRIMROSE trials enabled pooling of the efficacy data (individual patient data) up to Week 24, which helped to improve the precision of the treatment effect estimates for the efficacy outcomes and to evaluate whether overall positive results are also seen in specific subgroups. While the pooled efficacy analyses are exploratory, results from

the individual trials (see Appendix M) confirmed the statistical significance of the key efficacy outcomes across the linzagolix treatment groups versus the placebo group.

Overall, results from PRIMROSE 1 and 2 trials showed that linzagolix is efficacious and well tolerated regardless of concomitant ABT. The results support the use of the drug's flexible dosing combinations and provide certainty in clinical outcomes across a broad range of potential patients with symptomatic UFs.

B.2.12.2.2 Potential limitations of the evidence base

Although the PRIMROSE 2 trial had few patients of Black race, the pooled efficacy results showed that linzagolix response rates in the subgroup of patients of Black/African American race were similar to the overall pooled population.[25]

Despite the AH method being a recommended method for assessing MBL in clinical trials, it does have some limitations and may contribute to the placebo effect observed in the PRIMROSE trials. Approximately 32% of women in the placebo group (Pooled FAS) were classified as responders, which is similar to the placebo responder rates reported in other studies.[25] The higher bleeding burden in placebo groups may result in lower adherence to the collection of sanitary products in the placebo groups and lead to over-estimation of days with no bleeding.[25] Sensitivity analyses (using two different methods of imputation) were carried out to check for the robustness of the analysis results under alternative assumptions with regard to missing data.[25] In both individual trials, results of these supported those of the primary efficacy analysis, with a significant reduction in HMB observed in each active treatment group compared with the placebo group.[56]

Uterine and fibroid volumes were assessed using ultrasonography, which could have high interobserver variability across the more than 90 clinical sites involved in each study,[25] but does reflect clinical practice. Furthermore, fibroid volume was estimated for up to the three largest fibroids, so the total fibroid volume might have been underestimated in some participants.[25]

In the pooled analysis, there were small increases in the EQ-5D-5L index values and the VAS score in all linzagolix groups and the placebo group at Week 24, but no noticeable differences between the linzagolix groups and the placebo group.[56] EQ-5D was only captured at baseline, Week 12 and Week 24.[25] As the effects of fibroids are complex, and patients may report differently depending on exactly which timepoint in their menstrual cycle they complete the EQ-5D assessment, a singular measurement on a single day may not truly reflect patients' overall QoL. These issues raise questions as to the degree of validity and reliability of the EQ-5D scores from the PRIMROSE RCTs. The disease-specific UFS-QoL is felt to be a more reliable and appropriate scale to use in the assessment of QoL for patients with UFs.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic review of the literature was conducted to identify published economic evaluations of potential relevance to the decision problem addressed within this technology appraisal. Electronic database searches were initially conducted on 21 July 2021. An update of the SLR was run for the period 01 August 2021 to 09 March 2022, for GnRH antagonists. A second update of the SLR was run for the period 01 March 2022 to 07 February 2023 using the same search strings as the original SLR. Full details on the search strategies, inclusion and exclusion criteria and the PRISMA flow diagram are provided in Appendix G.

Following searches, exclusion of duplicates, title and abstract screening, and full-text screening, 20 relevant economic evaluations were identified and included for data extraction. Of these studies, 5 were cost-effectiveness or cost-minimisation analyses assessing pharmacological treatments for UFs. The remaining studies assessed interventional/surgical procedures.

In addition to the economic evaluations published in the literature, one prior NICE appraisal in moderate to severe symptoms of UFs was identified as relevant to this appraisal (TA832) - relugolix-estradiol-norethisterone acetate (referred to as relugolix CT hereon) was appraised for the treatment of moderate to severe symptoms of UFs in adults of reproductive age.[22] Throughout this submission, insights and learnings are drawn from this appraisal.

Table 46 provides a summary of the published economic evaluations identified in the review of the literature which were considered relevant to this submission and assessed pharmacological treatments for UFs (n=6). Further details of all 20 studies (including those assessing interventional/surgical procedures) are provided in Appendix G.

Table 46: Summary list of published cost-effectiveness/cost-minimisation evaluations

Study (country)	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
NICE TA832[22] (England)	NR (GBP)	Cohort-level Markov model with treatment-based states (on pharmacologic treatment, BSC), surgery, post-surgery, menopause and death	Premenopausal women with moderate to severe symptoms associated with UFs who have failed or are unsuitable for conventional hormonal therapy including contraceptives (42 years)	**Company (corrected post clarification)**: Relugolix CT, 16.894; Goserelin, 16.530 **ERG**: Relugolix CT, 17.037; Goserelin, 16.968	**Company (corrected post clarification)**: Relugolix CT, £9,854; Goserelin, £7,742 **ERG**: Relugolix CT, £6,573; Goserelin, £6,379	**Company (corrected post clarification)**: £5,796 **ERG**: £2,795
Badiani et al. 2018[75] (Italy)	NR (EUR)	Markov model with seven health states relating to controlled or uncontrolled bleeding, and the need for surgery	Women with symptomatic fibroids, excessive uterine bleeding (42 years)	UPA, 0.221 Placebo, 0.201 Incremental, 0.019	UPA, €3,836 Placebo, €3,485 Incremental, €351	€18,177
Nagy et al. 2014[76] (Hungary)	2012 (EUR)	Markov model consisting of 11 health states relating to excessive bleeding surgery menopause, and death	Women with a PBAC score >100 during days 1–8 of menstruation (NR)	UPA, 6.32 Placebo, 6.30 Incremental, 0.021 Immediate hysterectomy, 6.16 Incremental, 0.18	UPA, €1,238 Placebo, €842 Incremental, €397 Immediate hysterectomy, €609 Incremental, €630	€19,200 (vs placebo €3,575 (vs immediate hysterectomy)
Tsoi et al. 2015[77] (Canada)	2013 (CAD)	Decision tree in which all patients experienced either controlled or uncontrolled bleeding, both with	Premenopausal female patients with heavy uterine bleeding due to their fibroids (NR)	UPA, 0.177 Leuprolide, 0.165 Incremental, 0.012	UPA, CAN $1,273 Leuprolide, CAN $1,366 Incremental, $–92	Dominant

		and without hot flushes				
Geale et al. 2017[78] (England)	NR (GBP)	Treatment-based states (UPA, BSC, surgery, post-surgery and death)	Women eligible for treatment with UPA who are contraindicated for, or wish to avoid, surgery and do not experience sufficient response to standard pharmaceutical treatments (41.5 years)	Intermittent UPA, 6.696 BSC, 6.610 Incremental, 0.087	Intermittent UPA, £6,669 BSC, £5,555 Incremental, £1,115	£12,850
Zakiyah et al. 2017[79] (Netherlands)	2012 (EUR)	CMA, decision tree model with health states for each treatment	Premenopausal women with heavy uterine bleeding caused by fibroids (NR)	-	UPA, €4,216,027 Leuprolide, €4,218,095 Incremental, €2068	-

Note: In this table and throughout the submission, 'ERG' is used when referencing previous submissions. The terms ERG and EAG can be considered interchangeable
Abbreviations: BSC, best support care; CAN, Canadian; CMA, cost-minimisation analysis; CT, combination therapy; EAG, External Assessment Group; ERG, Evidence Review Group; EUR, Euro; GBP, Great British Pounds; ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; NR, not reported; PBAC, pictorial blood assessment chart; QALYs, quality-adjusted life years; TA, technology appraisal; UPA, ulipristal acetate; vs, versus

B.3.2 Economic analysis

The final scope issued by NICE included three subgroups of interest, which are each considered in the economic analysis (as described in the decision problem in Table 1, and summarised in Section B.3.2.1 below). The appropriate form of economic evaluation varies depending on the distinct subgroup being considered, and consequently depending on the relevant comparators of interest. A blended approach to addressing the decision problem (namely, an STA with cost-comparison methodology for a portion of the marketing authorisation population), was therefore suggested by NICE and explored at the decision problem stage.

The systematic review of the literature did not identify any published economic evaluations considering linzagolix for the treatment of moderate to severe symptoms of UFs. It was therefore necessary to develop *de novo* economic models to compare linzagolix with existing treatment options in the relevant patient populations, in line with the decision problem addressed within this appraisal (Table 1).

The patient populations (B.3.2.1), intervention and comparators (B.3.2.2), and corresponding economic evaluation type and model structure (B.3.2.3), by subgroup, are detailed in the subsections that follow, and summarised in Table 47.

B.3.2.1 Patient population

The overarching patient population considered in the analysis is adults of reproductive age with moderate to severe symptoms of UFs, in line with the marketing authorisation for linzagolix and final scope issued by NICE.

The final scope issued by NICE considers three distinct subgroups of patients:

- People having short-term treatment of 6 months or less (referred to as Population #1)
- People having longer-term treatment, with hormone-based therapy (referred to as Population #2)
- People having longer-term treatment, without hormone-based therapy (referred to as Population #3).

To align with the final scope, and due to the differences between populations in the treatment pathway and suitable type of economic evaluation, the economic analysis considers the three populations described above individually.

The overarching patient population is also aligned with patients included in the PRIMROSE 1 and 2 studies, which demonstrated the efficacy and safety of linzagolix. As described in Section B.2.3.1, PRIMROSE 1 and 2 were Phase 3, multicentre, randomised, parallel, double-blind, placebo-controlled trials that enrolled patients with HMB associated with UFs.

B.3.2.2 Intervention technology and comparators

The intervention considered in the analysis is linzagolix, which is incorporated into the evaluation in line with its marketing authorisation, and in line with the decision problem in the final scope issued by NICE.

In June 2022, linzagolix received marketing authorisation by the European Commission for the treatment of moderate to severe symptoms of UFs in adult women of reproductive age.

Linzagolix has flexible licensed dosing regimens as follows:

- 100 mg
- 100 mg + ABT
- 200 mg (for short-term use, less than 6 months)
- 200 mg + ABT.

Based on the comparators included within the final scope from NICE and clinical feedback received, the distinct patient populations considered align with different comparators in NHS England clinical practice:

1. For Population #1 (patients receiving short-term treatment of 6 months or less), the primary comparator of interest is relugolix CT, based on the recommendations in NICE TA832. In the TA832 final appraisal document, it was noted that although there is a paucity of evidence for the short-term use of relugolix CT in a presurgical setting, it is likely to be used in clinical practice irrespective of whether surgery is planned or not.[22] As GnRH agonists (goserelin, leuprorelin and triptorelin) were determined to be the most relevant comparators for relugolix CT in TA832 (with similar effectiveness concluded between the treatments), it is recognised that GnRH agonists are also used in this treatment setting. It is understood that treatment in the short-term setting would be administered with the intention of patients achieving a reduction in fibroid or uterine volume ahead of procedural/surgical intervention.
2. For Population #2 (patients receiving long-term treatment with hormone-based therapy), the relevant existing treatment option is relugolix CT. In TA832, relugolix CT was recommended as an option for treating moderate to severe symptoms of UFs in adults of reproductive age.[22] Clinical opinion indicates that patients would receive relugolix CT as a long-term treatment option with the aim of symptom resolution/reduced menstrual bleeding, while preventing or delaying surgical intervention.
3. For Population #3 (patients receiving longer-term treatment without hormone-based therapy), there is a clear unmet need for safe and effective treatment options. The current established clinical management would be non-hormonal treatments such as pain management and iron supplements. As all longer-term treatment with GnRH analogues currently requires the inclusion of hormone-based therapy, for these patients there are currently no active long-term treatment options. In this setting, linzagolix offers an effective treatment strategy due to its flexible dosing regimens for patients currently unable to receive anything but established clinical management (referred to as best supportive care [BSC] hereon).

B.3.2.3 Model structure

Table 47 presents a summary of the modelling approach and comparators, by subgroup, for the economic analysis. A blended approach to evaluating the economic case has been taken.

Within two of the subgroups specified by NICE in the final scope (Populations #1 and #2), there is population overlap between linzagolix and relugolix CT. With overlap in populations,

and similar (or greater) outcomes anticipated, a cost-comparison analysis was considered suitable to reflect the economic case for linzagolix, and in line with recommended guidance from the NICE methods.[80,81] The justification for this approach was three-fold:

1. Clinical expert opinion to the company supported that both GnRH antagonists (linzagolix and relugolix CT) would be considered clinically comparable in NHS practice (with regards to reduced menstrual blood loss).[73] Notably, clinical experts indicated that the linzagolix 200 mg dose (when administered without ABT) may achieve better outcomes with regards to fibroid shrinkage (a goal of pre-surgical treatment) compared with relugolix CT (which is formulated in combination with hormonal ABT).
2. As described in Section B.2.9, the findings of the ITC further support clinical comparability between linzagolix and relugolix CT, as the results did not generally indicate differences in treatment efficacy (with the majority of comparative results having shown no substantial differences between the treatment arms). Notably, those treated with linzagolix 200 mg (without ABT) achieved a larger decrease in fibroid volume than those treated with relugolix (and the credible interval did not contain zero), which is consistent with clinical expert opinion described above.
3. In NICE TA832, it was determined in the final appraisal document that relugolix CT is similarly effective to GnRH agonists.[22] This assumption is consistent with clinical expert opinion for the reduced menstrual blood loss endpoint.[73] This supports the assumption that there is expected to be at least similar outcomes across all comparators within the given populations.

As described in Section B.1.3.4, relugolix CT is formulated as a fixed-dose combination with ABT (and as such cannot be taken without ABT). Therefore, there are limited active treatment options for patients in Population #3 (those requiring longer-term treatment without hormone-based therapy). As linzagolix has the benefit of flexible dosing regimens (100 mg and 200 mg options, both with and without ABT), linzagolix has the potential to offer benefit to patients who are currently unable to receive relugolix CT. Consequently, for Population #3, linzagolix has been assessed using a cost-effectiveness framework and is compared with BSC (as defined in Section B.3.2.2).

Table 47: Modelling approach and comparators, by subgroup

#	Population	Comparators	Approach taken	Justification
1	Patients having short-term treatment of 6 months or less	GnRH antagonists (primary analysis): • Relugolix CT GnRH agonists (supplementary comparison): • Leuprorelin • Goserelin • Triptorelin	Cost-comparison analysis	• Explored by NICE at the decision problem stage, due to population overlap with relugolix CT • The ITC findings do not generally indicate differences in efficacy between GnRH antagonists (Section B.2.9) • Clinical opinion indicated clinical comparability between GnRH antagonists with regards to reduced menstrual blood loss (and potential for greater benefits with linzagolix 200 mg regarding fibroid shrinkage)[73]
2	Patients having longer-term treatment, with hormone-based therapy	GnRH antagonists: • Relugolix CT		

				• TA832 determined that relugolix CT is similarly effective to GnRH agonists[22]
3	Patients having longer-term treatment, without hormone-based therapy	BSC* • NSAIDs • Iron supplements	Cost-effectiveness analysis	There are no active treatment options (i.e. GnRH analogues) currently available in NHS England practice for long-term use without ABT

Note: *In line with NICE TA832, BSC is represented by the placebo arm of the clinical trial (with regards to clinical effectiveness), and pain management and iron supplements (with regards to costs)
Abbreviations: ABT, add-back therapy; BSC, best supportive care; CT, combination therapy; GnRH, gonadotropin-releasing hormone; ITC, indirect treatment comparison; TA, technology appraisal

In each of the three populations, patients can receive surgery. There are several types of procedural/surgical interventions available for treating UFs, which are captured within the model and summarised below:

- UAE
- MRgFUS
- Myomectomy
- Hysterectomy.

In practice, the choice of surgery type is dependent on a range of factors including both disease characteristics and patient preferences. For example, for patients in which a reduction in fibroid volume is achieved due to pharmacological treatment, it may be feasible to undergo a laparoscopic myomectomy rather than open/abdominal myomectomy. Similarly, for patients in which uterine volume is seen due to pharmacological treatment, it may be more feasible to undergo a laparoscopic hysterectomy (rather than open/abdominal hysterectomy). Alternatively, patients who wish to preserve future fertility options may prefer to avoid a hysterectomy. As such, it is possible that different patients receive different types of surgery. Therefore, within the economic models, the data informing surgery inputs are weighted by a distribution of surgery types (discussed further in Section B.3.3.3).

Clinical opinion suggests that fibroids tend to shrink due to low estrogen levels, and as such, after menopause it is assumed that no further surgeries, pharmacological treatments, or healthcare resource usage are required.

B.3.2.3.1 Population #1: Short-term treatment of 6 months or less

A cost-comparison model has been developed to estimate the costs associated with treatment for moderate to severe symptoms of UFs for patients receiving short-term therapy of 6 months or less (i.e. treatment ahead of surgery). The cost categories included in the base-case analysis are aligned with guidance from the NICE methods and are as follows[80,81]:

- Drug acquisition costs
- Administration costs
- Healthcare resource use costs
- Costs associated with surgery.

The model outcomes are costs associated with each treatment arm, aggregated and disaggregated by cost category. The time horizon for the cost-comparison analysis for Population #1 is 6 months, as this was deemed sufficient to capture differences in costs between arms, when assessing a treatment setting of 6 months or less. Although the NICE manual recommends costs are discounted at 3.5% per annum, specific NICE cost-comparison guidance indicates that discounting of costs is not normally required in a cost-comparison analysis. As such, costs are not time-preference discounted in the base-case cost-comparison model. Cost inputs are presented in Section B.3.5.

B.3.2.3.2 Population #2: Long-term treatment with hormone-based therapy

Consistent with Population #1, a cost-comparison analysis has been conducted for patients receiving long-term treatment with hormone-based therapy. In line with the short-term model (and NICE methods guidance), costs categories included are:

- Drug costs
- Administration costs
- Healthcare resource use costs
- Costs associated with surgery.

As described above, costs are not time-preference discounted in the cost-comparison analysis. For the analysis of Population #2, the time horizon is 10 years, which is sufficient for capturing differences in costs between arms for patients receiving long-term treatment. The time horizon was selected based on the baseline age in the PRIMROSE 1 and 2 studies (42 years)[25], and the average age of menopause in the UK (51 years).[82] It is clinical understanding that fibroids tend to shrink due to low estrogen levels, and as such, after menopause it is assumed that no further pharmacological treatment or surgery would be required for treating symptoms of UFs.

B.3.2.3.3 Population #3: Long-term treatment without hormone-based therapy

A *de novo* cost-effectiveness model was constructed in Microsoft Excel® to reflect costs and health outcomes associated with linzagolix or BSC, for patients with moderate to severe symptoms of UFs in the long-term treatment without hormone-based therapy setting (Population #3). The clinical effectiveness of BSC is represented by the placebo arm of PRIMROSE (discussed further in Section B.3.3.2.3), and the costs reflected by concomitant pain management and iron supplements (discussed further in Section B.3.5.1).

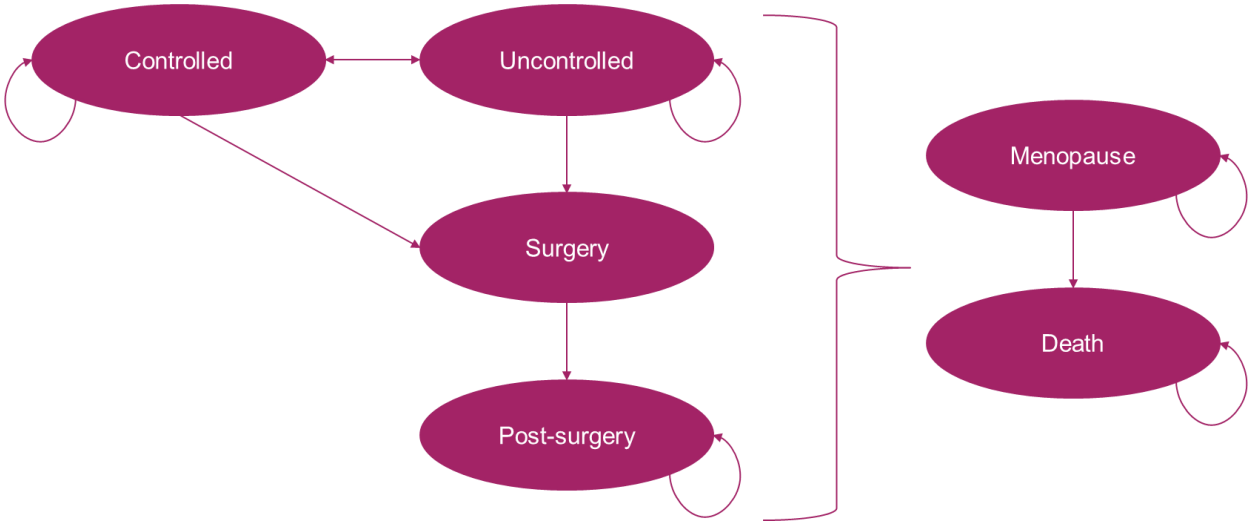
As illustrated in Figure 25, a cohort-level Markov model was designed with four primary health states relating to symptom control and movement to surgery, with further health states for menopause and death.

As shown in Table 46, the model structure in prior economic evaluations in UFs has varied; some analyses used models with health states based on symptom/bleeding control, while other models were based on treatment-based states. In TA832, the company submitted a model based on treatment status (pharmacological treatment, BSC, and movement to surgery) rather than health status, which was criticised by the Evidence Review Group (ERG). The NICE documentation in TA832 indicated that, in clinical practice, management of UFs was likely to be based on clinical need determined by symptom control and not by treatment status.[22] Furthermore, the ERG suggested that they would have considered a model structure like that of Nagy et al. 2014 to be more appropriate, in which patients

transition through a series of mutually exclusive health outcome states based on bleeding symptoms or symptom control.[76]

The cost-effectiveness model structure used for Population #3 in this submission therefore attempts to directly address the ERG critique of the model structure in TA832[22], by comprising health states based on disease/symptom control (Figure 25).

Figure 25: Cost-effectiveness model structure (Population #3, linzagolix versus BSC)



Abbreviations: BSC, best supportive care

All patients enter the model with 'uncontrolled' moderate to severe symptoms of UFs and receive pharmacologic treatment with either linzagolix or BSC. Within the model, a patient's symptoms can remain uncontrolled, or their symptoms may be 'controlled' by pharmacological treatment. It is assumed that uncontrolled symptoms are defined by HMB (>80 mL MBL per cycle), while patients with controlled disease are categorised by those who achieve MBL ≤80 mL and ≥50% reduction from baseline (which is aligned with the primary endpoint definition in the PRIMROSE 1 and 2). The clinical effectiveness data informing transitions between model health states is described further in Section B.3.3. Patients can move to surgery, menopause or the death health state from the uncontrolled symptoms state.

Patients with controlled disease may remain in a controlled state, or they may lose response to pharmacological treatment and re-enter the uncontrolled symptoms state, or move to surgery, menopause or death.

Surgery is assumed to last for one model cycle (28-days), after which patients enter the 'post-surgery' state. In the base case, a 10-year time horizon is applied based on the average age at baseline from PRIMROSE 1 and 2 (42 years) and average age of menopause in the UK (51 years). A time horizon to the average age of menopause was deemed long enough to sufficiently capture differences in costs and outcomes between treatment arms. In scenario analysis, longer time horizons are explored (30 years and 60 years), whereby all patients enter the 'menopause' state when the age of the modelled cohort reaches the average age of menopause, after which patients are assumed to experience outcomes that are in line with the age-matched general population.

Table 48 presents a summary of the features of the cost-effectiveness analysis for Population #3, compared with the single prior NICE appraisal in UFs (TA832).[22]

Table 48: Features of the economic analysis (Population #3, linzagolix versus BSC, cost-effectiveness analysis)

Factor	TA832[22]	Chosen values	Justification
Model type	Cohort-level Markov model based on treatment status (pharmacological treatment, BSC, surgery [with waiting time], post-surgery, menopause and death)	• Cohort-level Markov model based on health status (controlled, uncontrolled, surgery, post-surgery, menopause and death) • Symptom control defined as MBL ≤80 mL and -50% from baseline, in line with the primary endpoint in PRIMROSE	In TA832, the model using treatment-based states was criticised by the ERG and Committee as being unconventional without justification. The ERG expressed a preference for a model structure defined using health states based on bleeding symptoms or symptom control
Perspective	NHS and PSS on costs	NHS and PSS on costs and direct health effects for patients	Consistent with NICE reference case
Time horizon	Lifetime	To menopause (10 years), based on the average age of the cohort at baseline, and the average age of menopause based on NHS data (51 years)[82]	The NICE reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long enough to reflect any differences in costs or outcomes between the technologies being compared. It is understood that fibroids tend to shrink due to low estrogen levels, and as such, after menopause it is assumed that no further surgeries, pharmacological treatments, or healthcare resource usage are required
Cycle length	Monthly	28-days	• Considered short enough to adequately capture changes in health status • Aligns with linzagolix pack size, allowing for accurate dosing calculations for costs
Discount rates	3.50% for costs and outcomes	3.50% for costs and QALYs	Consistent with NICE reference case
Outcome measure	Change in MBL volume (used to derive utility values only)	Response (defined as reduced MBL ≤80 mL and ≥50% reduction from baseline)	• Used to define symptom control in the economic model. • Aligns with the primary endpoint in the PRIMROSE 1 and 2 studies
Source of utilities	LIBERTY (UFS-QoL mapped to EQ-5D-3L)	PRIMROSE (UFS-QoL mapped to EQ-5D-3L)	• The reference case states that EQ-5D is the preferred measure of HRQoL in adults. While EQ-5D-5L data were available from the PRIMROSE study, mapping from UFS-QoL to EQ-5D-3L was

Factor	TA832[22]	Chosen values	Justification
			preferred, as the EQ-5D lacks sensitivity to measure the impact of patient symptoms on HRQoL, given inappropriate timing of questionnaires and the single day EQ-5D recall • EQ-5D-5L mapped EQ-5D-3L utility values are tested in scenario analysis for completeness
Source of costs	NHS drug tariff for drug costs, NHS reference costs and PSSRU for administration, HCRU, surgery costs, and adverse event costs	BNF for branded drug costs, eMIT for generic drug costs, NHS reference costs and PSSRU for administration, HCRU, surgery costs, and adverse event costs	Consistent with NICE reference case

Abbreviations: BNF, British National Formulary; BSC, best supportive care; eMIT, drugs and pharmaceutical electronic market information tool; EQ-5D-5L, EuroQol-5 Dimension-5-Level; ERG, Evidence Review Group; HCRU, health care resource use; HRQoL, health-related quality of life; MBL, menstrual blood loss; mL, millilitre; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; PSSRU; Personal Social Services Research Unit; QALYs, quality-adjusted life years; QoL, quality of life; RMBL, reduced menstrual blood loss; TA, technology appraisal; UFS-QoL, Uterine Fibroid Symptom and Quality of Life questionnaire

B.3.3 Clinical parameters and variables

As described in Section B.3.2, to align with the final scope issued by NICE, the three sub-populations were modelled individually. As the appropriate type of economic evaluation varied between populations, the clinical data required to inform the economic evaluation differs. The clinical parameters used to inform the analyses by population are summarised in Table 49, and described in further detail throughout this section.

Table 49: Summary of clinical data informing the economic analyses, by subgroup

#	Population	Approach taken	Clinical data required to inform the model
1	Patients having short-term treatment of 6 months or less	Cost-comparison analysis	• Proportion of patients receiving surgery (used to determine surgery costs by treatment arm) • Distribution of types of surgery (used to determine the weighted average cost of surgery)
2	Patients having longer-term treatment, with hormone-based therapy		• Proportion of patients receiving surgery (used to determine surgery costs by treatment arm) • Distribution of types of surgery (used to determine the weighted average cost of surgery)
3	Patients having longer-term treatment, without hormone-based therapy	Cost-effectiveness analysis	• Baseline characteristics (to estimate age-matched general population mortality and utility) • Response rate defined by reduced HMB (to inform transitions from the uncontrolled to controlled health state) • Recurrence rate (to inform transitions from the controlled to uncontrolled health state) • Proportion of patients receiving surgery (used to determine surgery costs by treatment arm) • Distribution of types of surgery (used to determine the weighted average cost of surgery) • Adverse event data (to reflect the costs of managing AEs and consequences)

Abbreviations: AEs, adverse events; HMB, heavy menstrual bleeding

B.3.3.1 Baseline patient characteristics

B.3.3.1.1 Population #1: Short-term treatment of 6 months or less

Baseline patient characteristics were not required to inform the cost-comparison analysis comparing linzagolix with relugolix CT (and with GnRH agonists in supporting analysis) in the population of patients having short-term treatment of 6 months or less. As a simplifying assumption, background mortality rates (which would be applied equally across treatment arms) are not applied in the cost-comparison model.

B.3.3.1.2 Population #2: Long-term treatment with hormone-based therapy

In line with Population #1, baseline patient characteristics were not required to inform the cost-comparison analysis.

B.3.3.1.3 Population #3: Long-term treatment without hormone-based therapy

In the cost-effectiveness analysis comparing linzagolix with BSC in patients receiving long-term treatment without hormone-based therapy, the baseline age of the cohort was aligned with the population in the pooled PRIMROSE 1 and 2 studies (42.25 years; SD, 5.60).

The age at baseline is used to derive age-matched general population mortality rates, which inform transitions to death from alive model health states.[83] Furthermore, baseline age is used to calculate age-matched general population utility values, which in turn are used to age-adjust health-state utility values over time.[84]

The average age of menopause in the model is 51 years, in line with UK-based data, and consistent with NICE TA832.[22,82] Also, in line with TA832, it is assumed that all patients transition to the menopause state when the age of the modelled cohort reaches the average age of menopause. After this timepoint, patients are assumed to no longer experience disease-related symptoms (due to low estrogen levels shrinking UFs). As such, the model assumes that all further outcomes after menopause are the same on each treatment arm and are assumed equivalent to the age-matched outcomes of the general population.

B.3.3.2 Efficacy

B.3.3.2.1 Population #1: Short-term treatment of 6 months or less

Clinical effectiveness data were not directly required to inform the cost-comparison model. As described in Section B.2.9.8, the ITC findings do not generally indicate substantial differences in efficacy between GnRH antagonists. In addition to this, in NICE TA832, it was determined in the final appraisal document that relugolix CT is similarly effective to GnRH agonists.[22] Furthermore, clinical expert opinion indicated clinical comparability between linzagolix and relugolix CT, and relugolix CT and GnRH agonists with regards to reduced menstrual blood loss.

B.3.3.2.2 Population #2: Long-term treatment with hormone-based therapy

In line with Population #1, clinical effectiveness data were not directly required to inform the cost-comparison model.

B.3.3.2.3 Population #3: Long-term treatment without hormone-based therapy

Clinical data informing the linzagolix and BSC arms of the cost-effectiveness analysis, in the population of patients having long-term treatment without hormone-based therapy, were primarily based on pooled data from the PRIMROSE 1 and 2 studies. Clinical effectiveness results from PRIMROSE 1 and 2 are reported in Section B.2.6.

As described in Section B.2.3.1, PRIMROSE 1 and 2 are completed Phase 3, multicentre, randomised, parallel-group, double-blind, placebo-controlled trials. The trials included two treatment periods and a follow-up period (in which patients were not on treatment).

Although PRIMROSE 1 and 2 included four active treatment arms (100 mg, 100 mg + ABT, 200 mg, and 200 mg + ABT), only linzagolix 100 mg and 200 mg data are used to inform clinical effectiveness estimates in the linzagolix arm of the cost-effectiveness analysis in Population #3 (patients having long-term treatment without hormone-based therapy).

It is assumed the placebo arm of PRIMROSE 1 and 2 is representative of the clinical effectiveness of BSC, for patients having long-term treatment without hormone-based therapy. This assumption is necessary due to the lack of active treatment options for patients for whom hormone-based therapy is not appropriate. Therefore, in this context, BSC is a

general term used to describe concomitant pain management and iron supplements. This approach is consistent with the approach to capturing BSC in the prior NICE appraisal for relugolix CT (TA832).[22]

Within the modelling framework, the primary study endpoint is used to determine the proportion who enter the controlled health state (MBL ≤80 mL and ≥50% reduction from baseline at 24 weeks). The model considers patients who achieve response as having 'controlled disease' and patients who do not have a response or those who achieve but subsequently lose their response are categorised as having 'uncontrolled disease'.

The model uses 24-week response data from the pooled PRIMROSE studies for several reasons. Firstly, as described in Section B.2.4.1.1, the pooled analysis (efficacy and safety) of PRIMROSE 1 and 2 at Week 24 was performed in accordance with Statistical Analysis Plans. Pooling of efficacy data (individual patient data) up to Week 24 from both trials is appropriate as both studies have the same design up to Week 24, the same inclusion/exclusion criteria, no difference in study conduct, and efficacy results were generally similar.

Furthermore, although it is acknowledged that later follow-up data are available, these data are not suitable for informing a comparison in patients receiving treatment without hormone-based therapy, due to treatment switching rules in the trial program. In PRIMROSE 1, 50% of patients in the placebo arm switched to 200 mg + ABT at Week 24, while in PRIMROSE 2, this value was 100%. Similarly, in both PRIMROSE 1 and 2, 100% of patients switched from linzagolix 200 mg to linzagolix 200 mg + ABT at Week 24. Thus, there are no longer-term follow-up data to inform efficacy in the population of patients not receiving ABT for linzagolix 200 mg or placebo (BSC).

In the cost-effectiveness model, an exponential assumption (Equation 1) was used to estimate the per 28-day cycle probability of moving from the uncontrolled to controlled health state, based on the 24-week PRIMROSE response rate. In clinical expert interviews conducted to validate the modelling approach taken in this submission, clinical experts indicated that, in practice, it could typically take patients 3-6 months to respond to treatment.[73] The model extrapolates the estimated per 28-day cycle response probability for linzagolix and BSC beyond the trial period, in the absence of longer-term follow-up data.

Equation 1: Exponential formula

$$Probability = 1 - e^{-rate * time}$$

Linzagolix and placebo (BSC) response data and the corresponding 28-day probability of achieving response are presented in Table 50Table 50: PRIMROSE 1 and 2, response defined by reduced MBL at 24-weeks and corresponding 28-day .

Table 50: PRIMROSE 1 and 2, response defined by reduced MBL at 24-weeks and corresponding 28-day probabilities

Treatment arm	24-week response	28-day cycle probability
Placebo (BSC)	32.2%	6.3%
Linzagolix 100 mg	56. 5%	13.0%
Linzagolix 200 mg	74.5%	20.4%

Abbreviations: BSC, best supportive care; MBL, menstrual blood loss; mg, milligram

Recurrence rates of UF symptoms, which are used to derive the probability of losing response and moving from 'controlled' to 'uncontrolled' within the model health states, are

informed by expert opinion elicited from a market research survey with UK gynaecologists (n=50), which reported the rate of recurrence of symptoms for GnRH antagonists and BSC.[39] In scenario analysis, equivalent recurrence rates between treatment arms are tested (Section B.3.11.3.3).

In line with the response endpoint described above, recurrence rates were converted into 28-day cycle probabilities (using an exponential assumption) to inform transition probabilities from the controlled to uncontrolled health state within the model (Table 51).

Table 51: Recurrence rates used in the cost-effectiveness model

Treatment arm	Recurrence rate	28-day cycle probability
Placebo (BSC)	[redacted]	[redacted]
Linzagolix	[redacted]	[redacted]

Abbreviations: BSC, best supportive care

B.3.3.3 Surgery

B.3.3.3.1 Proportion of patients receiving surgery

As described in Section B.3.2.3.1, in addition to drug acquisition and administration costs, the economic analyses across all populations consider the cost of surgery.

Surgery rates are not available from the PRIMROSE studies, as the requirement for surgery within 6 months regardless of the treatment provided was an exclusion criterion. Therefore, in the base case, the probability of surgery is taken from PEARL II, a study which compared ulipristal acetate with leuprorelin acetate for the pre-operative treatment of symptomatic fibroids. In PEARL II, 45.10% of patients went on to have surgery, as reported in NICE TA832.[22] In the cost-comparison models, surgery costs are applied as a one-off cost, while the cost-effectiveness model is able to consider surgery costs on a per-cycle basis.

Although PEARL II is the most relevant study available to inform the proportion of patients receiving surgery, based on clinical understanding of the disease and positioning, it is possible that the PEARL II rate is most applicable to the short-term setting (Population #1), given PEARL II was conducted in a pre-operate setting. Therefore, to capture uncertainty, scenario analyses considering lower surgery proportions in the long-term populations are considered (discussed in Sections B.3.3.3.4 and B.3.3.3.5 respectively).

B.3.3.3.2 Distribution of surgery type received

As there are several procedural/surgical interventions for patients with moderate to severe symptoms of UFs, the model estimates a weighted average input cost of surgery (see Section B.3.5.4). The rationale for patients having different surgeries is subject to many factors (including disease characteristics and patient preference). In the base case, surgery type distributions are sourced from NICE TA832 (based on values report in the company submission [base case] and ERG report [scenario analysis]).[22]

In the base-case analysis, it is assumed that surgery type distributions are the same across treatment arms (Table 52). Therefore, while the inclusion of surgery costs provides a more accurate representation of total costs for each treatment arm in the cost-comparison model (Populations #1 and #2), the impact of surgery on incremental costs is zero.

However, in clinical practice, the type of surgery received may vary by pharmacological treatment arm. Clinical expert opinion indicated that, while the choice between hysterectomy

and myomectomy is primarily driven by patient preference (namely, the desire to preserve future fertility options), the decision between laparoscopic and open/abdominal surgery is often driven by disease characteristics (namely, fibroid/uterine size). Clinical expert opinion suggested that fibroid/uterine shrinkage plays a role in the simplification of surgery, and a higher proportion of patients would undergo laparoscopic myomectomy/hysterectomy where fibroid/uterine volume is reduced by pharmacological therapy.[73]

As linzagolix and GnRH agonists can be administered without hormonal ABT, it is possible to achieve larger fibroid shrinkage compared with treatments administered alongside hormonal therapy. This was demonstrated for linzagolix compared with relugolix CT in the ITC for primary fibroid volume [largest fibroid at baseline] percentage change from baseline, as reported in Section B.2.9.6.4). This was further supported by clinical expert opinion, which indicated that, while linzagolix and relugolix CT may be considered comparable with respect to reduced menstrual blood loss, linzagolix at the 200 mg dose (without ABT) could achieve greater fibroid shrinkage. Furthermore, the flexible dosing regimen of linzagolix (200 mg and 100 mg dose options, both with and without ABT), should allow for maintenance of fibroid/uterine size in the longer-term setting.

Clinical expert opinion has indicated that the role of fibroid shrinkage in the type of surgery a patient undergoes is particularly relevant due to the growth of NHS waiting lists in gynaecology. In April 2022, it was reported that the waiting list for hospital-based gynaecological services was just under half a million patients, which is almost double the pre-COVID-19 pandemic figure observed in April 2019.[85] Furthermore, clinical expert opinion indicated surgery wait times of up to 18 months in NHS England practice.[73] In addition to worsening of symptoms, it is reported that fibroid growth over time may result in more invasive and time-consuming medical, hormonal and surgical interventions for a larger proportion of patients with UFs, further highlighting the importance of fibroid shrinkage or maintenance through pharmacological therapy in a pre-surgical treatment setting.[20]

The base case across all three populations takes a conservative approach assuming that surgery distributions are the same between treatments. Therefore, scenario analyses are explored which assume a higher proportion of linzagolix patients (and GnRH agonist patients in Population #1) receive laparoscopic rather than open/abdominal surgery, compared with the base case distribution (a movement of 10% from open/abdominal to laparoscopic surgery).

Table 52: Distribution of surgery types

Treatment arm	Base case (TA832, company submission)[22]	Scenario (TA832, ERG report)[22]
UAE	4.8%	0.0%
MRgFUS	3.0%	0.0%
Open/abdominal myomectomy	25.7%	27.0%
Laparoscopic myomectomy	8.2%	43.0%
Open/abdominal hysterectomy	51.8%	2.0%
Laparoscopic hysterectomy	6.4%	27.0%

Note: In TA832, the company estimated separate surgery distributions for vaginal/abdominal myomectomy/hysterectomy but applied consistent unit costs to both sub-types. As a simplifying assumption, these surgery sub-types have therefore been combined under open/abdominal surgery for the company submission estimates.
Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; TA, technology appraisal; UAE, uterine artery embolisation

B.3.3.3.3 Population #1: Short-term treatment

In the cost-comparison model base case, it is assumed that the proportion of patients who would receive surgery after short-term pharmacological treatment is equivalent across arms (Table 52). As the subgroup of patients receiving short-term treatment of 6 months or less refers to a pre-surgical treatment setting, increased surgery rates (i.e. assuming all patients in Population #1 receive surgery) are tested in scenario analysis (Section B.3.11.3.1). Surgery in Population #1 is applied as a one-off cost.

Scenario analysis explores an adjustment of 10% of patients who would receive open/abdominal surgery types (hysterectomy and myomectomy) instead being eligible for laparoscopic surgery for linzagolix and GnRH agonists (based on the reduction in fibroid volume).

B.3.3.3.4 Population #2: Long-term treatment with hormone-based therapy

In line with Population #1, the cost-comparison analysis considers the cost of surgery. In the absence of alternative data, it is assumed that 45.10% of people experience surgery costs (over the 10-year time horizon) across the linzagolix and relugolix CT arms, based on PEARL II and in line with the short-term analysis. Surgery costs are applied as a one-off cost within the cost-comparison analysis. In clinical practice, it is likely that the surgery probability would be lower in the longer-term setting than in the short-term treatment setting. Therefore, in scenario analysis, exploratory lower surgery probabilities of 25% and 35% are tested.

Surgery type distributions are also consistent with the short-term model in the base case analysis, as reported in Table 52 above, meaning surgery costs do not influence incremental costs in the base case.

In the cost-comparison analysis for Population #2, linzagolix 200 mg + ABT is compared with relugolix CT in the base case analysis. Due to the flexibility of the linzagolix dosing regimens and in line with the linzagolix license, the option to use the linzagolix 200 mg dose for 6 months before adding hormone-based therapy (200 mg + ABT) is test in scenario analysis. As described in Section B.3.3.3.2, linzagolix at the 200 mg dose (without ABT) could achieve greater fibroid shrinkage, which may allow a higher proportion of patients to receive less invasive surgery. As such, an exploratory scenario is tested which assumes for patients receiving linzagolix 200 mg for 6 months followed by linzagolix 200 mg + ABT, a higher proportion receive laparoscopic versus open/abdominal surgery (see Section B.3.11.3.2).

B.3.3.3.5 Population #3: Long-term treatment without hormone-based therapy

In the longer-term cost-effectiveness model for Population #3, the PEARL II surgery rate is used in line with the cost-comparison analyses described above and consistent with TA832.[22] In the cost-effectiveness model, a per 28-day cycle probability of experiencing surgery (and entering the 'surgery' health state) is estimated based on the proportion of patients expected to receive surgery (45.10%) and the estimated surgery wait time of up to 18 months, as reported by two clinical experts in interviews conducted to validate the modelling approach.[73] The resulting per 28-day cycle probability of surgery (3.02%) is applied in the cost-effectiveness model up to the average age of menopause.

In the base case, it is assumed that the probability of experiencing surgery from the 'controlled' and 'uncontrolled' health states is equivalent. However, clinical expert opinion indicated that patients with controlled symptoms (reduced menstrual bleeding) may be less likely to experience surgery in NHS practice. Therefore, in exploratory scenario analyses, lower per 28-day surgery probabilities of 1% and 2% for patients with controlled symptoms

are tested, to reflect the assumption that a higher proportion of patients would delay or avoid surgery and continue long-term pharmacological treatment.

The cost-effectiveness model conservatively assumes that the distribution of surgery types would be equivalent between patients receiving linzagolix and BSC (which is comprised of non-active treatment options such as NSAIDs and iron supplements). As linzagolix is more likely to achieve fibroid shrinkage than BSC/placebo (with substantial reductions in fibroid and uterine volume observed with linzagolix 200 mg as reported in Section B.2.6.2.1), scenario analyses are presented assuming a higher distribution of linzagolix patients receive laparoscopic surgery compared with open/abdominal surgery (consistent with the scenarios presented in the cost-comparison analyses for Populations #1 and #2).

B.3.3.4 Mortality

B.3.3.4.1 Population #1: Short-term treatment

UFs are benign tumours and are therefore not expected to be associated with an increased mortality rate beyond that of the age-matched general population. Furthermore, no data have been identified within the literature which suggest UFs alter life expectancy.

Therefore, as a simplifying assumption in the cost-comparison analysis, mortality rates are not considered, because any effects would be equivalent across arms and have no impact on incremental costs.

B.3.3.4.2 Population #2: Long-term treatment with hormone-based therapy

Consistent with short-term cost-comparison analysis describe above.

B.3.3.4.3 Population #3: Long-term treatment without hormone-based therapy

In the cost-effectiveness model, death is incorporated based on background mortality rates derived from the latest general population ONS data for England (2018-2020)[83], and movements to death do not differ by health state (except surgery) or by treatment arm.

It is possible that surgery-related complications (procedural-related death) may result in a heightened risk of mortality within the surgery health state. Therefore, in addition to background mortality, the model accounts for procedural-related death (which may occur when patients exit the surgery state). Procedure-related death estimates sourced from TA832 and incorporated a small risk of death associated with some surgeries (summarised in Table 53).[22] Within the modelling framework, procedural death varies based on the type of surgery encountered, and as such a weighted average mortality rate is estimated.

Table 53: Risk of procedural death

Treatment arm	Risk of death	Source
UAE	0.0200%	TA832[22]/Zowall et al., 2008[86]
MRgFUS	0.0000%	TA832[22]/Gorny et al., 2011[87]
Open/abdominal myomectomy	0.0028%	TA832[22]/Assumption
Laparoscopic myomectomy	0.0000%	TA832[22]/Assumption
Open/abdominal hysterectomy	0.0028%	TA832[22]/Settnes et al 2020[88]
Laparoscopic hysterectomy	0.0020%	TA832[22]/Settnes et al 2020[88]

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; UAE, uterine artery embolisation

B.3.3.5 Summary of transition probabilities applied in the model

B.3.3.5.1 Population #1: Short-term treatment of 6 months or less

Not applicable in the cost-comparison analysis.

B.3.3.5.2 Population #2: Long-term treatment with hormone-based therapy

Not applicable in the cost-comparison analysis.

B.3.3.5.3 Population #3: Long-term treatment without hormone-based therapy

Table 54 summarises transition probabilities used the cost-effectiveness model for Population #3, which are based on the efficacy, surgery, and mortality data described in the previous sections.

Table 54: Summary of transition probabilities in the cost-effectiveness model (Population #3)

FROM / TO	Controlled	Uncontrolled	Surgery	Post-surgery	Procedural death
Linzagolix					
Controlled	[redacted]	[redacted]	[redacted]	0.000%	0.000%
Uncontrolled	[redacted]	[redacted]	[redacted]	0.000%	0.000%
Surgery	0.000%	0.000%	0.000%	99.999%	0.001%
Post-surgery	0.000%	0.000%	0.000%	100.000%	0.000%
Procedural death	0.000%	0.000%	0.000%	0.000%	100.000%
BSC					
Controlled	[redacted]	[redacted]	[redacted]	0.000%	0.000%
Uncontrolled	[redacted]	[redacted]	[redacted]	0.000%	0.000%
Surgery	0.000%	0.000%	0.000%	99.999%	0.001%
Post-surgery	0.000%	0.000%	0.000%	100.000%	0.000%
Procedural death	0.000%	0.000%	0.000%	0.000%	100.000%

Note: Transition matrix does not include background mortality which is applied separately within the model calculations
Abbreviations: BSC, best supportive care

B.3.3.6 Adverse events

B.3.3.6.1 Population #1: Short-term treatment of 6 months or less

Adverse event rates are not incorporated into the cost-comparison model, as it is assumed that treatments included in the cost-comparison analysis are clinically comparable with regards to efficacy and safety.

B.3.3.6.2 Population #2: Long-term treatment with hormone-based therapy

Not applicable (consistent with short-term cost-comparison analysis describe above).

B.3.3.6.3 Population #3: Long-term treatment without hormone-based therapy

In the cost-effectiveness analysis comparing linzagolix with BSC in patients receiving long-term treatment without hormone-based therapy, the costs and HRQoL consequences of AEs are captured.

AEs for linzagolix are informed by the pooled PRIMROSE 1 and 2 trials (100 mg and 200 mg arms), which reported treatment-emergent AEs by treatment arm. The placebo arm of PRIMROSE 1 and 2 was used to inform BSC AEs within the model. Treatment-emergent AEs occurring in 5% or more of patients across the treatment arms relevant to Population #3 (100 mg, 200 mg, and placebo) are used to inform the cost-effectiveness model.

Table 55: Treatment-emergent adverse events included within the cost-effectiveness model

Adverse event	Linzagolix 100 mg	Linzagolix 200 mg	Placebo (BSC)
Anaemia	10.05%	2.86%	6.70%
Headache	6.03%	11.90%	5.74%
Hot flush/flash	10.05%	33.33%	5.26%
Nausea	1.51%	5.24%	0.96%

Abbreviations: BSC, best supportive care

B.3.4 Measurement and valuation of health effects

The measurement and valuation of health effects is presented throughout this section. As cost-comparison methodology is considered appropriate for Populations #1 and #2, this section is only relevant to Population #3, the cost-effectiveness component comparing linzagolix to BSC in the patients having long-term treatment without hormone-based therapy.

B.3.4.1 Health-related quality of life data from clinical trials

In PRIMROSE 1 and 2, HRQoL outcome data were assessed using the Uterine Fibroid Symptom-Quality of Life questionnaire (UFS-QoL) and the EuroQol-5 Dimension-5-Level (EQ-5D-5L) questionnaire. HRQoL data collected at baseline and Weeks 12, 24, 36, and 52 were used to inform the cost-effectiveness analysis.

The UFS-QoL is a self-reported disease-specific measure that assesses the severity of symptoms and HRQoL of patients with UFs. The measure consists of an 8-item severity scale of symptoms (with a 5-point Likert scale ranging from ‘not at all’ to ‘a very great deal’ and 29-item HRQoL scale (reported as a Likert scale related to frequency ranging from ‘none of the time’ to ‘all of the time’), which links to six domains[89]:

1. Concern
2. Activities
3. Energy/mood
4. Control
5. Self-consciousness
6. Sexual function.

In the PRIMROSE studies, symptom severity and HRQoL were assessed using the 3-month recall version of the UFS-QoL questionnaire.

B.3.4.2 Mapping

The following two methods of mapping were conducted using the HRQoL data from PRIMROSE 1 and PRIMROSE 2:

1. Mapping of the UFS-QoL to EQ-5D-3L (base case)
2. Mapping of the EQ-5D-5L to EQ-5D-3L (scenario analysis)

In both instances, patients were categorised based on the primary endpoint of the trial (MBL ≤80 mL and ≥50% reduction from baseline), which allows estimation of health-state utility values, as the definition is aligned with the modelled health states ('controlled' and 'uncontrolled').

B.3.4.2.1 Mapping the UFS-QoL to EQ-5D-3L

The UFS-QoL was mapped to the EQ-5D using the same approach as was taken in TA832. This was based on an unpublished algorithm reported in Rowen and Brazier 2011, that was submitted as part of the TA832 submission.[22] The authors reported an ordinary least squares (OLS) model based on Equation 2. Using the information provided in TA832 (Clarification Question B10), the same methodology was applied using the UFS-QoL data collected in the PRIMROSE 1 and 2 trials.

Equation 2: UFS-QoL to EQ-5D-3L mapping algorithm

$$EQ-5D_i < -0.974 -$$
$$0.062 * [Q24 = 2]i - 0.075 * [Q24 = 3]i - 0.243 * [Q24 = 4]i - 0.151 * [Q24 = 5i] -$$
$$0.059 * [Q5 = 2]i - 0.061 * [Q5 = 3]i - 0.094 * [Q5 = 4]i - 0.323 * [Q5 = 5]i -$$
$$0.047 * [Q8 = 2]i - 0.040 * [Q8 = 3]i - 0.071 * [Q8 = 4]i - 0.100 * [Q8 = 5]i$$

In the PRIMROSE 1 and 2 studies, there were [redacted] UFS-QoL observations from [redacted] patients across timepoints (Table 56). A descriptive analysis of utility values by response status is presented in Table 57.

Table 56: Summary of UFS-QoL observations (PRIMROSE 1 and 2)

Follow-up	Number of observations
Baseline	[redacted]
Week 12	[redacted]
Week 24	[redacted]
Week 36	[redacted]
Week 52	[redacted]

Abbreviations: UFS-QoL, uterine fibroid symptom and quality of life

Table 57: Summary of utility values by response (UFS-QoL mapped to EQ-5D-3L)

Health state	Number of patients	Number of observations	Mean	Median
RMBL = Yes (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
RMBL = No (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D-3L, EuroQoL 5 dimensions; RMBL, reduced menstrual blood loss; UFS-QoL, uterine fibroid symptom and quality of life

A linear mixed model (LMM) was used to estimate health-state utility values from the PRIMROSE data using the mapped EQ-5D values. A linear mixed model was considered appropriate as it accounts for within-patient repeated measures (a critique raised by the EAG in the TA832 appraisal was that an OLS model was presented which did not account for repeated measures).[22] Outcomes of the analysis are presented in Table 58.

Base case utility values are discussed in Section B.3.4.5.3.

Table 58: LMM outcomes for UFS-QoL (mapped to EQ-5D) by RMBL

Health State	Utility value
Controlled (patients with RMBL)	[redacted]
Uncontrolled (patients without RMBL)	[redacted]

Abbreviations: EQ-5D, EuroQol-5 Dimensions; LMM, linear mixed model; RMBL, reduced menstrual blood loss; UFS-QoL, Uterine Fibroid Symptom and Quality of Life

B.3.4.2.2 Mapping the EQ-5D-5L to EQ-5D-3L

In line with the NICE methods guidance[80], the EQ-5D-5L responses collected in PRIMROSE 1 and 2 were mapped to produce EQ-5D-3L utility values, using the algorithm developed by Hernandez-Alava et al 2017.[90]

In total, [redacted] EQ-5D-5L observations were available from [redacted] patients (Table 59). A tabulated summary of the EQ-5D-5L mapped values are provided in Table 60.

Table 59: Summary of UFS-QoL observations (PRIMROSE 1 and 2)

Follow-up	Number of observations
Baseline	[redacted]
Week 12	[redacted]
Week 24	[redacted]
Week 36	[redacted]
Week 52	[redacted]

Abbreviations: EQ-5D, EuroQol-5 Dimensions

Table 60: Summary of utility values by response (EQ-5D-5L mapped to EQ-5D-3L)

Health state	Number of patients	Number of observations	Mean	Median
RMBL = Yes (Controlled)	[redacted]	[redacted]	[redacted]	[redacted]
RMBL = No (Uncontrolled)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EQ-5D, EuroQol-5 Dimensions; EQ-5D-3L, EuroQol-5 Dimensions-3-Level; EQ-5D-5L, EuroQol-3-Dimensions-5-Level; RMBL, reduced menstrual blood loss

A regression model was used to estimate health-state utility values based on RMBL (response) which, by definition (see Section B.3.2.3.3), categorises patients into modelled health states ('controlled' and 'uncontrolled'). Consistent with the UFS-QoL mapped to EQ-5D-3L utility analysis described above, a LMM was used to estimate utility values from the

PRIMROSE data using the mapped EQ-5D values (given that individual patients may provide multiple HRQoL assessments). Outcomes of the analysis are presented in Table 61.

Table 61: LMM outcomes for EQ-5D by RMBL

Health state	Utility value
Controlled (patients with RMBL)	[redacted]
Uncontrolled (patients without RMBL)	[redacted]

Abbreviations: EQ-5D, EuroQol-5 Dimensions; LMM, linear mixed model; RMBL, reduced menstrual blood loss; UF, uterine fibroids

B.3.4.3 Health-related quality of life studies

In line with the search for economic evaluations, an SLR to identify relevant HRQoL data was conducted. Appendix H provides full details of the methods, an overview of the studies and results, alongside a quality assessment of the studies identified. The original searches were performed in August 2021. An update of the SLR was run for the period August 2021 to March 2022, for GnRH antagonists. A further update of the SLR was run for the period March 2022 to February 2023.

B.3.4.3.1 Health state (controlled/uncontrolled) utility values from the literature

In total, the SLR identified 47 HRQoL studies of potential relevance to the decision problem (see Appendix H). One of the 47 studies, Hux et al. 2015, reported health-state utility values associated with moderate to severe UFs, although this was a Canadian study which estimated mapped US utility weights (Table 62).[91] While these data did not wholly meet the requirements of the NICE reference case, the health-state utility values for uncontrolled bleeding (0.55) and controlled bleeding (0.73) were included in the cost-effectiveness model in scenario analysis, to allow exploration of alternative utility values to those derived from the PRIMROSE 1 and 2 studies.

Table 62: Summary of health-state utility values from the literature

Author, year (country)	Study population	Number	Treatments	HRQoL instrument	Results, mean (SD)
Hux et al. 2015 (Canada)[91]	Women aged 20–49 years and of mixed ethno-cultural backgrounds, diagnosed with UFs and having received treatment in the last 5	Uncontrolled & Controlled bleeding: 909 Controlled bleeding with hot flashes: 296 Controlled bleeding with smaller fibroids: 312 Controlled bleeding with oral medication: 297	-	EQ-5D-5L	**Overall** Uncontrolled bleeding: 0.55 (0.21) Controlled bleeding: 0.73 (0.13) Controlled bleeding with hot flashes: 0.67 (0.17) Controlled bleeding with smaller fibroids: 0.76 (0.15) Controlled bleeding with oral medication: 0.74 (0.13)

Abbreviations: EQ-5D-5L, EuroQol-5 Dimensions-5-Level; HRQoL, health-related quality of life; SD, standard deviation

As well as consideration of the utility values reported within the literature, utility values were also reported in the TA832 NICE submission for relugolix CT. In TA832, data from the

LIBERTY 1 and 2 trials were pooled, and UFS-QoL data mapped to EQ-5D were used in the base case. In TA832, the company then used a further OLS linear additive regression model as a utility function to predict treatment-state utility values based on MBL and baseline age in their 'treatment-state based' model structure. Although the ERG in TA832 was generally satisfied that the underlying mapping process (UFS-QoL to EQ-5D) was reasonable, the ERG raised several concerns with the company's approach to the estimation of treatment-state utility values using an OLS regression.[22] Therefore, as described in Section B.3.4.2.1, the mapping algorithm reported in TA832 was used in this submission, but a LMM used estimate health-state utility values from the PRIMROSE data using the mapped EQ-5D values.

B.3.4.3.2 Surgery/post-surgery utility values from the literature

As there were no surgery or post-surgery HRQoL data collected in PRIMROSE 1 and 2, it was necessary to identify utility values from the literature for these states. As described in Section B.3.2.3, model inputs (including HRQoL data) are weighted across the following surgery types: UAE, MRgFUS, myomectomy, and hysterectomy.

Six identified studies from the HRQoL SLR reported EQ-5D utility values associated with surgical/interventional procedures. Of these six, only one (Manyonda et al. 2020) was a UK-based study. This study (summarised in Table 63) compared EQ-5D-3L values in patients who received UAE or myomectomy in women with symptomatic UFs.[92]

For completeness, the studies identified in the economic evaluation SLR (described in Section B.3.1 and further in Appendix G), were also examined to understand if any further HRQoL data may be appropriate for consideration to the decision problem. The economic evaluation SLR identified six UK-based economic evaluations, one of which compared UAE with myomectomy for treating symptomatic fibroids and used the utility values reported in Manyonda et al. 2020.[92,93] Another identified study (Cooper et al. 2019) which assessed the clinical and cost-effectiveness of laparoscopic supracervical hysterectomy (LASH) with endometrial ablation in an economic evaluation alongside a RCT (HEALTH) reported EQ-5D-3L utility values for women with HMB.[94] In addition, a further study reported utility values for patients receiving MRgFUS (Zowall et al. 2008), although it should be noted that, unlike previously described studies, this analysis was conducted in 2008, used the SF-6D rather than the EQ-5D to assess HRQoL, and reported utility values for 'post-treatment' and 'fully recovered' (rather than at baseline and a specified timepoint following surgery).

Nevertheless, in the absence of surgery-specific data from the PRIMROSE studies, these studies, which provided surgery and post-surgery specific utility values (summarised in Table 63) were considered appropriate to inform the cost-effectiveness analysis.

Table 63: Summary of relevant surgery/post-surgery utility values from the literature

Author, year (country)	Study population	Number	Treatments	HRQoL instrument	Results, mean (SD)
Manyonda et al. 2020 (UK)[92]	Women who had symptomatic UFs and did not want to undergo hysterectomy	**Patients** 254	UAE Myomectomy	EQ-5D-3L	**UAE** Baseline: 0.62 (0.34) 6 months: 0.77 (0.30) 1 year: 0.77 (0.30) 2 years: 0.80 (0.29) **Myomectomy** Baseline: 0.63 (0.32) 6 months: 0.85 (0.17) 1 year: 0.85 (0.23) 2 years: 0.88 (0.20)
Cooper et al. 2019 (UK)[94]	Women aged <50 years with HMB who were eligible for EA and willing to be randomised between LASH and EA	**Observations** Baseline: 641 6 weeks post-surgery: 497 6 months post-surgery: 488 15 months post-randomisation: 562	LASH EA	EQ-5D-3L	**LASH** Baseline: 0.7065 (0.30) 6 weeks post-surgery: 0.8279 (0.22) 6 months post-surgery: 0.8315 (0.27) 15 months post-randomisation: 0.8357 (0.24) **EA** Baseline: 0.6983 (0.31) 6 weeks post-surgery: 0.8282 (0.28) 6 months post-surgery: 0.8269 (0.25) 15 months post-randomisation: 0.8005 (0.28)
Zowall et al. 2008 (informed by UF002)[86,95,96]	Women for whom surgical treatment for uterine fibroids is being considered	NR	MRgFUS	SF-36 to SF-6D	**MRgFUS*** Post-treatment: 0.783 (NR) Fully recovered: 0.802 (NR)

* Only HRQoL data in the MRgFUS arm was informed by the UF002 clinical trial data in the cost-utility analysis (as such, only the MRgFUS arm utility values are presented within this table)
Abbreviations: EA, endometrial ablation; EQ-5D, EuroQol-5 Dimensions; HMB, heavy menstrual bleeding;

HRQoL, health-related quality of life; LASH, laparoscopic supracervical hysterectomy; MRgFUS, magnetic resonance-guided focused ultrasound; NR, not reported; SD, standard deviation; SF, short form; UAE, uterine artery embolisation; UF, uterine fibroid; UK, United Kingdom

B.3.4.4 Adverse reactions

The impact of adverse events (AEs) on HRQoL was explored in the cost-effectiveness model (Population #3). As trial-based utilities derived from PRIMROSE 1 and 2 are applied in the controlled and uncontrolled model health states across both arms in the base-case analysis (see Section B.3.4.5.3), the individual impact of toxicities associated with AEs are not captured within the health-state specific values. As such, AE disutility values have been included within the cost-effectiveness model (with the exclusion of these values considered in scenario analysis, see Section B.3.11.3).

The disutility values of AEs applied for linzagolix versus BSC were identified from published sources and are presented in Table 64. The frequency of AEs for both arms was obtained from the pooled PRIMROSE 1 and 2 studies (as outlined in Section B.3.3.6.3). As a simplifying approach, the duration of AEs was assumed to be one model cycle (28-days) and resulting QALY decrements were applied as a one-off in the first model cycle.

Table 64: Adverse event disutility values

AE	Disutility	Source
Anaemia	-0.0209	Sullivan et al. 2006[97] ICD-9 185
Headache	-0.0297	Sullivan et al. 2006[97] ICD-9 346
Hot flush/flash	-0.0600	Hux et al. 2015[91]
Nausea	-0.0480	Nafees et al. 2008[98]

Abbreviations: AE, adverse event; ICD; International Classification of Diseases

Using the AE frequencies from the PRIMROSE 1 and 2 trials (for linzagolix 200 mg [in the base case] as reported in Table 55), and the disutility values (Table 64), a one-off QALY decrement per treatment arm was calculated and applied in the first cycle of the cost-effectiveness model (reported in Table 65).

Table 65: AE QALY decrement

Treatment arm	AE disutility
Linzagolix (100 mg, scenario)	-0.001
Linzagolix (200 mg, base case)	-0.002
BSC	-0.001

Abbreviations: AE, adverse event; BSC, best supportive care; mg, milligram

B.3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

B.3.4.5.1 Population #1: Short-term treatment

Not applicable in a cost-comparison framework.

B.3.4.5.2 Population #2: Long-term treatment with hormone-based therapy

Not applicable in a cost-comparison framework.

B.3.4.5.3 Population #3: Long-term treatment without hormone-based therapy

Health-state utility values for controlled and uncontrolled patients

HRQoL within the cost-effectiveness model (Population #3) is based on health-state occupancy (the proportion of patients in each health state in each model cycle) and corresponding utility values assigned to the respective health states. The values derived from PRIMROSE 1 and PRIMROSE 2 are based on the collected UFS-QoL (mapped to EQ-5D) data.

The HRQoL values obtained from the EQ-5D-5L are not deemed suitable to inform the base-case analysis, as the EQ-5D measure does not have the sensitivity to fully evaluate the impact of UFs on a patients' HRQoL. One of the primary reasons for this, and aligned with rationale provided in TA832, is that the EQ-5D is limited by asking patients what they are experiencing 'today', which may not provide an accurate reflection of a patients overall HRQoL over a menstrual cycle. The UFS-QoL is more specific than the EQ-5D and asks patients to recall their outcomes based on the prior 3 months. In addition, the UFS-QoL is specific to symptoms associated with UFs, which are difficult to capture within the restricted domains of the EQ-5D (examples include: inconvenience associated with the disease related to the need to carry additional hygiene products, concerns and anxiousness related to soiling outer clothes, and diminished sexual desire). These limitations of the generic EQ-5D measure raise questions as to the degree of internal validity and reliability of the EQ-5D-5L scores from the PRIMROSE trials and the applicability to patients suffering with moderate to severe symptoms of UFs. The disease-specific UFS-QoL provides a more reliable and appropriate measure to use in the assessment of HRQoL for patients with UFs and is therefore included as the model base case (mapped to EQ-5D-3L values in line with NICE requirements, as described in Section B.3.4.2.1). In TA832, the ERG was generally satisfied with the underlying mapping process (UFS-QoL to EQ-5D). However, for completeness, EQ-5D-5L (mapped to 3L, as described in Section B.3.4.2.2) utility values are tested in scenario analysis.

HRQoL for surgery/post-surgery

For health states related to surgery and post-surgery, utility values informing the base-case cost-effectiveness model are informed by the literature (Table 66) and are dependent on the type of surgery received (see Section B.3.3.3). Where the literature provided multiple post-surgery HRQoL assessments, the last timepoint was used to represent utility in the post-surgery state (see Table 63), to utilise the longest available follow-up data and as a simplifying assumption.

Table 66: Health-state utility values for surgery/post-surgery

Surgery	Health state	Value	Reference
UAE	Surgery	0.620	Manyonda et al. 2020[92]
	Post-surgery	0.800	
	Post-surgery	0.801	
MRgFUS	Surgery	0.783	Zowall et al. 2008[86]
	Post-surgery	0.802	
Open/abdominal myomectomy	Surgery	0.628	Assumption based on the reported disutility difference between abdominal and laparoscopic myomectomy in TA832
	Post-surgery	0.878	
Laparoscopic Myomectomy	Surgery	0.630	Manyonda et al. 2020[92]
	Post-surgery	0.880	
Open/abdominal Hysterectomy	Surgery	0.705	Assumption based on the reported disutility difference between abdominal and laparoscopic hysterectomy in TA832
	Post-surgery	0.834	
Laparoscopic hysterectomy	Surgery	0.707	Cooper et al. 2019[94]
	Post-surgery	0.836	

Abbreviations: MRgFUS, magnetic resonance-guided focused ultrasound; UAE, uterine artery embolisation

Based on the distribution of surgery types for each treatment arm (Table 51), weighted average utility values are obtained for the surgery and post-surgery health states. Alternative post-surgery utility values are tested in scenario analysis, including assuming HRQoL returns to that of the general population post-surgery, and assuming HRQoL returns to that of the controlled health state.

Age-adjusted utilities

Age-related utility decrements have also been included in the model base case to account for the natural decline in quality of life associated with age. Utility values from the general population at each age were calculated using the algorithm by Ara and Brazier, 2010.[84] The utility multiplier was the calculated per increase in age and applied in each cycle throughout the model time horizon. A scenario analysis is considered which excludes the adjustment for age-related disutility.

$$General\ population\ utility\ value = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

Summary of utility values for cost-effectiveness (Population #3 base case)

Table 67: Summary of utility values for cost-effectiveness analysis (Population #3)

Health state	Treatment arm	Utility value	Source	Justification
Controlled	Linzagolix (200 mg)	[redacted]	PRIMROSE 1 and 2 (UFS-QoL mapped to EQ-5D)	Utilises clinical trial data in a relevant population. Aligns with model health states EQ-5D questionnaire lacks sensitivity in UFs.
	BSC	[redacted]		
Uncontrolled	Linzagolix (200 mg)	[redacted]		
	BSC	[redacted]		
Surgery	Surgery and post-surgery utility values are non-treatment specific in the base case	0.677	Literature	It is necessary to source surgery-specific utility values from the literature in the absence of surgery or post-surgery data in the PRIMROSE 1 and 2 studies.
Post-surgery		0.846	Literature	

Abbreviations: BSC, best supportive care; EQ-5D, EuroQol-5 Dimension; mg, milligram; UF, uterine fibroid; UFS-QoL, Uterine Fibroid Symptom-Quality of Life

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

In line with the NICE reference case, the perspective on costs is that of the NHS and PSS in England.[80] Costs are taken from typical UK sources used in previous NICE appraisals, including:

- The British National Formulary (BNF) for branded treatment costs[99]
- The drugs and pharmaceutical electronic market information tool (eMIT) for generic treatment costs[100]
- National Schedule of NHS costs (or NHS reference costs) 2021/22 for service/healthcare activity costs[101]
- The PSS Research Unit (PSSRU) Unit Costs of Health and Social Care 2022 for staff costs[102]
- Other published literature sources where necessary

B.3.5.1 Intervention and comparators' costs and resource use

Unit costs used in the cost-comparison analysis and cost-effectiveness analysis are presented in Table 68. Furthermore, hormonal ABT and concomitant medication unit costs are presented in Table 69. For relugolix CT, it is assumed that the cost of ABT is included in the combined formulation, therefore no additional ABT costs are applied in the relugolix CT arm. For linzagolix 100 mg + ABT and 200 mg + ABT, the cost of estradiol 1 mg and norethisterone 0.5 mg is applied in line with the license. In the cost-comparison analysis for Population #1, it is assumed that patients receiving short-term treatment do not require hormonal ABT; and as such, no ABT costs are applied in the GnRH agonist arms.

As described in NICE TA832, patents with moderate to severe symptoms of UFs may require supplementary drugs for symptom management such as pain and blood loss. In the

base case analysis, it is assumed all patients across all treatment arms receive concomitant ibuprofen (assuming 200 mg taken 3 times a day for 4 days per model cycle in line with TA832) and iron supplements (200 mg daily). However, in scenario analysis (Section B.3.11.3), treatment-specific concomitant medication proportions from the relevant clinical trials are applied (Table 70).

Administration costs are incorporated within the cost-comparison and cost-effectiveness models and are summarised in Table 71. It is assumed that oral medicines (GnRH antagonists) do not require any administration cost as they are self-administered. For the GnRH agonists, which are administered via subcutaneous injection, the models assume that treatment is administered in a local GP setting, requiring 10 minutes of nurse time.[102]

Table 68: Drug unit costs

Treatment	Units and pack size	Dose	Pack cost	Source	Description
Linzagolix	100 mg x 28 tablets	100 mg daily	List price: [redacted] PAS price: [redacted]	Theramex	Yselty 100 mg
Linzagolix	200 mg x 28 tablets	200 mg daily	List price: [redacted] PAS price: [redacted]	Theramex	Yselty 200 mg
Relugolix CT	40 mg x 28 tablets	40 mg daily	£72.00	BNF 2023[99]	Ryeqo 40 mg/1 mg/0.5 mg
Relugolix CT	40 mg x 84 tablets	40 mg daily	£216.00	BNF 2023[99]	
Leuprorelin	3.75 mg x 1 injection	3.75 mg once monthly	£75.24	BNF 2023[99]	Prostap SR DCS 3.75 mg
Leuprorelin	11.25 mg x 1 injection	11.25 mg once every 3 months	£225.72	BNF 2023[99]	Prostap 3 DCS 11.25 mg
Goserelin	3.6 mg x 1 injection	3.6 mg once monthly	£70.00	BNF 2023[99]	Zoladex 3.6 mg
Goserelin	10.8 mg x 1 injection	10.8 mg once every 3 months	£235.00	BNF 2023[99]	Zoladex LA 10.8 mg
Triptorelin	3.8 mg x 1 injection	3.8 mg once monthly	£81.69	BNF 2023[99]	Gonapeptyl Depot 3.75 mg
Triptorelin	11.3 mg x 1 injection	11.3 mg once every 3 months	£207.00	BNF 2023[99]	Decapeptyl SR 11.25 mg

Note: Prostap SR DCS = leuprorelin acetate (powder and solvent for prolonged-release suspension for injection); Prostap 3 DCS = leuprorelin acetate (powder and solvent for prolonged-release suspension for injection).
Abbreviations: BNF, British National Formulary; CT, combination therapy; mg, milligram; PAS, patient access scheme

Table 69: Hormonal ABT and concomitant medication unit costs

Treatment	Units and pack size	Pack cost	Source	Description
Oestradiol/ norethisterone	1 mg / 0.5 mg x 84 tablets	£13.20	BNF 2023[99]	Kliovance tablets
Ibuprofen	200 mg x 24 tablets	£0.36	eMIT 2023[100]	Quantity: 78,257 SD: £0.21
Ferrous sulfate	200 mg x 28 tablets	£0.54	eMIT 2023[100]	Quantity: 584,493 SD: £0.28

Abbreviations: ABT, add-back therapy; BNF, British National Formulary; eMIT, electronic marketing information tool; mg, milligram; SD, standard deviation

Table 70: Treatment-specific concomitant medication proportions (applied in scenario analysis)

Treatment	Ibuprofen	Ferrous sulfate	Source
Linzagolix 100 mg	[redacted]	[redacted]	PRIMROSE 1 and 2 (pooled)
Linzagolix 100 mg + ABT	[redacted]	[redacted]	
Linzagolix 200 mg	[redacted]	[redacted]	
Linzagolix 200 mg + ABT	[redacted]	[redacted]	
Relugolix CT	61.30%	30.10%	LIBERTY 1 and 2 (pooled); TA832
GnRH agonists	27.70%	24.80%	
BSC	[redacted]	[redacted]	PRIMROSE 1 and 2 (pooled)

Note: It is assumed 100% of patients across treatment arms require concomitant medication in the base case, treatment-specific proportions are applied in scenario analysis
Abbreviations: ABT, add-back therapy; BSC, best supportive care; CT, combination therapy; GnRH; gonadotropin-releasing hormone

Table 71: Administration costs

Administration type	Cost	Reference
Oral	£0.00	Zero cost (assumption that patients will self-administer)
Subcutaneous injection	£7.67	PSSRU 2022[102]: Nurse GP (assumed 10 minutes of hourly unit cost of £46)

Abbreviations: GP, general practitioner; PSSRU; Personal Social Services Research Unit

B.3.5.1.1 Treatment discontinuation rates

Population #1: Short-term treatment of 6 months or less

For simplicity, it is assumed that no discontinuation occurs in the base case for Population #1. Given the short treatment duration (expected ahead of surgery), the impact of considering discontinuation is expected to be minimal.

Population #2: Long-term treatment with hormone-based therapy

It is not anticipated that 100% of patients receiving linzagolix or relugolix CT in a longer-term treatment setting would remain on treatment for the full 10-year time horizon. Furthermore, it is expected that discontinuation rates would be comparable between linzagolix and relugolix CT (based on the withdrawal rates observed in the relevant clinical trials). As such, treatment discontinuation rates from PRIMROSE 1 and 2 (linzagolix) are applied to both treatment arms for the population of patients receiving long-term treatment with hormone-based therapy. To inform treatment discontinuation within the model, the discontinuation

data from the observed period of the trial (24-weeks) is converted in to a 28-day cycle probability (Table 72).

Table 72: Discontinuation rates from PRIMROSE 1 and 2 from 24-week follow-up (Population #2)

Treatment arm	Discontinuation rates from PRIMROSE 1 and 2 (linzagolix 200 mg + ABT)	Converted 28-day discontinuation rate
GnRH antagonists	[redacted]	[redacted]

Abbreviations: ABT; add-back therapy; GnRH; gonadotropin-releasing hormone

Population #3: Long-term treatment without hormone-based therapy

For Population #3, discontinuation of linzagolix is considered using withdrawal data from the pooled PRIMROSE 1 and 2 studies (presented in Table 73). The discontinuation data from the observed period of the trial (24-weeks) is converted in to a 28-day probability (in line with the model cycle length outlined in Section B.3.2.3.3) for linzagolix 200 mg up to 6 months followed by 100 mg (base case analysis) and 100 mg throughout (scenario analysis). The 28-day probability is then applied throughout the time horizon for all patients in the *'Controlled'* and *'Uncontrolled'* health states on both treatment arms. It is assumed that on entry to the *'Surgery'* or *'Menopause'* states, pharmacological therapy is no longer required.

In TA832, the company modified discontinuation based on the assumption that withdrawals in the trial are an overestimate of clinical practice. However, the ERG preferred method was to use the data obtained directly from the trial. As such, in the economic model base case, unadjusted treatment withdrawal rates from PRIMROSE 1 and 2 are used to estimate discontinuation in the linzagolix arm. However, a scenario analysis is applied whereby only withdrawals due to AEs in PRIMROSE 1 and 2 are used to inform discontinuation rates. As BSC comprises concomitant medication costs (which are applied to all patients across treatment arms) but no active therapy, placebo discontinuation rates do not influence costs in the BSC arm of the cost-effectiveness model.

Table 73: Discontinuation rates from PRIMROSE 1 and 2 from 24-week follow-up

Treatment arm	Discontinuation rates from PRIMROSE 1 and 2	Converted 28-day discontinuation rate
Linzagolix 100 mg	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]
Linzagolix 100 mg (withdrawals due to AEs scenario)	[redacted]	[redacted]
Linzagolix 200 mg (withdrawals due to AEs scenario)	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; mg, milligram

B.3.5.2 Health-state unit costs and resource use

A systematic review of the literature was conducted to identify relevant published cost and resource use studies. Searches were conducted alongside those presented in Section B.3.1 (and Appendix G) for economic evaluations. Further details of the cost and resource use SLR are reported in Appendix I.

The cost and resource use SLR identified 18 studies; however, none of these studies were conducted in the UK and were therefore considered to be of limited relevance to the decision

problem in this appraisal. Furthermore, most of the identified studies reported surgery costs (non-UK) but not healthcare resource estimates.

Therefore, the single prior NICE STA in moderate to severe symptoms of UFs (TA832) was considered the most relevant source of cost and resource use identification to this appraisal.[22]

B.3.5.2.1 Population #1: Short-term treatment of 6 months or less

Although there is no evidence identified to suggest differences in monitoring between the GnRH antagonists and GnRH agonists in a short-term treatment setting, for completeness healthcare resource use has been included within the cost-comparison model. Health care resource use is based on those presented as the ERG-preferred resource use from the prior NICE appraisal for relugolix CT (TA832).[22] Values applied in the model are included and are summarised in Table 74.

B.3.5.2.2 Population #2: Long-term treatment with hormone-based therapy

In line with Population #1, healthcare resource use is not expected to differ between treatment arms within the cost-comparison model (linzagolix and relugolix CT) for Population #2. However, healthcare resource use costs have been included for completeness. Resource usage is based on values from TA832 (using the ERG-preferred assumptions) and is aligned with Population #1 and #3 (Table 74).

B.3.5.2.3 Population #3: Long-term treatment without hormone-based therapy

Healthcare resource use costs in the cost-effectiveness analysis for patients having long-term treatment with hormonal based therapy are assumed to be the same as those presented in the prior NICE appraisal in UFs (TA832).[22] ERG-preferred resource use assumptions used in the model are presented in Table 74. Corresponding unit costs sourced from NHS reference costs 2021/22 are presented in Table 75. In line with the ERG's preferred resource use assumptions from TA832, costs are aggregated and applied as a one-off in the first cycle of the model.

Table 74: Health care resource usage

Resource	GnRH antagonists	BSC
Gynaecologist consultation	Once only	Once only
GP visits	None	None
DEXA scans	One after 1 year*	None
Ultrasound	Once (67% of patients)	Once (67% of patients)
Full blood count	Once	Once
Hysteroscopy	Once (17% of patients)	Once (17% of patients)
MRI	Once (17% of patients)	Once (17% of patients)

* Applied to 100% of patients in the first model cycle as a conservative assumption
Abbreviations: BSC, best supportive care; DEXA, dual-energy X-ray absorptiometry; GnRH; gonadotropin-releasing hormone; GP, general practitioner; MRI, magnetic resonance imaging

Table 75: Health care resource use, unit costs

Resource	Cost	Descriptions
Gynaecologist consultation	£185.51	NHS schedule of NHS costs 2021/22[101]: Consultant led. Gynaecology (502). WF01A. Non-admitted face-to-face attendance, follow-up

GP visits	£42.00	PSSRU 2022.[102] Per surgery consultation lasting 9.22 minutes
DEXA scans	£95.45	NHS schedule of NHS costs 2021/22[101]: Total HRGs. RD50Z. DEXA Scan
Ultrasound	£235.60	NHS schedule of NHS costs 2021/22[101]: Outpatient. Gynaecology (502). MA36Z. Transvaginal Ultrasound
Full blood count	£2.96	NHS schedule of NHS costs 2021/22[101]: DAPS05. Haematology
Hysteroscopy	£286.41	NHS schedule of NHS costs 2021/22[101]: Outpatient. Gynaecology (502). MA31Z. Diagnostic Hysteroscopy
MRI	£197.34	NHS schedule of NHS costs 2021/22[101]: Total HRGs. RD01A. Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over

Abbreviations: BSC, best supportive care; BSC, best supportive care; DEXA, dual-energy X-ray absorptiometry; HRG, Healthcare Resource Group; MRI, magnetic resonance imaging; NHS, National Health Service; PSSRU, Personal Social Services Research Unit

B.3.5.3 Adverse reaction unit costs and resource use

B.3.5.3.1 Population #1: Short-term treatment of 6 months or less

Not applicable as discussed in Section B.3.3.6.1.

B.3.5.3.2 Population #2: Long-term treatment with hormone-based therapy

Not applicable as discussed in Section B.3.3.6.2.

B.3.5.3.3 Population #3: Long-term treatment without hormone-based therapy

Adverse event management costs are reflected within the cost-effectiveness model and are captured as a one-off cost in the first model cycle, as a simplifying assumption.

Adverse event unit costs (presented in Table 76 below) are combined with the AE probabilities reported in Section B.3.3.6.3 to estimate adverse event management costs in the linzagolix and BSC arms. The total AE management costs by treatment arm are provided in Table 77.

Table 76: Individual treatment-related adverse event costs applied in the cost-effectiveness model (Population #3)

AE	Cost	Reference
Anaemia	£42.00	PSSRU 2022.[102] Assumed to be the cost of a GP appointment (surgery consultation lasting 9.22 minutes). In line with TA832
Headache	£0.00	Assumed no cost incurred (self-managed/no treatment sought). In line with TA832[22]
Hot flush/flash	£0.00	Assumed no cost incurred (self-managed/no treatment sought). In line with TA832[22]
Nausea	£0.96	Treatment with metclopramadine (cost from BNF assuming 10 mg pack size 28) in line with TA832[22,99]

Abbreviations: AE, adverse event; BNF, British National Formulary; GP, general practitioner; mg, milligram; PSSRU, Personal Social Services Research Unit; TA, technology appraisal

Table 77: Total treatment-related adverse event costs applied in the cost-effectiveness model (Population #3)

Treatment	AE cost

Linzagolix (100 mg, scenario)	£4.24
Linzagolix (200 mg, base case)	£1.25
BSC	£2.82

Abbreviations: AE, adverse event; BSC, best supportive care; mg, milligram

B.3.5.4 Surgery costs

As outlined in Section B.3.3.3, several types of surgery are included within the cost-comparison and cost-effectiveness models. The total cost of surgery is calculated based on a weighted average of surgery types (and can vary by treatment). For the cost-comparison models (Population #1 and Population #2) costs are estimated and aggregated based on an overarching assumption related to the proportion of patients requiring surgery (see Section B.3.3.3). For the cost of surgery in Population #3, costs are estimated based on the proportion of patients moving to the surgery state in each model cycle (Section B.3.3.3.5). A breakdown of the surgery costs by type of surgery are provided in Table 78.

Table 78: Costs by surgery type (applied to cost-comparison model and cost-effectiveness model)

Surgery type	Cost	Reference
UAE	£2,786	NHS schedule of NHS costs 2021/2022.[101] Uterine Artery Embolisation (YR55Z). Total HRGs.
MRgFUS	£1,131	NHS schedule of NHS costs 2021/2022.[101] Radiofrequency Ablation or Cryoablation, for Pain Management (AB15Z). Total HRGs.
Open/abdominal myomectomy	£4,670	NHS schedule of NHS costs 2021/2022.[101] Intermediate Open Upper Genital Tract Procedures (MA11Z). Total HRGs.
Laparoscopic myomectomy	£3,496	NHS schedule of NHS costs 2021/2022.[101] Intermediate, Laparoscopic or Endoscopic, Upper Genital Tract Procedures, with CC Score 2+ (MA08A) and 0-1 (MA08B). Total HRGs.
Open/abdominal hysterectomy	£6,336	NHS schedule of NHS costs 2021/2022.[101] Major Open Upper Genital Tract Procedures with CC score 5+ (MA07E), 3-4 (MA07F), and 0-2 (MA07G). Total HRGs.
Laparoscopic hysterectomy	£5,273	NHS schedule of NHS costs 2021/2022.[101] Major, Laparoscopic or Endoscopic, Upper Genital Tract Procedures with CC score 2+ (MA08A) and 0-1 (MA08B). Total HRGs.

B.3.5.4.1 Population #1: Short-term treatment of 6 months or less

Table 79 summarises the surgery costs applied to the proportion of patients receiving surgery as a one-off cost to each treatment arm in Population #1, based on the distribution of surgery types provided in Table 52.

Table 79: Surgery costs associated with short-term treatment (Population #1)

Approach	Treatment arm	Total surgery cost
Base case (treatment independent surgery distributions from the TA832 company submission)	All	£5,278.12
Scenario analysis (treatment-specific surgery distributions, assuming a 10% switch from open/abdominal to laparoscopic surgery for patients receiving linzagolix or GnRH agonists)	Linzagolix	£5,054.46
	Relugolix CT	£5,278.12
	GnRH agonists	£5,054.46

Abbreviations: CT, combination therapy; GnRH; gonadotropin hormone releasing hormone

B.3.5.4.2 Population #2: Long-term treatment with hormone-based therapy

Table 80 summarises the surgery costs applied to the proportion of patients receiving surgery as a one-off cost to each treatment arm in Population #2, based on the distribution of surgery types provided in Table 52.

Table 80: Surgery costs associated with longer-term treatment (Population #2)

Approach	Treatment arm	Total surgery cost
Base case (treatment independent surgery distributions from the TA832 company submission)	All	£5,278.12
Scenario analysis (linzagolix 200 mg for 6 months following by 200 mg + ABT, and treatment-specific surgery distributions assuming a 10% switch from open/abdominal to laparoscopic surgery for patients receiving linzagolix or GnRH agonists)	Linzagolix	£5,054.46
	Relugolix CT	£5,278.12

Abbreviations: CT, combination therapy; GnRH; gonadotropin hormone releasing hormone

B.3.5.4.3 Population #3: Long-term treatment without hormone-based therapy

In the base-case analysis, it is assumed that surgery type distributions are the same across treatment arms. However, in practice, the type of surgery received may vary by pharmacological treatment arm as described in Section B.3.3.3.2. The costs of surgery for the base case and scenario assuming treatment independent surgery distributions (using the distributions provided in Table 52) and scenario assuming treatment dependent surgery distributions) are provided below in Table 81 (applied to the proportion of patients in the surgery state each model cycle).

Table 81: Surgery costs associated with long-term treatment without hormone-based therapy (Population #3)

Approach	Treatment arm	Surgery cost
Base case (treatment independent surgery distributions from the TA832 company submission)	Linzagolix and BSC	£5,278.12
Scenario 1 (treatment independent surgery distributions from the TA832 ERG report)	Linzagolix and BSC	£4,358.15
Surgery 2 (treatment-specific surgery distributions, assuming a 10% switch from open/abdominal to laparoscopic surgery for patients receiving linzagolix or GnRH agonists)	Linzagolix	£5,054.46
	BSC	£5,278.12

Abbreviations: BSC, best supportive care

B.3.6 Severity

In assessment of the proportional and absolute QALY shortfall, it is not anticipated that the treatment of UFs will be applicable for any form of severity weighting.

B.3.7 Uncertainty

The PRIMROSE 1 and 2 studies, which are Phase 3, multicentre, 52-week, randomised, parallel-group, double-blind, placebo-controlled trials, provide robust efficacy and safety data supporting the four linzagolix treatment options (100 mg, 100 mg +ABT, 200 mg, 200mg + ABT).[25]

However, when measuring blood loss using the AH method (as per the PRIMROSE studies), patients must collect, store and then submit used sanitary products for MBL analysis. Collection of used feminine products may not be acceptable, feasible, or may be burdensome for many women. Furthermore, as discussed in Section B.2.9.7, patients treated with placebo likely experienced more bleeding and therefore used more products than those on active treatment. As such, there will have been a greater burden to return all used products within the constraints set in the PRIMROSE trial protocols which may mean that MBL is underestimated in the placebo arms of PRIMROSE 1 and 2. This would lead to the relative treatment effect of linzagolix versus placebo being an underestimation in the PRIMROSE trials.

B.3.8 Managed access proposal

Not applicable.

B.3.9 Summary of base-case analysis inputs and assumptions

B.3.9.1 Summary of base-case analysis inputs

B.3.9.1.1 Population #1: Short-term treatment of 6 months or less

A summary of the inputs used to inform the cost-comparison model for Population #1 are provided in Appendix N.

B.3.9.1.2 Population #2: Long-term treatment with hormone-based therapy

A summary of the inputs used to inform the cost-comparison model for Population #2 are provided in Appendix N.

B.3.9.1.3 Population #3: Long-term treatment without hormone-based therapy

A summary of the inputs used to inform the cost-effectiveness model for Population #3 are provided in Appendix N.

Extensive scenario and sensitivity analyses have been conducted within the cost-effectiveness model which test the structural and parameter uncertainty associated with Population #3. Table 82 summarises the cost-effectiveness model parameter components and the methods taken to quantify uncertainty.

Table 82: Approach to uncertainty within the cost-effectiveness model: Population #3

Component	Parameter types	Tested in OWSA	Tested in PSA	Tested in scenario analysis
Model settings	Time horizon	×	×	✓

	Discount rates	×	×	✓
	Cycle length	×	×	×
	Linzagolix regimen	×	×	✓
Patient characteristics	Mean age at baseline	×	×	×
	Menopause Age	×	×	×
Transitions	Movements to controlled	✓	✓	×
	Movements to uncontrolled	✓	✓	×
Adverse events	Frequencies	✓	✓	×
	Duration	✓	✓	×
	Costs	✓	✓	×
	Utility decrements	✓	✓	✓
Drug costs	eMIT (generic)	✓	✓	×
	BNF (branded)	×	×	×
Discontinuation	Withdrawal rate	✓	✓	✓
Surgery	Surgery proportion	✓	✓	✓
	Surgery types	×	✓	✓
	Surgery costs	✓	✓	×
Other costs	Administration	✓	✓	×
	Resource use	✓	✓	×
Utility values	Controlled	×	✓	✓
	Uncontrolled	×	✓	✓
	Surgery	✓	✓	✓
	Age-adjustment	×	✓	✓

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; OWSA, one-way sensitivity analysis; PSA, probabilistic sensitivity analysis

B.3.9.2 Assumptions

B.3.9.2.1 Population #1: Short-term treatment of 6 months or less

Table 83 provides a summary of key assumptions for the cost-comparison analysis for Population #1.

Table 83: Summary of key assumptions (Population #1)

Assumption	Description	Justification
Cost-comparison methodology	For Population #1 (short-term treatment of 6 months or less), cost-comparison methodology is appropriate for comparing linzagolix with existing relevant treatment options	• The blended approach to addressing the decision was explored by NICE at the decision problem stage, due to population overlap with relugolix CT • The indirect comparison findings do not generally indicate differences in efficacy between GnRH antagonists • Clinical opinion indicated clinical comparability between GnRH antagonists with regards to reduced menstrual blood loss (and potential for greater benefits with linzagolix 200 mg regarding fibroid shrinkage) • In NICE TA832, it was determined in the that relugolix CT is similarly effective to GnRH agonists
Time horizon	The time horizon for the cost-comparison analysis for Population #1 is 6 months	When comparing linzagolix with existing treatment options in a short-term treatment setting, 6 months is sufficient for capturing differences in costs between treatment arms, as no pharmacological treatment is received beyond 6 months
Surgery	Surgery type distributions are assumed to be equal across treatment arms in the Population #1 base case.	• This is a conservative assumption in the comparison with relugolix CT, as the indirect comparison results and supporting clinical opinion indicate linzagolix 200 mg can achieve greater fibroid shrinkage. • Clinical expert opinion indicated that fibroid/uterine shrinkage can impact the type of surgery a patient would receive. Treatment-specific surgery type distributions are therefore tested in scenario analysis.
Mortality	Mortality rates are excluded from the cost-comparison model	UFs are not associated with a heightened risk of mortality. Mortality rates are not considered as a simplifying assumption, because any effects would be equivalent across arms and have no impact on incremental costs
Treatment discontinuation	Treatment discontinuation rates are excluded from the cost-comparison model for Population #1	Given the short treatment duration (expected ahead of surgery), the impact of considering discontinuation on costs is expected to be minimal

Abbreviations: GnRH, gonadotropin releasing hormone; NHS, National Health Service; STA, single technology appraisal; TA, technology appraisal; UF, uterine fibroid

B.3.9.2.2 Population #2: Long-term treatment with hormone-based therapy

Table 84 provides a summary of key assumptions for the cost-comparison analysis for Population #2.

Table 84: Summary of key assumptions (Population #2)

Assumption	Description	Justification
Cost-comparison methodology	For Population #2 (long-term treatment with hormone-based therapy), cost-comparison methodology is appropriate for comparing linzagolix with existing relevant treatment options	• The blended approach to addressing the decision was explored by NICE at the decision problem stage, due to population overlap with relugolix CT • The indirect comparison findings do not generally indicate differences in efficacy between GnRH antagonists • Clinical opinion indicated clinical comparability between GnRH antagonists with regards to reduced menstrual blood loss (and potential for greater benefits with linzagolix 200 mg regarding fibroid shrinkage) • In NICE TA832, it was determined in the that relugolix CT is similarly effective to GnRH agonists
Time horizon	The time horizon for the cost-comparison analysis for Population #2 is 10 years	10 years is sufficient for capturing differences in costs between treatment arms, based on the average age at baseline (42 years) and the average age of menopause based on NHS data (51 years). After menopause, no further treatment costs are applied due to fibroid shrinkage because of estrogen levels
Surgery	Surgery type distributions are assumed to be equal across treatment arms in the Population #2 base case.	• This is a conservative assumption in the comparison with relugolix CT, as the indirect comparison results and supporting clinical opinion indicate linzagolix 200 mg can achieve greater fibroid shrinkage. • Clinical expert opinion indicated that fibroid/uterine shrinkage can impact the type of surgery a patient would receive. Treatment-specific surgery type distributions are therefore tested in scenario analysis.
Mortality	Mortality rates are excluded from the cost-comparison model	UFs are not associated with a heightened risk of mortality. Mortality rates are not considered as a simplifying assumption, because any effects would be equivalent across arms and have no impact on incremental costs
Treatment discontinuation	Treatment discontinuation rates are excluded from the cost-comparison model base case	In the long-term, it is expected that discontinuation rates between linzagolix and relugolix CT would be similar, and therefore the impact on the cost-comparison results would be negligible. For completeness, a scenario analysis is conducted which considers discontinuation rates from the clinical trials

Abbreviations: CT, combination therapy; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; STA, Single Technology Appraisal

B.3.9.2.3 Population #3: Long-term treatment without hormone-based therapy

Table 85 provides a summary of key assumptions for the cost-comparison analysis for Population #3.

Table 85: Summary of key assumptions (Population #3)

Assumption	Description	Justification
Model structure	Patients transition through mutually exclusive health states based on symptom control	In NICE TA832, the EAG criticised the company's decision to model 'treatment states', rather than health states, and specified that a model based on bleeding/symptom control would be considered more appropriate[22]
	'Uncontrolled' symptoms are defined by HMB (>80 mL MBL per cycle), while the 'controlled' health state is categorised by those who achieve MBL ≤80 mL and ≥50% reduction from baseline	• Directly addresses EAG critique of the model structure in NICE TA832 (see above).[22] • Aligns the model health states with the primary endpoint in the PRIMROSE studies
Time horizon and menopause	A time horizon of 10 years is sufficient for capturing differences in costs and outcomes between treatments In the menopause state, patients experience outcomes in line with the age-matched general population and do not require further treatment or monitoring	It is understood that patients no longer experience disease-related symptoms (due to low estrogen levels shrinking UFs). Therefore, costs and outcomes are consistent beyond the average age of menopause
Cycle length	It is assumed that a 28-day cycle length is appropriate, and adequate for capturing meaningful changes in health status	Aligns with clinical trial endpoint definitions, and pack sizes for calculating drug acquisition cost
Surgery	Surgery type distributions are assumed to be equal across treatment arms in the Population #3 base case.	• This is a conservative assumption in the comparison with BSC, as the findings from PRIMROSE indicate linzagolix 200 mg can achieve larger fibroid shrinkage. • Clinical expert opinion indicated that fibroid/uterine shrinkage can impact the type of surgery a patient would receive. Treatment-specific surgery type distributions are therefore tested in scenario analysis.
Efficacy data	The 24-week response data from the PRIMROSE 1 and 2 studies is most suitable for informing the cost-effectiveness analysis	• The pooled analysis (efficacy and safety) of PRIMROSE 1 and 2 at Week 24 was performed in accordance with Statistical Analysis Plans. • Pooling of efficacy data (individual patient data) up to Week 24 from both trials is appropriate as both studies have the same design up to Week 24, the same inclusion/exclusion criteria, no difference in study conduct, and efficacy results were generally similar • Although it is acknowledged that later follow-up data are available, these data are not suitable for informing a comparison in patients receiving treatment without

		hormone-based therapy, due to treatment switching rules in the trial program. • In PRIMROSE 1, 50% of patients in the placebo arm switched to 200 mg + ABT at Week 24, while in PRIMROSE 2, this value was 100%. Similarly, in both PRIMROSE 1 and 2, 100% of patients switched from linzagolix 200 mg to linzagolix 200 mg + ABT at Week 24
Transition probabilities	An exponential assumption is used to derive per 28-day cycle transition probabilities between health states, based on the 24-week response rate from PRIMROSE	• Aligns with clinical opinion which indicated in practice it may take 3-6 months to achieve response • The assumption is applied consistently across treatment arms

Abbreviations: ABT, add-back therapy; EAG, External Assessment Group; CT, combination therapy; HMB, heavy menstrual bleeding; MBL, menstrual blood loss; mg, milligram; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; UF, uterine fibroids

B.3.10 Base-case results

B.3.10.1 Population #1: Short-term treatment of 6 months or less

Base-case cost-comparison results for Population #1 are presented in Table 86, using the submitted linzagolix PAS price. In the short-term treatment setting, it is anticipated that linzagolix will be administered without hormone-based therapy in clinical practice. Due to the flat-pricing structure, cost-comparison results are consistent across the linzagolix 100 mg and 200 mg arms.

In the primary comparison of linzagolix versus relugolix CT, costs were comparable between treatment arms (incremental costs of [redacted]) over the 6-month time horizon.

In the supporting analysis, costs were similar across the linzagolix and GnRH agonist arms (incremental costs of [redacted], [redacted], and [redacted] versus leuprorelin, goserelin, and triptorelin, respectively).

A breakdown of costs by treatment category is presented in Appendix J, while a range of key scenario analyses demonstrating the robustness of the cost-comparison results are provided in Section B.3.11.3.1.

Table 86: Base-case cost-comparison results (Population #1), with PAS

Treatment	Total costs (£)	Incremental costs, linzagolix versus (£)
Linzagolix	[redacted]	-
Relugolix CT	£3,411	[redacted]
Leuprorelin	£3,441	[redacted]
Goserelin	£3,407	[redacted]
Triptorelin	£3,482	[redacted]

Abbreviations: CT, combination therapy; PAS, patient access scheme

B.3.10.2 Population #2: Long-term treatment with hormone-based therapy

Base-case cost-comparison results for Population #2 are presented in Table 87, comparing linzagolix with relugolix CT in the long-term treatment setting for patients having hormone-

based therapy. Base-case cost-comparison results are presented for the 200 mg + ABT linzagolix arm; however due to the flat-pricing structure, cost-comparison results are consistent across the linzagolix 100 mg + ABT and 200 mg + ABT arms. Cost-comparison results using the linzagolix 200 mg dose for 6 months followed by 200 mg + ABT are presented in scenario analysis.

In the comparison of linzagolix versus relugolix CT in the long-term treatment setting, costs were broadly similar between treatment arms. Incremental costs were [redacted] over the full 10-year time horizon.

A breakdown of costs by treatment category is presented in Appendix J, while a range of key scenario analyses are provided in Section B.3.11.3.2.

Table 87: Base-case cost-comparison results (Population #2), with PAS

Treatment	Total costs (£)	Incremental costs, linzagolix versus (£)
Linzagolix	[redacted]	-
Relugolix CT	£4,752	[redacted]

Abbreviations: CT, combination therapy; PAS, patient access scheme

B.3.10.3 Population #3: Long-term treatment without hormone-based therapy

The base-case deterministic cost-effectiveness results for linzagolix versus BSC in Population #3 are presented in Table 88 at the submitted PAS price. Base-case results are presented for linzagolix 200 mg for 6 months followed by linzagolix 100 mg. Probabilistic results are reported in Section B.3.11.1.3. Alternative linzagolix doses are tested in scenario analysis.

The results demonstrate that compared with BSC over the 10-year time horizon, linzagolix is associated with a QALY gain of [redacted] at an incremental cost of [redacted], which translates to an ICER of £15,392. Table 88 presents the net-health benefit (NHB) at the £20,000/QALY and £30,000/QALY willingness-to-pay (WTP) thresholds. Clinical outcomes in comparison to the trial and disaggregated results are presented in Appendix J.

Results show that at a WTP threshold of £20,000-£30,000 per QALY gained, the introduction of linzagolix would increase the overall population health and is a cost-effective use of NHS resources.

Table 88: Base-case results (Population #3), with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
BSC	[redacted]	9.97	[redacted]						
Linzagolix	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,392	0.02	0.04

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NHB, net-health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years

B.3.11 Exploring uncertainty

Several methods have been considered to ensure that uncertainty is adequately explored throughout each patient population.

B.3.11.1 Probabilistic sensitivity analysis

B.3.11.1.1 Population #1: Short-term treatment

Not applicable for cost-comparison framework.

B.3.11.1.2 Population #2: Long-term treatment with hormone-based therapy

Not applicable for cost-comparison framework.

B.3.11.1.3 Population #3: Long-term treatment without hormone-based therapy

Joint parameter uncertainty in the cost-effectiveness model for Population #3 was explored through probabilistic sensitivity analysis (PSA), in which all parameters are varied jointly within their assigned probability distributions (see Appendix N). PSA was run for 1,000 iterations, by which point results had stabilised.

The mean PSA results are presented in Table 89 and the cost-effectiveness plane showing the 1,000 iterations is presented in Figure 26. The probabilistic results show consistency with the deterministic analysis with a mean QALY gain of [redacted] at a mean incremental cost of [redacted]. This results in a probabilistic ICER of £15,357, supporting that linzagolix is a cost-effective use of NHS resources at the £20,000-£30,000/QALY WTP threshold.

Figure 27 presents the cost-effectiveness acceptability curve (CEAC) for linzagolix versus BSC. Based on the 1,000 PSA iterations, linzagolix is projected to be 99.9% cost-effective at the £30,000/QALY WTP threshold.

Table 89: PSA results (Population #3), with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	9.97	[redacted]				
Linzagolix	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,357

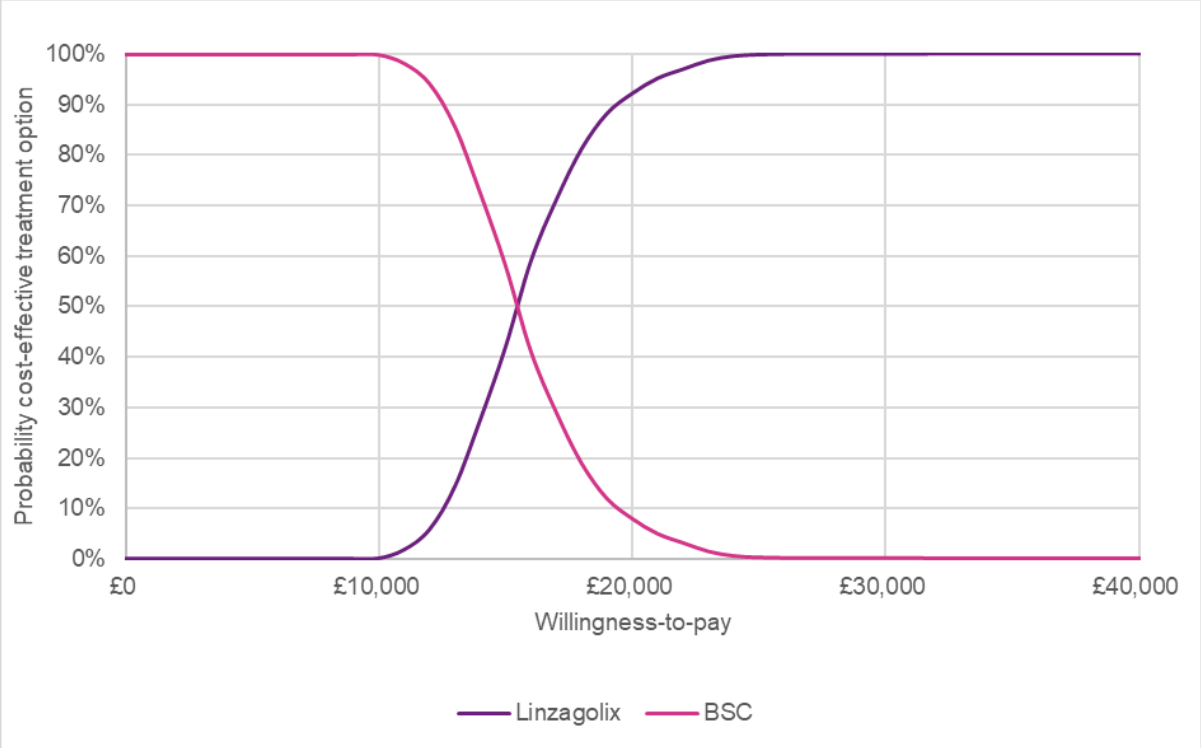
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 26: Cost-effectiveness plane (Population #3), with PAS

[redacted]

Abbreviations: PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 27: Cost-effectiveness acceptability curve (Population #3), with PAS



Abbreviations: BSC, best supportive care; PAS, patient access scheme

B.3.11.2 Deterministic sensitivity analysis

B.3.11.2.1 Population #1: Short-term treatment

Not applicable for cost-comparison framework.

B.3.11.2.2 Population #2: Long-term treatment with hormone-based therapy

Not applicable for cost-comparison framework.

B.3.11.2.3 Population #3: Long-term treatment without hormone-based therapy

One-way sensitivity analysis (OWSA) was conducted to test the impact of individual parameters at their lower and upper limits of the confidence intervals (see Appendix N.3). If the variance of any input was not published or available, a simplified assumption was made assuming the standard error was 10% of the mean value.

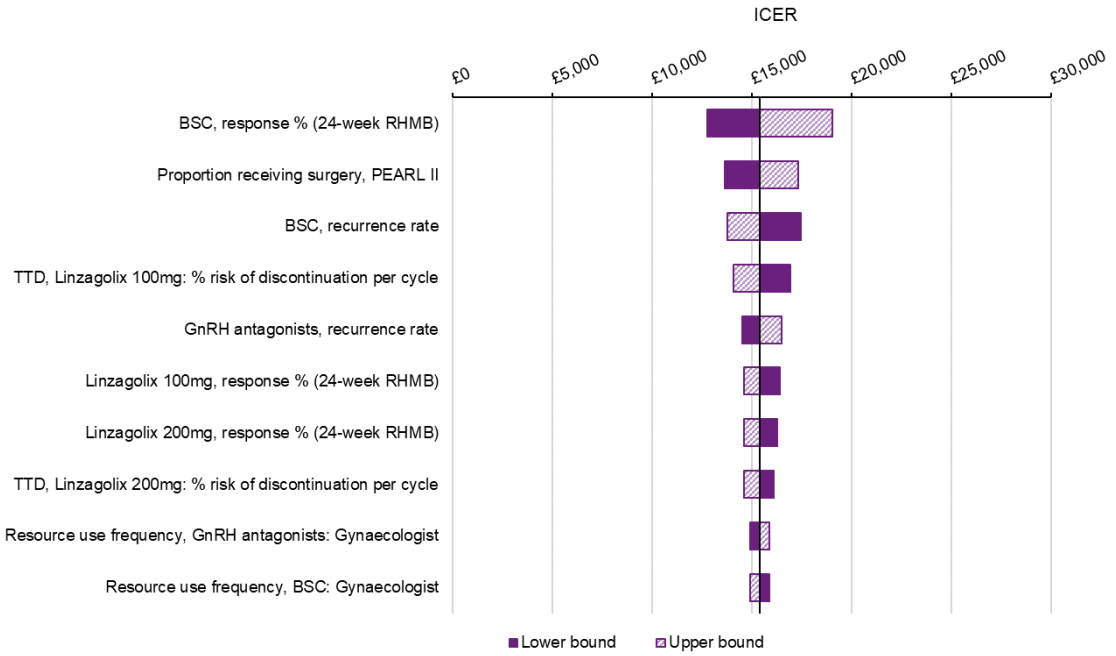
Table 90 and Figure 28 present the ICERs and tornado plot of the top 10 parameters which had the largest impact on the ICER. BSC response rates had the largest impact on the ICER, followed by the probability of receiving surgery and the BSC recurrence rate. Across all parameters varied at their 95% confidence intervals, linzagolix remained cost-effective at the £30,000/QALY threshold, with all corresponding ICERs below £20,000. This outcome demonstrates the robustness of results to individual parameter uncertainty.

Table 90: OWSA results (Population #3), with PAS

Parameter	Lower bound ICER	Upper bound ICER
BSC, response % (24-week RHMB)	£12,750	£19,035
Proportion receiving surgery, PEARL II	£13,622	£17,327
BSC, recurrence rate	£17,460	£13,755
TTD, Linzagolix 100 mg, % risk of discontinuation	£16,932	£14,090
GnRH antagonists, recurrence rate	£14,504	£16,480
Linzagolix 100 mg, response % (24-week RHMB)	£16,416	£14,600
Linzagolix 200 mg, response % (24-week RHMB)	£16,293	£14,610
TTD, Linzagolix 200 mg: % risk of discontinuation	£16,089	£14,618
Resource use frequency, GnRH antagonists: Gynaecologist	£14,925	£15,860
Resource use frequency, BSC: Gynaecologist	£15,860	£14,925

Abbreviations: BSC, best supportive care; GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis; mg, milligram; PAS, patient access scheme; RHMB, reduced heavy menstrual bleeding; TTD, time to treatment discontinuation

Figure 28: Tornado plot (Population #3), with PAS



Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; mg, milligram; OWSA, one-way sensitivity analysis; PAS, patient access scheme; RHMB, reduced heavy menstrual bleeding; TTD, time to treatment discontinuation

B.3.11.3 Scenario analysis

Scenario analyses were performed to test key structural assumptions in both the cost-comparison analyses and cost-effectiveness analysis.

B.3.11.3.1 Population #1: Short-term treatment

The list of scenarios tested and corresponding results for Population #1 are presented in Table 91.

Results were consistent with the base-case analysis when reducing the time horizon/maximum treatment duration to 3 months across treatments in the short-term setting, and when assuming the 3-month formulations of GnRH agonists would be used. In the scenario which adjusts the distribution of surgery types to assume a higher proportion of linzagolix and GnRH agonist patients are able to receive less invasive laparoscopic surgery (rather than open/abdominal surgery), due to fibroid shrinkage, linzagolix was marginally cost saving compared with relugolix CT. The impact of applying treatment-specific concomitant medicine proportions on cost-comparison results was negligible.

The scenario analysis results demonstrate the robustness of the base case cost-comparison analysis in the short-term treatment setting, with incremental costs for linzagolix remaining below [redacted] across all scenarios across all comparators.

Table 91: Scenario analysis results (Population #1), with PAS

Base case	Scenario	Total costs					Incremental costs (versus linzagolix)			
		Linzagolix	Relugolix CT	Leuprorelin	Goserelin	Triptorein	Relugolix CT	Leuprorelin	Goserelin	Triptorein
Base case		[redacted]	£3,411	£3,441	£3,407	£3,482	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon/treatment duration, 6 months	3 months	[redacted]	£3,193	£3,210	£3,191	£3,234	[redacted]	[redacted]	[redacted]	[redacted]
GnRH agonist formulation, 1 monthly	3 monthly	[redacted]	£3,411	£3,408	£3,428	£3,368	[redacted]	[redacted]	[redacted]	[redacted]
Surgery probability, 45.1%	100%	[redacted]	£6,309	£6,339	£6,305	£6,380	[redacted]	[redacted]	[redacted]	[redacted]
Distribution of surgery types, treatment independent (TA832, company submission)	10% switch from open/abdominal to laparoscopic surgery for patients receiving linzagolix or GnRH agonists	[redacted]	£3,411	£3,340	£3,306	£3,382	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medication, 100% of patients	Treatment-specific %	[redacted]	£3,408	£3,437	£3,404	£3,479	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CT, combination therapy; GnRH, gonadotropin-releasing hormone; TA, technology appraisal

B.3.11.3.2 Population #2: Long-term treatment with hormone-based therapy

The list of scenarios tested and corresponding cost-comparison results for Population #2 are presented in Table 92.

Costs remain broadly comparable between linzagolix and relugolix CT in the longer-term treatment setting. A reduction in the time horizon leads to a reduction in incremental costs for linzagolix.

Testing the linzagolix 200 mg dose for 6 months before patients receive 200 mg + ABT in the longer-term and assuming a higher proportion of patients receiving linzagolix are able to receive laparoscopic surgery due to fibroid shrinkage has the largest impact on cost-comparison results of the scenarios tested, resulting in incremental costs of [redacted].

Table 92: Scenario analysis results (Population #2), with PAS

Base case	Scenario	Total costs, linzagolix (£)	Total costs, relugolix CT (£)	Incremental costs, linzagolix versus (£)
Base case		[redacted]	£4,752	[redacted]
Time horizon, 10 years	1 year	[redacted]	£3,693	[redacted]
	5 years	[redacted]	£4,609	[redacted]
Surgery probability, 45.1%	35%	[redacted]	£4,219	[redacted]
	25%	[redacted]	£3,691	[redacted]
Linzagolix dose, 200 mg + ABT	200 mg for 6 months followed by linzagolix 200 mg + ABT	[redacted]	£4,922	[redacted]
Linzagolix dose, 200 mg + ABT and treatment independent surgery type distributions	200 mg for 6 months followed by linzagolix 200 mg + ABT, and a 10% switch from open/abdominal to laparoscopic surgery for patients receiving linzagolix	[redacted]	£4,922	[redacted]
Concomitant medication, 100% of patients	Treatment-specific %	[redacted]	£4,701	[redacted]

Abbreviations: ABT, add-back therapy; CT, combination therapy; mg, milligram; PAS, patient access scheme

B.3.11.3.3 Population #3: Long-term treatment without hormone-based therapy

Structural uncertainty within the cost-effectiveness model is explored through scenario analysis. Results of the scenario analysis for Population #3 are presented in Table 93. The results demonstrate the robustness of the base case cost-effectiveness results, for the population of patients receiving longer-term treatment without hormone-based therapy. Several scenarios are presented which explore various time horizons, discount rates, linzagolix dosing regimens, transition probabilities, utility value sources and assumptions. In the majority of scenarios explored, linzagolix remains a cost-effective treatment option within the £20,000 per QALY gained threshold (16 out of 19 scenarios) and £30,000 per QALY gained threshold (18 out of 19 scenarios).

The source of utility values, which is a key driver of the QALY gain in the comparison versus BSC for Population #3 has the largest impact on cost-effectiveness results, with the change

in ICER from base case ranging from -£5,295 when exploring utility values from the literature to +£15,411 when testing EQ-5D-5L mapped to 3L utility values. However, these results should be interpreted with a degree of caution, given that the utility values from the literature were taken from a Canadian study, and the EQ-5D is not considered to have the sensitivity to fully evaluate the impact of UFs on a patients' HRQoL, as described in Section B.3.4.5.3.

In scenarios exploring a lower proportion of patients experiencing surgery from the controlled health state (which are explored in line with clinical expert opinion), the ICER for linzagolix versus BSC decreases by -£4,251 (28-day cycle surgery probability of 1% from the controlled health state) and -£863 (28-day cycle surgery probability of 2% from the controlled health state).

Notably, in the scenario exploring a change in the surgery distribution for patients receiving linzagolix (where a higher proportion of patients receiving laparoscopic surgery due to fibroid shrinkage), the ICER for linzagolix versus BSC falls by -£2,873. This scenario is of particular relevance in the context of increased NHS waiting times for surgery in gynaecology services, as it is reported that fibroid growth over time may result in more invasive and time-consuming surgical interventions for a larger proportion of patients with UFs.

Table 93: Scenario analysis results (Population #3), with PAS

Parameter	Base case	Scenario	Linzagolix			BSC			Incremental			ICER (£/QALY)	Change from base case
			Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs		
Base case			[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,392	-
Time horizon	10 years	30 years	[redacted]	28.75	[redacted]	[redacted]	28.75	[redacted]	[redacted]	0.00	[redacted]	£15,392	-£0
		60 years	[redacted]	41.86	[redacted]	[redacted]	41.86	[redacted]	[redacted]	0.00	[redacted]	£15,392	£0
Discount rates	3.5%	1.5%	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,064	-£328
		6.00%	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,786	£393
Linzagolix dosing	200 mg for 6 months followed by 100 mg	200 mg for 6 months followed by BSC	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£16,835	£1,443
		100 mg	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£17,365	£1,973
Recurrence rate	By treatment class	Assume equal to BSC	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£20,707	£5,315
Surgery probability (per 28-day cycle): controlled → surgery	3.02%	1%	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£11,141	-£4,251
		2%	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£14,529	-£863
Source of surgery distribution	TA832, company submission	TA832, ERG report	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,392	-£0
		10% switch from open/abdominal to laparoscopic surgery for patients receiving linzagolix	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£12,519	-£2,873
Concomitant medicine distribution	Treatment-specific	Assume 100%	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,261	-£131

Parameter	Base case	Scenario	Linzagolix			BSC			Incremental			ICER (£/QALY)	Change from base case
			Costs	LYs	QALYs	Costs	LYs	QALYs	Costs	LYs	QALYs		
Treatment withdrawal rates	Trial %	Modified trial % (AEs as the reason for discontinuation	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£25,828	£10,436
PRIMROSE utility model	UFS-QoL to EQ-5D-3L	EQ-5D-5L to EQ-5D-3L	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£30,803	£15,411
Utility source	PRIMROSE	Hux et al.	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£10,098	-£5,295
Post-surgery utility	Literature	General population	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,392	-£0
		Equal to controlled	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,392	£0
AE disutility	Include	Exclude	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,096	-£297
Utility age adjustment	Include	Exclude	[redacted]	9.97	[redacted]	[redacted]	9.97	[redacted]	[redacted]	0.00	[redacted]	£15,283	-£110

Abbreviations: AE, adverse event; BSC, best supportive care; GP, general practitioner; EQ-5D-3L, EuroQol-5 Dimensions-3 level; EQ-5D-5L, EuroQol-5 Dimensions-5 level; ICER, incremental cost-effectiveness ratio; KOL, key opinion leaders; LYs, life-years; mg, milligram; QALYs, quality-adjusted life-years; TA, technology appraisal; UFS-QoL, Uterine Fibroid Symptom-Quality of Life

B.3.12 Subgroup analysis

Subgroup analyses have been presented as part of the main results section and in line with the NICE final scope.

B.3.13 Benefits not captured in the QALY calculation

There are likely several additional benefits of linzagolix which are not captured in the QALY calculation and may impact a patients' health-related quality of life.

Firstly, linzagolix is administered orally, which when compared to GnRH agonists, avoids the use of needles (which is particularly relevant for patients who suffer from trypanophobia). As the oral treatment is self-administered, the need for repeated visits to the hospital/GP practice throughout the course of a patients' disease is avoided (which is relevant when considering NHS capacity, and also levels of productivity within the UK population given the disease primarily affects women of a working age who may require time off due to healthcare visits).

Linzagolix also offers a well-tolerated long-term treatment option for patients with UFs who may want to avoid surgical routes. Although it is difficult to quantify, these benefits are highly meaningful to patients, particularly those who want to preserve their uterus and fertility options.

A further key benefit of linzagolix is the flexible licensed dosing regimen. With high and low dose options, both with and without hormone-based treatment, linzagolix can be used across a range of treatment settings. Short-term treatment (in a pre-operative setting) with linzagolix can reduce heavy menstrual bleeding while also reducing uterus and UF volume ahead of surgery. This reduction in volume can reduce complications associated with surgery, as well as potentially increasing the number of surgical options available to patients (e.g. it is expected that patients with reduced uterine and UF volume may be able to receive less invasive laparoscopic surgery, instead of open/abdominal surgery). This is of particular importance in the context of increased NHS waiting times of up to 18 months to 2 years for gynaecology services,[20] whereby UF and uterine growth over time may result in more invasive and time-consuming medical, hormonal and surgical interventions for a larger proportion of patients with UFs.

In the context of longer-term treatment, linzagolix meets a clear need for patients who may want to avoid surgery, and particularly for those for whom hormone-based therapy is not appropriate. A long-term treatment option which does not require additional hormone-based therapy is not offered by current pharmacological therapies and is a setting in which linzagolix can offer a flexible treatment option for patients with UFs.

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The cost-effectiveness and cost-comparison models (Microsoft Excel® workbooks) were quality assured as part of the internal processes of the model development team. As part of this quality-control process, the model was reviewed for potential coding errors, inconsistencies, and the plausibility of inputs by an economist who was not involved in the model development process. The review comprised of a sheet-by-sheet check and a checklist (based on publicly available and peer review checklists). Examples of the basic validity checks followed included:

- Extreme value testing
- Logical relationship testing (e.g. if intervention drug costs are increased, do total costs in the intervention arm increase? Consequently, does the ICER increase accordingly?)
- Consistency checks (e.g. is an input parameter value in one cell reflected elsewhere/used consistently throughout the model?).

In addition to technical validation, clinical experts (experienced in treating moderate to severe symptoms of UFs in NHS England practice) have been consulted as part of the submission process to help inform and validate model inputs and assumptions.

B.3.15 Interpretation and conclusions of economic evidence

Despite current therapies, there remains an unmet need for effective, well tolerated pharmacological treatments that meet the individualised treatment needs of people with UFs, that can avoid or simplify surgery, and that address the residual unmet need for patients for whom hormonal therapy is not appropriate.

The clinical efficacy and safety of linzagolix (100 mg or 200 mg, with or without ABT) have been demonstrated in the large, well-controlled and robust PRIMROSE 1 and 2 RCTs.[25] The pooled results of these pivotal trials clearly demonstrated the efficacy and safety of linzagolix, the only GnRH antagonist providing flexible dosing options (once daily oral dose of 100 mg or 200 mg with or without ABT), to meet the personalised treatment needs of people with moderate to severe symptoms of UFs.[25,55,56]

In the absence of head-to-head clinical trial data, the comparative efficacy of linzagolix versus relugolix CT was assessed by an ITC and supported by clinical opinion received by the company. The evidence aligns on the conclusion that linzagolix provides similar or greater health benefits than relugolix CT, and therefore also versus GnRH agonists (which were deemed equivalent to relugolix CT in NICE TA832). Furthermore, due to the flexible licensed dosing regimen, it is possible that linzagolix can achieve greater health benefits due to fibroid shrinkage, compared with treatments administered alongside hormonal therapy, which is particularly relevant in the context of pre-operative pharmacological treatment and surgery wait times. Additionally, linzagolix provides an option to fulfil an unmet need for people with moderate to severe UFs for whom hormone-based therapy is not appropriate.

Based on the findings of the ITC, supporting clinical expert opinion, and cost-comparison analyses, linzagolix meets the requirements of a cost-comparison case for patients with moderate to severe symptoms of UFs receiving short-term treatment of 6 months or less (Population #1) and longer-term treatment with hormone-based therapy (Population #2), by providing similar or greater health benefits at similar cost to relevant comparators.

For Population #3 (patients receiving longer-term treatment without hormone-based therapy), the ICER of £15,392 for linzagolix versus BSC falls below the NICE decision-making threshold – indicating that linzagolix can provide a cost-effective treatment option for a patient group with limited existing active therapies.

Overall, the findings of the economic analysis support the expectation that linzagolix provides a cost-effective treatment option in NHS England practice, for patients with moderate to severe symptoms of UFs.

B.4 References

1. Dababou S, Garzon S, Laganà AS, Ferrero S, Evangelisti G, Noventa M, et al. Linzagolix: a new GnRH-antagonist under investigation for the treatment of endometriosis and uterine myomas. Expert Opin Investig Drugs. 2021 Sep 2;30(9):903–11.

2. Williams ARW. Uterine fibroids – what's new? F1000Research. 2017 Dec 7;6:2109.

3. Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. BMC Womens Health. 2012 Mar 26;12(1):6.

4. Wise LA, Laughlin-Tommaso SK. Epidemiology of Uterine Fibroids – From Menarche to Menopause. Clin Obstet Gynecol. 2016 Mar;59(1):2–24.

5. Stewart EA, Nicholson WK, Bradley L, Borah BJ. The Burden of Uterine Fibroids for African-American Women: Results of a National Survey. J Womens Health. 2013 Oct;22(10):807–16.

6. Stewart E, Cookson C, Gandolfo R, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG Int J Obstet Gynaecol. 2017;124(10):1501–12.

7. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. Int J Gynecol Obstet. 2020;149(1):3–9.

8. Hunsche E, Rakov V, Scippa K, Witherspoon B, McKain L. The Burden of Uterine Fibroids from the Perspective of US Women Participating in Open-Ended Interviews. Womens Health Rep. 2022 Mar 4;3(1):286–96.

9. Al-Hendy A, Myers ER, Stewart E. Uterine Fibroids: Burden and Unmet Medical Need. Semin Reprod Med. 2017 Nov;35(6):473–80.

10. Marsh EE, Al-Hendy A, Kappus D, Galitsky A, Stewart EA, Kerolous M. Burden, Prevalence, and Treatment of Uterine Fibroids: A Survey of U.S. Women. J Womens Health 2002. 2018 Nov;27(11):1359–67.

11. Borah BJ, Nicholson WK, Bradley L, Stewart EA. The impact of uterine leiomyomas: a national survey of affected women. Am J Obstet Gynecol. 2013 Oct;209(4):319.e1-319.e20.

12. Ghant MS, Sengoba KS, Recht H, Cameron KA, Lawson AK, Marsh EE. Beyond the physical: a qualitative assessment of the burden of symptomatic uterine fibroids on women's emotional and psychosocial health. J Psychosom Res. 2015 May;78(5):499–503.

13. Strong SM, Sideris M, Magama W, Rouabhi S, Odejinmi F. Surgical Intervention for Uterine Fibroids. Our 4-Year Experience and Literature Review: Is It Time to Centralise Care Provision Via Specialist Fibroid Centres? In Vivo. 2020 Mar 3;34(2):695–701.

14. Fernandez H, Farrugia M, Jones SE, Mauskopf JA, Oppelt P, Subramanian D. Rate, Type, and Cost of Invasive Interventions for Uterine Myomas in Germany, France, and England. J Minim Invasive Gynecol. 2009 Jan 1;16(1):40–6.

15. Soliman AM, Yang H, Du EX, Kelkar SS, Winkel C. The direct and indirect costs of uterine fibroid tumors: a systematic review of the literature between 2000 and 2013. Am J Obstet Gynecol. 2015 Aug;213(2):141–60.

16. Downes E, Sikirica V, Gilabert-Estelles J, Bolge SC, Dodd SL, Maroulis C, et al. The burden of uterine fibroids in five European countries. Eur J Obstet Gynecol Reprod Biol. 2010 Sep;152(1):96–102.

17. Leyland N, Leonardi M, Murji A, Singh SS, Al-Hendy A, Bradley L. A Call-to-Action for Clinicians to Implement Evidence-Based Best Practices When Caring for Women with Uterine Fibroids. Reprod Sci Thousand Oaks Calif. 2022 Apr;29(4):1188–96.

18. NICE NG88. HMB: assessment and management. 2018 Mar 14 [cited 2022 Sep 22]; Available from: https://www.nice.org.uk/guidance/ng88/resources/heavy-menstrual-bleeding-assessment-and-management-pdf-1837701412549

19. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update. 2016 Nov 20;22(6):665–86.

20. Royal College of Obstetricians and Gynaecologists. Left for too long: understanding the scale and impact of gynaecology waiting lists [Internet]. 2022 Apr [cited 2023 Feb 20]. Available from: https://rcog.shorthandstories.com/lefttoolong/index.html

21. Lethaby A, Vollenhoven B, Sowter MC. Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst Rev [Internet]. 2001 [cited 2023 Apr 6];(2). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000547/full

22. Gedeon Richter Limited. NICE Single technology appraisal. Relugolix with oestradiol and norethisterone acetate for treating uterine fibroids [ID3842; GID-TA10734]. Available at: https://www.nice.org.uk/guidance/ta832 (Last accessed: 3 April 2022). 2021.

23. Department of Health and Social Care. Women's Health Strategy for England [Internet]. 2022 Aug [cited 2023 Feb 20]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1100721/Womens-Health-Strategy-England-web-accessible.pdf

24. Department of Health and Social Care. Our Vision for the Women's Health Strategy for England [Internet]. GOV.UK. 2021 [cited 2023 Feb 20]. Available from: https://www.gov.uk/government/publications/our-vision-for-the-womens-health-strategy-for-england/our-vision-for-the-womens-health-strategy-for-england

25. Donnez J, Taylor HS, Stewart EA, Bradley L, Marsh E, Archer D, et al. Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. The Lancet. 2022 Sep 17;400(10356):896–907.

26. Linzagolix SPC [Internet]. EMA; 2023 [cited 2023 May 23]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/yselty

27. Keam SJ. Linzagolix: First Approval. Drugs [Internet]. 2022 Aug 23 [cited 2022 Sep 5]; Available from: https://link.springer.com/10.1007/s40265-022-01753-9

28. Donnez J, Dolmans MM. Endometriosis and Medical Therapy: From Progestogens to Progesterone Resistance to GnRH Antagonists: A Review. J Clin Med. 2021 Mar 5;10(5):1085.

29. Fibroids [Internet]. nhs.uk. 2017 [cited 2022 Sep 13]. Available from: https://www.nhs.uk/conditions/fibroids/

30. Pérez-López FR, Ornat L, Ceausu I, Depypere H, Erel CT, Lambrinoudaki I, et al. EMAS position statement: Management of uterine fibroids. Maturitas. 2014 Sep;79(1):106–16.

31. Fibroids - Diagnosis [Internet]. nhs.uk. 2017 [cited 2022 Sep 29]. Available from: https://www.nhs.uk/conditions/fibroids/diagnosis/

32. Navarro A, Bariani MV, Yang Q, Al-Hendy A. Understanding the Impact of Uterine Fibroids on Human Endometrium Function. Front Cell Dev Biol. 2021 May 25;9:633180.

33. Munro MG, Critchley HOD, Broder MS, Fraser IS, Disorders for the FWG on M. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynecol Obstet. 2011;113(1):3–13.

34. Martín-Merino E, Wallander MA, Andersson S, Soriano-Gabarró M, Rodríguez LAG. The reporting and diagnosis of uterine fibroids in the UK: an observational study. BMC Womens Health. 2016 Dec;16(1):45.

35. Ghosh S, Naftalin J, Imrie R, Hoo WL. Natural History of Uterine Fibroids: A Radiological Perspective. Curr Obstet Gynecol Rep. 2018;7(3):117–21.

36. Catherino WH, Eltoukhi HM, Al-Hendy A. Racial and ethnic differences in the pathogenesis and clinical manifestations of uterine leiomyoma. Semin Reprod Med. 2013 Sep;31(5):370–9.

37. Joel Noutakdie Tochie. Physiopathology and Management of Uterine Fibroids. In: Gaelle Therese Badjang, editor. Fibroids [Internet]. Rijeka: IntechOpen; 2020 [cited 2022 Sep 20]. p. Ch. 7. Available from: https://doi.org/10.5772/intechopen.94162

38. Soliman AM, Margolis MK, Castelli-Haley J, Fuldeore MJ, Owens CD, Coyne KS. Impact of uterine fibroid symptoms on health-related quality of life of US women: evidence from a cross-sectional survey. Curr Med Res Opin. 2017 Nov 2;33(11):1971–8.

39. Data on File: Uterine Fibroids Market Research Survey for Yselty (Linzagolix) Full Report. 2022.

40. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014 Jan 30;123(5):615–24.

41. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. The Lancet. 2011 Oct 15;378(9800):1396–407.

42. Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015 Oct 22;126(17):1981–9.

43. Tolkien Z, Stecher L, Mander AP, Pereira DIA, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PloS One. 2015;10(2):e0117383.

44. Brookes MJ, Farr A, Phillips CJ, Trudgill NJ. Management of iron deficiency anaemia in secondary care across England between 2012 and 2018: a real-world analysis of Hospital Episode Statistics. Frontline Gastroenterol. 2020 Oct 26;12(5):363–9.

45. McWilliams MM, Chennathukuzhi VM. Recent Advances in Uterine Fibroid Etiology. Semin Reprod Med. 2017 Mar;35(2):181–9.

46. Fraser IS, Mansour D, Breymann C, Hoffman C, Mezzacasa A, Petraglia F. Prevalence of heavy menstrual bleeding and experiences of affected women in a European patient survey. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2015 Mar;128(3):196–200.

47. Bonine NG, Banks E, Harrington A, Vlahiotis A, Moore-Schiltz L, Gillard P. Contemporary treatment utilization among women diagnosed with symptomatic uterine fibroids in the United States. BMC Womens Health. 2020 Aug 13;20(1):174.

48. Brito LGO, Panobianco MS, Sabino-de-Freitas MM, Barbosa H de F, de Azevedo GD, Brito LMO, et al. Uterine leiomyoma: understanding the impact of symptoms on womens' lives. Reprod Health. 2014 Jan 30;11(1):10.

49. Williams VSL, Jones G, Mauskopf J, Spalding J, DuChane J. Uterine fibroids: a review of health-related quality of life assessment. J Womens Health 2002. 2006 Sep;15(7):818–29.

50. Lee DW, Ozminkowski RJ, Carls GS, Wang S, Gibson TB, Stewart EA. The Direct and Indirect Cost Burden of Clinically Significant and Symptomatic Uterine Fibroids. J Occup Environ Med. 2007 May;49(5):493–506.

51. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the United States. Am J Obstet Gynecol. 2012 Mar;206(3):211.e1-9.

52. Duhan N. Current and emerging treatments for uterine myoma – an update. Int J Womens Health. 2011 Aug 8;3:231–41.

53. Data on File: PRIMROSE 1 and 2 Pooled Efficacy Analysis, Statistical Analysis Plan. 2021 Mar.

54. Data on File: PRIMROSE 1 and 2 Pooled Safety Analysis up to Week 52, Statistical Analysis Plan.

55. Data on File: PRIMROSE 1 and 2 Pooled Analysis, 16-OBE2109-008_and_16-OBE2109-009_Combined. 21-09-08. 2021.

56. Linzagolix EPAR [Internet]. 2022 Jul [cited 2022 Dec 28]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/yselty

57. Data on File: PRIMROSE 3 CSR. 2023 Mar.

58. Tsai HW, Wang PH, Huang BS, Twu NF, Yen MS, Chen YJ. Low-dose add-back therapy during postoperative GnRH agonist treatment. Taiwan J Obstet Gynecol. 2016 Feb 1;55(1):55–9.

59. Data on File: PRIMROSE 1 CSR Week 24, v2.0. 2021 Jun.

60. Data on File: PRIMROSE 1 CSR Week 52 v2.0. 2021 Jul.

61. Data on File: PRIMROSE 1 CSR Week 76. 2021 Jun.

62. Al-Hendy A, Bradley LD, Taylor HS, Catherino W, Humberstone A, Garner E. A107. Quality of life improvements in women with uterine fibroids: results of two phase 3 trials with linzagolix. Obstet Gynecol. 2022 May;139(1):31S-31S.

63. Taylor HS, Donnez J, Bestel E, Humberstone A, Garner E. A108. Post-treatment Efficacy and Safety Follow-up in Women with Uterine Fibroids Treated for 52 Weeks With Linzagolix. Obstet Gynecol. 2022 May;139:31S.

64. Data on File: PRIMROSE 2 CSR Week 52, v2.0. 2021 May.

65. Data on File: PRIMROSE 2 CSR Week 76. 2021 Mar.

66. National Institute for health and Care Excellence. Health Technology Evaluation. Linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190]. Final scope [Internet]. 2023 Jul [cited 2023 Jul 10]. Available from: https://www.nice.org.uk/guidance/gid-ta11131/documents/final-scope

67. Lukes AS, Baker J, Eder S, Adomako TL. Daily menstrual blood loss and quality of life in women with heavy menstrual bleeding. Womens Health Lond Engl. 2012 Sep;8(5):503–11.

68. Lukes AS, Muse K, Richter HE, Moore KA, Patrick DL. Estimating a meaningful reduction in menstrual blood loss for women with heavy menstrual bleeding. Curr Med Res Opin. 2010 Nov;26(11):2673–8.

69. Carr BR, Stewart EA, Archer DF, Al-Hendy A, Bradley L, Watts NB, et al. Elagolix Alone or With Add-Back Therapy in Women With Heavy Menstrual Bleeding and Uterine Leiomyomas: A Randomized Controlled Trial. Obstet Gynecol. 2018 Nov;132(5):1252–64.

70. Appendix C Methodology checklist: randomised controlled trials | The social care guidance manual | Guidance | NICE [Internet]. NICE; 2013 [cited 2023 Jul 25]. Available from: https://www.nice.org.uk/process/pmg10/chapter/appendix-c-methodology-checklist-randomised-controlled-trials

71. Phillippo DM. multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data [Internet]. 2023 [cited 2023 Jul 25]. Available from: https://cran.r-project.org/web/packages/multinma/index.html

72. Data on File: 2.7.4 Summary of Clinical Safety (D121).

73. Data on File: UF KOL interview full report. 2023 Aug.

74. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol. 2002 Feb;99(2):290–300.

75. Badiani B, Chiumente M, Messori A. Ulipristal acetate for pre-operative management of uterine fibroids: Modeling outcomes and costs. Eur J Obstet Gynecol Reprod Biol. 2018 Mar;222:84–8.

76. Nagy B, Timár G, Józwiak-Hagymásy J, Kovács G, Merész G, Vámossy I, et al. The cost-effectiveness of ulipristal acetate tablets in treating patients with moderate to severe symptoms of uterine fibroids. Eur J Obstet Gynecol Reprod Biol. 2014 Apr 1;175:75–81.

77. Tsoi B, Blackhouse G, Ferrazzi S, Reade CJ, Chen I, Goeree R. Incorporating ulipristal acetate in the care of symptomatic uterine fibroids: a Canadian cost-utility analysis of pharmacotherapy management. Clin Outcomes Res CEOR. 2015 Apr 17;7:213–25.

78. Geale K, Saridogan E, Lehmann M, Arriagada P, Hultberg M, Henriksson M. Repeated intermittent ulipristal acetate in the treatment of uterine fibroids: a cost-effectiveness analysis. Clin Outcomes Res CEOR. 2017;9:669–76.

79. Zakiyah N, van Asselt ADI, Postma MJ. Ulipristal acetate for pre-operative treatment of moderate-to-severe uterine fibroids in women of reproductive age in The Netherlands: cost minimization analysis and budget impact analysis. J Med Econ. 2017 Mar;20(3):280–7.

80. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual [Internet]. [cited 2022 Oct 25]. Available from: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741

81. National Institute for Health and Care Excellence. methods-guide-addendum-cost-comparison.pdf [Internet]. [cited 2023 Aug 30]. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf

82. NHS Inform. Menopause [Internet]. [cited 2022 Nov 25]. Available from: https://www.nhsinform.scot/healthy-living/womens-health/later-years-around-50-years-and-over/menopause-and-post-menopause-health/menopause

83. Office for National Statistics (ONS). National life tables: England [Internet]. [cited 2022 Nov 25]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables

84. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2010 Aug;13(5):509–18.

85. Kulakiewicz A, Powell T. Waiting lists for gynaecological services. 2023 Aug 30 [cited 2023 Aug 30]; Available from: https://commonslibrary.parliament.uk/research-briefings/cdp-2022-0127/

86. Zowall H, Cairns JA, Brewer C, Lamping DL, Gedroyc WMW, Regan L. Cost-effectiveness of magnetic resonance-guided focused ultrasound surgery for treatment of uterine fibroids. BJOG Int J Obstet Gynaecol. 2008 Apr;115(5):653–62.

87. Gorny KR, Woodrum DA, Brown DL, Henrichsen TL, Weaver AL, Amrami KK, et al. Magnetic resonance-guided focused ultrasound of uterine leiomyomas: review of a 12-month outcome of 130 clinical patients. J Vasc Interv Radiol JVIR. 2011 Jun;22(6):857–64.

88. Settnes A, Topsoee MF, Moeller C, Dueholm M, Kopp TI, Norrbom C, et al. Reduced Complications Following Implementation of Laparoscopic Hysterectomy: A Danish Population-based Cohort Study of Minimally Invasive Benign Gynecologic Surgery between 2004 and 2018. J Minim Invasive Gynecol. 2020;27(6):1344-1353.e3.

89. Harding G, Coyne KS, Thompson CL, Spies JB. The responsiveness of the uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL). Health Qual Life Outcomes. 2008 Nov 12;6(1):99.

90. Hernández-Alava M, Pudney S. Econometric modelling of multiple self-reports of health states: The switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. J Health Econ. 2017 Sep;55:139–52.

91. Hux M, Ng C, Ortega GL, Ferrazzi S, Goeree R. Utility values for pre-menopausal women suffering from symptomatic uterine fibroids. Expert Rev Pharmacoecon Outcomes Res. 2015 Feb;15(1):181–9.

92. Manyonda I, Belli AM, Lumsden MA, Moss J, McKinnon W, Middleton LJ, et al. Uterine-Artery Embolization or Myomectomy for Uterine Fibroids. N Engl J Med. 2020 Jul 30;383(5):440–51.

93. Rana D, Wu O, Cheed V, Middleton LJ, Moss J, Lumsden MA, et al. Uterine artery embolisation or myomectomy for women with uterine fibroids wishing to avoid hysterectomy: a cost-utility analysis of the FEMME trial. BJOG Int J Obstet Gynaecol. 2021 Oct;128(11):1793–802.

94. Cooper K, Breeman S, Scott NW, Scotland G, Hernández R, Clark TJ, et al. Laparoscopic supracervical hysterectomy compared with second-generation endometrial ablation for heavy menstrual bleeding: the HEALTH RCT. Health Technol Assess Winch Engl. 2019 Sep;23(53):1–108.

95. Stewart EA, Rabinovici J, Tempany CMC, Inbar Y, Regan L, Gostout B, et al. Clinical outcomes of focused ultrasound surgery for the treatment of uterine fibroids. Fertil Steril. 2006 Jan;85(1):22–9.

96. Hindley J, Gedroyc WM, Regan L, Stewart E, Tempany C, Hynyen K, et al. MRI guidance of focused ultrasound therapy of uterine fibroids: early results. AJR Am J Roentgenol. 2004 Dec;183(6):1713–9.

97. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. Med Decis Mak Int J Soc Med Decis Mak. 2006;26(4):410–20.

98. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008 Oct 21;6:84.

99. BNF content published by NICE [Internet]. 2023 [cited 2023 Jul 25]. Available from: https://bnf.nice.org.uk/

100. Drugs and pharmaceutical electronic market information tool (eMIT) [Internet]. GOV.UK. 2023 [cited 2023 Jul 25]. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

101. NHS England. National Cost Collection for the NHS [Internet]. [cited 2022 Nov 25]. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/

102. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit Costs of Health and Social Care 2022 Manual [Internet]. Personal Social Services Research Unit; 2022 [cited 2023 Jul 25]. Available from: https://kar.kent.ac.uk/id/eprint/100519

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190]

Summary of Information for Patients (SIP)

September 2023

File name	Version	Contains confidential information	Date
ID6190_Linzagolix_UF_SIP v2.0	2.0	No	11-Sep-23

Summary of Information for Patients (SIP):
The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from National Institute for Health and Care Excellence (NICE) for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The SIP template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Linzagolix (Yselty)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Linzagolix is used for the treatment of moderate to severe symptoms of uterine fibroids (UFs) in adults of reproductive age (1). UFs are common non-cancerous tumours that develop in the womb during a woman's reproductive years (2,3). Linzagolix does not need to be taken in combination with hormone-based therapy, unlike other existing therapies; the patient population being appraised by NICE therefore includes patients who are not able to, or prefer not to, take hormone-based therapies and who are under-served by existing therapies (2).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The European Commission issued a marketing authorisation for linzagolix throughout the European Union on June 14, 2022.

The UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued a marketing authorisation for linzagolix on June 27, 2022.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Working with patient groups

As a responsible pharmaceutical company, Theramex partners with relevant patient organisations to support endeavours to improve treatment and care and to improve understanding of patients. This is common practice, and we adhere closely to industry guidelines and regulations that are in place.

However in the UK, despite reaching out to potential patient groups for people with UFs, none appear to be currently active.

No collaborations exist that could be considered a potential conflict of interest.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Uterine fibroids

UFs are common, non-cancerous tumours that develop in the uterus (womb) during a women's reproductive years (2,3). They can grow in clusters or alone, and range in size from a few millimetres in length to large growths of more than 20 cm in diameter (3). The most common symptom is chronic heavy menstrual bleeding (HMB) (4). HMB can lead to a low red blood cell count (iron-deficiency anaemia), causing excessive tiredness and lack of energy; in severe cases this can be life-threatening (4,5). Other UF symptoms include pain (e.g., pelvic pain, period pain and discomfort, or pain during sexual intercourse). Larger fibroids can lead to 'bulk symptoms' causing pelvic pressure, bloating, leg or back pain, increased need to urinate, and constipation (6–8).

Number of patients with UFs

UFs is a common condition, but the true number of people with UFs is unknown, as people sometimes don't have symptoms and remain undiagnosed (4,9). Nearly 70% of White women and more than 80% of Black women will have had at least one fibroid by the age of 50 (4). In a large online study that included 2,500 women from the UK, the proportion of women who reported having UFs was 4.5% for those aged 15 to 49 years, and 9.4% in those aged 40 to 49 years (8).

Linzagolix is being assessed for people with moderate to severe symptoms of UFs. Approximately 25% to 30% of women with UFs experience symptoms although the type and severity of symptoms depends on the size, location and number of UFs (7,10). Black women typically have more severe symptoms than White women (11). In online studies, 33% of the women with diagnosed UF reported a moderate or severe negative impact of their symptoms (8) and 43% rated the most common symptoms as being moderate or severe (12).

Linzagolix is being assessed in three subgroups of patients with moderate to severe symptoms of UFs:

- People having short-term treatment of 6 months or less
- People having longer-term treatment, with hormone add-back therapy (ABT)

- People having longer-term treatment, without hormone ABT.

Impact of UFs on patients

The bleeding, pain, and other symptoms of UFs can cause significant distress for patients and have a negative impact on their daily lives.(4,11) UFs can have a negative impact on physical and social activities, intimate relationships, productivity at work, emotional well-being and health-related quality of life (HRQoL) (4,7,8,11). They can also affect fertility (up to 10% of infertility cases are associated with UFs) and are associated with miscarriages and complications during pregnancy (4,13). UFs can affect mental health and well-being, as having them can result in concerns about health, body image, sense of femininity and sexuality, feelings of sadness, hopelessness and loss of control (4,14).

While UFs are benign tumours and are not expected to be associated with an increased death rate beyond that of the age-matched general population, there is an increased risk of mortality associated with surgical and interventional procedures used to remove them, which is likely to be higher if patients are anaemic before undergoing surgery (15,16).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Diagnosis and testing

If a GP suspects fibroids in people with symptoms, they'll carry out a pelvic examination to look for any obvious signs. They will usually refer the patient to a local hospital for further tests to confirm a diagnosis. These tests include an ultrasound scan (abdominal or via the vagina), hysteroscopy (a small telescope is inserted into the uterus through the vagina and cervix) or laparoscopy (a small telescope is inserted through a small cut in the abdomen [tummy]) (9). In some cases, a biopsy (small tissue sample) may be removed during hysteroscopy or laparoscopy for closer investigation under a microscope (9). Sometimes UFs are only discovered during routine vaginal examinations or tests for other problems (9).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Treatment of UFs

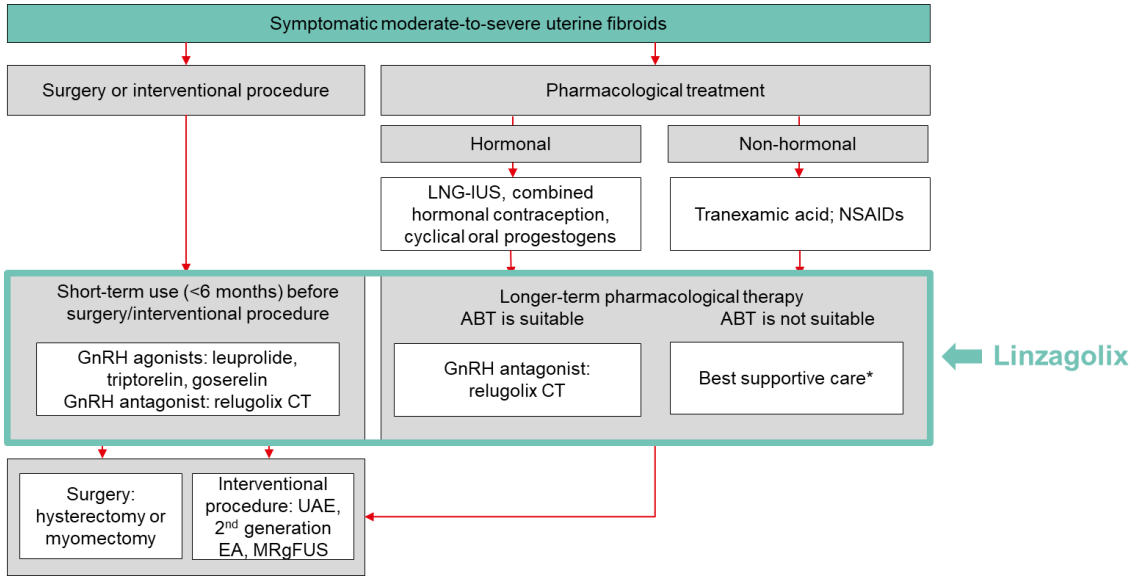
The aim of treatment is to improve quality of life (17) by reducing or eliminating the symptoms caused by UFs, maintaining or improving fertility if desired, removing UFs with surgery, or reducing uterine and fibroid size before surgery. Treatment options should take the person's preferences into consideration.

Current treatment options include non-surgical treatment (non-hormonal or hormonal treatments), surgical procedures such as removal of UFs (myomectomy) or removal of the uterus (hysterectomy), and interventional procedures such as uterine artery embolisation (blocking the blood vessels supplying the UFs) (17). Hormonal therapy includes gonadotropin-releasing hormone (GnRH) agonists and GnRH antagonists; although ulipristal acetate is also licensed in the UK, it is rarely used in clinical practice (17). GnRH agonists (including leuprolide, triptorelin and goserelin) are given by an injection and are typically used for short periods (less than 6 months) before surgery (hysterectomy and myomectomy) if UFs are causing an enlarged or distorted uterus (17). The only GnRH antagonist recommended by NICE for the treatment of moderate to severe symptoms of UFs is relugolix CT (18). This is a combined tablet of relugolix with hormonal ABT (known as relugolix CT) and is not suitable for people who have an elevated risk of estrogen- and progestogen-related side effects, cannot take these hormones, or who prefer to avoid hormonal ABT (19).

The most relevant UK guideline is the NICE guideline 88 (NG88), which was originally published in 2018 and updated in May 2021 (17).

Linzagolix would be used to manage symptoms and reduce UF size in people waiting for surgery or an interventional procedure, or in people who wish to avoid surgery as an alternative to other treatments (see the figure below). Unlike relugolix CT, linzagolix can be given without hormonal ABT.

Place of linzagolix in the current treatment pathway



*Best supportive care includes NSAIDs for pain management and iron supplements for blood loss
Abbreviations: EA, endometrial ablation; GnRH, gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; MRgFUS; magnetic resonance guided focused ultrasound; NSAIDs, non-steroidal anti-inflammatory drugs; relugolix CT, relugolix in a combined tablet with hormonal add-back therapy; UAE, uterine artery embolisation

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Furthering our understanding of UFs

Theramex has a strong commitment to working with people with UFs to better understand the condition and to gather evidence that is relevant to them about the impact of UFs and how they are treated. For example, Theramex actively engages with a French patient group called the L'association Fibrome Info France.

Published evidence

Several online studies have provided important information about patients' experience of living with UFs (8,14,20).

In a large cross-sectional online survey that included 1,533 people with UFs, 43% stated that their sexual life was negatively affected, 28% reported impaired

performance at work, 27% said UFs had negatively affected relationships and family and 26% that it had impaired their ability to carry out activities of daily living (8).

Another internet-based survey involving 330 women with HMB from five European countries (France, Germany, Netherlands, Spain, and Switzerland) reported heavy bleeding to have a major negative impact on sexual life (62%), physical activities (53%), productivity at work (39%), sleep and ability to travel (both 35%), productivity at home (31%), relationship with spouse/and or children (28%) and social life (23%) (20).

In a cross-sectional survey of 968 women with UFs in the US, most women reported fears due to their UF diagnosis, including fears around the growth of their UFs (79%), future health complications (63%), and needing a hysterectomy (55%). In the same survey, 19% of women reported feeling sad, discouraged or hopeless, 37% felt conscious about the size and appearance of their stomach, 34% were concerned about soiling clothes or bedding, 20% felt not in control of life and 21% reported that their UFs negatively affected their sense of femininity or sexuality, all or most of the time (14).

Example quotes from women taking part in an open-ended interview study involving 30 women from the US with heavy bleeding and UFs illustrate the negative impacts of UFs symptoms on their daily lives and emotional well-being (7):

- “No matter how many sanitary towels you put in, when the blood comes out, it drains down to your feet because it pours”.
- “I used to have clots as big as a jellyfish, where I could just stand up at work, like I said, and they would just fall out”.
- “I sleep every night with that baby diaper [nappy] on me… I cannot go out because blood falls under my panties, it goes out and spills a lot, you know…Because tampon cannot control it”.
- “I pretty much paid rent with the amount of money I was [spending on] buying for pads and tampons”.
- “It would be like a stabbing pain. like something literally is trying to rip out of me – or it’s a sharp, stabbing pain. And it would be crippling”.
- “I would have to say I’m not in a relationship because of my uterine fibroids because I don’t care to have sex because it’s painful”.
- “As it got worse and worse, I just stopped doing things”.

Commitment to patient-based outcomes

Data for linzagolix come principally from the PRIMROSE 1 and 2 trials, as well as PRIMROSE 3, where patients were followed for longer after treatment with linzagolix (21,22).

In both PRIMROSE 1 and 2, data on the effects of linzagolix on quality of life were collected using the Uterine Fibroid Symptom-quality of life (UFS-QoL) scale, Patient Global Impression of Improvement (PGI-I) questionnaire and the EuroQol-5 Dimensions-5 level scale (EQ-5D-5L). These are all patient-reported measures that help to assess the impact of UFs on patients and whether treatments are improving people's HRQoL.

The UFS-QoL is a UF-specific, self-reported questionnaire for detecting differences in symptom severity and HRQoL among patients with UFs. It measures both a patient's pre-treatment and post-treatment symptoms (bleeding, cramping) and emotional experiences (feeling 'blue' or less productive') (23).

Additionally, safety data were collected to ensure that the safety profile of linzagolix is well-understood, and appropriate for patients with UFs.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

The cause of UFs

The exact cause of UFs is unknown, but they have been linked to the hormone estrogen (24). Estrogen is the female reproductive hormone produced by the ovaries (the female reproductive organs). UFs usually develop during a woman's reproductive years (from around the age of 16 to 50) when estrogen levels are at their highest. They tend to shrink when estrogen levels are low, such as after the menopause when a woman's monthly period stops (24).

How does linzagolix work?

Linzagolix is a new oral, once daily GnRH antagonist (1), this means it blocks the action of GnRH, a hormone that helps to regulate the release of female sex hormones estradiol and progesterone. These hormones trigger women’s periods (menstruation). When blocked, the levels of the hormones estrogen and progesterone circulating in the body are reduced. By decreasing their levels, linzagolix stops or reduces menstrual bleeding and decreases pain and pelvic discomfort and other symptoms associated with UFs (1).

How is linzagolix innovative and how might this be important to people with UFs?

Linzagolix is the first and only GnRH antagonist that provides flexible dosing options for short- or long-term use with or without ABT. It provides an alternative treatment option to injectable GnRH agonists and the GnRH antagonist, relugolix CT, as well as being suitable for people wishing to avoid surgery. Relugolix CT is only available at one dose and can only be given in as a tablet combined with hormonal ABT (19). Linzagolix provides benefits at two different doses with and without ABT (1).

Having a treatment that offers flexible dosing options, with or without ABT, will give doctors the ability to tailor treatment to the needs of people with UFs. In particular, a treatment option without ABT would give an option for people with moderate to severe UFs who 1) prefer not to take hormonal therapy; 2) are high risk of ABT side effects or contraindicated to ABT (should not use it) — including people with obesity, hypertension (high blood pressure), and dyslipidaemia (abnormal level of

fat in the blood) as they increase the chance of thrombosis (blood clot in blood vessel), stroke (when blood supply to part of the brain is cut off) and cardiac events (19), which disproportionately affect Black women, and 3) women with an elevated risk of estrogen- and progestogen-related side effects.

Linzagolix therefore helps to address equality and inclusion issues associated with relugolix CT, which is only available in combination with hormonal ABT

Please refer to the Linzagolix Summary of Product Characteristics (SPC), Patient Information Leaflet and Public Assessment Report for more details about the way the treatment works.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3 g) focus on data that relate to the combination rather than the individual treatments.

Patients in the PRIMROSE 1 and 2 trials (see Section 3d below) had been receiving standard non-surgical treatments for UFs and still had symptoms when they entered the studies (21). They stopped all other treatment for treating UFs during the studies.

Linzagolix can be taken with or without hormonal ABT, a combination of the hormones estrogen and progestogen (see below for the different linzagolix dosing options) (1). Hormonal ABT is used to prevent the menopause-like side effects that can occur with GnRH antagonists, such as hot flushes, increased sweating, muscle stiffness, vaginal dryness, and osteoporosis (thinning of the bones). Hormonal ABT is readily available and has a well-known side-effect profile (including breast tenderness, headaches, feeling sick, indigestion, abdominal [tummy] pain and vaginal bleeding; these usually pass within 3 months of starting treatment).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Linzagolix is available as tablets to be taken by mouth once a day. Treatment should preferably start during the first week of the menstrual period. Before

starting treatment with linzagolix, pregnancy must be ruled out. The recommended dose of linzagolix is 100 mg, or if needed 200 mg, once a day, with hormonal ABT, which comprises estradiol 1 mg and norethisterone acetate 0.5 mg taken once daily (1). For people in whom ABT is not appropriate, the dose is 100 mg once daily (1). Linzagolix 100 mg with or without ABT, and linzagolix 200 mg with ABT can be used long term. Linzagolix 200 mg once daily without ABT can be used short term (<6 months) when a reduction in UF size is desired (1). In patients with risk factors for osteoporosis or bone loss, a dual X-ray absorptiometry (DXA) scan is recommended before starting linzagolix, and a DXA scan is also recommended for all patients after 1 year of treatment with linzagolix.

As an oral therapy, linzagolix with or without hormonal ABT can be taken at the patient's home, eliminating the need for patients and their caregivers to visit a clinic or hospital for treatment.

Individualised dosing

The recommended dose of linzagolix varies depending on individual's needs (1):

- Starting dose for patients able and willing to take ABT: 100 mg with hormonal ABT (estradiol 1 mg and norethisterone acetate 0.5 mg tablet once daily)
- If a higher dose is needed to control symptoms: 200 mg once daily with hormonal ABT (as above)
- For people in whom ABT is not recommended or who prefer to avoid hormonal therapy: 100 mg once daily
- For short-term use (<6 months) when reduction of uterine and UF volume is desired: 200 mg once daily (UF size may increase when the treatment is stopped). The 200 mg dose without ABT should not be prescribed for longer than 6 months due to the risk of bone mineral density (BMD) decrease with prolonged use.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria, completion dates, etc. Please provide references to further information about the trials or publications from the trials.

The table below summarises the two main completed clinical trials upon which the evidence for linzagolix is based (PRIMROSE 1 and 2) (21). These trials were nearly identical but differed with respect to the countries in which they occurred and a small difference in treatment switch design between Week 24 and Week 52 of the trials. An additional follow-up trial, PRIMROSE 3 provided longer-term safety

information about the effects on BMD after linzagolix treatment had stopped (for results, see Section B.2.11.1 of the company submission).

Linzagolix clinical trials

Trial	PRIMROSE 1 (NCT03070899) Donnez et al. (2022) (21)	PRIMROSE 2 (NCT03070951) Donnez et al. (2022) (21)
Trial design	Phase 3, randomised, parallel-group, double-blind, placebo-controlled, multicentre	
Population	Women aged ≥18 years with ultrasound confirmed UFs and HMB (defined as ≥80 mL of MBL per cycle for at least two menstrual cycles)	
Countries	US only	US and eight European countries
Intervention(s)	Patients in the trials received one of the following four treatment regimens, taken orally once daily for up to 52 weeks: • Linzagolix 100 mg • Linzagolix 100 mg + ABT (1 mg E2/0.5 mg NETA) • Linzagolix 200 mg • Linzagolix 200 mg + ABT (1 mg E2/0.5 mg NETA)	
Comparator	Placebo	
Treatment switch	At Week 24, 50% of patients allocated to the placebo group at baseline remained in the placebo group and 50% of patients allocated to the placebo group at baseline switched to linzagolix 200 mg + ABT (selected at random assignment) to Week 52 At Week 24, all patients allocated to linzagolix 200 mg at baseline switched to linzagolix 200 mg + ABT to Week 52	At Week 24, all patients allocated to the placebo group or linzagolix 200 mg group at baseline switched to linzagolix 200 mg + ABT to Week 52
Number of patients	511 (full analysis set)	501 (full analysis set)
Completion date	April 2021	October 2020
Main reported outcomes	• Change in MBL volume • Time to MBL response • Pain • UF volume • Haemoglobin levels • Change in BMD • Mortality • AEs of treatment	

	• HRQoL improvement
Inclusion/exclusion criteria	Patients had to be premenopausal and aged over 18 with a diagnosis of UFs and HMB defined as ≥80 mL of MBL per cycle for at least two cycles. They had to have at least one UF with a diameter of at least 2 cm (but no larger than 12 cm) or multiple small fibroids with calculated uterus volume ≥200 cm^3. Uterus size had to be less than the size of a 20-week pregnancy (or <20 cm from bottom to top of the uterus [womb] as measured by ultrasound) Patients could not be pregnant, breast-feeding or planning a pregnancy, have had recent surgery or undiagnosed uterine bleeding or be at substantial risk or have osteoporosis, and they had to stop oral contraceptives and other sex hormones during the trial and be able to take hormonal ABT For more detail on inclusion and exclusion criteria, please refer to the trial entries in clinicaltrials.com (reference numbers: NCT03070899 and NCT03070951)

Abbreviations: ABT, add-back therapy; AE, adverse events; BMD, bone mineral density; E2, estradiol; HMB, heavy menstrual bleeding; HRQoL, health-related quality of life; MBL, menstrual blood loss; NCT, National Clinical Trials; NETA, norethisterone acetate; UFs, uterine fibroids; US, United States of America

3e) Efficacy

Efficacy measures how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Linzagolix was studied in two nearly identical trials called PRIMROSE 1 and 2 (see above for trial details) (21). Across both trials, 1,012 people with UFs received 100 mg or 200 mg of linzagolix with and without hormonal ABT (making four different treatment groups) or an inactive dummy treatment (referred to as placebo) given the same way as linzagolix (with and without hormonal ABT) (21). The study was double blinded, meaning neither the patients nor the doctors knew whether it was linzagolix or placebo being administered (and they didn't know who was receiving hormonal ABT either) (21). All patients in the trials had diagnosed UFs that were at least 2 cm but less than 12 cm in diameter, and were causing symptoms including HMB (MBL had been measured by collecting all sanitary products for at least two menstrual cycles and was ≥80 mL per cycle) (21).

How treatment was given

Linzagolix was given by mouth once a day for 24 weeks. At 24 weeks, treatment changed for some of the patients (as linzagolix 200 mg without ABT should not be taken for longer than 6 months) (21):

- In PRIMROSE 1, half of patients allocated to the placebo group at baseline remained in the placebo group and the other half switched to linzagolix

200 mg + ABT (selected at randomly). All patients allocated to linzagolix 200 mg at baseline switched to linzagolix 200 mg + ABT.

- In PRIMROSE 2, all patients allocated to the placebo group or linzagolix 200 mg group at baseline switched to linzagolix 200 mg + ABT.

All patients then continued to receive their new or existing treatment/placebo for the next 24 weeks of the trials, up to Week 52. After that, all patients stopped treatments/placebo but continued to be assessed up to Week 64.

Significant improvement demonstrated vs. placebo

The patients who received linzagolix (with and without ABT) had significantly less bleeding compared with those who received placebo at Week 24 in the PRIMROSE 1 and 2 trials (21). The bleeding endpoint was considered to be clinically meaningful and has been used for approval for other drugs, including relugolix CT (18,25,26). Furthermore, the reduction in HMB (the most common symptom of UFs) (21) with linzagolix treatment is likely to be particularly meaningful for patients given how much is affects people with UFs.

On average, patients treated with linzagolix (all dose groups) had less days of bleeding, more days without bleeding, and quicker time to no bleeding, compared with the placebo group. In patients who had a low red blood cell count (anaemia) at the beginning of the trials, improvements in blood iron (haemoglobin) levels were seen in all linzagolix treatment groups at Week 24 compared with the placebo group.

All patients treated with linzagolix (all dose groups) had reductions in average fibroid volume and uterine volume. A reduction in the fibroid and uterine volume may help to reduce pressure effects (such as bloating, leg or back pain, increased urinary frequency, and constipation) and may prevent, delay or facilitate surgery. The linzagolix 200 mg without ABT group had substantial and clinically meaningful reductions in average fibroid volumes (48% reduction) and uterine volumes (39% reduction) after 24 weeks of treatment (21).

Improvements compared with placebo also occurred in UF-related pain scores, and in HRQoL assessed using the UFS-QoL symptom severity and HRQoL total scores (see below) (21).

Comparison against relugolix CT

There are no head-to-head trials comparing linzagolix against relugolix CT. In the absence of direct comparisons, Theramex has carried out indirect treatment comparisons using well-established methodology. The results of these analyses have not been published and are available in Section B.2.9 of the company submission. Overall, the comparisons indicate that relugolix CT and linzagolix have similar efficacy, although the results vary across different trial outcomes due to differences between the relugolix and linzagolix trial designs.

Comparison against GnRH agonists

There are no head-to-head trials comparing linzagolix against GnRH antagonists. NICE's appraisal of relugolix CT (TA832) concluded that GnRH agonists and relugolix CT have similar efficacy (18), and as indirect comparisons indicate that relugolix CT and linzagolix have similar efficacy (see above), it is also very likely that linzagolix and GnRH agonists have similar efficacy

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for t potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease-specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient-reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Information on patient quality of life during the PRIMROSE 1 and 2 trials was gathered using patient-reported questionnaires UFS-QoL (symptom severity score and HRQoL total score), EQ-5D-5L and PGI-I.

The UFS-QoL is a disease-specific self-reported questionnaire for detecting differences in symptom severity and HRQoL among patients with UFs. It measures both a patient's objective pre-treatment and post-treatment symptoms (bleeding, cramping) and subjective experience (feeling 'blue' or less productive'). There were marked decreases in the symptom severity scores (indicating improvement) and increases in the HRQoL scores (indicating improvement) from baseline at Week 24 in all the linzagolix groups with and without ABT compared with the placebo group, demonstrating that linzagolix reduced symptom severity and improved HRQoL in women with UFs compared with placebo. Increases in HRQoL were seen across all areas (concern, activities, energy and mood, control, self-consciousness, and sexual function) in the linzagolix groups compared with the placebo group. Increases were most pronounced in the concern and activities areas and tended to be higher in the linzagolix 200 mg and 200 mg + ABT groups (21,27).

The PGI-I questionnaire asks patients to assess the overall impact of UF symptoms over a 4-week period in comparison to before starting trial treatment; possible responses are 'very much better', 'much better', 'a little better', 'no change', 'a little worse', 'much worse' and 'very much worse'. In both trials, the proportion of patients reporting being 'much better' or 'very much better' was higher across all linzagolix groups compared with the placebo group (27).

In the pooled analysis, there were small increases in the EQ-5D-5L index values and the visual analogue scale (VAS) score in all linzagolix groups and the placebo group at Week 24, but there were no noticeable differences between the linzagolix

groups and the placebo group (27). In the PRIMROSE 1 and 2 trials, EQ-5D was assessed at baseline, Week 12 and Week 24. As the effects of UFs are complex, and patients may report differently depending on exactly which timepoint in their menstrual cycle (period) they complete the EQ-5D assessment, a single measurement on a single day may not truly reflect patients' overall HRQoL. The disease-specific UFS-QoL is likely to be a more reliable and appropriate measure to use in the assessment of HRQoL for patients with UFs.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment about its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Generally, linzagolix for the treatment of HMB associated with UFs was well tolerated by women (27). Few serious side effects occurred across the PRIMROSE trials and very few were considered related to linzagolix.

The most frequently reported side effect with the use of linzagolix was hot flushes (PRIMROSE 1; 11.4% and PRIMROSE 2; 14.1%) at Week 24 (21). This was more common with higher doses of linzagolix and off-set by the addition of ABT. Other common side effects included nausea, headache, anaemia (expected in patients with UFs), and excessive sweating. The incidence of hot flushes and headaches was lower at Week 52 than at Week 24, suggesting that these side effects mainly occur at the start of treatment and do not increase with extended use. Changes in BMD were small in the trials, and were not considered to be clinically meaningful except in patients treated with linzagolix 200 mg. There was a trend to recovery of BMD loss at Week 76 when patients were off treatment. Other side effects, such as increases in liver function tests, cholesterol and blood fat profile, and mood changes, are also consistent with the drug class, and generally can be managed with appropriate monitoring by doctors (27).

The overall incidence of side effects leading to patients stopping linzagolix treatment was low up to Week 24 and comparable to rates in the placebo group (21).

3h) Summary of key benefits of treatment for patients

<u>Addressing the unmet need</u>

Current pharmacological treatment options have limitations and are not suitable for all people with UFs leaving a need for a flexible dosing option, and flexibility for

people with UFs who can't or don't want to take hormonal ABT. Linzagolix offers a new flexible oral treatment option for short- or long-term use with or without ABT (2).

Effectiveness and tolerability shown in robust clinical trials

The beneficial impact of linzagolix – both on the symptoms of UFs and on the quality of life of people with UFs – has been shown in two large controlled clinical trials against a placebo comparator (21).

Linzagolix provided rapid, sustained and clinically meaningful decreases in bleeding, and many patients experienced marked improvement in their pain symptoms and in their quality of life (21). The linzagolix 200 mg without hormonal ABT group had substantial and clinically meaningful reductions in UF volume (21).

Linzagolix was generally well tolerated with few serious side effects occurring across the PRIMROSE trials and very few considered related to linzagolix (27).

Simplifies/avoids the need for surgery due to reduction in UF size

As noted in Section 3e, linzagolix 200 mg without ABT group provides a substantial and clinically meaningful reduction in average fibroid and uterine volumes after 24 weeks of treatment (21). As well as reducing bulk-related symptoms, short-term use (<6 months) of linzagolix at this dose before surgery is likely to delay surgery, or simplify it, such that patients may be more likely to have keyhole surgery rather than open surgery.

Individualised, flexible dosing

Linzagolix also offers an individualised approach to treatment due to its flexible dosing options (1). This means that it is suitable for a variety of people with UFs, including previously under-served people with UFs who do not want surgery and should not or do not wish to use hormonal ABT, and therefore are unable to use relugolix CT.

Addresses equality concerns

By providing an option for people with UFs who currently can't or prefer not to use hormonal ABT (1), linzagolix addresses equality and inclusion concerns associated with relugolix CT, which is only available in combination with hormonal ABT (19).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities compared with current treatments. Which disadvantages are most important to patients and carers?

- Please include disadvantages related to the mode of action, effectiveness, side effects and method of administration
- What is the impact of any disadvantages highlighted compared with current treatments

People who take linzagolix without hormonal ABT are more likely to experience menopausal-like side effects – but these are likely to diminish over time. People taking linzagolix will need a scan after one year of treatment to check for bone thinning (this is also the case for people taking relugolix CT (19)) and long-term follow-up for monitoring to check for this and other potential side effects (1), which is time-consuming for patients and requires hospital visits.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness/cost-comparison assessment of new medicines

In assessing whether a medicine represents a cost-effective use of NHS resources, NICE refers to a measure called the incremental cost-effectiveness ratio (ICER) (28). This looks at the cost-effectiveness of the product in question – in this case, linzagolix – against other treatments currently used to treat the condition.

The ICER is measured in terms of what needs to be spent to gain one quality-adjusted life year (QALY). The QALY is a measure of disease burden and includes both the quality and quantity of life lived. A treatment can increase the number of QALYs a patient experiences by extending life, increasing the quality of life, or both.

If a new medicine is likely to provide similar or greater health benefits at similar or lower cost to existing treatment options, a cost-comparison analysis may be carried out.

How the economic assessment of linzagolix in UFs was conducted

There are no existing economic models which assess the costs (or cost-effectiveness) of linzagolix for treating patients with moderate to severe symptoms of UFs. Therefore, new economic models were developed for this submission.

The economic models were designed to assess linzagolix in the three groups of patients with moderate to severe symptoms of UFs that were specified by NICE:

- People having short-term treatment of 6 months or less (Population #1)
- People having longer-term treatment, with hormone-based therapy (Population #2)
- People having longer-term treatment, without hormone-based therapy (Population #3)

Cost-comparison analysis for Population #1 and #2

For the population of patients having short-term treatment and the population of patients having longer-term treatment with hormone-based therapy, it is assumed based on clinical opinion and statistical analysis that linzagolix is at least similarly effective to the existing medicines that are available for treating moderate to severe symptoms of UFs.

Therefore, cost-comparison analyses were conducted in these populations. The costs captured within the analysis include the cost of treatment, the cost of administering the treatment, other healthcare resource use (or monitoring) costs, and the costs associated with having surgery.

In Population #1 (short-term treatment), costs were compared between linzagolix, relugolix CT, and the GnRH agonists (leuprorelin, goserelin, and triptorelin). In Population #2 (longer-term treatment with hormone-based therapy), costs were compared between linzagolix and relugolix CT.

Cost-effectiveness analysis for Population #3

In the population of patients receiving longer-term treatment without hormone-based therapy, there are limited existing treatment options. Therefore, a cost-effectiveness model was designed to compare linzagolix with best supportive care (BSC). It was assumed that the effectiveness of BSC is represented by the placebo arm of the PRIMROSE clinical trials.

The model was structured using ‘health states’, which help to capture both the costs to the NHS and the impact on quantity and quality of life for patients receiving different medicines.

The costs captured within the analysis include drug costs, administration costs, healthcare resource use costs, surgery costs, and the costs associated with managing adverse events.

The model health states were uncontrolled disease, controlled disease, surgery, post-surgery, menopause, and death. These show how the disease can develop over time and are a simplified reflection of the course of the disease in real life.

Assumptions and limitations

The key assumption in cost-comparison analyses for Populations #1 and #2 is that linzagolix is at least similarly effective to relugolix CT and the GnRH agonists for treating moderate to severe symptoms of UFs.

In practice, the type of surgery a patient receives depends on a range of factors including disease characteristics and patient preferences. The cost-comparison and cost-effectiveness models assume the distribution of surgery types are consistent between treatment arms in the base case.

There are several key assumptions in the cost-effectiveness analysis for Population #3, as follows:

- The effectiveness of BSC is represented by the placebo arm of the PRIMROSE studies, while the costs of BSC are represented by pain relief (ibuprofen) and iron supplements.
- Uncontrolled symptoms of UFs are represented by HMB (>80 ml), and controlled symptoms are represented by reduced HMB (<80 ml and a ≥50% reduction from baseline), consistent with the primary endpoint in the PRIMROSE studies
- A time horizon to the average age of menopause is sufficient for capturing differences in costs and outcomes between treatments, as fibroids tend to shrink due following menopause due to lower estrogen levels (and therefore no further treatment, surgery, or resource usage is assumed)

Summary

Clinical and economic evaluations are presented within the submission documents. Theramex believes that interpretation of the clinical and economic evidence should also consider the flexibility in dosing that linzagolix allows, offering people a treatment choice without hormone-based therapy and meeting an unmet need in people with UFs for whom hormone-based therapy is not appropriate.

In order to fulfil our commitment to ensuring that patients can have access to linzagolix, Theramex have put forward a price that will be part of an effectapproved Patient Access Scheme (PAS).

NICE and its assessors will review the cost-effectiveness and cost-comparison models and their underlying assumptions/inputs to determine whether they are suitable for decision making. NICE will then make a recommendation based on the outputs using the committee's preferred assumptions.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Individualised treatment to match patient needs and preferences

Linzagolix is the first and only GnRH antagonist for people with UFs that provides flexible dosing options for short- or long-term use with or without ABT. It therefore provides an alternative treatment option to injectable GnRH agonists and the GnRH antagonist, relugolix CT, as well as being suitable for people wishing to avoid surgery.

Meets an unmet clinical need

There is a specific unmet need for treatments that offer flexible dosing options with or without ABT that would give doctors the ability to tailor treatment to needs of women with UFs. In particular, linzagolix given without ABT fulfils an unmet need for women with moderate to severe UFs who 1) prefer not to take hormonal therapy; 2) are contraindicated to ABT (should not use it) — contraindications include obesity, hypertension (high blood pressure), and dyslipidaemia (abnormal level of fat in the blood) as they increase the chance of thrombotic, stroke and cardiac events, which disproportionately affect Black women, and 3) women with an elevated risk of estrogen- and progestogen-related side effects.

Addresses equality and inclusion issues

Linzagolix helps to address equality and inclusion issues associated with relugolix CT, which is only available in combination with hormonal ABT.

3l) Equalities

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 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

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

Recommending linzagolix would adequately address equality concerns that were highlighted in the relugolix CT NICE TA:

1) Should be available to everyone with UFs who is eligible; this may potentially include people who are trans or non-binary (although there are no clinical data in this population).

2) Black women are two or three times more likely to develop UFs than White women and may be more opposed to surgery because of cultural beliefs.

3) The clinical experts highlighted that clinic visits for injectable treatment with GnRH agonists can result in significant financial and time costs – this could be a particular problem for people from lower socioeconomic groups and may increase the 'did not attend' rate at clinics.

4) Clinical experts highlighted the need for a more effective non-surgical treatment option for people not wanting to have a hysterectomy. Patient organisation submission for relugolix CT noted the need for ‘equality of esteem’ with ‘men’s’ conditions. For example, prostatectomies are rare unless there is progressive cancer. But removal of the uterus and other reproductive organs is common and often the only option because of a lack of other treatment choices.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

British Fibroid Trust resources

- UF FAQs: http://www.britishfibroidtrust.org.uk/Fib_info/fibroid
- Treatment summary information: http://www.britishfibroidtrust.org.uk/Fib_info
- Treatment factsheets: http://www.britishfibroidtrust.org.uk/Resources/factsheets

External resources

- NHS website: https://www.nhs.uk/conditions/fibroids/
- Practical information on prescriptions: https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/who-can-get-free-prescriptions/

Further information

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment – an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Adenomyosis – a condition that causes the lining of the womb (the endometrium) to bury into the muscular wall of the womb.

Bone mineral density (BMD) – is a measure of how strong your bones are. The more dense your bones, the stronger and less likely they are to break.

Double-blind – a clinical study where the patients being treated in the study and the researchers conducting the study do not know which of the study medicines the patient is receiving (e.g., they are unaware whether they are receiving linzagolix or placebo).

Full analysis set (FAS) – the FAS in the PRIMROSE 1 and 2 trials included all randomly assigned patients who received at least one dose of the trial drug and who did not meet the exclusion criteria for liver function or BMD based on the results of pre-treatment baseline assessments reported after Day 1 (patients who met these exclusion criteria were immediately withdrawn from the trial).

GnRH agonists – (gonadotropin-releasing hormone agonists) – a group of drugs given by injection, which reduce a woman's estrogen levels; these drugs are used to reduce the size of fibroids.

GnRH antagonists – (gonadotropin-releasing hormone antagonists) – a group of drugs, usually given by mouth to reduce the size and symptoms of UFs, by reducing estrogen levels.

Hormonal ABT – this stands for add-back therapy, and is a treatment to relieve menopause-like symptoms brought about by GnRH agonists/antagonists. It replaces hormones that are at a lower level due to these treatments.

Hysterectomy – A surgical operation to remove the uterus (womb). During a simple hysterectomy only the uterus and cervix are removed, during a total hysterectomy the uterus and cervix are removed along with the ovaries and fallopian tubes. To treat UFs, only a simple hysterectomy is usually required. It can be done through the vagina, through multiple small incisions (surgical cuts) in the abdomen (tummy) (keyhole surgery) or through a single large incision (open surgery).

Hysteroscopy – a procedure to examine the inside of the uterus (womb), that involves inserting a small telescope with a light at the end into the uterus through the vagina and cervix.

ICER – incremental cost-effectiveness ratio. Measure of the cost-effectiveness of a medicine against other treatments currently used to treat the condition.

Iron-deficiency anaemia – A low red blood cell count, caused by HMB or other blood loss; the most obvious symptoms are excessive tiredness and lack of energy.

Laparoscopy – a procedure to examine the organs in the abdomen (tummy), including the uterus (womb), that involves inserting a small telescope with a light at the end through a small cut in the abdomen.

Levonorgestrel intrauterine system (LNG-IUS) – plastic coil which is inserted into the uterus via the cervix that releases synthetic progesterone. It is used as a form of contraception and sometime to treat UFs.

Licence/Licensed – see **Marketing authorisation** (29).

Myomectomy – The surgical removal of a UF from the wall of the uterus (womb).

Marketing authorisation – permission to sell a medicine after the evidence around it (on safety, quality, and efficacy) has been assessed. This is different from NICE's appraisal of a medicine, which also considers whether the medicine is cost-effective for the NHS (29).

Open-label – a clinical study where both patients and researchers know what study medicine the patient is receiving (30).

Phase 3 – a clinical study that investigates how safe and efficacious a medicine is. The medicine will previously have been tested in Phase 1–2 studies, which test whether the medicine is safe enough to use in humans and whether it has an effect on the disease (31).

Placebo-controlled – when a patients in a clinical study receive either the medicine or a fake, dummy medicine (a placebo) in order to test the study medicine (29).

QALY – quality-adjusted life year. A measure of disease burden, including both the quality and quantity of life lived, used for the economic assessment of medicines.

Randomised – when patients in a clinical study are randomly assigned to a group in the trial (e.g., the group being given the medicine or the group being given a placebo) (29).

Relugolix CT – a fixed-dose combination tablet containing relugolix (a GnRH antagonist), and hormonal ABT (treatment to relieve menopause-like symptoms)

Uterine artery embolisation (UAE) – An interventional procedure that involves blocking the blood vessels supplying UFs so that the UFs shrink.

Uterine fibroids (UFs) – non-cancerous tumours of the uterus (womb).

Uterus – The female organ that holds and sustains a developing baby (foetus), also known as the womb.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Linzagolix SPC [Internet]. EMA; 2023 [cited 2023 May 23]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/yselty

2. Dababou S, Garzon S, Laganà AS, Ferrero S, Evangelisti G, Noventa M, et al. Linzagolix: a new GnRH-antagonist under investigation for the treatment of endometriosis and uterine myomas. Expert Opin Investig Drugs. 2021 Sep 2;30(9):903–11.

3. Williams ARW. Uterine fibroids – what's new? F1000Research. 2017 Dec 7;6:2109.

4. Al-Hendy A, Myers ER, Stewart E. Uterine Fibroids: Burden and Unmet Medical Need. Semin Reprod Med. 2017 Nov;35(6):473–80.

5. Leyland N, Leonardi M, Murji A, Singh SS, Al-Hendy A, Bradley L. A Call-to-Action for Clinicians to Implement Evidence-Based Best Practices When Caring for Women with Uterine Fibroids. Reprod Sci Thousand Oaks Calif. 2022 Apr;29(4):1188–96.

6. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update. 2016 Nov 20;22(6):665–86.

7. Hunsche E, Rakov V, Scippa K, Witherspoon B, McKain L. The Burden of Uterine Fibroids from the Perspective of US Women Participating in Open-Ended Interviews. Womens Health Rep. 2022 Mar 4;3(1):286–96.

8. Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. BMC Womens Health. 2012 Mar 26;12(1):6.

9. nhs.uk [Internet]. 2017 [cited 2022 Sep 29]. Fibroids - Diagnosis. Available from: https://www.nhs.uk/conditions/fibroids/diagnosis/

10. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. Int J Gynecol Obstet. 2020;149(1):3–9.

11. Marsh EE, Al-Hendy A, Kappus D, Galitsky A, Stewart EA, Kerolous M. Burden, Prevalence, and Treatment of Uterine Fibroids: A Survey of U.S. Women. J Womens Health 2002. 2018 Nov;27(11):1359–67.

12. Soliman AM, Margolis MK, Castelli-Haley J, Fuldeore MJ, Owens CD, Coyne KS. Impact of uterine fibroid symptoms on health-related quality of life of US women: evidence from a cross-sectional survey. Curr Med Res Opin. 2017 Nov 2;33(11):1971–8.

13. McWilliams MM, Chennathukuzhi VM. Recent Advances in Uterine Fibroid Etiology. Semin Reprod Med. 2017 Mar;35(2):181–9.

14. Borah BJ, Nicholson WK, Bradley L, Stewart EA. The impact of uterine leiomyomas: a national survey of affected women. Am J Obstet Gynecol. 2013 Oct;209(4):319.e1-319.e20.

15. O'Sullivan AK, Thompson D, Chu P, Lee DW, Stewart EA, Weinstein MC. Cost-effectiveness of magnetic resonance guided focused ultrasound for the treatment of uterine fibroids. Int J Technol Assess Health Care. 2009 Jan;25(1):14–25.

16. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. The Lancet. 2011 Oct 15;378(9800):1396–407.

17. NICE NG88. HMB: assessment and management. 2018 Mar 14 [cited 2022 Sep 22]; Available from: https://www.nice.org.uk/guidance/ng88/resources/heavy-menstrual-bleeding-assessment-and-management-pdf-1837701412549

18. Gedeon Richter Limited. NICE Single technology appraisal. Relugolix with oestradiol and norethisterone acetate for treating uterine fibroids [ID3842; GID-TA10734]. Available at: https://www.nice.org.uk/guidance/ta832 (Last accessed: 3 April 2022). 2021.

19. Ryeqo SPC [Internet]. EMA; 2023 [cited 2023 Jul 4]. Available from: https://www.ema.europa.eu/en/documents/product-information/ryeqo-epar-product-information_en.pdf

20. Fraser IS, Mansour D, Breymann C, Hoffman C, Mezzacasa A, Petraglia F. Prevalence of heavy menstrual bleeding and experiences of affected women in a European patient survey. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 2015 Mar;128(3):196–200.

21. Donnez J, Taylor HS, Stewart EA, Bradley L, Marsh E, Archer D, et al. Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. The Lancet. 2022 Sep 17;400(10356):896–907.

22. Data on File: PRIMROSE 3 CSR. 2023 Mar.

23. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol. 2002 Feb;99(2):290–300.

24. nhs.uk [Internet]. 2017 [cited 2022 Sep 13]. Fibroids. Available from: https://www.nhs.uk/conditions/fibroids/

25. Lukes AS, Baker J, Eder S, Adomako TL. Daily menstrual blood loss and quality of life in women with heavy menstrual bleeding. Womens Health Lond Engl. 2012 Sep;8(5):503–11.

26. Lukes AS, Muse K, Richter HE, Moore KA, Patrick DL. Estimating a meaningful reduction in menstrual blood loss for women with heavy menstrual bleeding. Curr Med Res Opin. 2010 Nov;26(11):2673–8.

27. Linzagolix EPAR [Internet]. 2022 Jul [cited 2022 Dec 28]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/yselty

28. NICE. Guide to the methods of technology appraisal. Available Httpswwwniceorgukprocesspmg36 Last Accessed 01042022. 2022;

29. NICE [Internet]. NICE; [cited 2023 Feb 11]. Glossary. Available from: https://www.nice.org.uk/glossary?letter=b

30. Definition of open label study - NCI Dictionary of Cancer Terms - NCI [Internet]. 2011 [cited 2023 Feb 11]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/open-label-study

31. National Institute on Aging [Internet]. [cited 2023 Feb 11]. What Are Clinical Trials and Studies? Available from: https://www.nia.nih.gov/health/what-are-clinical-trials-and-studies

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190]

Response to clarification questions

October 2023

File name	Version	Contains confidential information	Date
ID6190 Linzagolix_Response to clarification questions_[CON]	1.0	No	10/10/2023

Section A: Clarification on effectiveness data

Clinical documents

A1. In the European Public Assessment Report (EPAR) some concerns are noted relating to "potential different versions of the Clinical Study Reports (CSRs) for the pivotal studies, apparent discrepancies in treatment-emergent adverse events (TEAEs), and some miscoding of reasons for treatment discontinuation/trial withdrawal". We appreciate that these concerns were resolved during the European regulatory process. However, please would you confirm that all CSRs provided for the PRIMROSE trials are the latest, corrected, versions.

Theramex confirms that all the CSRs submitted are the latest and final versions. Please note that 'Data on File PRIMROSE 2 CSR Week 24, 2020 Oct..pdf' was included in the reference pack in error – but it has not been cited in the submission documents. 'Data on File PRIMROSE 2 CSR Week 52, v2.0. 2021 May..pdf' is the latest version of data for PRIMROSE 2 for Week 24 and Week 52 data.

A2. Please provide unredacted trial protocols for PRIMROSE 1 and PRIMROSE 2 (the PRIMROSE 1 protocol is included as Appendix 2 of Donnez et al. 2022 but is a redacted version).

Please refer to the following documents included with this response:

- 16-OBE2109-008_Working Protocol_v8.0_Amend07_12May2020_Final
- 16-OBE2109-009_WorkingProtocol_v6.0_Amend10_27Nov2019

A3. Statistical analysis plans (SAPs) have been provided for the pooled analysis only. Please provide the individual SAPs for PRIMROSE 1 and PRIMROSE 2.

Please refer to the following documents included with this response:

- PRIMROSE 1_16-OBE2109-008_Statistical-Analysis-Plan_Final Version 8.0_signed

- PRIMROSE 2_16-OBE2109-009_Statistical-Analysis-Plan_V5.0 2020-11-06 clean

Pivotal trials

A4. Please explain the purpose of the following treatment switches in the PRIMROSE 1 and PRIMROSE 2 trials. Do these regimens represent therapy scenarios envisaged in clinical practice?

(a) **The switch from placebo to 200mg linzagolix + add-back therapy (ABT) in both PRIMROSE trials after 24 weeks.**

(b) **The switch from linzagolix 200mg to linzagolix 200mg + ABT in both PRIMROSE trials after 24 weeks.**

(a) The switch from placebo to 200 mg linzagolix + add-back therapy (ABT) after 24 weeks in both PRIMROSE trials was a measure taken to support study subjects who received placebo to continue therapy for 24 weeks and therefore avoid high discontinuation rates in that arm of the trials.

(b) The switch from linzagolix 200 mg to linzagolix 200 mg + ABT is consistent with the product label that states that 200 mg alone should be limited to a treatment duration of 24 weeks. If a patient requires continuation of the 200 mg dose beyond 24 weeks, ABT should be administered concomitantly, to avoid hypoestrogenic side effects, such as bone mineral density (BMD) loss.

A5. Please clarify the following aspects of masking/blinding in the PRIMROSE trials:

(a) Were the outcome assessors and statistical data analysts masked to the patient groups in PRIMROSE 1 and PRIMROSE 2?

(b) Why was PRIMROSE 1 unmasked earlier (week 24) than PRIMROSE 2 (week 52)? (as stated in the trial publication, Donnez et al. 2022, page 898).

(c) What role did the study sponsor have in the data collection and analysis?

(a) PRIMROSE 1 trial was double-blinded (see Section 9.4.6 of the PRIMROSE 1 Week 24 CSR).[1] The Sponsor and study team were only unblinded after all subjects had completed the first treatment period (Week 24) and the database had been locked. Importantly, the Investigator and the subject were fully blinded until the trial was complete and the database was locked.

In PRIMROSE 2, an analysis of the Week 24 data, including the primary endpoint and bone mineral density (BMD) endpoint, was performed after all subjects had completed Week 24 or terminated the trial. This analysis was performed by an unblinded team that was not involved in the conduct, randomisation, interpretation of the results, or reporting of the trial. Information provided to the Sponsor and the study team concerning this analysis was restricted to prevent identification of individual subjects.

Subsequently, the Sponsor and study team was unblinded at the time of the database lock for the Week 52 analysis. Importantly, however, the Investigator and the subject were fully blinded until the trial was complete. Thus, treatment allocation, individual progesterone (P4) and estradiol (E2) levels and alkaline haematin (AH) results (as of Study Day 1) were not communicated to the Investigators or subjects until after the database lock.

As the primary endpoint of reduction of menstrual bleeding was based on the collection of menstrual material and assessed by the central laboratory (blinded to study treatment), and key secondary endpoints such as amenorrhoea, time to menstrual blood loss, number of days of bleeding, haemoglobin levels and other endpoints were hard endpoints that were assessed by the central laboratory or by the subject's bleeding profile, the unblinding of the Sponsor at Week 24 (PRIMROSE 1) and Week 52 (PRIMROSE 2) was considered to have no impact on the trial results.

(b) The PRIMROSE 2 trial was conducted mainly in Europe (91% of randomly assigned subjects from 72 European clinical sites, versus 5% of randomly assigned subjects from 23 clinical sites in the US), and subject recruitment was more rapid than in the PRIMROSE 1 trial. As the primary and key secondary

endpoints were assessed at Month 6, and the Month 12 data concerned only maintenance of effect and long-term safety, the Dutch Medicines Evaluation Board (CBG-MEB) and Swedish Medical Products Agency (MPA) were consulted in 2020 to assess whether an initial submission with Week 24 and Week 52 data for PRIMROSE 2, and only Week 24 data for PRIMROSE 1, was acceptable at initial Marketing Authorisation Application, with the later provision of PRIMROSE Week 52 data during the Marketing Authorisation process. As the number of subjects met ICH E1 criteria for exposure to 6 months and 12 months of linzagolix (E 1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (europa.eu), both Agencies agreed to this proceeding.

(c) The Sponsor contracted several CROs; these are detailed in Section 6 of the CSRs,[1,2] including the respective responsibilities for each. Data collection and monitoring was performed by Covance Inc, and data management and analysis was performed by Cytel Inc. The Sponsor managed these CROs. Decisions on protocol deviations were performed prior to unblinding of the data.

A6. Please clarify whether the PRIMROSE 3 trial has been completed (the PRIMROSE 3 CSR states that the "last subject completed" on 19th September 2022 but it is unclear whether "completed" refers to the specific analysis reported in the CSR or to the whole trial). If the trial is ongoing, please clarify when the final results will be available.

The PRIMROSE 3 trial is completed, and the final CSR was provided in the NICE reference pack.[3]

A7. The PRIMROSE trials provide a maximum duration of efficacy outcome assessments of 52 weeks, although most of the efficacy outcomes reported in the CS are for assessments at 24 weeks. According to the Summary of Product Characteristics (SmPC), linzagolix may be used for more than one year in clinical practice (subject to regular bone mineral density [BMD] monitoring). Given the limited duration of clinical efficacy evidence reported in the CS, please explain the rationale for concluding that linzagolix is efficacious beyond 52 weeks in clinical practice.

The number of patients exposed and the duration of treatment in the PRIMROSE studies, as well as the intended indication for the treatment of uterine fibroids, had

been discussed with the Dutch Medicines Evaluation Board (CBG-MEB) and Swedish Medical Products Agency (MPA) prior to initiating the PRIMROSE studies and fulfils the requirement of the ICH guidelines E8 (General considerations for clinical studies) E1 (Population Exposure: The Extent of Population Exposure to Assess Clinical Safety).

Linzagolix is a selective, non-peptide small molecule GnRH receptor antagonist, that binds competitively to GnRH receptors in the pituitary gland and inhibits endogenous GnRH signalling.[4,5] This leads to dose-dependent suppression of serum luteinising hormone and follicle-stimulating hormone, which then leads to a dose-dependent reduction in serum estradiol (E2) and progesterone.[4,5] The onset of action is rapid,[5] treatment effect was maintained over 52 weeks, and dose-dependent E2 suppression is expected to continue as long as treatment is maintained. Efficacy is expected to be durable throughout long-term treatment with linzagolix, and there is no biological reason to suggest that efficacy will decrease over time provided that E2 suppression is maintained, because it is well known that fibroids are hormone-dependent benign tumours.

Relugolix CT, which has a similar mechanism of action to linzagolix, has 2-year data from its Phase 3 LIBERTY randomised withdrawal study.[6] This shows that relugolix CT has a durable effect in maintaining low MBL volume in women with symptomatic UF over 2 years.[6] At Week 104, 69.8% of women on relugolix CT maintained MBL <80 mL versus 11.8% in the placebo group ($p<0.0001$).[6] The proportion of women who achieved or maintained amenorrhoea was 58.3% for relugolix CT versus 10.6% for placebo at Week 104 ($p<0.0001$).[6] It is expected that linzagolix will similarly maintain efficacy when taken long-term.

A8. CS section B.2.12.2.2 states that the alkaline haematin (AH) method for assessing menstrual blood loss (MBL) may have contributed to the placebo effect in the PRIMROSE trials (32% placebo-responder rate in the pooled placebo arms) and that this placebo responder rate is similar to other studies. However, we note that a similarly pronounced placebo effect was not evident for MBL in the LIBERTY trials of relugolix CT (Al-Hendy et al. 2021; https://doi.org/10.1056/NEJMoa2008283). Please explain this discrepancy.

Although the LIBERTY trials[7] used the same primary endpoint as the PRIMROSE trials, there were differences in blood collection and the way that menstrual blood loss was analysed, particularly with respect to missing data. As described in the LIBERTY trial protocols,[7] (Section 6.8.1.1 of the protocol in the appendix), the collection of menstrual protection products was performed once monthly at study visits, as this was very convenient for study subjects. As described in Section 6.3.1.1 of the PRIMROSE 1 and 2 trial protocols,[8,9] the sanitary products had to be received by the laboratory (a different laboratory from the one used in the LIBERTY trials) within 3 weeks of collection. The subject was instructed to return the collection containers and the transportation box to the Investigator's site either once it was full or after a collection period of a maximum of 12 days. This suggests that subjects in the PRIMROSE trials had a higher burden than the subjects who participated in the LIBERTY trials, as they had to bring back the menstrual protection pads to the laboratory outside of the study visits. This difference in methodology is likely to have contributed to a higher burden in the placebo groups of the PRIMROSE trials.

In the LIBERTY trials, the primary endpoint was referred to as responder rate and was derived on the basis of the total MBL volume measured at the Week 24/EOT visit window, taking into consideration the subject's compliance with return of feminine sanitary products and completion of the eDiary (see Section 7.3.2 and Section 7.3.4 of the SAP for details).[7] For the evaluation of the primary endpoint, missing data handling rules were implemented for deriving responder status at Week 24/EOT as described in Section 7.3.5 of the SAP. These rules stated that for subjects with <4 weeks of treatment who withdrew from the study prematurely due to lack of efficacy or to undergo surgical intervention for UFs were considered as non-responders. For subjects with a feminine sanitary product return rate of 100%, responder status was determined based on the observed MBL volume; **for subjects**

who had incomplete feminine product collection, responder status was derived based on either imputed or observed MBL volume (those with an MBL volume ≥80 mL or <50% reduction from baseline were considered to be non-responders; those with an MBL volume <80 mL and ≥50% reduction from baseline were imputed for partial or complete missing MBL volume; and for subjects who did not return a feminine product collection, responder status was determined depending on the reason reported on the Feminine Product Collection eCRF).

In the PRIMROSE trials, if there was no data from the AH method from the central laboratory for any particular day; it was assumed that there was no bleeding/zero blood loss on that day. Subjects who discontinued prematurely due to lack of efficacy or adverse events or who underwent operative or radiological interventions for UFs were considered to be non-responders. In order to consider all randomised and treated subjects in the analysis, the assessment of the primary endpoint for subjects who discontinued prior to Week 24 or at Week 24 for a reason other than lack of efficacy or adverse events or who underwent operative or radiological interventions for UFs was based on the results from the last 28 days prior to the last daily diary entry. Subjects who had less than 28 days of data were counted as non-responders (see Section 4.6.1.1 of the PRIMROSE SAPs).[10,11]

Therefore, in the PRIMROSE trials, any missing return of menstrual blood loss was considered as ‘no bleeding’ whereas in the LIBERTY trials, missing return of menstrual products was imputed. Notably, this difference in blood loss assessment leads to differences in responder rates, particularly in the placebo group where subjects typically did not stop bleeding and consequently were the subjects who were most likely to be non-compliant in returning their sanitary products for evaluation of menstrual bleeding.

Analysis of PRIMROSE trial outcomes

A9. Priority question. The Full analysis set (FAS) in PRIMROSE 1 and PRIMROSE 2 appears to approximate a per protocol population. Please explain why an intention to treat (ITT) analysis was not also conducted, as this would provide confidence in the robustness of the trial findings to missing data. Please provide an ITT analysis for PRIMROSE 1 and PRIMROSE 2 for the

primary and secondary outcomes, using conservative approaches for imputing missing data (e.g. assuming missing observations are non-responders, and/or using multiple imputation methods).

The reason Theramex preferred using the Full Analysis Set (FAS; N = 511 in PRIMROSE 1 and N = 501 in PRIMROSE 2) as defined in the SAPs in Section 3.1,[10,11] in preference to the FAS as initially planned in the protocol (FASPP),[12,13] which is equivalent to the ITT population (N = 526 in PRIMROSE 1 and N = 511 in PRIMROSE 2; see Table 1), was due to the exclusion of a small numbers of subjects who entered the trial without meeting all the inclusion criteria. For example:

- Fifteen subjects in PRIMROSE 1 and 10 subjects in PRIMROSE 2 met exclusion criteria 19 or 20, but the results of assessments to determine eligibility were only received after the subjects had received the study drug. These subjects did not meet the eligibility criteria for the trials and would not comprise the population of patients who would receive linzagolix in routine clinical practice.

- According to the protocol, and for logistical reasons (i.e. need for repeated scans; see Section 6.4.5 of the trial protocols), it was possible that subjects received their final baseline DXA assessment after the trial had started, not before. During the trial conduct, the FDA requested the Company include an additional exclusion criterion based on z-scores. When this additional exclusion criterion was implemented (Amendment 2), subjects who received their baseline DXA results after treatment start had to be excluded. As the exclusion criterion on z-scores was added at the request of the FDA, it was considered acceptable to exclude the few subjects with a baseline DXA result arriving after treatment start subjects – who had received only few days of study drug – from the FAS.

- Results of blood samples taken on Day 0 were received a few days after inclusion. In the unlikely event that after a normal screening blood sample, the subject demonstrated increased liver enzymes at Day 0 (and consequently met an exclusion criterion), it was decided to discontinue these subjects from the FAS.

Theramex considers that the FAS as determined in the SAPs and trial protocols is the most appropriate population to conduct the analyses. A general description of an ITT population is that it is considered to represent suitable subjects and to be reflective of what might be seen if the treatment was used in clinical practice. Given the very small number of subjects excluded due to the reasons above, and that the FAS is representative of the patients who would receive linzagolix in clinical practice, the Company believes that the FAS as defined in the PRIMROSE trials is the appropriate population for the analysis. Moreover, the MAIC analyses (reported in Appendix D.3.8 and Response A12) provide further reassurance by controlling for the possibility of any imbalances between treatment groups as they are adjusted for patients lost after randomisation.

For the above reasons, we believe that any attempt to impute missing endpoints for non-FAS patients would be inappropriate. Even if this analysis was conducted the Company believes that it would have minimal impact, and – moreover - potentially increase uncertainty rather than reduce it. As would be anticipated, given the double-blind nature of the trial, the number of patients excluded from the FAS is relatively evenly split between the four trial arms and, where baseline characteristics are available, these appear not to vary significantly according to whether patients were included in the FAS. A summary of patients, according to whether they are on the FAS of not, is provided below for PRIMROSE 1 and 2 pooled.

Simple imputation of missing endpoints (e.g. no change from baseline) would have a similar impact across all arms, and so relative effects would be minimally changed in the case of continuous variables. Multiple imputation to model missing values would be impractical due to the paucity of data for non-FAS patients.

Table 1: PRIMROSE 1 and 2 FAS and FASPP set

PRIMROSE 1	**Placebo**	**100 mg**	**100 mg + ABT**	**200 mg**	**200 mg + ABT**	**Total**
FAS	N = 103	N = 94	N = 107	N = 105	N = 102	N = 511
FASPP	N = 104	N = 100	N = 109	N = 107	N = 106	N = 526
PRIMROSE 2	**Placebo**	**100 mg**	**100 mg + ABT**	**200 mg**	**200 mg + ABT**	**Total**
FAS	N = 102	N = 97	N = 101	N = 103	N = 98	N = 501
FASPP	N = 105	N = 99	N = 102	N = 104	N = 101	N = 511

Abbreviations: ABT, add-back therapy; FAS, full analysis set; FASPP, FAS as initially planned in the protocol.

Table 2: Summary of selected baseline characteristics for FAS PP patients according to whether in the FAS (Pooled data)

Characteristic	FAS	Placebo	100 mg	100 mg + ABT	200 mg	200 mg + ABT
Overall	N	N = 4	N = 8	N = 3	N = 3	N = 7
	Y	N = 205	N = 191	N = 208	N = 208	N = 200
Age	N	N = 4 43.5 (4.7)	N = 8 39.2 (5.4)	N = 3 41.3 (3.5)	N = 3 42.3 (8.1)	N = 7 43.9 (4.6)
	Y	N = 205 42.5 (5.5)	N = 191 42.3 (5.7)	N = 208 42.1 (5.6)	N = 208 42.0 (6.0)	N = 200 42.4 (5.4)
Black	N	N = 4 25%	N = 8 38%	N = 3 33%	N = 3 33%	N = 7 29%
	Y	N = 205 34%	N = 191 34%	N = 208 36%	N = 208 36%	N = 200 33%
BMI	N	N = 4 26.6 (6.0)	N = 8 30.7 (6.4)	N = 3 31.4 (5.6)	N = 3 28.9 (2.2)	N = 7 27.6 (4.9)
	Y	N = 205 29.5 (6.7)	N = 191 30.3 (7.2)	N = 208 30.1 (6.8)	N = 208 29.7 (6.6)	N = 200 29.9 (7.1)
Fibroids >= 2cm	N	N = 0 -%	N = 0 -%	N = 0 -%	N = 0 -%	N = 0 -%
	Y	N = 205 98%	N = 191 98%	N = 208 98%	N = 208 97%	N = 200 98%
Menstrual blood loss	N	N = 4 233 (87)	N = 8 247 (139)	N = 3 112 (26)	N = 3 153 (52)	N = 7 182 (79)
	Y	N = 205 206 (120)	N = 191 221 (141)	N = 208 198 (104)	N = 208 211 (128)	N = 200 204 (130)
Haemoglobin	N	N = 4 12.1 (1.0)	N = 8 12.0 (1.4)	N = 3 11.9 (0.8)	N = 3 12.1 (2.4)	N = 7 10.7 (2.1)
	Y	N = 205 11.3 (1.6)	N = 191 10.9 (1.7)	N = 208 10.9 (1.9)	N = 208 11.1 (1.8)	N = 200 11.1 (1.7)

Table presents proportion for binary variables or mean (standard deviation) for continuous variables.

Network meta-analyses (NMAs)

A10. Priority question. The PRIMROSE 1 and PRIMROSE 2 trials differ in some important respects as noted in the EPAR (e.g. race, weight, BMI, proportion anaemic, dropout rates). Following the methodological approach reported in CS sections B.2.9.5 and B.2.9.6, please provide separate NMAs for PRIMROSE 1 and PRIMROSE 2 for the 24-week assessments of the primary and secondary outcomes.

Results from separate NMAs for PRIMROSE 1 and PRIMROSE 2 are presented in Table 3 to Table 8 (alongside the pooled PRIMROSE NMA results reported in the CS), for the outcomes presented in Document B Section B.2.9.6.

Table 3: Fixed-effects network meta-analysis for response

Median odds ratio (95% CrI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Placebo	Relugolix CT	Placebo	Relugolix CT	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted]					
Linzagolix 100 mg + ABT	[redacted]					
Linzagolix 200 mg	[redacted]					
Linzagolix 200 mg + ABT	[redacted]					

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 4: Fixed-effects network meta-analysis for percentage change in menstrual blood loss

Median relative effect (95% CrI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Placebo	Relugolix CT	Placebo	Relugolix CT	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted]					
Linzagolix 100 mg + ABT	[redacted]					
Linzagolix 200 mg	[redacted]					
Linzagolix 200 mg + ABT	[redacted]					

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 5: Fixed-effects network meta-analysis for pain

Median odds ratio (95% CrI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Placebo	Relugolix CT	Placebo	Relugolix CT	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 6: Fixed-effects network meta-analysis for percentage change in primary fibroid volume

Median relative effect (95% CrI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Placebo	Relugolix CT	Placebo	Relugolix CT	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 7: Fixed-effects network meta-analysis for percentage change in haemoglobin

Median relative effect (95% CrI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Placebo	Relugolix CT	Placebo	Relugolix CT	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 8: Fixed-effects network meta-analysis for change in uterine fibroid symptom and quality of life (UFS-QoL) total score

Median relative effect (95% CrI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Placebo	Relugolix CT	Placebo	Relugolix CT	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

(a) For each NMA please conduct a sensitivity analysis using the randomised (i.e. intention to treat) population to confirm robustness of the full analysis set results to missing data. For any missing data imputations please use appropriate conservative methods (e.g. multiple imputation, non-response assumption).

As described in response to Question A9, the FAS as determined in the SAPs and trial protocols is considered the most appropriate population to conduct the analyses.

(b) The credible intervals for the reported NMA outcomes are generally wide making it unclear for some of the drug arm and outcome combinations whether linzagolix has similar clinical efficacy to relugolix CT. To assist interpretation of clinical similarity, please provide an estimate of the probability of treatment effect for each NMA outcome.

To assist interpretation, posterior probabilities of each treatment having a given rank within the network are presented in Appendix 1.

(c) Please provide the full R / Stan code and the input data used for each NMA.

R code used for each NMA is presented in Appendix 2.

A11. Priority question. The NICE guidance for relugolix CT (TA832) states that the committee was concerned that the most robust methods to characterise uncertainty in the comparative effectiveness of relugolix CT compared with GnRH agonists may not have been used. There is therefore a risk of propagating unresolved uncertainty around the similarity of GnRH analogues if linzagolix is compared solely to relugolix CT without considering the other relevant comparators.

Please conduct NMAs, separately for PRIMROSE 1 and PRIMROSE 2, that extend the network shown in CS Appendix Figure 5 to include all GnRH analogues relevant to the NICE scope so that the effectiveness of linzagolix can be compared against all relevant comparators.

Results from pooled and separate NMAs for PRIMROSE 1 and PRIMROSE 2, when extending the network to include GnRH agonists, are presented in Table 9 to Table 11.

An extended network including the PRIMROSE, LIBERTY, and PEARL studies could be formed; however, based on the available published outcomes, only the response endpoint could be assessed (Table 9). A network was considered with only the PRIMROSE (linzagolix) and PEARL (GnRH agonist) studies, for which total fibroid volume (Table 10) and haemoglobin (Table 11) could be considered.

With regard to the ITC for response, it is important to note that the methods of recording MBL differed between the studies in the network. Differences between the PRIMROSE and LIBERTY studies are highlighted in the response to question A8 above, however there are further limitations which exist across the wider network. In the PRIMROSE and LIBERTY studies, MBL was measured using the AH technique, which is perceived as the gold-standard measure.[7,14,15] Yet, in PEARL II, MBL was assessed using the PBAC method.[16] When using the AH technique, patients must collect, store and then submit all their used feminine products for MBL analysis, whereas the PBAC method involves a visual scoring system whereby patients can directly record the number of used feminine items and the degree to which they are bloodstained.[15] The PBAC method is based on the subjective response of patients as opposed to the direct assessment of the volume of menstrual blood loss by comparing haematin from menstrual products, as such the comparability of the two methods is limited. This difference in measurement methods (and sourcing an appropriate conversion between the PBAC and AH) was the predominant reason an NMA was not conducted on response measures within the TA832 appraisal to compare relugolix with GnRH agonists (as cited by the company in the response to CQs Question A12 and A13).[17] Instead, a simple Bucher comparison was provided by the company, from which, the ERG and committee in TA832 concluded that relugolix CT and GnRH agonists were likely to be equally effective in reducing menstrual blood loss volume.

To address the questions raised by the EAG, despite differences in methods of assessing MBL (and the corresponding limitations), the requested NMA has been conducted, however results should be interpreted with considerable caution.

Table 9: Fixed-effects network meta-analysis for response

Median odds ratio (95% CrI)	Placebo	Leuprolide acetate	Relugolix CT
PRIMROSE 1 & 2 (Pooled)			
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]
PRIMROSE 1			
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]
PRIMROSE 2			
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 10: Fixed-effects network meta-analysis for total fibroid volume

Median relative effect (95% CrI)	Placebo	Leuprolide acetate	Relugolix CT
PRIMROSE 1 & 2 (Pooled)			
Linzagolix 100 mg	[redacted]	[redacted]	-
Linzagolix 100 mg + ABT	[redacted]	[redacted]	-
Linzagolix 200 mg	[redacted]	[redacted]	-
Linzagolix 200 mg + ABT	[redacted]	[redacted]	-
PRIMROSE 1			
Linzagolix 100 mg	[redacted]	[redacted]	-
Linzagolix 100 mg + ABT	[redacted]	[redacted]	-
Linzagolix 200 mg	[redacted]	[redacted]	-
Linzagolix 200 mg + ABT	[redacted]	[redacted]	-
PRIMROSE 2			
Linzagolix 100 mg	[redacted]	[redacted]	-
Linzagolix 100 mg + ABT	[redacted]	[redacted]	-
Linzagolix 200 mg	[redacted]	[redacted]	-

Linzagolix 200 mg + ABT	[redacted]	[redacted]	-

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 11: Fixed-effects network meta-analysis for haemoglobin

Median relative effect (95% CrI)	Placebo	Leuprolide acetate	Relugolix CT
PRIMROSE 1 & 2 (Pooled)			
Linzagolix 100 mg	[redacted]	[redacted]	-
Linzagolix 100 mg + ABT	[redacted]	[redacted]	-
Linzagolix 200 mg	[redacted]	[redacted]	-
Linzagolix 200 mg + ABT	[redacted]	[redacted]	-
PRIMROSE 1			
Linzagolix 100 mg	[redacted]	[redacted]	-
Linzagolix 100 mg + ABT	[redacted]	[redacted]	-
Linzagolix 200 mg	[redacted]	[redacted]	-
Linzagolix 200 mg + ABT	[redacted]	[redacted]	-
PRIMROSE 2			
Linzagolix 100 mg	[redacted]	[redacted]	-
Linzagolix 100 mg + ABT	[redacted]	[redacted]	-

Linzagolix 200 mg	[redacted]	[redacted]	-
Linzagolix 200 mg + ABT	[redacted]	[redacted]	-

Abbreviations: ABT, add-back therapy; CrI, credible interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

(a) For each NMA please conduct a sensitivity analysis using the randomised (i.e. intention to treat) population to confirm robustness of the full analysis set results to missing data.

As described in response to Question A9, the FAS as determined in the SAPs and trial protocols is considered the most appropriate population to conduct the analyses.

(b) Please provide an estimate of the probability of treatment effect for each NMA outcome.

Posterior probabilities of each treatment having a given rank within the network are presented in Appendix 3.

(c) Please provide the full R / Stan code and the input data used for each NMA.

R code used for each NMA is presented in Appendix 4.

Matching-adjusted indirect comparisons (MAICs)

A12. Priority question. To account for the differences between the PRIMROSE 1 and PRIMROSE 2 trials, please provide separate MAIC analyses for PRIMROSE 1 and PRIMROSE 2 for the 24-week assessments of the same outcomes as reported in CS Appendix D.3.8.

Results from separate MAICs for PRIMROSE 1 and PRIMROSE 2, alongside the Pooled MAIC results, are presented in Table 12 to Table 17, for the same outcomes presented in CS Appendix D.3.8.

Table 12: Matching adjusted indirect comparison of response, linzagolix versus relugolix CT anchored via placebo

Odds ratios (95% CI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Before weighting	After weighting	Before weighting	After weighting	Before weighting	After weighting
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CI, confidence interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 13: Matching adjusted indirect comparison of the percentage change in menstrual blood loss, linzagolix versus relugolix CT anchored via placebo

Mean difference (95% CI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Before weighting	After weighting	Before weighting	After weighting	Before weighting	After weighting
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CI, confidence interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 14: Matching adjusted indirect comparison of pain, linzagolix versus relugolix CT anchored via placebo

Odds ratios (95% CI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Before weighting	After weighting	Before weighting	After weighting	Before weighting	After weighting
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CI, confidence interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 15: Matching adjusted indirect comparison of the percentage change in primary fibroid volume, linzagolix versus relugolix CT anchored via placebo

Mean difference (95% CI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Before weighting	After weighting	Before weighting	After weighting	Before weighting	After weighting
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CI, confidence interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 16: Matching adjusted indirect comparison of the percentage change in haemoglobin, linzagolix versus relugolix CT anchored via placebo

Mean difference (95% CI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Before weighting	After weighting	Before weighting	After weighting	Before weighting	After weighting
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CI, confidence interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 17: Matching adjusted indirect comparison of the change in uterine fibroid symptom and quality of life (UFS QoL) total score, linzagolix versus relugolix CT anchored via placebo

Mean difference (95% CI)	PRIMROSE 1 & 2 (Pooled)		PRIMROSE 1		PRIMROSE 2	
	Before weighting	After weighting	Before weighting	After weighting	Before weighting	After weighting
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CI, confidence interval; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

(a) For each MAIC please provide evidence that the key prognostic variables and effect modifiers have been accounted for where possible and that the population characteristics are adequately matched.

Pre- and post-matched baseline characteristics are presented in Table 18 (PRIMROSE 1 and 2), Table 19 (PRIMROSE 1), and Table 20 (PRIMROSE 2).

Table 18: Summary of baseline characteristics in PRIMROSE 1 and 2, matched on the proportion of black patients, menstrual blood loss, haemoglobin, total fibroid volume, and uterine volume

Characteristic (matched on - ✓)			PRIMROSE 1 and 2 – before weighting						PRIMROSE 1 and 2 – after weighting						LIBERTY 1 and 2	
			Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg	Linzagolix 200 mg + ABT	p-value	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg	Linzagolix 200 mg + ABT	p-value	Placebo	Relugolix CT
N/WSS; ESS			205	191	208	208	200		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		257	254
Age (years)			42.5	42.3	42.1	42.0	42.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42.0	42.5
BMI (kg/m^2)			29.5	30.3	30.1	29.7	29.9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32.2	31.3
Race	White		65.4%	63.4%	61.1%	63.0%	65.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40.9%	48.0%
	Black	✓	34.1%	33.5%	36.1%	35.6%	33.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54.1%	47.6%
Ethnicity (Hispanic or Latino)			12.7%	10.5%	11.5%	13.0%	11.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21.0%	20.5%
Menstrual blood loss (mL)		✓	205.9	221.1	197.6	210.6	203.5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	215.6	242.9
Menstrual blood loss <225mL			71.7%	66.5%	71.6%	69.7%	74.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	66.5%	64.6%
Haemoglobin (g/dL)		✓	11.3	10.9	10.9	11.1	11.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11.2	11.2
Total fibroid volume (cm^3)		✓	95.8 (N=200)	110.2 (N=182)	103.9 (N=202)	88.2 (N=204)	97.8 (N=196)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73.0	72.8
Uterine volume (cm^3)		✓	338.3 (N=203)	351.4 (N=185)	320.6 (N=207)	321.4 (N=208)	311.2 (N=198)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	402.8	383.4
Pain score ≥4			74.4% (N=203)	80.4% (N=184)	79.4% (N=204)	79.0% (N=200)	72.4% (N=196)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73.9%	69.7%
Bone mineral density (g/cm^3)	Lumbar spine		1.19 (N=189)	1.19 (N=179)	1.19 (N=191)	1.19 (N=194)	1.18 (N=179)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.24	1.19
	Total hip		1.06 (N=192)	1.07 (N=184)	1.07 (N=194)	1.06 (N=194)	1.07 (N=184)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.07	1.04

									[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			

Abbreviations: ABT, add-back therapy; BMI, body mass index; dL, decilitre; ESS, effective sample size; g, gram; kg, kilogram; m, meter; mg, milligram; mL, millilitre; relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate); WSS, weighted sample size

Table 19: Summary of baseline characteristics in PRIMROSE 1, matched on the proportion of black patients, menstrual blood loss, haemoglobin, total fibroid volume, and uterine volume

Characteristic (matched on - ✓)			PRIMROSE 1 – before weighting						PRIMROSE 1 – after weighting						LIBERTY 1 and 2	
			Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg	Linzagolix 200 mg + ABT	p-value	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg	Linzagolix 200 mg + ABT	p-value	Placebo	Relugolix CT
N/WSS; ESS			103	94	107	105	102		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		257	254
Age (years)			42.0	41.3	41.7	41.3	41.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42.0	42.5
BMI (kg/m^2)			32.2	33.3	32.7	32.4	33.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32.2	31.3
Race	White		35.9%	29.8%	29.9%	32.4%	35.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	40.9%	48.0%
	Black	✓	63.1%	63.8%	64.5%	64.8%	60.8%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54.1%	47.6%
Ethnicity (Hispanic or Latino)			22.3%	21.3%	19.6%	24.8%	20.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21.0%	20.5%
Menstrual blood loss (mL)		✓	195.0	197.0	202.2	204.6	194.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	215.6	242.9
Menstrual blood loss <225mL			75.7%	71.3%	69.2%	70.5%	73.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	66.5%	64.6%
Haemoglobin (g/dL)		✓	11.0	10.6	10.5	10.7	10.8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11.2	11.2
Total fibroid volume (cm^3)		✓	98.7 (N=98)	127.1 (N=88)	120.5 (N=101)	90.2 (N=102)	103.4 (N=99)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73.0	72.8
Uterine volume (cm^3)		✓	413.5 (N=101)	454.3 (N=91)	397.3 (N=106)	378.3 (N=105)	361.9 (N=101)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	402.8	383.4
Pain score ≥4			81.4% (N=102)	89.0% (N=91)	88.3% (N=103)	87.1% (N=101)	84.8% (N=99)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73.9%	69.7%

Bone mineral density (g/cm^3)	Lumbar spine		1.21 (N=90)	1.21 (N=84)	1.20 (N=96)	1.20 (N=96)	1.19 (N=86)								1.24	1.19
	Total hip		1.09 (N=93)	1.11 (N=89)	1.10 (N=98)	1.09 (N=96)	1.09 (N=91)								1.07	1.04

Abbreviations: ABT, add-back therapy; BMI, body mass index; dL, decilitre; ESS, effective sample size; g, gram; kg, kilogram; m, meter; mg, milligram; mL, millilitre; relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate); WSS, weighted sample size

Table 20: Summary of baseline characteristics in PRIMROSE 2, matched on the proportion of black patients, menstrual blood loss, haemoglobin, total fibroid volume, and uterine volume

Characteristic (matched on - ✓)			PRIMROSE 2 – before weighting						PRIMROSE 2 – after weighting						LIBERTY 1 and 2	
			Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg	Linzagolix 200 mg + ABT	p-value	Placebo	Linzagolix 100 mg	Linzagolix 100 mg + ABT	Linzagolix 200 mg	Linzagolix 200 mg + ABT	p-value	Placebo	Relugolix CT
N/WSS; ESS			102	97	101	103	98								257	254
Age (years)			42.9	43.4	42.5	42.7	43.1								42.0	42.5
BMI (kg/m^2)			26.8	27.4	27.2	26.8	26.8								32.2	31.3
Race	White		95.1%	95.9%	94.1%	94.2%	95.9%								40.9%	48.0%
	Black	✓	4.9%	4.1%	5.9%	5.8%	4.1%								54.1%	47.6%
Ethnicity (Hispanic or Latino)			2.9%	0.0%	3.0%	1.0%	1.0%								21.0%	20.5%
Menstrual blood loss (mL)		✓	216.8	244.5	192.8	216.8	212.7								215.6	242.9
Menstrual blood loss <225mL			67.6%	61.9%	74.3%	68.9%	74.5%								66.5%	64.6%
Haemoglobin (g/dL)		✓	11.7	11.2	11.4	11.6	11.3								11.2	11.2
Total fibroid volume (cm^3)		✓	93.1 (N=102)	94.3 (N=94)	87.3 (N=101)	86.1 (N=102)	92.1 (N=97)								73.0	72.8

Uterine volume (cm^3)		✓	263.8 (N=102)	251.7 (N=94)	240.1 (N=101)	263.5 (N=103)	258.5 (N=97)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	402.8	383.4
Pain score ≥4			67.3% (N=101)	72.0% (N=93)	70.3% (N=101)	70.7% (N=99)	59.8% (N=97)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73.9%	69.7%
Bone mineral density (g/cm^3)	Lumbar spine		1.17 (N=99)	1.17 (N=95)	1.17 (N=95)	1.17 (N=98)	1.18 (N=93)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.24	1.19
	Total hip		1.04 (N=99)	1.03 (N=95)	1.03 (N=96)	1.04 (N=98)	1.05 (N=93)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.07	1.04

Abbreviations: ABT, add-back therapy; BMI, body mass index; dL, decilitre; ESS, effective sample size; g, gram; kg, kilogram; m, meter; mg, milligram; mL, millilitre; relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate); WSS, weighted sample size

(b) Please provide the R code used for the MAIC analyses described in CS Appendix D.3.8.

R code used for the MAIC is presented in Appendix 5.

A13. Priority question. According to the Summary of Product Characteristics (SmPC), linzagolix may be used for more than one year in clinical practice, but the longest-term data available on the clinical efficacy of linzagolix is for 52 weeks. The design of the PRIMROSE 1 and PRIMROSE 2 trials does not permit an NMA comparing linzagolix against relugolix CT for 52-week outcome data and the CS instead focuses on 24-week outcomes. However, we believe unanchored MAIC analyses should be feasible for the 52-week outcomes, utilising the non-randomised relugolix CT arm from the LIBERTY Extension Study as the comparator.

Please conduct unanchored MAIC analyses, for PRIMROSE 1 and PRIMROSE 2 separately, to compare 52-week outcomes for linzagolix against 52-week outcomes for relugolix CT. Data are available from the linzagolix and linzagolix + ABT arms of PRIMROSE 1 and PRIMROSE 2 and from the relugolix CT arm (N=133) of the LIBERTY Extension Study (reported by Al-Hendy et al. 2022 (https://doi.org/10.1097/AOG.0000000000004988). Baseline characteristics and outcomes for this arm of the LIBERTY Extension Study can be found in the study publication and its appendices. Please conduct these analyses for the same outcomes as reported in CS Appendix D.3.8.

> **(a) (BMD) is an important safety outcome for assessments of GnRH analogues. Please include 52-week BMD outcomes in the MAICs if feasible. If not feasible, please explain why.**
>
> **(b) For each MAIC please provide evidence that the key prognostic variables and effect modifiers have been accounted for where possible and that the population characteristics are adequately matched.**
>
> **(c) Please provide the R code used for the MAIC analyses described in CS Appendix D.3.8.**

It has not been possible to perform the requested unanchored MAIC in the time available within the schedule, as this would require further data extraction, reassessment of weighting variables, derivation and examination of revised weights, and execution of weighted analyses. However, the Company also suggest that such an analysis would be of limited value and would most likely introduce further uncertainty as unanchored MAICs are considered to be a weaker form of evidence relative to anchored analyses. Nonetheless, a selection of unadjusted outcomes at 52 weeks are presented below as a crude comparison.

Table 21: Summary of naive (unweighted) outcomes at 52 weeks

Outcome	PRIMROSE trials				LIBERTY trials
	Linzagolix 100mg	Linzagolix 100mg + ABT	Linzagolix 200mg + ABT after 6 months	Linzagolix 200mg + ABT	Relugolix CT
PRIMROSE 1 & 2 (Pooled)	**N = 191**	**N = 208**	**N = 208**	**N = 200**	**N = 163**
Response	N = 140 56.4%	N = 144 91.0%	N = 163 80.4%	N = 149 89.3%	87.7%
Percentage change in menstrual blood loss	N = 140 -56.2 (3.92)	N = 144 -93.6 (3.86)	N = 163 -84.2 (3.63)	N = 149 -90.7 (3.80)	-89.9 (5.11)
Percentage change in primary fibroid volume	N = 90 -41.5 (10.38)	N = 95 -39.7 (10.41)	N = 91 -65.8 (6.04)	N = 107 -47.8 (8.50)	-18.3 (5.75)
Percentage change in haemoglobin	N = 37 20.8 (3.64)	N = 37 35.8 (3.64)	N = 33 36.9 (3.86)	N = 44 38.1 (3.35)	28.4 (3.03)
Change in uterine fibroid symptom and quality of life (UFS-QoL) total score	N = 101 18.5 (2.12)	N = 101 32.0 (2.12)	N = 103 29.0 (2.10)	N = 114 35.5 (1.99)	40.4 (2.65)
Percentage change in BMD (hip)	N = 93 -1.26 (0.34)	N = 87 -0.03 (0.35)	N = 91 -1.48 (0.34)	N = 95 0.23 (0.34)	-0.15 (0.29)
Percentage change in BMD (spine)	N = 92 -2.28 (0.32)	N = 83 -0.97 (0.34)	N = 91 -2.72 (0.32)	N = 93 -1.60 (0.32)	-0.80 (0.23)
PRIMROSE 1	**N = 94**	**N = 107**	**N = 105**	**N = 102**	**N = 163**
Response	N = 61 60.7%	N = 64 90.6%	N = 75 76.0%	N = 66 86.4%	87.7%
Percentage change in menstrual blood loss	N = 61 -55.2 (7.11)	N = 64 -89.8 (6.95)	N = 75 -77.7 (6.40)	N = 66 -87.0 (6.83)	-89.9 (5.11)
Percentage change in primary	N = 33	N = 27	N = 31	N = 38	-18.3 (5.75)

Outcome	PRIMROSE trials				LIBERTY trials
	Linzagolix 100mg	**Linzagolix 100mg + ABT**	**Linzagolix 200mg + ABT after 6 months**	**Linzagolix 200mg + ABT**	**Relugolix CT**
fibroid volume	-42.1 (24.81)	-29.1 (34.08)	-41.6 (25.84)	-37.8 (24.93)	
Percentage change in haemoglobin	N = 18 23.1 (5.11)	N = 20 27.0 (4.85)	N = 20 35.5 (4.85)	N = 24 35.5 (4.46)	28.4 (3.03)
Change in uterine fibroid symptom and quality of life (UFS-QoL) total score	N = 47 22.3 (3.45)	N = 36 35.2 (3.97)	N = 43 28.0 (3.63)	N = 44 39.6 (3.59)	40.4 (2.65)
Percentage change in BMD (hip)	N = 39 -1.74 (0.68)	N = 34 0.58 (0.73)	N = 39 -1.96 (0.68)	N = 36 0.86 (0.72)	-0.15 (0.29)
Percentage change in BMD (spine)	N = 38 -2.10 (0.52)	N = 30 0.08 (0.59)	N = 38 -2.25 (0.52)	N = 34 -0.85 (0.55)	-0.80 (0.23)
PRIMROSE 2	**N = 97**	**N = 101**	**N = 103**	**N = 98**	**N = 163**
Response	N = 79 53.2%	N = 80 91.3%	N = 88 84.1%	N = 83 91.6%	87.7%
Percentage change in menstrual blood loss	N = 79 -57.0 (3.98)	N = 80 -96.7 (3.96)	N = 88 -89.8 (3.77)	N = 83 -93.6 (3.88)	-89.9 (5.11)
Percentage change in primary fibroid volume	N = 57 -40.9 (8.95)	N = 68 -42.5 (7.99)	N = 60 -74.2 (3.81)	N = 69 -53.0 (6.47)	-18.3 (5.75)
Percentage change in haemoglobin	N = 19 18.3 (4.77)	N = 17 46.9 (5.04)	N = 13 36.5 (5.77)	N = 20 41.0 (4.65)	28.4 (3.03)
Change in uterine fibroid symptom and quality of life (UFS-QoL) total score	N = 54 16.0 (2.60)	N = 65 29.9 (2.37)	N = 60 29.8 (2.47)	N = 70 32.9 (2.29)	40.4 (2.65)
Percentage change in BMD (hip)	N = 54 -0.90 (0.33)	N = 53 -0.42 (0.33)	N = 52 -1.14 (0.34)	N = 59 -0.17 (0.32)	-0.15 (0.29)

Outcome	PRIMROSE trials				LIBERTY trials
	Linzagolix 100mg	**Linzagolix 100mg + ABT**	**Linzagolix 200mg + ABT after 6 months**	**Linzagolix 200mg + ABT**	**Relugolix CT**
Percentage change in BMD (spine)	N = 54 -2.40 (0.40)	N = 53 -1.61 (0.40)	N = 53 -3.04 (0.40)	N = 59 -2.05 (0.38)	-0.80 (0.23)

Table presents proportion for binary variables or mean (standard deviation) for continuous variables.

Section B: Clarification on cost-effectiveness data

B1. Priority question. The EAG are unable to replicate the results reported for the following scenarios:

- **CS Table 91. Scenario: GnRG agonist formulation for 3 monthly.**
- **CS Table 92. Scenario: 200mg for 6 months followed by linzagolix 200mg +ABT, and a 10% switch from open/abdominal to laparoscopic surgery for patients receiving linzagolix.**

Please explain the steps to run these scenarios within the cost consequence analysis model.

CS Table 91. Scenario: GnRH agonist formulation for 3 monthly.

The following steps can be taken to manually run the 3-monthly GnRH agonist formulation scenario (an automated scenario analysis is also programmed on the 'ScA' sheet):

1. Set the model settings to Population #1 using the '*Set to Population #1 (short-term setting) base case*' button which is located at the top of the model 'Controls' sheet
2. Set the value in the following cells to "0%"
    a. Controls J62 ('con_leup_prop_1m')
    b. Controls J63 ('con_gose_prop_1m')
    c. Controls J64 ('con_trip_prop_1m')
3. Results (corresponding to the scenario in CS Table 91) can be seen on the 'Results' sheet (Cells E44:I48)

CS Table 92. Scenario: 200mg for 6 months followed by linzagolix 200mg +ABT, and a 10% switch from open/abdominal to laparoscopic surgery for patients receiving linzagolix.

The following steps can be taken to manually run the 200mg for 6 months followed by linzagolix 200mg +ABT, and a 10% switch from open/abdominal to laparoscopic surgery for patients receiving linzagolix scenario (an automated scenario is also programmed on the 'ScA (2)' sheet):

1. Set the model settings to Population #2 using the '*Set to Population #2 (long-term setting) base case*' button which is located at the top of the model 'Controls' sheet

2. Change the dropdown in cell Controls J30 ('con_linzagolix_dose') to "Linzagolix 200mg"

3. If it is not already set, change the dropdown in cell Controls J31 ('con_linzagolix_200_subs') to "Linzagolix 200mg + ABT"

4. Change the dropdown in cell Controls J67 ('con_surgdist') to "User-defined treatment specific" (the user-defined surgery distributions which are located on the 'Surgery' sheet were set to a 10% switch from open/abdominal to laparoscopic surgery for linzagolix 200 mg in the submitted version of the model)

5. Results (corresponding to the scenario in CS Table 92) can be seen on the 'Results' sheet (Cells E25:J26)

B2. Priority question. The transition probability in CS Table 54 for surgery to procedural death is given as 0.001%, whereas the corresponding transition probability in the model is given as 0.003%. Please clarify which figure is correct.

Thank you for raising this clarification, the value in the model (0.003%) is correct, based on the corresponding surgery inputs reported in the model and in CS Document B Table 53. As such, the reported value of 0.001% in CS Document B Table 54 is a typographical error.

Section C: Textual clarification and additional points

C1. Priority question. The base case for concomitant medicine distribution is "assume 100%". However, in CS Table 93 the base case for concomitant medicine distribution is stated as "treatment-specific", while the scenario is labelled "assume 100%". It appears that the base case and scenario in the table have been entered the wrong way around. Please clarify this.

Thank you for raising this textual clarification, the EAG's interpretation is correct. For the concomitant medicine distribution scenario in Table 93, the base case column should read "assume 100%", and the scenario column should read "treatment-specific".

References

1. Data on File: PRIMROSE 1 CSR Week 24, v2.0. 2021 Jun.
2. Data on File: PRIMROSE 2 CSR Week 52, v2.0. 2021 May.
3. Data on File: PRIMROSE 3 CSR. 2023 Mar.
4. Linzagolix SPC [Internet]. EMA; 2023 [cited 2023 May 23]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/yselty
5. Keam SJ. Linzagolix: First Approval. Drugs [Internet]. 2022 Aug 23 [cited 2022 Sep 5]; Available from: https://link.springer.com/10.1007/s40265-022-01753-9
6. Al-Hendy A, Venturella R, Ferreira JCA, Li Y, Wagman RB, Lukes AS. LIBERTY RANDOMIZED WITHDRAWAL STUDY: 2-YEAR EFFICACY AND SAFETY OF RELUGOLIX COMBINATION THERAPY IN WOMEN WITH HEAVY MENSTRUAL BLEEDING ASSOCIATED WITH UTERINE FIBROIDS. Fertil Steril. 2021 Sep 1;116(3):e2.
7. Al-Hendy A, Lukes AS, Poindexter AN, Venturella R, Villarroel C, Critchley HOD, et al. Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy. N Engl J Med. 2021 Feb 18;384(7):630–42.
8. Data on File: 16-OBE2109-008_Working Protocol_v8.0_Amend07_12May2020_Final. 2020 May.
9. Data on File: 16-OBE2109-009_WorkingProtocol_v6.0_Amend10_27Nov2019. 2019 Nov.
10. Data on File: PRIMROSE 1_16-OBE2109-008_Statistical-Analysis-Plan_Final Version 8.0_signed. 2021 Feb.
11. Data on File: PRIMROSE 2_16-OBE2109-009_Statistical-Analysis-Plan_V5.0 2020-11-06 clean.
12. Data on File: ObsEva_16-OBE2109-008_Week24_Supplemental_Analysis_2021-04-22. 2021 Apr.
13. Data on File: ObsEva_16-OBE2109-009_Tables_Supplemental_Analysis_2021-04-22. 2021 Apr.
14. Donnez J, Taylor HS, Stewart EA, Bradley L, Marsh E, Archer D, et al. Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. The Lancet. 2022 Sep 17;400(10356):896–907.
15. Magnay JL, O'Brien S, Gerlinger C, Seitz C. Pictorial methods to assess heavy menstrual bleeding in research and clinical practice: a systematic literature review. BMC Womens Health. 2020 Feb 10;20:24.
16. Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med. 2012 Feb 2;366(5):421–32.
17. Gedeon Richter Limited. NICE Single technology appraisal. Relugolix with oestradiol and norethisterone acetate for treating uterine fibroids [ID3842; GID-TA10734]. Available at: https://www.nice.org.uk/guidance/ta832 (Last accessed: 3 April 2022). 2021.

Appendices

Appendix 1: PRIMROSE 1 and PRIMROSE 2 NMAs – posterior rank distribution (Question A10, Part B)

Table 22: Fixed-effects network meta-analysis for response – rank distribution

	Rank					
Treatment	**1**	**2**	**3**	**4**	**5**	**6**
PRIMROSE 1 & 2 (Pooled)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 1						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 2						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 23: Fixed-effects network meta-analysis for percentage change in menstrual blood loss – rank distribution

	Rank					
Treatment	**1**	**2**	**3**	**4**	**5**	**6**
PRIMROSE 1 & 2 (Pooled)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 1						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 2						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 24: Fixed-effects network meta-analysis for pain – rank distribution

	Rank					
Treatment	**1**	**2**	**3**	**4**	**5**	**6**
PRIMROSE 1 & 2 (Pooled)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 1						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 2						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 25: Fixed-effects network meta-analysis for percentage change in primary fibroid volume – rank distribution

	Rank					
Treatment	**1**	**2**	**3**	**4**	**5**	**6**
PRIMROSE 1 & 2 (Pooled)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 1						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 2						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 26: Fixed-effects network meta-analysis for percentage change in haemoglobin – rank distribution

Treatment	Rank					
	1	2	3	4	5	6
PRIMROSE 1 & 2 (Pooled)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 1						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 2						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 27: Fixed-effects network meta-analysis for change in uterine fibroid symptom and quality of life (UFS-QoL) total score – rank distribution

	Rank					
Treatment	**1**	**2**	**3**	**4**	**5**	**6**
PRIMROSE 1 & 2 (Pooled)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 1						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 2						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Appendix 2: Separate PRIMROSE 1 and PRIMROSE 2 NMAs – NMA code (Question A10, Part C)

Binary outcomes:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Continuous outcomes:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 3: Pooled and separate PRIMROSE 1 and PRIMROSE 2 NMAs – network included GnRH agonists - posterior rank distribution (Question A11, Part B)

Table 28: Fixed-effects network meta-analysis for response – rank distribution

	Rank						
Treatment	**1**	**2**	**3**	**4**	**5**	**6**	**7**
PRIMROSE 1 & 2 (Pooled)							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leuprolide acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 1							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leuprolide acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 2							
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leuprolide acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relugolix CT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; mg, milligram; Relugolix CT, relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate).

Table 29: Fixed-effects network meta-analysis for total fibroid volume – rank distribution

	Rank					
Treatment	**1**	**2**	**3**	**4**	**5**	**6**
PRIMROSE 1 & 2 (Pooled)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leuprolide acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 1						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leuprolide acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 2						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leuprolide acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; mg, milligram.

Table 30: Fixed-effects network meta-analysis for haemoglobin – rank distribution

	Rank					
Treatment	**1**	**2**	**3**	**4**	**5**	**6**
PRIMROSE 1 & 2 (Pooled)						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leuprolide acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 1						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leuprolide acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PRIMROSE 2						
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leuprolide acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 100 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; mg, milligram.

Appendix 4: Pooled and separate PRIMROSE 1 and PRIMROSE 2 NMAs – network included GnRH agonists – R code (Question A11, Part C)

Binary outcomes:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Continuous outcomes:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 5: MAICs – R code (Question A12, Part B)

Calculating weights:

[redacted]

Generating pseudo data for the comparator:

[redacted]

Comparing binary outcomes:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Comparing continuous outcomes:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CONFIDENTIAL UNTIL PUBLISHED

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Linzagolix for treating moderate to severe symptoms of uterine fibroids

---

Produced by	**Southampton Health Technology Assessments Centre (SHTAC)**
Authors	Lois Woods, Senior Research Assistant, Evidence Synthesis and Information Specialist Neelam Kalita, Senior Research Fellow, Health Economics Asyl Hawa, Research Fellow, Health Economics David Alexander Scott, Principal Research Fellow, Statistics Geoff Frampton, Principal Research Fellow, Evidence Synthesis
Correspondence to	Dr Geoff Frampton Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation University of Southampton Alpha House, Enterprise Road, University of Southampton Science Park, Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	9th November 2023 (updated 28th November 2023 after factual accuracy check)
Source of Funding	This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number 136078.

Acknowledgements

We thank the following for providing expert clinical advice to the project team and for reading and commenting on a draft of the report:

Mr Sameer Umranikar, Consultant Gynaecologist, Princess Anne Hospital, University Hospital Southampton NHS Foundation Trust.

We also thank Fay Chinnery and Karen Pickett, Southampton Health Technology Assessments Centre (SHTAC), for reading and commenting on a draft of this report for quality assurance.

Declared competing interests of the authors and advisors

The authors and clinical expert advisor have no conflicts to declare

Rider on responsibility for the report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Woods LE, Kalita N, Hawa A, Scott DA, Frampton G. Linzagolix for treating moderate to severe symptoms of uterine fibroids. A Single Technology Appraisal. Southampton Health Technology Assessments Centre, 2023

Contributions of authors

Lois Woods critically appraised the company searches and the clinical effectiveness systematic review, and drafted the report; Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; Asyl Hawa critically appraised the health economic systematic review, critically appraised the economic evaluation, and drafted the report; David Alexander Scott critically appraised the clinical effectiveness systematic review and drafted the report; Geoff

Frampton critically appraised the clinical effectiveness systematic review, drafted the report and is the project co-ordinator and guarantor.

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ABT	Add-back therapy
AE	Adverse event
AH	Alkaline haematin
AIC	Academic in confidence
BMD	Bone mineral density
BNF	British National Formulary
CI	Confidence interval
CIC	Commercial in confidence
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Combination therapy
DSU	Decision Support Unit
DEXA or DXA	Dual energy X-ray absorptiometry
EAG	External Assessment Group
EMC	Electronic Medicines Compendium
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
EQ-VAS	EuroQol Visual Analogue Scale
FAS	Full Analysis Set
FIGO	International Federation of Gynecology and Obstetrics
Hb	Haemoglobin
HMB	Heavy menstrual bleeding
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient level data
ITC	Indirect treatment comparison
ITT	Intention to treat

MAIC	Matching-adjusted indirect comparison
MBL	Menstrual blood loss
mITT	Modified intention to treat
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NRS	Numeric Rating Scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
PBAC	Pictorial blood-loss assessment chart
PGI-I	Patient Global Impression of Improvement scale
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk/risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
UF	Uterine fibroid(s)
UFS-QoL	Uterine Fibroid Symptom-Quality of Life
UK	United Kingdom
US	United States
VAS	Visual analogue scale

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG'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, health technology, evidence and information on the issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

The EAG's Key Issues refer to two different types of economic analysis since the company's submission (CS) includes both cost-comparison and cost-effectiveness analysis approaches. In the cost-comparison analysis the comparators are relugolix-CT and other gonadotrophin releasing hormone (GnRH) analogues. In the cost-effectiveness analysis the comparator is established clinical management, which the company refer to as best supportive care (BSC). An overview of how the economic analysis approaches map to the comparators and sub-populations of the CS is given in Table 3 of this report.

Table 1 Summary of Key Issues identified by the EAG

ID	Summary of issue	Report sections
1	Uncertain whether linzagolix has similar clinical effectiveness to relugolix CT and other GnRH analogues	2.3 (summary), 3.4, 3.5 (details)
2	Uncertain market share of relugolix CT	2.3
3	Issue 3 Uncertain relevance of the PRIMROSE pivotal trials to the three population subgroups that inform the company's economic analyses	2.2.3 (summary), 3.2.1.1.5.1 (details)
4	Uncertain whether patients can experience recurrence after undergoing surgery	4.2.5.2.4
5	Uncertainty surrounding the utility function	4.2.6

The key difference between the company's assumption and the EAG's conclusion for the cost-comparison analysis is that we are uncertain about the similarity in clinical efficacy between linzagolix and relugolix-CT for Populations #1 and #2.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions for the cost-effectiveness analysis for Population #3 are:

- Inclusion of prophylactic regimens of calcium and vitamin D in the BSC arm.
- Distribution of surgery types.
- Use of healthcare resources.
- Unit costs of gynaecological consultation and MRI as identified by the EAG.
- Using EQ-5D-5L data from the PRIMROSE trial to estimate the health state utilities.

1.2 Overview of key model outcomes for the cost-effectiveness analysis

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:

- Improving symptoms (based on menstrual blood loss) and affecting patients' transition through the health states (based on the response and recurrence rates).
- Reducing the overall probability of surgery, which is associated with a risk of mortality.
- Switching the surgery types, from open/abdominal to laparoscopic, which is associated with an improved quality of life.
- Utility associated with the controlled, uncontrolled, and post-surgery health states and disutility associated with adverse effects.

Overall, the technology is modelled to affect costs by:

- Increase in drug acquisition costs and health state resource use.
- Treatment discontinuation rates.
- Distribution of surgery types.

The modelling assumptions that have the greatest effect on the ICER are:

- Recurrence rate.
- Choice of the HRQoL data from the pivotal company trials (PRIMROSE) used to estimate EQ-5D values for the health states, and the source of utility (whether trial-based or published literature).

- Treatment withdrawal rates.
- Changing the probability associated with surgery and changing the distribution of surgery types.

1.3 The decision problem: summary of the EAG's key issues

The EAG have identified three key issues that are related both to the decision problem and the clinical efficacy evidence, summarised in the following tables.

Issue 1 Uncertain whether linzagolix has similar clinical efficacy to relugolix CT and other GnRH analogues

Report section	Sections 2.3 (summary), 3.4 and 3.5 (details)
Description of issue and why the EAG has identified it as important	According to the NICE Methods Guide[1] a cost comparison analysis is appropriate for technologies that are likely to provide similar or greater health benefits at similar or lower cost than the relevant comparator(s). Relugolix CT is considered by the company to be a relevant comparator to support their cost-comparison analyses. Cost comparisons were conducted for two population subgroups: those receiving linzagolix for short-term treatment (≤6 months) prior to surgical intervention (referred to in the CS as Population #1); and those receiving linzagolix for longer-term treatment (Population #2). No studies exist that directly compare linzagolix against relugolix CT in these populations so the company conducted network meta-analyses (NMAs) to make this comparison. Matching-adjusted indirect comparisons (MAICs) were also provided as a sensitivity analysis to help understand how sensitive the NMA results might be to heterogeneity in the trial characteristics. Results of the NMAs are generally highly uncertain and only convincingly show clinical similarity of linzagolix to relugolix CT for one outcome, the reduction in fibroid volume. Clinical similarity does not appear to be supported for key outcomes related to menstrual blood loss, including the company trials' primary outcome. However, interpreting clinical similarity from NMA results is challenging because a non-inferiority analysis should ideally have been pre-specified which, as far as we are aware, is uncommon in NMAs. Although not stated explicitly in the CS, the company appear to assume that statistical non-significance of NMA results implies similarity in clinical efficacy. Such an assumption would be very sensitive to statistical heterogeneity, and conclusions on clinical similarity may not be possible when NMA results have wide credible intervals that include the null, as was frequent in the NMAs provided by the company. The CS does not provide any

	explicit guidance on how the NMA results are expected to be interpreted.
What alternative approach has the EAG suggested?	The company had conducted the NMAs and MAICs using pooled data from the pivotal trials PRIMROSE 1 and PRIMROSE 2 but did not explore opportunities for reducing uncertainty in the NMA results. These trials, although of similar designs, differ in some aspects of their population baseline characteristics. The EAG requested the company to rerun the NMA analyses separately for the PRIMROSE 1 and PRIMROSE 2 trials. We also requested that the company explore alternative approaches for accounting for missing data, and for the company to provide posterior probabilities for the NMA and MAIC results to assist in judgements of the statistical similarity of the therapies. These analyses were provided by the company but do not reduce the uncertainty.
What is the expected effect on the cost-effectiveness estimates?	The existing cost-comparison analyses for Population #1 and Population #2 make the key assumption that linzagolix has similar clinical efficacy when compared to relugolix CT. If this assumption is not supported, then cost-comparison analyses might not be appropriate.
What additional evidence or analyses might help to resolve this key issue?	We requested extended NMAs from the company to include alternative comparators specified in the NICE scope. The company provided NMAs for one comparator, leuprolide acetate, but with almost no explanation of the methodology employed so the results are difficult to interpret. Results of these NMAs are highly uncertain and it is unclear whether other comparators could have been included in the evidence networks. A more thorough and transparent approach to the evidence synthesis, exploring ways to reduce uncertainty in the NMA results would be helpful. If uncertainty of the comparative clinical efficacy evidence for Populations #1 and #2 cannot adequately be resolved, then a cost-effectiveness modelling approach might be more appropriate for these population subgroups.

Issue 2 Uncertain market share of relugolix CT

Report section	Section 2.3
Description of issue and why the EAG has identified it as important	An assumption of NICE cost comparisons is that the selected comparator therapy, i.e. relugolix CT, should have an adequate market share. The EAG's clinical expert commented that most patients in his experience (around 90%) currently receive goserelin or leuprorelin, although relugolix CT is relatively new

	and its use would likely increase. The expert also commented that general practitioners are not yet aware of relugolix CT.
What alternative approach has the EAG suggested?	Consultation with further clinical experts to clarify the extent of relugolix CT use.
What is the expected effect on the cost-effectiveness estimates?	The cost comparison approach might not be appropriate if relugolix CT is not widely used in clinical practice.
What additional evidence or analyses might help to resolve this key issue?	Market share data if available.

Issue 3 Uncertain relevance of the PRIMROSE pivotal trials to the three population subgroups that inform the company's economic analyses

Report section	Sections 2.2.3 (summary) and 3.2.1.1.5.1 (details)
Description of issue and why the EAG has identified it as important	The company submission specifies three population subgroups are relevant to this technology appraisal, consistent with the NICE scope, and these influence the economic analysis approaches employed by the company: • Population #1: Patients having short-term treatment of 6 months or less whilst awaiting a surgical intervention (cost-comparison analysis); • Population #2: Patients having longer-term treatment with hormone-based therapy (cost-comparison analysis); • Population #3: Patients having longer-term treatment without hormone-based therapy (cost-utility analysis). The pivotal PRIMROSE trials do not explicitly and fully include any of these subgroups of patients, for the following reasons: • Population #1: Patients included in the trials were not eligible to receive surgery for their fibroids within 6 months regardless of the treatment provided. • Population #2: These patients, taking longer-term therapy, are not fully represented in the PRIMROSE trials since the trials had maximum duration 52 weeks, with most outcomes reported at 24 weeks. Patients who would take linzagolix for longer than 52 weeks are not specifically represented, although some limited efficacy outcomes data are available up to 64 weeks.

	• Population #3: People who were contraindicated to hormonal add-back therapy (ABT) were excluded from the PRIMROSE trials. The company assume that patients in the PRIMROSE trials randomised to receive linzagolix (100mg or 200mg) without ABT are suitable as a proxy for those contraindicated to ABT. The company do not provide a rationale for this assumption, and the EAG are uncertain whether the assumption is valid. Furthermore, there is uncertainty in the size of this sub-population in clinical practice. The EAG's clinical expert believed the sub-population unable to receive HRT to be very small, as he had not encountered this patient group in his clinical practice.
What alternative approach has the EAG suggested?	The CS does not discuss explicitly whether Population #1 and Population #2 are represented in the PRIMROSE trials and whether the trial outcomes can be applied to these population subgroups. The CS also does not discuss whether clinical efficacy or safety responses to linzagolix would differ according to patients' ability or willingness to receive ABT. It is therefore unclear whether the population in the PRIMROSE trials who could receive hormonal ABT is an appropriate proxy for those in Population #3. The EAG sought feedback from a clinical expert.
What is the expected effect on the cost-effectiveness estimates?	The company's approaches to economic analysis might not be appropriate if the clinical trial populations are not reflective of the modelled populations. In particular, the company's cost-effectiveness analysis for Population #3 might not be appropriate if: (1) patients who are unable or able to receive HRT differ in their response to linzagolix therapy; or (2) very few, or no, patients in clinical practice would be unable to receive ABT.
What additional evidence or analyses might help to resolve this key issue?	The EAG received advice from one clinical expert. Wider consultation with further clinical experts might help to understand whether the clinical trial populations can be extrapolated to the company's three sub-populations.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified three key issues relating to both the decision problem and the clinical effectiveness evidence, summarised in section 1.3 above.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The EAG have identified two key issues relating to the cost-effectiveness evidence, summarised in the following tables.

Issue 4 Uncertain whether patients can experience recurrence after undergoing surgery

Report section	Section 4.2.5.2.4
Description of issue and why the EAG has identified it as important	The company's assumption that both linzagolix and BSC arms have similar distributions of surgery types is reasonable. With respect to patient distributions across the different surgery types, the EAG's clinical expert considered that some of the surgery types, e.g. laparoscopic hysterectomy and UAE, are more common than others. Furthermore, patients are also likely to undergo hysteroscopic myomectomy, which is not listed in the company's analyses. Lastly, our clinical expert suggested that recovery time after different types of surgery varies between 4 and 8 weeks. For example, the recovery time after laparoscopic surgery could be 4-6 weeks; open surgery: 6-8 weeks, UAE: 4-6 months. We have conducted scenario analyses changing the distributions across the different surgery types based on our expert's advice. While this impacts the total costs and total QALYs, the change is proportional as the distributions are similar for both the treatment arms and therefore there is no overall impact on the ICER (see Section 6) In their cost-utility analysis for Population #3, the company assume that after patients undergo surgery, they transition to the 'post-surgery' state until the onset of menopause. The EAG are uncertain if this is clinically plausible as patients undergoing different surgery types may have a different prognosis. While some may be completely cured (e.g., those undergoing hysterectomies), others may experience a recurrence of the symptoms post-surgery.
What alternative approach has the EAG suggested?	We suggest the company consider adding 'recurrence' from the post-surgery state to the cost-effectiveness model for Population #3. This would be appropriate if recurrence is found to be frequent, based on further discussion with clinicians and the NICE committee.
What is the expected effect on the cost-effectiveness estimates?	The direction and magnitude of the overall cost-effectiveness results are unclear as it depends on the recurrence rate(s) applied in both the treatment arms- Linzagolix and BSC. The EAG suspect the overall impact is unlikely to be significant if a similar recurrence rate is applied to both the treatment arms.
What additional evidence or analyses might	Further discussion and clarification of patients' prognosis after undergoing different surgery types in clinical practice, particularly with respect to the proportion of patients who may experience a recurrence of the symptoms, might enable a more accurate

help to resolve this key issue?	reflection of clinical practice. We suggest the company conduct scenario analyses by adding percentage(s) of recurrence in the post-surgery state for both arms.

Issue 5 Uncertainty surrounding the utility function

Report section	Section 4.2.6
Description of issue and why the EAG has identified it as important	In their base case, the company mapped UFS-QoL data from the PRIMROSE trials to EQ-5D-3L utility values using an unpublished algorithm that was applied in a previous NICE appraisal TA832. They also reported a scenario analysis using EQ-5D-5L data collected in the PRIMROSE trials, mapped to EQ-5D-3L utility values estimated using the NICE-preferred (Hernández-Alava) method. The EAG has some concerns over the use of utility estimates mapped from a disease-specific measure when EQ-5D data are available from the PRIMROSE trials. We also have some concerns about the lack of transparency of the UFS-QoL mapping algorithm. We note the use of the UFS-QoL mapped estimates in TA832, but question whether the TA832 committee's concerns about the availability of EQ-5D-5L data from the clinical trials apply in the current appraisal. The company applied a linear mixed model to analyse both mapped UFS-QoL and EQ-5D utility estimates from the PRIMROSE trials to estimate utilities for the 'controlled' and 'uncontrolled' health states. The same health state utilities were used in the economic model for both the treatment arms. The EAG have some concerns about the reporting of the utility analysis. The company did not define or justify the specification for the linear mixed model regression of utility data. It is not clear why they chose to include a single independent variable- reduction in menstrual blood loss (RMBL), or whether additional co-variates would have improved the model fit. Furthermore, no sensitivity or scenario analyses were reported for alternative specifications of the utility function, and uncertainty over the regression coefficients was not included in the probabilistic sensitivity analysis.
What alternative approach has the EAG suggested?	The EAG suggest that the base case should use utility estimates derived from EQ-5D data collected in the trial. Scenario analysis should also be reported to explore uncertainty over the coefficients from the linear mixed model analyses of trial utility data.
What is the expected effect on the cost-	Due to lack of information on the model specification, the EAG conducted a range of exploratory scenarios changing the coefficients of the utility function. The EAG's exploratory analyses

effectiveness estimates?	have an impact on the ICER, ranging between £13,968 per QALY and £34,376 per QALY.
What additional evidence or analyses might help to resolve this key issue?	Further information on the model specification for the linear mixed model utility function along with exploration of alternative specifications.

1.6 Other key issues: summary of the EAG's view

- The company's interpretation of BSC may not fully reflect clinical practice, as it does not include prophylactic doses of calcium and vitamin D, which are also given to the patients as well as NSAID and iron supplements, to protect against bone loss.

- There are no data to support the company's assumption that the treatment effect (i.e. response) of linzagolix is maintained beyond 1 year, although it may be biologically plausible.

- There is uncertainty about the recurrence rate in patients with uterine fibrosis.

- With respect to patient distributions across the different surgery types, advice from our clinical expert suggests that some of the surgeries (e.g., laparoscopic hysterectomy and umbilical artery embolization (UAE)) may be more common than others.

- The company's assumptions regarding healthcare resource use may not be reflective of the UK clinical practice. Their assumptions that patients would not have any GP visits, have full blood count and MRI scan once each, and people in the linzagolix arm receive one DEXA scan after 1 year may not be an appropriate representation of the clinical practice. We conduct scenario analysis on resource use, based on the advice of our clinical expert, see Section 6.

1.7 Summary of EAG's preferred assumptions and resulting ICER

The following changes were made to the company's base case to form the EAG preferred base case for Population #3:

- Inclusion of vitamin D and calcium in the BSC arm.
- Applying the distribution of surgery types based on the advice of the EAG's clinical expert.
- Using the health care resource use based on the EAG's clinical expert advice.
- Change in the unit costs for gynaecologist consultation and MRI scan.

- Using EQ-5D-5L data from the PRIMROSE trial to estimate the utilities for the controlled and uncontrolled health states.

Table 2 Company and EAG base case results for Population #3

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case	[redacted]	[redacted]	£15,392
EAG's preferred base case	[redacted]	[redacted]	£28,973

For further details of the EAG's exploratory and sensitivity analyses see Section 6.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This report is a critique of the company's submission (CS) to NICE from Theramex on the clinical effectiveness and cost effectiveness of linzagolix for treating moderate to severe symptoms of uterine fibroids. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the external assessment group (EAG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the EAG via NICE on 21st September 2023. A response from the company via NICE was received by the EAG on 11th October 2023 and this can be seen in the NICE committee papers for this appraisal.

2.2 Background

2.2.1 Background information on uterine fibroids

The CS provides an accurate overview of the disease in CS sections B.1.3.1 and B.1.3.2.

2.2.1.1 Overview of the condition

Uterine fibroids (also called myomas or leiomyomas) are non-malignant smooth muscle tumours of the uterus. The exact cause is not known but they have been linked to oestrogen and progesterone, occur in people of reproductive age, and can become smaller after menopause. Around 2 in 3 women develop at least one uterine fibroid. Incidence of fibroids increases with age until the menopause, with a peak in those aged in their 40s.

Uterine fibroids are classified according to their site of origin (CS Figure 2). Intramural fibroids (the most common type) develop within the uterine wall; subserosal fibroids develop on the outside of the uterus, projecting into the pelvis, where they can become very large; and submucosal fibroids develop from inside the uterus and protrude into the uterine cavity. Submucosal and subserosal fibroids may or may not have a stalk (pedunculate fibroids) and some fibroids may encompass more than one uterine location. Generally, fibroids in the uterus can cause bleeding symptoms, whereas fibroids outside the uterus can cause pressure symptoms. The EAG's clinical expert advisor confirmed that the International Federation of Gynecology and Obstetrics (FIGO) classification system for uterine fibroids (CS Figure 3) is used in clinical practice to guide treatment decisions.

2.2.1.2 Risk factors

Major risk factors for uterine fibroids, as confirmed by the EAG's clinical expert, are age up to menopause, family history, nulliparity and Black race. Specifically, Black women have an increased risk of developing uterine fibroids, are more likely to have large and multiple fibroids, develop these 5-6 years earlier, and experience higher rates of hospitalisation and surgical intervention compared to White women. The risk of developing uterine fibroids is also increased in women who have obesity, early menarche (first menstrual period), time since last birth more than 5 years, hypertension, and exposure to oestrogen-like chemicals (e.g. phytoestrogens in soy milk) (CS section B.1.3.1.3).

2.2.1.3 Symptoms and burden of disease

Most women with uterine fibroids do not experience symptoms, but for the 25% to 30% with fibroids who do, their symptoms can be moderate or severe [2] (this is the population specified in the NICE scope for this appraisal). The CS does not explicitly define severity of uterine fibroids. The EAG's clinical expert said severity of symptoms are judged according to their impact on a patient's quality of life and their work. If the patient needs to take time off work or their symptoms are causing disruption to their regular activity then these would be classed as moderate to severe. Symptoms that are often considered moderate or severe include heavy menstrual bleeding which can lead to anaemia, bladder or bowel pressure, pain, or infertility. For pain related to uterine fibroids, a numerical rating scale can be used for quantifying severity (CS Table 10) whilst symptom severity can also be assessed using a subscale of the UFS-QoL instrument (described in section 3.2.3.2). Black people typically present with more severe symptoms than White people.[3] The position, type, size, and number of fibroids present influences the type and severity of symptoms experienced.[4, 5] According to the recent (October 2022) NICE Technology Appraisal (TA) of relugolix CT for uterine fibroids (TA832), symptoms are broadly classed into heavy and prolonged menstrual bleeding, pelvic pain and pressure, and reproductive dysfunction. The CS (section B.1.3.2.1) notes that people with uterine fibroids can experience a wide range of symptoms including frequent menstrual cycles, bloating, increased urinary frequency, constipation, fatigue, anxiety or stress, and various types of pain (leg or back pain, menstrual pain or cramping, pelvic pain, or pain during intercourse).[6]

Iron deficiency anaemia (IDA) is an important complication in around two thirds of those who experience HMB caused by uterine fibroids and can lead to increased morbidity and mortality following surgery. Uterine fibroids can also cause infertility and pregnancy complications, including miscarriage, pre-term and caesarean delivery.

As reported in CS section B.1.3.2.1 and CS Table 3, the symptoms and sequelae of uterine fibroids can have a range of negative impacts on patients' wellbeing, including physical, social and emotional impacts which can interfere with sleep, relationships, social life and work or school. These can have a negative impact on patients' health-related quality of life (HRQoL) and productivity. The NICE Committee in TA832 concluded that uterine fibroids represent a significant burden for people who have them, affecting both physical and psychological aspects of quality of life.

2.2.2 Background information on linzagolix

Linzagolix (brand name Yselty®) is a gonadotrophin releasing hormone (GnRH) receptor antagonist which binds competitively to GnRH receptors in the pituitary gland. This alters GnRH signalling between the hypothalamus and pituitary, leading to a dose-dependent reduction in the production of serum luteinising hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary gland. LH and FSH are key regulators of the production of estradiol and progesterone in the ovary. The effect of linzagolix on the production of LH and FSH causes immediate dose-dependent suppression of ovarian estradiol secretion and subsequent progesterone secretion, with the changes in hormone levels quickly reversible on stopping the therapy. The overall mode of action of linzagolix (as with all GnRH analogues) is therefore to reduce the levels of the hormones that are thought to be responsible for fibroid development, effectively inducing a controlled menopause.

GnRH analogues fall into two groups, agonists and antagonists, which differ in the way that they interact with pituitary GnRH receptors and modulate the secretion of LH and FSH. The GnRH agonists, such as leuprolide acetate and goserelin (which are potential comparators to linzagolix) cause an initial, transient, increase in sex hormone production before levels of estradiol and progesterone decrease, which can lead to a transient initial increase in symptoms such as heavy menstrual bleeding. In contrast, the more recently-developed GnRH antagonists, which include linzagolix and relugolix, do not cause a transient increase in oestradiol and progesterone levels or the associated initial symptom flare.

The use of GnRH analogues has the downside that patients may experience symptoms of early menopause (i.e. hot flashes, weight gain, fluid retention, among others) as well as potential adverse events related to early menopause, notably decreased bone mineral density (BMD) and increased risk of osteoporosis. Long-term use of GnRH analogues therefore requires a balancing act between management of uterine fibroids and management of menopausal sequelae. To achieve this, GnRH analogues are usually co-administered with hormonal therapy, except for short-term use (≤6 months). A linzagolix

tablet contains the GnRH antagonist without the hormonal therapy, and it is intended by the company that the hormonal therapy can be administered separately, referred to as "add-back therapy" (ABT). In contrast, relugolix CT is formulated as a combined therapy (CT) that includes both the GnRH antagonist and the hormonal therapy (estradiol-norethisterone acetate) in the same tablet.

As noted in the Summary of Product Characteristics (SmPC),[7] linzagolix is available as a daily oral therapy in two doses, 100mg and 200mg, each of which may be prescribed with or without ABT (where ABT comprises estradiol 1 mg and norethisterone acetate 0.5 mg).

The company have submitted a confidential Patient Access Scheme (PAS) discount of [redacted] to NHS England.

2.2.3 The position of linzagolix in the treatment pathway

According to CS Table 2, the four possible regimens of linzagolix (i.e. 2 doses, with or without ABT) allow for flexible dosing options to support the individualised treatment need of women with uterine fibroids. In summary:

• The 100mg and 100mg + ABT regimens enable "partial suppression" of estradiol, controlling uterine fibroids while minimising BMD loss. The CS states that this is suitable for either short-term (≤6 months) or long-term (>6 months) treatment.

• The 200mg dose can be used for "full suppression" of estradiol but for long-term use (> 6 months) concomitant ABT is required to control symptoms whilst minimising BMD loss.

• The 200mg dose without ABT is suitable for short-term use when reduction of uterine and fibroid volume is desired, e.g. prior to surgery (such as myectomy or hysterectomy). NB this implies that whilst the 100mg dose without ABT can achieve symptom control, it does not provide the same magnitude of uterine or fibroid volume reduction as the 200mg dose.

According to the CS, the recommended dose of linzagolix is "100mg, or if needed 200mg, once daily with concomitant ABT". The CS does not provide any criteria for selecting whether the 100mg + ABT or 200mg + ABT dose is appropriate. The EAG assume that patients would likely be tried first on 100mg + ABT and if required for further symptom control the dose would be increased to 200mg + ABT, considering the patient's individual circumstances such as risk of osteoporosis. The SmPC recommends performing a dual X-ray absorptiometry (DXA) scan for patients with risk factors for osteoporosis, it does not recommend any particular dose of linzagolix.[7]

For patients in whom ABT therapy is not recommended, or those who prefer to avoid hormonal therapy, the recommended linzagolix dose is 100mg daily without ABT (CS Table 2). The CS specifies that contraindications to ABT include obesity, hypertension and dyslipidaemia; and women with an elevated risk of oestrogen- and progestogen-related side-effects (CS B.1.3.4.5) The size of this group of patients is uncertain and discussed further in section 3.2.1.1.5.1.

The care pathway is described in detail in CS section B.1.3.4, references the current NICE Guideline for heavy menstrual bleeding (NG88)[8], and is best summarised in CS Figure 5.

As suggested above, the CS has identified three relevant sub-populations for linzagolix therapy, i.e. patients having short-term treatment of 6 months or less (referred to by the company as Population #1); patients having longer-term treatment with hormone-based therapy (referred to as Population #2); and patients having longer-term treatment without hormone-based therapy (referred to as Population #3). The position of linzagolix in the treatment pathway for each of these sub-populations is summarised in CS Figure 6, which we have reproduced below in Figure 1.

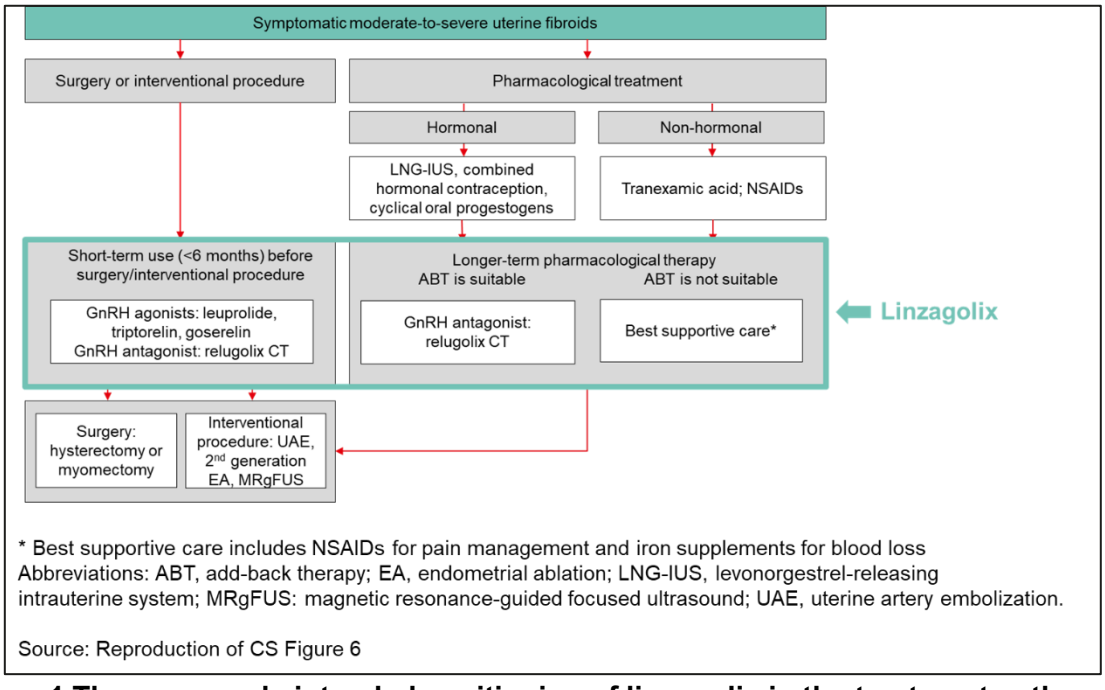


Figure 1 The company's intended positioning of linzagolix in the treatment pathway

As shown in Figure 1, different comparators are relevant for each of these sub-populations. Furthermore, the company have used different economic analysis approaches for the sub-populations (cost comparisons for Populations #1 and #2 and cost-utility analysis for

Population #3). To help clarify the company's approach to the technology appraisal and assist interpretation of the company's Decision Problem (section 2.3 below), Table 3 provides an overview of the sub-populations, their relevant linzagolix dose regimens, comparators, and the company's economic analysis approaches.

Table 3 Summary of the company's approach to the technology appraisal

Sub-populations	Applicable linzagolix dose regimens	Comparators considered relevant by the company	Economic analysis approaches employed by the company
Population #1: Adults of reproductive age with moderate to severe symptoms associated with uterine fibroids having short-term treatment of 6 months or less	The company assume that patients receiving short-term treatment do not require ABT (CS section B.3.5.1) and the CS suggests 200mg would be used, without ABT, if shrinkage of uterine and fibroid volume is the primary aim (prior to surgery) (CS Table 2).	**Relugolix CT** (as explained later in this report, no direct in-trial comparisons exist so this comparison is made via network meta-analysis (NMA) comparing linzagolix in the pivotal placebo-controlled PRIMROSE trials against relugolix CT in the placebo-controlled LIBERTY trials using placebo as the common comparator) For detailed discussion of the PRIMROSE and LIBERTY trials see section 3.2.1; for explanation of the NMA approach see section 3.3.	**Cost comparison** Assumes linzagolix has similar clinical efficacy and safety to relugolix CT.
Population #2: Adults of reproductive age with moderate to severe symptoms associated with uterine fibroids having longer-term treatment, with hormone-based therapy	Either 100mg + ABT or 200mg + ABT		
Population #3: Adults of reproductive age	Either 100mg or 200mg, without ABT. The 200mg	**Best supportive care (BSC)[a]** (no alternative	**Cost-utility analysis** Follows the standard approach for Single

with moderate to severe symptoms associated with uterine fibroids having longer-term treatment, without hormone-based therapy	regimen is likely to be used short-term (the company base case assumes 200mg for 6 months followed by 100 mg, with a scenario of 100 mg all the way through) (CS B.3.5.1.1).	comparator without hormone-based therapy exists). This comparison is directly from the PRIMROSE trials assuming that the placebo arm represents BSC.	Technology Appraisals
a The company refer to established clinical management as 'best supportive care' (BSC) and we use this term in the current report for consistency. BSC is synonymous with established clinical management as stated in the NICE scope ABT: add-back therapy; BSC: best supportive care (=established clinical management); CT: combination therapy; NMA: network meta-analysis			

2.2.4 Characteristics of the appraisal populations

The CS does not discuss the size of these sub-populations in clinical practice. We note particular uncertainty regarding Population #3, i.e. those patients who are unable to or prefer not to receive hormonal ABT. The EAG's clinical expert thought Population #3 likely to be very small, since he had not seen many such patients with moderate or severe symptoms of uterine fibroids in his clinical practice. In contrast, the company's Market Research Survey[9] suggests that in the UK [redacted] of patients might be contraindicated and [redacted] unable to take ABT or would prefer to avoid hormone therapies, although it is unclear how relevant these data are to patients with moderate or severe symptoms, and methodological details of the company's survey are lacking. We have noted this uncertainty in the size of Population #3, together with uncertainty in how well Population #3 is supported with clinical evidence (discussed in detail section 3.2.1.1.5.1 below), as a key issue for further consideration (see Key Issue 3). The EAG are satisfied that Population #1 and Population #2 are relevant in clinical practice as they would cover most patients who would receive GnRH analogues,[9, 10] including those with moderate or severe symptoms of uterine fibroids, although the size of these groups in clinical practice is unclear. The EAG's clinical exert suggested that more patients would likely be in Population #1 than Population #2 but did not quantify this.

EAG conclusion on the condition and treatment pathway

The CS provides an accurate and thorough description of uterine fibroids and the associated symptoms. Details on the current treatment pathway are also accurate. The proposed position of linzagolix in the treatment pathway is either for short term use prior to surgery where the current treatments are GnRH agonists or relugolix CT, or for longer-term use where the current treatment is relugolix CT, or BSC if the

patient is contraindicated for hormonal therapy. Linzagolix has four dose regimens that enable this flexibility of use across the treatment pathway, however it is unclear what proportions of the indicated population correspond to each dose regimen.

2.3 Critique of the company's definition of the decision problem

For this appraisal, the company have submitted a cost-comparison analysis for Populations #1 and #2, and a cost-utility analysis for Population #3, as summarised in Table 3 above.

In a cost-comparison NICE appraisal, companies are not expected to provide a comparison of the intervention against all the comparators specified in the NICE scope.[10] Only one of the scoped comparators need be selected and should represent NICE recommended treatments as a whole in terms of costs and effects, and which has a significant market share. In the company's decision problem they have selected relugolix CT (relugolix combination therapy, i.e. includes hormonal add-back therapy; ABT) as the comparator in the cost-comparison analysis for Populations #1 and #2. CS section B.3.2.2 states that the selection of relugolix CT was based on the recommendations of NICE TA832 and clinical opinion.

The NICE guidance on cost-comparison appraisals[10] indicates that the intervention of interest (i.e. linzagolix regimens with or without ABT) should have similar clinical effectiveness and safety to the selected comparator(s) (i.e. relugolix CT). However, the EAG note that the clinical similarity of linzagolix to relugolix CT is uncertain, as explained in detail in section 3.5 of this report. This could have a bearing on whether cost-comparison analysis is an appropriate economic analysis approach for Population #1 and Population #2. We have therefore raised this as a key issue for further consideration (see Key Issue 1).

The company have not provided an estimate of the market share for relugolix CT when treating people with moderate or severe symptoms of uterine fibroids. The EAG's clinical expert estimated that relugolix CT currently has a low market share, with around 90% of patients in his practice receiving goserelin or leuprorelin, but he noted that, as relugolix CT is a relatively new therapy, its market share could increase. The expert also thought that general practitioners (GPs) are currently unfamiliar with relugolix CT. The EAG are uncertain whether the expert's observations are reflective of the use of GnRH analogues more widely in the NHS. As the market share of relugolix CT and other comparators could have a bearing on whether cost-comparison analysis is an appropriate economic analysis approach for Population #1 and Population #2 we have raised this as a key issue for further consideration (see Key Issue 2).

Table 4 below summarises the decision problem addressed by the company in the CS in relation to the final scope issued by NICE and the EAG's comments on this.

Table 4 Summary of the decision problem

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Population	People of reproductive age with moderate to severe symptoms associated with UFs	People of reproductive age with moderate to severe symptoms associated with UFs	Not applicable	The trial populations in the clinical evidence reported in the CS are mostly consistent with the NICE scope but exclude people at risk of BMD loss, and those with very large fibroids (see exclusion criteria CS Appendix M.1). It is also unclear whether they include people with pressure symptoms of uterine fibroids – see section 3.2.1 of this report.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Subgroups	If the evidence allows the following subgroups will be considered: • People having short-term treatment of 6 months or less • People having longer-term treatment, with hormone-based therapy • People having longer-term treatment, without hormone-based therapy	• 1: People having short-term treatment of 6 months or less • 2: People having longer-term treatment, with hormone-based therapy • 3: People having longer-term treatment, without hormone-based therapy	Not applicable	The subgroups are consistent with the NICE scope. They are represented in the CS and in this report as Population #1, Population #2, and Population #3 – with respect to the numbering in the company's decision problem column to the left. The EAG are uncertain of the extent to which the trial populations represent populations #1, #2, and #3, see sections 3.2.1.1.4 and 3.2.1.1.5.
Intervention	Linzagolix (with or without hormone-based therapy)	Linzagolix (with or without hormone-based therapy)	Not applicable	This is consistent with the NICE scope.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Comparators [a]	GnRH agonists (off-label for some GnRH agonists) [a] Relugolix-estradiol-norethisterone acetate Where hormone-based therapy is not suitable: established clinical management without linzagolix	GnRH agonists (off-label for some GnRH agonists) [a] Relugolix CT (relugolix-estradiol-norethisterone acetate) Where hormone-based therapy is not suitable: established clinical management without linzagolix (NSAIDs and iron supplements)	The company considers NSAIDs and iron supplements to be established clinical management for patients who cannot receive hormone-based therapy, based on guidelines and discussion with clinical experts	The CS includes relugolix-estradiol-norethisterone acetate (relugolix CT) as the main comparator for Population #1 (with GnRH agonists leuprorelin, goserelin and triptorelin in a supplementary comparison, CS Table 47) and relugolix CT as the only comparator for Population #2 which is appropriate for the NICE cost-comparisons if the intervention and comparator can be demonstrated to have similar clinical efficacy and safety. The company included other GnRH analogues as comparators for Population#1 and Population #2 in a clarification response. For Population #3 the company included best supportive care

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
				(BSC) as the sole comparator which is appropriate for the cost-utility analysis for this population (which could not receive comparators containing hormone-based therapy). The EAG's clinical expert agreed with the company's definition of BSC except noting that tranexamic acid (an antifibrinolytic drug that reduces bleeding) would also be included in BSC in clinical practice, whilst iron supplements would be given specifically to anaemic patients. The EAG note that patients were prohibited from receiving tranexamic acid in the pivotal trials (PRIMROSE 1 CSR section 9.3.2).

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
Outcomes	The outcome measures to be considered include: • Change in MBL volume • Time to MBL response • Pain • UF volume • Haemoglobin levels • Change in BMD • Rates and route of surgery • Impact on fertility and pregnancy and teratogenic effects • Mortality • AEs of treatment, including but not	• Change in MBL volume • Time to MBL response • Pain • UF volume • Haemoglobin levels • Change in BMD • Impact on pregnancy and teratogenic effects • Mortality • AEs of treatment, including but not limited to vasomotor symptoms and incontinence • HRQoL	Rates and route of surgery, impact on fertility, or pelvic organ prolapse were not specified endpoints in PRIMROSE 1 and PRIMROSE 2	The CS has only excluded outcomes which were not reported in the pivotal trials (impact on fertility and pregnancy and teratogenic effects; pelvic organ prolapse). Incontinence is reported in the CSRs, not the CS, as not enough adverse events occurred for the summary analysis. The EAG's clinical expert noted that pelvic organ prolapse may be a part of menopausal change and did not consider this to be important as an adverse effect of treatment.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	limited to vasomotor symptoms, incontinence and pelvic organ prolapse • HRQoL			
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	• The most suitable type of economic evaluation varies between subgroups • For people having short-term treatment of 6 months or less and people having longer-term treatment with hormone-based therapy, where relugolix CT is the primary comparator	The blended approach to addressing the decision problem (an STA with cost-comparison methodology for a portion of the marketing authorisation population) was suggested by NICE and explored at the decision problem stage, and was considered	The company's economic approaches for analysing the three population subgroups are appropriate in principle. However, there is uncertainty whether linzagolix and relugolix CT have similar efficacy and safety (see Key Issue Issue 1 and report sections 3.4 and 3.5.) which is an assumption required for the cost-comparisons for Population #1 and Population #2.

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
	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. The availability and cost of biosimilar and generic products should be taken into account	of interest, cost-comparison methodology is used. This is based on population overlap between linzagolix and relugolix CT, findings from an indirect treatment comparison, clinical expert opinion, and guidance from NICE at the decision problem stage • For people having longer-term treatment without hormone-based therapy, where	appropriate by the company	

	Final scope issued by NICE	Company's decision problem	Rationale if different from the final NICE scope	EAG comments
		existing treatment options are limited, cost-effectiveness analysis is used, and expressed in terms of incremental cost per quality-adjusted life year		

Source: Reproduced from CS Table 1 with additional EAG comments.
Abbreviations: AEs: adverse effects; BMD: bone mineral density; GnRH: gonadotropin-releasing hormone; HRQoL: health-related quality of life; MBL: menstrual blood loss; NSAIDs: non-steroidal anti-inflammatory drugs; Relugolix CT: relugolix combined therapy (i.e. relugolix plus hormonal add-back therapy); UFs: uterine fibroids.
[a] There is a typographical error in the company's responses. The NICE scope refers to "GnRH analogues" which includes both GnRH agonists and GnRH antagonists; the company's description "agonists" should therefore read "analogues".

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's literature review methods

The company carried out three systematic literature reviews:

• one to identify randomised controlled trials (RCTs) for the clinical effectiveness evidence comparing linzagolix to placebo (CS section B.2.1 and CS Appendix D) and for a network meta-analysis (NMA) comparing linzagolix to relugolix CT (CS section B.2.9.1 and CS Appendix D),

• one for cost-effectiveness, cost, and healthcare resource use (CS section B.3.1 and CS Appendix G) which is discussed in section 4.1 of this report,

• and another for health-related quality of life (CS section B.3.4.3 and Appendix H which is discussed in section 4.2.6.1 of this report).

The EAG's full assessment of the methods of the clinical effectiveness review is summarised in Appendix 1. The review is generally comprehensive and appropriate for the decision problem. Searches were six months out-of-date when received by the EAG but we do not believe any relevant clinical efficacy studies were missed.

3.2 Critique of studies of the technology of interest and the company's analysis and interpretation of these

3.2.1 Included studies

The company systematic literature review identified six publications relating to the two company pivotal trials PRIMROSE 1 and PRIMROSE 2, and unpublished data relating to the company's extension trial PRIMROSE 3, that provide evidence on the efficacy and safety of linzagolix compared to placebo (CS section B.2.2).

The company additionally identified 19 publications relating to 14 studies for four GnRH analogue comparator therapies (relugolix CT, goserelin, leuprolide acetate, and ulipristal acetate) listed within CS Appendix D Table 7. These included the LIBERTY trials providing evidence for relugolix CT compared to placebo for use in the cost-comparison, and the PEARL trials providing evidence for ulipristal acetate compared to placebo and ulipristal acetate compared to leuprolide acetate for the company's indirect treatment comparison provided in clarification response A11. We believe it is likely that all relevant comparator studies were included.

As noted above (Table 3), the PRIMROSE trials provide evidence for the company's cost-utility analysis relevant to Population #3 (long-term treatment without ABT); whilst the PRIMROSE trials, the LIBERTY trials, and the PEARL trials provide evidence for the company's cost-comparison analyses relevant to Population #1 (short-term treatment with or without ABT) and Population #2 (long-term therapy with ABT). Characteristics of the PRIMROSE, LIBERTY, and PEARL trials are discussed below.

3.2.1.1 PRIMROSE trials and extension study

3.2.1.1.1 Role of the trials in the technology appraisal

The placebo-controlled PRIMROSE trials provide evidence of the clinical effectiveness and safety of linzagolix compared to BSC, with the placebo arms assumed to reflect BSC in clinical practice. This comparison is relevant to the company's cost-utility analysis for Population #3. The PRIMROSE trials are also used in indirect treatment comparisons of linzagolix against relugolix CT to support the company's cost-comparison analyses for Population #1 and Population #2, which assume that linzagolix and relugolix CT have similar clinical effectiveness and safety.

3.2.1.1.2 Study designs

PRIMROSE 1 and PRIMROSE 2 are large, completed, company-sponsored, phase III, multicentre, double-blind, RCTs; they had identical study designs but differed in location and patient baseline characteristics. PRIMROSE 3 is a completed company-sponsored off-treatment extension study for women who completed PRIMROSE 1 or PRIMROSE 2. Study characteristics are summarised in Table 5 below.

Table 5 Overview of the PRIMROSE trials

Study characteristics	PRIMROSE 1	PRIMROSE 2	PRIMROSE 3
Study ID	NCT03070899	NCT03070951	EudraCT 2021-000452-19
Study designs	Double-blind RCTs: 4 different dosing regimens of linzagolix vs placebo		Single arm, open-label, off-treatment extension study
Locations	USA (94 sites)	95 sites in USA and 8 European countries (no UK sites)	USA and Europe (no UK sites)

Study characteristics	PRIMROSE 1	PRIMROSE 2	PRIMROSE 3
Populations	Women aged ≥18 years with ultrasound-confirmed uterine fibroids (between 2-12 cm diameter) and heavy menstrual bleeding (≥80 mL MBL per cycle for at least 2 cycles)		Women completing either PRIMROSE 1 or 2 and who had a DXA scan within 35 days from the last treatment administration
Randomisation	1:1:1:1:1; stratified according to race (Black or African American vs other)		Not applicable: open-label, off-treatment
Regimens and participants	Randomised N=574; FAS N=511 Placebo N=103 Linzagolix 100 mg N=94 Linzagolix 100 mg + ABT N=107 Linzagolix 200 mg N=105 Linzagolix 200 mg + ABT N=102	Randomised N=535; FAS N=501 Placebo N=102 Linzagolix 100 mg N=97 Linzagolix 100 mg + ABT N=101 Linzagolix 200 mg N=103 Linzagolix 200 mg + ABT N=98	[redacted] Enrolled: [redacted] Completed: [redacted]
Primary outcome	Reduction in heavy menstrual bleeding at 24 weeks, reported as response (proportion of patients achieving the outcome); measured by the alkaline haematin method		Change in BMD at 12, 18 and 24 months from end of treatment in PRIMROSE 1 or 2
Duration and treatment switching	After 24 weeks (primary outcome), a second treatment period ran up to week 52 where treatment switching occurred for linzagolix 200 mg → linzagolix 200 mg + ABT in both trials, for 50% of the placebo group in PRIMROSE 1→ linzagolix 200 mg + ABT, and for all of the placebo group in PRIMROSE 2. There was no treatment switching in any of the other trial arms which		24 months. The study is complete.

Study characteristics	PRIMROSE 1	PRIMROSE 2	PRIMROSE 3
	also ran up to week 52. After this there was a follow-up period of no treatment for all study arms up to week 76. The trials are complete.		

Sources: CS sections B.2.3.1, B.2.3.4, CS Appendix M, and trial publication (Donnez et al. 2022;[11]) CS section B.2.11; PRIMROSE 3 study CSR.[12]
Abbreviations: ABT: add-back therapy; BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; FAS: full analysis set; MBL: menstrual blood loss; RCTs: randomised controlled trials.

Treatment switching was applied for practical and ethical reasons (Clarification Response A4b). Full suppression of serum estradiol (200 mg linzagolix without ABT) cannot be received for >6 months due to the impact on bone mineral density. Hence the treatment switching for this treatment group to 200 mg with ABT. The company explained that the treatment switch from placebo to 200 mg linzagolix without ABT was to support study participants to continue therapy and therefore avoid high discontinuation rates in that group (Clarification Response A4a). However, this switch was applied differently in the two trials as only 50% (selected at randomisation) of the placebo group in PRIMROSE 1 was switched. Nonetheless, there is no placebo comparator data, with sufficient statistical power, beyond 24 weeks for either of the trials and therefore for the cost-utility analysis.

Thus the available evidence appears to be relatively short-term considering that some of the linzagolix dosing regimens may be used for more than one year in clinical practice (subject to regular bone mineral density monitoring).[7] The company argue that because linzagolix leads to a dose-dependent reduction in serum estradiol and progesterone, and because it is well-known that fibroids are hormone-dependent, then as long as serum estradiol suppression is maintained clinical effectiveness is also expected to be durable (Clarification Response A7). The EAG's clinical expert agreed that this is likely. The company also point to the LIBERTY randomised withdrawal study for relugolix CT, which has a similar mechanism of action to linzagolix, and those trial results show durable effect in maintaining low MBL volume and amenorrhoea for over two years (Clarification Response A7). The EAG view the long-term similarity of linzagolix to relugolix CT to be plausible but speculative because the group of patients in the 52-week LIBERTY randomised withdrawal study who received relugolix CT for the whole 2-year period (beginning with LIBERTY 1 or 2), was relatively small (N=46), with limited results reported for this group.[13]

3.2.1.1.3 Pooled analysis of the trials

The CS primarily focuses on pooled data from PRIMROSE 1 and PRIMROSE 2 up to week 24 (prior to treatment switching), with results of the individual PRIMROSE trials reported in CS Appendix M. The strengths and limitations of the pooled analysis approach are discussed in section 3.2.4.2 below.

3.2.1.1.4 Relevance of the placebo arms to BSC in clinical practice

The placebo treatment group in the PRIMROSE 1 and 2 trials represents BSC (the comparator for Population #3 in the cost-utility analysis) which the company describe as consisting of NSAIDs and iron supplements (CS Table 1).

The EAG's clinical expert suggested that the company's interpretation of BSC does not fully reflect clinical practice. As well as NSAIDs and iron supplements, tranexamic acid would be prescribed according to the NG88 guidelines for management of heavy menstrual bleeding,[8] with prophylactic doses of calcium and vitamin D also given to protect against bone loss (doses as noted in section 4.2.4 of this report relating to the economic model). Expert opinion reported in the company's market research survey suggests that [redacted] patients (around [redacted]) on long-term pharmacological treatment in the UK would receive tranexamic acid. However, tranexamic acid is not part of the company description of BSC and patients were not permitted to receive tranexamic acid in the PRIMROSE trials. The EAG conclude that the effects of tranexamic acid on bleeding control that could be experienced by patients in clinical practice would not be reflected in placebo arms of the PRIMROSE trials, although the significance of this is unclear.

3.2.1.1.5 Trial population characteristics

3.2.1.1.5.1 Exclusion of patients unable to take hormonal therapy (Population #3)

Patients with moderate to severe symptoms of uterine fibroids who could not take hormonal ABT or preferred not to take hormonal ABT were excluded from the PRIMROSE trials (CS Document A, section A.9). As noted above, this group is referred to by the company as Population #3 and is the subject of their cost-utility analysis (Table 3) but is not represented by any patients in the trials. According to CS Document A (section A.9) an unspecified number of clinical experts agreed that the patients in the 100mg and 200mg arms of the PRIMROSE trials (i.e. those not randomised to receive ABT) are a suitable proxy population for those patients who cannot or prefer not to take hormonal ABT. The EAG are uncertain whether this is a reasonable proxy and the company do not provide a rationale for why it should be. We note that there may be several reasons why patients are unable to take

hormonal ABT, including having a history or risk of thrombosis, having diabetes, being a smoker, having a history of cancer, or personal preference. Given the uncertainty in whether patients in the PRIMROSE trials are appropriate as a proxy for those who cannot or prefer not to take ABT, as well as uncertainty in the size of this patient group in clinical practice (section 2.2.3), we have highlighted this uncertainty relating to Population #3 as a key issue for further consideration (see Key Issue 3).

3.2.1.1.5.2 Exclusion of patients eligible for surgery or with large fibroids indicative of surgery (Population #1)

Patients were excluded from participating in the PRIMROSE trials if their condition was so severe that they would require surgery within 6 months regardless of the treatment provided. This means that patients relevant to Population #1 were excluded. In addition, patients with fibroids over 12 cm in diameter were also ineligible to participate in the PRIMROSE trials. Such patients could be eligible for surgery or might benefit from fibroid reduction provided by linzagolix 200 mg without ABT. The linzagolix SmPC does not exclude these people. We highlight this uncertainty relating to how well the PRIMROSE trials represent Population #1 as an additional issue for further consideration (see Key Issue 3).

3.2.1.1.5.3 Exclusion of patients receiving long-term therapy (Population #2)

The PRIMROSE trials had a relatively short duration and patients receiving therapy for longer than 52 weeks are not represented.

3.2.1.1.5.4 Participants' baseline characteristics

Patient baseline characteristics for the individual trials are reported in CS Appendix M.3.2. In PRIMROSE 1 all treatment groups had similar baseline characteristics including similarity of prognostic characteristics, and likewise for PRIMROSE 2. Therefore, we agree with the CS that the within-trial baseline characteristics are generally comparable and that there is low risk of bias for any imbalance across treatment groups.

Most patients in PRIMROSE 1 were of Black race (61% to 65% across all trial arms) which differs from the PRIMROSE 2 population (4% to 6% were of Black race across all trial arms). Black race is a key risk factor for the development of uterine fibroids (section 2.2.1.2). The EAG's clinical expert commented that both PRIMROSE trials could reflect the proportion of Black people seen in clinical practice: PRIMROSE 1 would reflect those NHS Trusts who see a lot of Black patients, e.g. in London, whereas PRIMROSE 2 would be more representative of the population in the expert's clinical practice in Southampton. There do

not appear to have been any Asian women included in the PRIMROSE trials, although the EAG's clinical expert estimated that Asian patients make up 5-10% of the patients at his clinical practice and noted that Asian women not receiving HRT have greater risk of BMD loss if they continue on any therapy that does not include HRT so have narrower treatment options than lower-risk patients. Overall, the EAG's clinical expert agreed that, aside from not including Asian patients, both PRIMROSE trials are generally representative of the population likely to be seen in NHS clinical practice: the individual trial results (CS Appendix M) would reflect local population characteristics whilst the pooled trial results would reflect the overall population mix.

The EAG's clinical expert noted that BMD in the trials was in the normal range for most patients: this is consistent with the trials' exclusion criteria for BMD loss (which we assume reflect ethical considerations relating to the risk of worsening osteoporosis in susceptible patients).

Important fibroid characteristics (location, number, size; i.e. FIGO classification) are not reported in the patient baseline characteristics, although the FIGO classification appears to have been assessed in the trials, as the SmPC (section 5.1)[7] states "97.5% had FIGO classification from 1-6", and there was a pre-specified subgroup of participants with submucosal fibroids, FIGO 0, 1 or 2 at baseline, to evaluate impact on the primary outcome. The EAG's clinical expert confirmed that the FIGO classification is routinely used in clinical practice, and it is important because (as noted above in section 2.2.1.1), the type and location of a fibroid has a major influence on a patient's symptoms and prognosis. This view is supported by an independent academic paper which further states that lack of this clinical information restricts the predictability of expected effectiveness in a real-world population.[14]

Pressure symptoms are not part of the inclusion or exclusion criteria of the PRIMROSE trials. These can range from discomfort to pain, and influence mobility, urination, and constipation issues. These symptoms may be implied in the pain and quality of life assessments at baseline and in the results although this is not made clear. Patients with only subserosal fibroids were excluded from the trials and the EAG's clinical expert confirmed that these fibroids may be completely asymptomatic or have pressure symptoms. It is unclear if patients with pressure symptoms are included in the trial population or if a patient group is missing.

3.2.1.2 LIBERTY trials and extension studies

3.2.1.2.1 Role of the trials in the technology appraisal

The LIBERTY trials are used in indirect treatment comparisons of linzagolix against relugolix CT to support the company's cost-comparison analyses for Population #1 and Population #2, which assume that linzagolix and relugolix CT have similar clinical effectiveness and safety.

3.2.1.2.2 Study designs

LIBERTY 1 and LIBERTY 2 are completed, international, multicentre, phase III, double-blind, randomised controlled trials that investigated the efficacy and safety of relugolix CT for 24 weeks. A critique of LIBERTY 1 and 2, as applicable to the NMA for which they provide evidence, is in section 3.3.2 of this report. Study characteristics are summarised in Table 6 below, with further details on eligibility criteria in CS Appendix D.3.3.2.

Table 6 Overview of the LIBERTY trials

Study characteristic	**LIBERTY 1**	**LIBERTY 2**
Study ID	NCT03049735	NCT03103087
Study designs	Replicate double-blind RCTs: 3 arms: placebo, relugolix CT, and delayed relugolix CT (relugolix monotherapy followed by relugolix CT at 12 weeks)	
Locations	Africa, Europe, North America, South America	
	80 sites, 1 in the UK (number of UK patients not stated)	99 sites, none in the UK
Populations	Premenopausal women aged 18-50 years with ultrasound-confirmed fibroids and heavy menstrual bleeding (≥80 mL per cycle for 2 cycles or ≥160 mL for 1 cycle)	
Randomisation	1:1:1, unstratified	
Regimens and participants	Randomised N=388 Completed N=308	Randomised N=382 Completed N=302
	Placebo N=127 Relugolix CT N=128 Delayed relugolix CT[a] N=132	Placebo N=129 Relugolix CT N=125 Delayed relugolix CT[a] N=127

Study characteristic	LIBERTY 1	LIBERTY 2
Primary outcome	Reduction in MBL at 24 weeks reported as response (proportion of patients achieving the outcome); measured by alkaline haematin method	
Duration	24 weeks	

Sources: CS Appendix D.3.3.2, trial publications (Al-Hendy et al. 2021[15], Stewart et al. 2022[16]).
Abbreviations: LTE: long-term extension; MBL: menstrual blood loss; RCTs: randomised controlled trials.
[a] delayed relugolix CT: relugolix monotherapy for 12 weeks followed by relugolix CT for 12 weeks.

3.2.1.2.3 Relevance of the placebo arms to BSC in clinical practice

The therapies received by patients in the placebo arms of the LIBERTY trials are not well described in the trial publications.[15, 16] However, the trial protocol (available from clinicaltrials.gov) confirms that patients in the LIBERTY trials could not receive tranexamic acid. Therefore, as with the PRIMROSE trials described above (section 3.2.1.1.4), the placebo arms in the LIBERTY trials are not fully reflective of clinical practice.

3.2.1.2.4 Trial population characteristics

Baseline characteristics for participants in the individual LIBERTY 1 and LIBERTY 2 trials are provided in CS Appendix Table 9. Baseline characteristics for LIBERTY 1 were similar in both treatment groups except that actual menstrual blood loss was slightly lower in the placebo group at 218.8 mL compared to 239.4 mL in the relugolix CT group, although a similar proportion of patients had MBL<225 mL in both groups (67% and 66% respectively). Likewise for LIBERTY 2, baseline characteristics were similar in both treatment groups except that actual menstrual blood loss was slightly lower in the placebo group at 211.8 mL compared to 246.7 mL in the relugolix CT group, although a similar proportion of patients had MBL<225 mL in both groups (67% and 64% respectively). The study publication states that the demographic and clinical characteristics of the participants at baseline were similar across the trial groups.[15] The EAG's clinical expert confirmed that the baseline characteristics that are reported are consistent with what he would expect to see in clinical practice.

The characteristics are similar to those of the participants in the PRIMROSE trials, except that there were proportionally more Black people (almost half the population was Black compared to approximately one third of the population in the pooled analysis of the PRIMROSE trials). Similarly, FIGO classification, number and location of fibroids are not

reported. For a comparison of the baseline population characteristics of the LIBERTY and PRIMROSE trials see section 3.3.3.1.

3.2.1.3 PEARL trials

3.2.1.3.1 Role of the trials in the technology appraisal

The PEARL trials are used in NMA comparisons of linzagolix against leuprolide acetate to support the company's cost-comparison analyses for Population #1 and Population #2 (Clarification Response A11), which assume that linzagolix and other GnRH analogues have similar clinical effectiveness and safety.

3.2.1.3.2 Study designs

PEARL I and PEARL II are completed, randomised, multi-centre, phase III, double-blind, RCTs. PEARL I evaluated two different doses of ulipristal acetate versus placebo (i.e. three arms) in an anaemic population with symptomatic uterine fibroids. PEARL II evaluated two different doses of ulipristal acetate versus leuprolide acetate in a non-anaemic population with symptomatic uterine fibroids. Study characteristics are summarised in Table 7 below, with further details on eligibility criteria in CS Appendix D.3.3.3 and D.3.3.4.

Table 7 Overview of the PEARL trials

Study characteristics	PEARL I	PEARL II
Study ID	NCT00755755	NCT00740831
Study designs	Double-blind RCT	Double-blind RCT
Locations	Czech Republic, Hungary, India, Romania, Russia, Ukraine. No UK sites.	Austria, Belgium, Germany, Israel, Italy, Netherlands, Poland, Spain. No UK sites.
Populations	Premenopausal women aged 18-50 years and BMI 18-40 with excessive uterine bleeding (PBAC score >100) caused by fibroids (at least one fibroid ≥3 cm, none >10 cm) and anaemia (Hb ≤10.2 g/dL) for whom surgery is indicated. All participants were eligible for surgery after week 13.	Premenopausal women aged 18-50 years and BMI 18-40 with excessive uterine bleeding (PBAC score >100) caused by fibroids (at least one fibroid ≥3 cm, none >10 cm) for whom surgery is indicated. All participants were eligible for surgery after week 13.

Study characteristics	PEARL I	PEARL II
		(Anaemia was not an inclusion criterion)
Randomisation	2:2:1; stratified for haematocrit level (≤28% or >28%) and for race (Black or other)	1:1:1; stratified for race or ethnic group [race and ethnic groups not specified]
Regimens and participants	Ulipristal acetate 5 mg N=96 Ulipristal acetate 10 mg N=98 Placebo N=48 All study arms included 80 mg iron tablets (participants were anaemic).	Ulipristal acetate 5 mg N=98 Ulipristal acetate 10 mg N=104 Leuprolide acetate N=101
Primary outcome	Co-primary outcomes: Proportion of patients with reduction in uterine bleeding (PBAC score <75) at week 13. Change in total fibroid volume at week 13.	Proportion of patients with control of uterine bleeding at week 13 (PBAC score <75). (Change in fibroid volume was a secondary outcome)
Duration	13 weeks; plus off-treatment follow up to week 38	13 weeks; plus off-treatment follow up to week 38

Sources: CS Appendix D.3.3.3 and Donnez et al. 2012[17]; CS Appendix D.3.3.4 and Donnez et al. 2012[18]
Abbreviations: Hb: haemoglobin; PBAC: pictorial blood-loss assessment chart; RCT: randomised controlled trial.

3.2.1.3.3 Trial population characteristics

There is slight variation in baseline characteristics (where reported) between the arms within each of the PEARL trials.[17, 18] The EAG conclude that although there is within-trial heterogeneity in baseline population characteristics in each PEARL trial, there is no indication of systematic differences between arms in disease severity or prognostic factors.

Due to differences in reporting, only haemoglobin, age, BMI, uterine volume, and race can be directly compared between the two PEARL trials. Age and BMI were similar in both trials. PEARL had lower haemoglobin, reflecting the anaemic population, and higher total uterine volume, than PEARL II. Most patients (≥84%) in both trials were White. PEARL I had 10% to

15% Asian and no Black patients; whilst PEARL II had few if any Asian patients (only reported as “other”), and 9% to 11% were Black patients.

For a comparison of baseline characteristics between the PEARL, PRIMROSE and LIBERTY trials see section 3.3.3.2.

The EAG believe that there were no major outliers in baseline characteristics in comparison with the PRIMROSE and LIBERTY trials which were assessed by our clinical expert as representative of UK clinical practice, and therefore consider that the PEARL trials are likely to represent UK clinical practice with the caveat that PEARL I represents an anaemic population and in which the placebo group was prohibited from receiving tranexamic acid.

EAG conclusion on the included trials

All included trials are RCTs with comparative data up to 24 weeks for PRIMROSE and LIBERTY, and up to 13 weeks for PEARL, which is short-term relative to expected longer-term treatment of >6 months outlined in the proposed position in the treatment pathway. However, patient subgroups identified by the company as relevant to their decision problem and economic analyses are missing from the PRIMROSE trials, namely those eligible to receive surgical interventions (Population #1), those who would receive long-term treatment (Population #2), those unable to receive hormonal therapy (Population #3), and patients who would receive tranexamic acid. It is unclear how important these exclusions are, for example whether patients in the trials could be a suitable proxy for those not included. We have highlighted this for further consideration; see Key Issue 3.

3.2.2 Risk of bias assessment

3.2.2.1 Risk of bias assessment for the PRIMROSE trials

A critical appraisal of PRIMROSE 1 and PRIMROSE 2, where they were assessed together as ‘identical’ trials, using the NICE checklist for RCTs, is reported in CS section B.2.5. The EAG have critically appraised the trials in Appendix 2 of this report. The company included an additional assessment of the PRIMROSE trials in the relevant ITC section (CS Appendix D.3.7), but this was based on conference abstracts for the trials and the full publications are now available. In general, we believe the trials are at low risk of bias, with a few exceptions. There is unclear risk of selection bias due to lack of reporting of fibroid characteristics, which are important prognostic factors, although in the reported characteristics including other prognostic factors such as race and BMI there was balance across the treatment groups.

There is unclear risk of detection bias and reporting bias due to the way in which fibroid volume was measured (see section 3.2.3.1.3). There is also unclear risk of attrition bias due to the imbalance in the number of dropouts between groups which mostly affects the uterine and fibroid volume outcomes in PRIMROSE 1 where there was the most missing data.

3.2.2.2 Risk of bias assessment for the LIBERTY trials

Risk of bias assessments for LIBERTY 1 and 2 are reported in CS Appendix D.3.7. The company has not included justifications for their assessments, nor provided any overall statement of risk of bias. Therefore the EAG has assessed the LIBERTY trials for risk of bias using the NICE checklist, consistent with use of the NICE checklist for the PRIMROSE trials, and our completed checklist is in Appendix 2. Overall, our assessment of the trials is that they are at low risk of bias in all domains. There was an unclear risk of selection bias due to lack of reporting of the method of randomisation and lack of reporting of important prognostic fibroid characteristics, however, the reported participant baseline characteristics were generally similar across the treatment groups within each trial (section 3.2.1.2.4).

3.2.2.3 Risk of bias assessment for the PEARL trials

The PEARL trials were included by the company in this technology appraisal in response to Clarification Question A11 to extend the NMA network to include all GnRH analogues relevant to the NICE scope. The EAG have assessed these trials for risk of bias using the NICE checklist (see Appendix 2), consistent with use of this checklist for the PRIMROSE and LIBERTY trials. Overall, our assessment of both trials is that PEARL I is at low risk of bias and that PEARL II is at low risk of bias except for unclear risk of bias around non-reporting of fibroid characteristics.

EAG conclusion on risk of bias

All trials in this appraisal (PRIMROSE 1 and 2, LIBERTY 1 and 2, PEARL I and II) are mostly at low risk of bias across the various domains of bias. Where risk of bias is unclear this is mainly due to lack of reporting of FIGO classification for prognostic fibroid characteristics which is a consistent omission across all trials except PEARL I.

3.2.3 Outcomes assessment

3.2.3.1 Clinical effectiveness outcomes

3.2.3.1.1 Primary outcome

Response. The primary outcome in PRIMROSE trials (also primary in the LIBERTY trials) was the proportion of patients who achieved a reduction of HMB at week 24, defined as MBL

≤80mL and with a ≥50% reduction in MBL from baseline in the last 28 days before the week 24 visit (also assessed at week 52). This dichotomous outcome is referred to by the company as response. The EAG's clinical expert agreed that this represents a clinically meaningful reduction in HMB.

In the PRIMROSE and LIBERTY trials MBL was assessed using the alkaline haematin (AH) method which involves chemically measuring the blood content of used sanitary products and is considered the 'gold standard' approach.[19] All used sanitary products were sent to a central laboratory masked to the trial treatment for analysis and assessment of daily MBL (CS Table 10). In the PEARL trials MBL was assessed using a different approach: the pictorial blood assessment chart (PBAC) score, which records the number of tampons or towels used and the degree to which they are stained with blood. The PEARL trials therefore used a different definition of response, which was a PBAC score less than 75 (in the normal range), summed over the preceding 28-day period.

Estimates of MBL using the PBAC and AH approaches are generally correlated.[19] However, as noted by the company in TA832, calibration coefficients from the PBAC to the AH method differ between studies and publicly available data are required to enable translation of PBAC into AH measurement to enable comparison of the MBL estimates. Such information is available from the PEARL trial publications but not for other studies that might potentially be included in evidence networks for NMA such as the studies identified by the company that were conducted in Japan.[20-22] As noted in TA832, the specific conversion factor is not likely to be the same between the PEARL and Japanese trials which would make it incorrect to use the same calculations and translations between PBAC and AH across them. The Evidence Review Group in TA832 suggested that it might be possible to convert from PBAC score to MBL volume, using the approach adopted in Magnay et al. 2020,[19] but this depends on data availability in the trial publications. For the Japanese study by Osuga et al. 2019 this information could not be found even when the EAG had access to the study protocol and CSR.

3.2.3.1.2 Ranked secondary outcomes

These secondary outcomes were assessed in the following sequence (highest priority first) to protect against the risk of multiple testing inflating the overall type 1 error rate (CS Table 11). For statistical discussion please see section 3.2.4.4.

Time to reduced HMB. This was defined as the number of days from Day 1 of treatment to the first day the woman reached the definition of HMB (as defined for the primary outcome) and MBL was maintained up to week 24 and up to week 52.

Amenorrhoea (absence of bleeding). This was defined as having no sanitary material returned or the MBL volume below the lower limit of quantification within at least a 35-day interval maintained up to week 24 and up to week 52.

Time to amenorrhoea, defined as the number of days from Day 1 to the first day the woman reached the definition of amenorrhoea and without having bleeding after this time up to week 24 and up to week 52.

Number of days of uterine bleeding in the last 28-day interval before week 24 and before week 52.

Haemoglobin concentrations were assessed in a subgroup of patients who had anaemia (defined in CS Table 10 as Hb<12g/dL) whose baseline Hb was <10.5 g/dL (CS section B.2.9.6.5). For the comparison of linzagolix against placebo the CS reports differences in the change from baseline in Hb concentration (CS Table 21). However, for the comparison of linzagolix against relugolix CT the CS reports only the percentage change in Hb concentration from baseline (CS section B.2.9.6.5). This is less clinically informative but appears to reflect that only the percentage change is available from the LIBERTY trials.[15]

3.2.3.1.3 Additional outcomes

Pain related to uterine fibroids was assessed by patient self-report using an on-site eDiary with a numerical rating scale (NRS) from 0 (no pain) to 10 (worst possible pain) over the preceding 28 days. The NRS scores were categorised as 0 = none, 1 to 3 = mild, 4 to 6 = moderate, 7 to 10 = severe. Assessed at several timepoints including weeks 24 and 52. The CS does not report any validation or testing of this scale, although the EAG's clinical expert commented that a similar basic scale would be used in clinical practice.

In the PRIMROSE trials pain was reported as the mean and categorical changes in scores as well as the proportion who achieved a clinically meaningful pain response, defined as those who had a numerical rating scale score of at least 4 (indicating moderate or severe pain) at baseline and achieved a score of 1 or less at Week 24. The EAG's clinical expert agreed that achieving an NRS score of 1 or less would represent a meaningful clinical improvement. In the LIBERTY trials only the proportion achieving a clinically meaningful improvement in pan score was reported.

Primary fibroid volume was estimated using the same ultrasonography approach as for uterine volume. CS Table 10 states that "up to the three largest fibroids were included in the volume calculation" without explanation of why or when more than one fibroid would be included in the calculation. The EAG are uncertain whether this could be a source of bias, for instance if certain subgroups of the population (e.g. those with specific race, BMI or other anatomical characteristics) might have differed systematically in the way that their fibroid volume was calculated. The EAG also note that patients with large fibroids >12 cm diameter were excluded from the trials, imposing a ceiling effect on this outcome. Moreover, the CS does not report which types of fibroids were the largest in a given patient, e.g. whether they were situated inside or outside of the uterus. Due to these limitations the EAG believe that results for this outcome might not be consistently reliable when making comparisons between therapies or patient groups, so we have noted this as being a potential, although unclear, risk of bias (section 3.2.2.1). We also note that the total fibroid volume, potentially a more reliable measure, depending on how it was calculated, was available for the PRIMROSE trials when used in the NMA comparison of linzagolix against relugolix CT (section 3.3.3.1) but not reported by the CS for the within-trial comparison of linzagolix against placebo.

The reporting of primary fibroid volume is not consistent between the PRIMROSE within-trial comparisons of linzagolix against placebo (section 3.2.5.2.1) and the company's indirect comparisons of linzagolix against GnRH analogues (section 3.5.1.4). In the PRIMROSE trials analyses, primary fibroid volume is reported as the least-squares mean ratio to placebo which has unclear clinical interpretation. It is unclear why the change in fibroid volume relative to the placebo arm, as used in the indirect treatment comparisons was not reported instead.

Uterine volume was estimated using ultrasonography (transvaginal, or abdominal if transvaginal was not available), done by the same operator at all visits where feasible. Due to the different ultrasound methods, operators and inherent imprecision of measurements the EAG believe some variation in this outcome is to be expected.

3.2.3.2 HRQoL outcomes

HRQoL outcomes are specified as a separate class of outcome (i.e. not "secondary" or "additional"). CS Table 11 does not mention any statistical interpretation criteria for these outcomes.

Disease-specific symptom severity and HRQoL were assessed using the 3-month recall version of the UFS-QoL (Uterine Fibroid Symptom-Quality of Life) questionnaire. Assessments were completed by participants on site using an eDiary set up by site staff. UFS-QoL is a validated measure comprising an 8-item symptom severity scale which measures a patient's objective symptoms (e.g. bleeding, cramping) and a 29-item HRQoL scale which measures a patient's subjective HRQoL experience based on six subdomains (concern, activities, energy/mood, control, self-consciousness, sexual function) (CS section B.2.6.2.7). Each symptom severity or HRQoL item is scored on a 5-point Likert scale and then scores are summed and transformed to give two 0-100 scales, one for symptom severity with improvement indicated by lower scores, and one for HRQoL with improvement indicated by higher scores. The CS does not state what a minimum clinically important difference or change in UFS-QoL score would be (results are presented in the CS as changes in mean scores without a numeric clinical interpretation). A recent (2023) study[23] states that a specific minimal clinically important difference for the UFS-QoL has not been established, but a difference of 10 points appears reasonable, whilst a previous study [24] suggested a change of 9-15 points could indicate a clinically meaningful improvement for the symptom severity or HRQoL scales. The EAG assume that the same minimum clinically important difference would apply to both the severity and HRQoL scales (this was not stated in the Anchan et al. study[23] but the results reported by Harding et al.[24] showed the severity and HRQoL scales to be within the 9-15 point range).

EQ-5D-5L index and visual analogue scale (VAS) scores were also assessed using on-site eDiaries. The company argue that "As the effects of fibroids are complex, and patients may report differently depending on exactly which timepoint in their menstrual cycle they complete the EQ-5D assessment, a singular measurement on a single day may not truly reflect patients' overall HRQoL. These issues raise questions as to the degree of validity and reliability of the EQ-5D scores from the PRIMROSE trials." As such the company favoured the UFS-QoL for assessing patients' HRQoL.

3.2.3.3 Safety outcomes

The CS reports the numbers of adverse events and the proportion of participants experiencing them that were reported by >2% in at least one active treatment group, for both treatment periods, up to Week 24 and Weeks 24-52 (CS B.2.10). This included vasomotor symptoms associated with hormonal treatment such as hot flushes and headache. Additionally, BMD was assessed as an adverse event of special interest due to the known effects of oestrogen suppression relating to osteoporosis. Assessments were made at three anatomic sites (lumbar spine, femoral neck, and total hip). The EAG's clinical expert

suggested that a 5% change in BMD would be clinically meaningful. Week 76 results from PRIMROSE 1 and 2, and unpublished data from the PRIMROSE 3 extension study, for which the primary outcome was change in BMD at 12, 18 and 24 months from end of treatment in PRIMROSE 1 or 2, were provided to support this safety outcome.

EAG conclusion on the outcomes assessment

The outcomes assessed are appropriate for the condition but the CS does not discuss the degree of change for each outcome that would be considered clinically meaningful. The EAG have particular concerns around the assessment and reporting of primary fibroid volume, which might be a source of bias. The company prefer the disease-specific UFS-QoL measure of HRQoL than the EQ-5D-5L, which the EAG agree is appropriate (based on precedent in TA832 and the opinion of the EAG's clinical expert).

3.2.4 Statistical methods of the included studies

3.2.4.1 Analysis populations

The intention to treat (ITT) population is not used in company analyses. Instead, the clinical effectiveness outcomes were analysed using the full analysis set (FAS) and safety outcomes were analysed using the safety analysis set (SAS).

The FAS was defined as all randomised patients in PRIMROSE 1 and PRIMROSE 2 who received at least one dose of double-blind study drug irrespective of the treatment received and who did not violate the following two exclusion criteria prior to first administration of double-blind study drug (based on the results of pre-treatment baseline assessments reported after Day 1): (1) significant risk, history of or known osteoporosis or other bone metabolic disease; (2) liver function test results ≥2 times the upper limit of normal. The difference in patient numbers between the randomised population (ITT) and the FAS ranged from 9 to 20 patients per trial arm (7% to 11%) in PRIMROSE 1 and from 4 to 10 patients per trial arm (4% to 9%) in PRIMROSE 2 (CS Appendix Table 51).

The EAG requested a sensitivity analysis using the ITT population to enable an assessment of the robustness of the FAS-based analyses to these missing data. Instead of providing this, the company provided a detailed explanation of why they believed an ITT analysis to be inappropriate - which was because the patients excluded from the FAS had failed the trial eligibility criteria after randomisation when they received delayed test results and therefore would be ineligible for inclusion. We note that the linzagolix EPAR does not provide an opinion on whether the FAS population is appropriate.[25] However, the EAG agree with the company's rationale for not employing an ITT analysis as reported in Clarification Response

A9. We note that the numbers of patients missing from the FAS were reasonably well-balanced across the trial arms and their baseline characteristics appear to be generally similar to those of the FAS population, with no clear signals of any systematic imbalances between the trial arms (Clarification Response Table 1). As noted above, the number of missing patients from the FAS was larger in PRIMROSE 1 than in PRIMROSE 2.

A per protocol (PP) population is also defined (CS Appendix M.3.1) and used in a sensitivity analysis (CS Appendix M.3.3.2) (see section 3.2.4.6 below).

The SAS was defined as all randomised patients in PRIMROSE 1 and 2 who received at least one dose of double-blind study drug irrespective of the treatment received. Patients were analysed according to treatment received.

3.2.4.2 Pooled analysis of PRIMROSE 1 and PRIMROSE 2

The analyses for all efficacy outcomes reported in the CS focus on a pooled FAS analysis of PRIMROSE 1 and PRIMROSE 2, which had identical study designs apart from their geographical locations and patient baseline characteristics. The EPAR states that the pooled analysis was done according to a statistical analysis plan written after the 24-week results from PRIMROSE 1 and 2 were available.[25] The CS primarily reports the pooled analysis, although individual analyses for PRIMROSE 1 and PRIMROSE 2 are provided in Appendix M. The CS is not explicit about how the two trials were combined in the pooled analysis but according to the statistical analysis plan it appears that the data from the individual trials were added together and statistical analyses were then run on the combined data.

Given that there are some differences between the individual PRIMROSE trials in the baseline characteristics, the EAG believe a meta-analysis of the PRIMROSE trials would be preferable to naïve pooling, to enable statistical heterogeneity of the trials and weighting of effects by sample size to be explored objectively. Meta-analysis would also clarify whether the naïve pooled analysis is appropriate. We note that the pooled analysis gives implausible results for two outcomes: effect estimates for the pooled analysis are outside the range of values in the individual trials for the response and UFS-QoL symptom severity score outcomes (Figure 2 and Figure 17 respectively in the results section of this report).

A pooled analysis of safety data was performed up to Week 52, with a supplemental post-hoc analysis including pooled data up to Week 76 for select BMD assessments. This was to provide a comprehensive overview and more precise estimates for the rates of adverse events and for potential bone BMD loss with linzagolix treatment (CS section B.2.4.1.1). The EAG agree that a pooled safety analysis is appropriate.

3.2.4.3 Sample size calculations

The sample size calculations ensured that the individual PRIMROSE trials had 90% statistical power to detect a difference between all four dose regimens of linzagolix and placebo for the primary outcome (MBL improvement response rate), assuming response rates of 30% for placebo and 70% for linzagolix (CS Table 11). After the exclusions noted above in section 3.2.4.1, sufficient patients remained in the FAS to achieve the intended statistical power.

3.2.4.4 Methods to account for multiplicity

For the individual PRIMROSE trials, secondary outcomes were analysed sequentially in ranked order within each linzagolix treatment group, to protect against an overall type I error. An outcome was only claimed to be statistically significant if the resulting p-value for that outcome and all outcomes higher up in the testing order (for a given treatment group) were less than 0·0125 (CS Table 11).

Additional efficacy outcomes in the individual PRIMROSE trials were tested using a p-value of less than alpha=0·0125 with no further adjustments for having multiple outcomes (CS Table 11). The CS does not clarify whether these outcomes were considered independently of the hierarchy for the preceding outcomes, or whether all outcomes in the preceding hierarchy would need to be statistically significant for the additional efficacy outcomes to be tested.

For the pooled analysis of week 24 outcomes, the company say that “as the analysis is to improve precision, statistical results are to be regarded from an exploratory perspective. No adjustment was made for multiplicity within the pooled analyses” (CS section B.2.4.1.1). This appears counterintuitive, as precision and exploration are opposite concepts. The EAG note that the need to protect against the effect of multiple testing resulting from analysing multiple linzagolix dose regimens and multiple outcomes is independent of whether the trials are pooled or not. Given that a specific statistical analysis plan was developed for the pooled analysis, the EAG are unclear why an objective approach to account for multiplicity was not included in the plan. The company’s statistical approach undermines their preferred (pooled trials) analyses by implying that these can only support “exploratory” inferences.

3.2.4.5 Outcome analyses

Overall, the statistical methods used for outcome analyses appear broadly appropriate. We note that the EPAR did not raise any concerns around the statistical methods used or their assumptions. [25] All outcome analyses appear to have used broadly consistent approaches

and included race (the randomisation stratification factor) as a covariate which is appropriate.

3.2.4.6 Handling of missing data

CS Table 11 states that in general missing data were not imputed. Patients who had less than 28 days of data were counted as non-responders. Patients who discontinued prematurely due to lack of efficacy or adverse events or who underwent operative or radiological interventions for uterine fibroids were considered as non-responders for the primary analysis and in a similar way for the secondary outcomes of amenorrhea and reduced MBL. These are appropriate assumptions.

Two sensitivity analyses were conducted for the primary outcome to assess the robustness of the primary clinical effectiveness analysis results under alternative assumptions for days on which there were no data from the AH method. The first was done by imputing daily bleeding data based on the eDiary responses for days when no sanitary products were returned but bleeding had been reported in the eDiary. The second was done by assigning patients who discontinued early or who did not return any sanitary protection tools and had missing bleeding information in the eDiary as non-responders. According to the EPAR and study CSRs these analyses confirmed the primary analysis finding of significantly reduced menstrual blood loss in each active treatment group compared to placebo.[25-27]

CS Appendix M.3.3.2 states, descriptively only, that results of sensitivity analyses imputing missing data and results in the per protocol set were consistent with those of the main analysis. Results of these analyses are not reported in the CS or trial publications. Missing values for continuous efficacy endpoints were handled within the analysis itself via mixed model repeated measures, with the assumption that the model specification was correct, and that the data were missing at random.

Outcomes with missing data are summarised in Table 8 (percentages missing are relative to the FAS population)

Table 8 Outcomes with missing data

Outcome	Missing data at week 24
Haemoglobin Pooled analysis (CS Table 21)	31 to 48 patients (24% to 33%) per arm
Pain score Pooled analysis (CS Table 22)	51-64 patients (25% to 31%) per trial arm

Primary fibroid volume (CS Appendix Table 63)	PRIMROSE 1: 33-52 patients (31% to 49%) per trial arm PRIMROSE 2: 13-20 patients (13% to 20%) per trial arm
Uterine volume (CS Appendix Table 63)	PRIMROSE 1: 32-47 patients (31% to 45%) per trial arm PRIMROSE 2: 13-20 patients (13% to 20%) pe trial arm
UFS-QoL symptom severity score	Same as for pain outcome
EQ-5D (CS Appendix Table 67)	Not reported NB for Week 52, around one third missing from placebo and 200mg + ABT arms in PRIMROSE 1 (as examples - treatment switching affected some other arms) (CS Appendix Table 68)

The EPAR noted a high rate of missing BMD measurements at week 24 and at week 52, for both PRIMROSE trials due to the dropout rate.[25] However, the clinical characteristics and baseline BMD of the patients missing week 24 BMD data and those with week 24 BMD data are very similar.

3.2.4.7 Sensitivity and post hoc analyses

Sensitivity analyses to assess the implications of missing data were conducted as noted in section 3.2.4.6 above. Results of pre-specified subgroup analyses on race, therapy cycle length, excessively heavy menstrual bleeding (defined by the third quartile of baseline MBL in the FAS), baseline FIGO classification, and fibroid size are reported in CS Appendix Figures 23 and 24 (CS Appendix E). Overall, the results show consistent effectiveness of the linzagolix compared to placebo for all the subgroups. There is a suggestion in CS Appendix Figure 23 that the strength of effect of linzagolix differs between the Black/Afro-American subgroup compared to the “Other” subgroup in PRIMROSE 1, as there appears to be less of a dose-response pattern evident in the Black/Afro-American group; this group did not achieve as high a response rate for the linzagolix 200mg plus ABT regimen as was achieved in the “Other” group.

EAG conclusion on study statistical methods

The company’s approach to trial statistics appears broadly appropriate for the individual PRIMROSE trials. However, the company’s approach to pooling the trials is not well explained and the company declared the results of the pooled analysis to be “exploratory” without requiring formal hypothesis testing or adjustment for multiple comparisons. The EAG believe that the same standard of statistical testing and adjustment for multiplicity used in the identical individual trials should have been applied

in the pooled analysis. We also suggest that a meta-analysis of the two individual PRIMROSE trials would be helpful to enable objective consideration of statistical heterogeneity and differences in sample sizes between the trials.

3.2.5 Efficacy results of the PRIMROSE studies

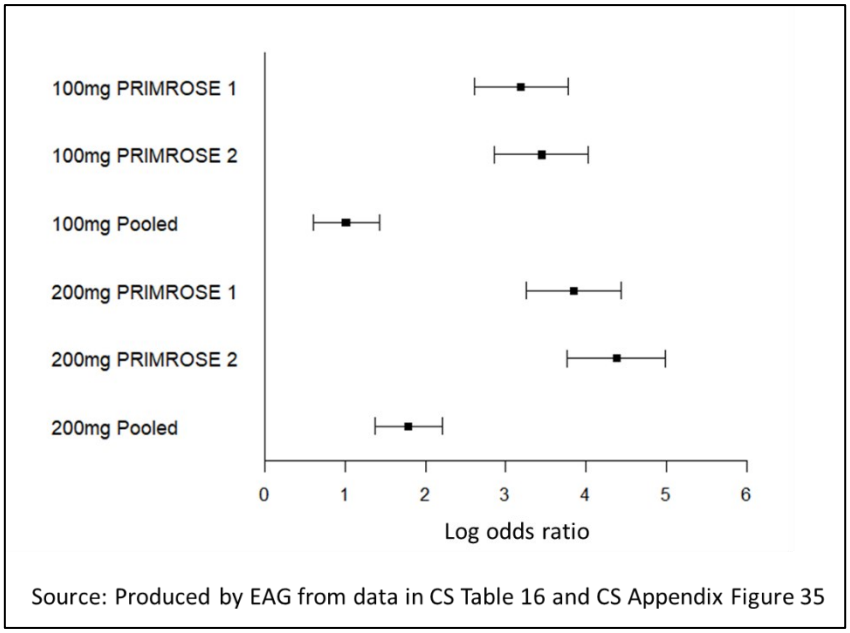
This section focuses on the evidence reported for the trial dosing regimen groups relevant to the cost-utility analysis of this appraisal, i.e. for Population #3, people receiving longer-term treatment without hormonal add-back therapy compared to placebo.

3.2.5.1 Primary outcome: clinically meaningful reduction in heavy menstrual bleeding (response) at Week 24

The primary outcome was the proportion of patients achieving a response (i.e. achieving a clinically meaningful reduction HMB). Response was defined as MBL $\leq$80 mL, with $\geq$50% reduction in MBL from baseline, at Week 24.

Odds ratios for the response outcome are reported in CS Table 16, but these are based on a skewed (non-normal) distribution. The log odds ratios, shown in Figure 2 below, are similar between the PRIMROSE 1 and PRIMROSE 2 trials, with no statistically significant differences between the regimens in the odds of achieving a response. However, there is a discrepancy in the data since the odds ratios provided by the company for the pooled trials analysis are outside the range of trial data, as shown for the log odds ratios in Figure 2. Nevertheless, overall, patients in the linzagolix groups have favourable odds of achieving a response compared to those in the placebo groups.

The response rates for the pooled analysis at Week 24 were 32.2% (66/205) in the placebo arm, 56.5% (108/191) in the linzagolix 100mg arm, and 74.5 (155/208) in the linzagolix 200mg arm (CS Figure 8 andCS Table 16). The results suggest a dose-response effect, as well as a placebo effect.



Source: Produced by EAG from data in CS Table 16 and CS Appendix Figure 35

Figure 2 Proportion achieving response: linzagolix versus placebo, Week 24

The placebo effect continued into the second treatment period increasing to 42% achieving response in the remainder of the placebo treatment group in PRIMROSE 1 at 52 weeks (CS Appendix M.3.3.1 Figure 36). The company argue that because of the high response rate in the placebo group the relative efficacy of linzagolix may be underestimated. They suggest that the high response rate in the placebo group may be due to patient non-compliance with the method of collecting used sanitary products, leading to overestimation of the number of days with no bleeding (CS sections B.2.12.2.2, and CS B.2.9.7, and clarification response A8). The EAG and our clinical expert considered that the reason for the observed placebo effect is uncertain, and the company's explanation is speculative. Regression to the mean might explain at least some of the placebo effect. The company conducted sensitivity analyses using two different methods of data imputation to check the robustness of the analysis to missing data and they found that the linzagolix versus placebo comparisons were not sensitive to missing data (CS section B.2.12.2.2).

Despite the response rate in the placebo group being 32.2%, the difference between placebo and each of the linzagolix treatment groups at Week 24 is statistically significant for all dose regimens in the pooled PRIMROSE trials ($p<0.001$) (CS Table 16) and in each of the individual PRIMROSE trials ($p<0.003$) (CS Appendix Figure 35).

At Week 52 The proportion of patients in the 100 mg treatment groups achieving a clinically meaningful reduction in HMB in the individual trials was maintained at 57% in PRIMROSE 1 and 53% in PRIMROSE 2 (compared with 56.5%, 56.4% and 56.7% in the pooled analysis, PRIMROSE 1, and PRIMROSE 2 respectively at Week 24). As noted above, there was an

unexplained increase in the proportion of responders in the PRIMROSE 1 placebo arm at Week 52.

3.2.5.2 Secondary and additional efficacy outcomes

3.2.5.2.1 Change in primary fibroid volume (additional outcome)

In the pooled analysis at Week 24, reductions in fibroid volume (limited to the largest three fibroids) were 25% and 48% (change from baseline) in the 100 mg and 200 mg linzagolix treatment groups (CS section B.2.6.2.1). Compared to placebo, the result for the 200mg linzagolix dose regimen is statistically significant (p<0.001) while the result for the 100mg dose is marginally significant (p=0.012) (the specified Bonferroni significance threshold was p≤0.0125) (CS Table 17).

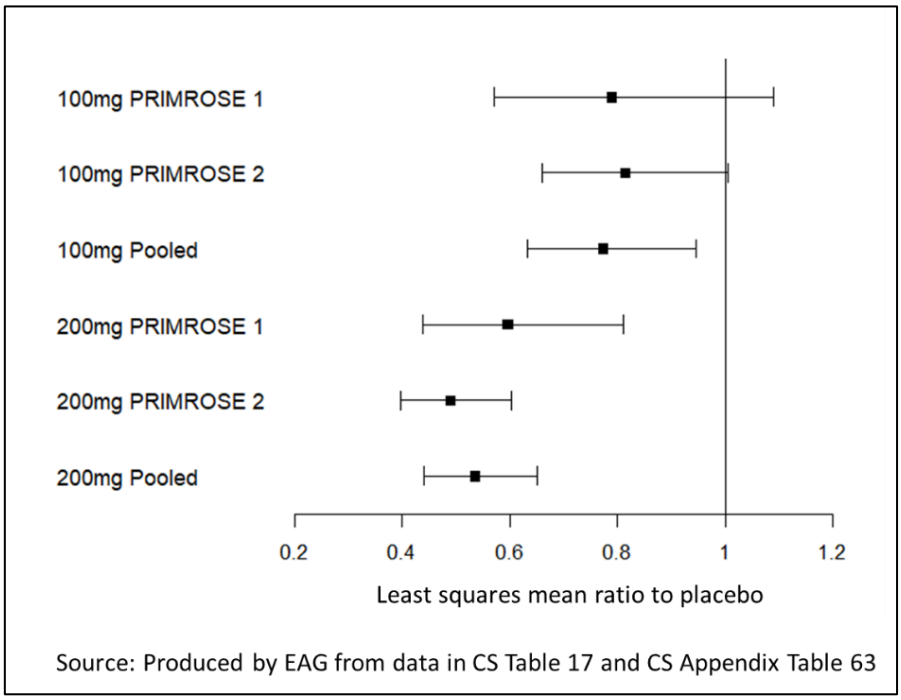


Figure 3 Primary fibroid volume, Week 24

Results for reduction in primary fibroid volume were similar at Week 24 for the individual PRIMROSE trials, with only the 200 mg group achieving a statistically significant result, although both doses achieved significant reduction in primary fibroid volume in the pooled analysis (Figure 3). There is a substantial amount of missing data, n/N: PRIMROSE 1 linzagolix 100 mg 58/94 and linzagolix 200 mg 72/105; and PRIMROSE 2 linzagolix 100 mg 79/97 and linzagolix 200 mg 85/103 (CS Appendix Table 63).

At Week 52, the change from baseline for primary fibroid volume (mean (SD)) was generally maintained at 9.42 mL (104.89) and -10.27 mL (55.53) in the linzagolix 100 mg groups of PRIMROSE 1 and PRIMROSE 2 respectively (CS Appendix Table 64). However, there was substantial missing data (19/61 missing in PRIMROSE 1 and 20/79 missing in PRIMROSE 2) (CS Appendix Table 64).

The EAG are uncertain how meaningful these results for the change in primary fibroid volume are, due to lack of clarity and potential inconsistency in how the primary fibroid(s) were selected and measured (section 3.2.3.1.3). We believe this outcome has potential for (but uncertain risk of) detection bias (section 3.2.2.1).

3.2.5.2.2 Change in uterine volume (additional outcome)

In the pooled analysis at Week 24, reductions in uterine volume (change from baseline) were 15% and 39% (change from baseline) in the 100 mg and 200 mg linzagolix treatment groups (CS section B.2.6.2.1). Compared to placebo, both results were statistically significant: p=<0.001 for both 100 mg and 200 mg linzagolix compared to placebo (CS Table 17). Results comparable across both trials and the pooled analysis were reported only as a ratio (Figure 4).

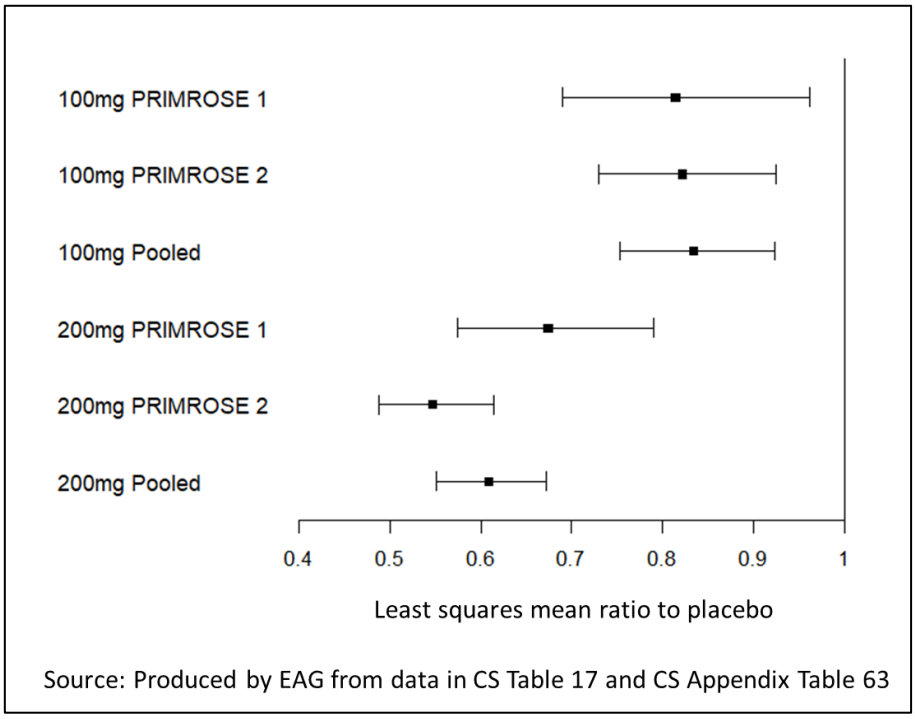


Figure 4 Uterine volume, Week 24

At Week 52, the change from baseline for uterine volume (mean (SD)) was generally maintained at 8.02 (229.05) mL and 94.98 (857.54) mL in the linzagolix 100 mg groups of PRIMROSE 1 and PRIMROSE 2 respectively (CS Appendix Table 64).

3.2.5.2.3 Secondary outcomes relating to reduction in heavy menstrual bleeding

Week 24 results for secondary outcomes related to reduction in HMB, are reported in CS sections B.2.6.2.2 to B.2.6.2.5. These are ranked secondary outcomes in the individual trials, in the following rank order:

- **Time to response (reduced HMB) (pooled analysis)** was significantly shorter in all linzagolix treatment groups compared to placebo. The 100 mg linzagolix group took a median 135.0 days (95% CI 119.0 to 146.0) and the 200 mg linzagolix group took a median 3.0 days (95% CI [redacted]). Median number of days to reduced HMB was non-evaluable in the placebo group (Pooled Analysis data on file Table 2.7.3.6.2.1).

- **Amenorrhoea (pooled analysis)** was achieved in a significantly larger proportion of patients in all linzagolix treatment groups compared to placebo. Amenorrhoea was achieved by 36.1% in the 100 mg linzagolix group and 65.4% in the 200 mg linzagolix group compared to 16.6% in the placebo group.

- **Time to amenorrhoea (pooled analysis)** was significantly shorter in all linzagolix treatment groups compared to placebo. KM estimates for the median number of days to achieve amenorrhoea was non-evaluable for the 100 mg linzagolix group and 33.0 days (95% CI 10.0 to 80.0) for the 200 mg linzagolix group (Pooled Analysis Data on file Table 2.7.3.6.4.1).

- **Number of days of uterine bleeding for the last 28 days (pooled analysis)** was significantly reduced in all linzagolix treatment groups compared to placebo. The percentage of patients with zero days of uterine bleeding was 76% in the 200mg group and 53% in the 100mg group. However, actual change from baseline in the mean number of days of uterine bleeding shows less difference between the dose regimens: 100 mg linzagolix -3.1 (3.2) days mean (SD), and 200 mg linzagolix -4.4 (2.6) days mean (SD) (Pooled Analysis Data on file Tables 2.7.3.6.5.1 and 2.7.3.6.5.2).

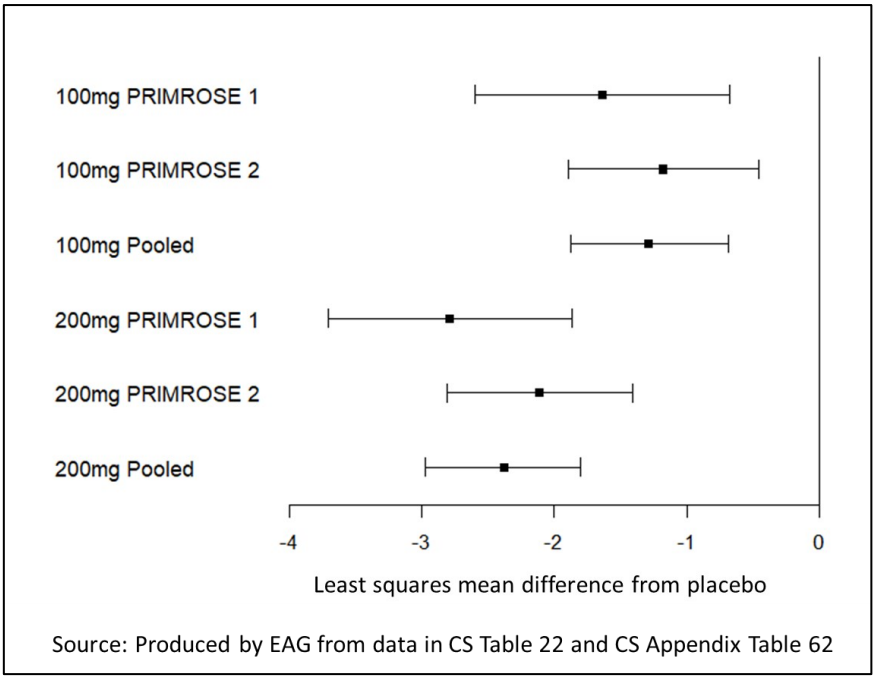
- **Haemoglobin concentrations in patients anaemic at baseline (Hb <12 g/dL) (pooled analysis)** were significantly improved in all linzagolix treatment groups at week 24. Summary values for Hb concentrations at 24 weeks show that the Hb levels only reach 12 g/dL in the linzagolix 100 mg plus ABT, 200 mg, and 200 mg plus ABT groups: mean g/dL (SD) 12.01 (1.57), 12.19 (1.46) and 12.25 (1.5) respectively (Tables 2.7.3.6.6.1 and 2.7.3.6.6.2 of Data on file PRIMROSE 1 and 2 Pooled

Analysis). Therefore, many patients remained anaemic or around the threshold for anaemia. Additionally, women with a haemoglobin level below 6 g/dL (severe anaemia) were excluded from the trials, so it is unclear if linzagolix is indicated for anaemia as a severe symptom of uterine fibroids.

These results support a meaningful reduction in HMB for all linzagolix treatment groups at Week 24 (CS Appendix M.3.3.3.1 to M.3.3.3.2). At week 52, CS Appendix M.3.3.3.1 to M.3.3.3.2 show that these results were sustained over a longer-term treatment period in the individual trials. Including the proportional differences between the PRIMROSE 1 and PRIMROSE 2 trials. However, the evidence is much weaker for this second treatment period as not all treatment groups had estimable results so there is less comparative evidence.

3.2.5.2.4 Uterine fibroid-associated pain (additional outcome)

In the pooled analysis, at Week 24 the uterine fibroid-associated pain score was statistically significantly reduced from baseline in all linzagolix treatment groups compared to the placebo group (CS section B.2.6.2.6). Results for the 100 mg and 200 mg linzagolix treatment groups also appear to be dose-dependent with linzagolix 200 mg effecting greater changes than linzagolix 100 mg compared to placebo (CS section B.2.6.2.6; CS Table 22). Results are broadly similar for the individual trials (Figure 5), and both 100 mg and 200 mg linzagolix treatment groups remained statistically significant in both PRIMROSE 1 and PRIMROSE 2 (CS Appendix Table 62).



Source: Produced by EAG from data in CS Table 22 and CS Appendix Table 62

Figure 5 Uterine fibroid-associated pain, Week 24

At week 52, these results were generally maintained in the linzagolix 100 mg treatment groups, although was a slight deterioration towards the end of the second treatment period in PRIMROSE 1 (CS Appendix Figure 41).

3.2.5.3 HRQoL outcomes

The company used UFS-QoL and EQ-5D-5L to measure HRQOL for the economic models. Choice of assessment tool, UFS-QoL or EQ-5D-5L, makes a difference as to whether any statistically significant changes were observed for the quality-of-life outcome: UFS-QoL scores show significant changes but EQ-5D-5L scores do not (see below). The explanation provided in the CS refers to the UFS-QoL score being based on a 3-month recall of overall pre-treatment and post-treatment experience, whereas the EQ-5D-5L score is based on a single measurement on a single day which may not adequately reflect a fluctuating menstrual cycle (CS Appendix M.3.3.3.6). However, the company base case uses the EQ-5D-5L data mapped to EQ-5D-3L which is according to NICE procedural preferences and is the most conservative option, with a scenario analysis using the UFS-QoL results.

3.2.5.3.1 UFS-QoL

In the pooled analysis, at Week 24 all the linzagolix treatment groups showed statistically significant improvements in both HRQoL scores (Figure 6) and symptom severity scores (Figure 7) compared to the placebo group (CS section B.2.6.2.7, CS Table 23). There is a discrepancy between the reported pooled and individual trial symptom severity scores; the pooled score is outside the range of the individual trial scores (Figure 7).

At Week 52, the linzagolix 100 mg group maintained the improved scores from baseline that were observed at Week 24, but they were not further improved during the second treatment period. This treatment group has the highest symptom severity score and lowest HRQoL score compared to all other treatment groups in both PRIMROSE 1 and PRIMROSE 2 (CS Appendix Table 66).

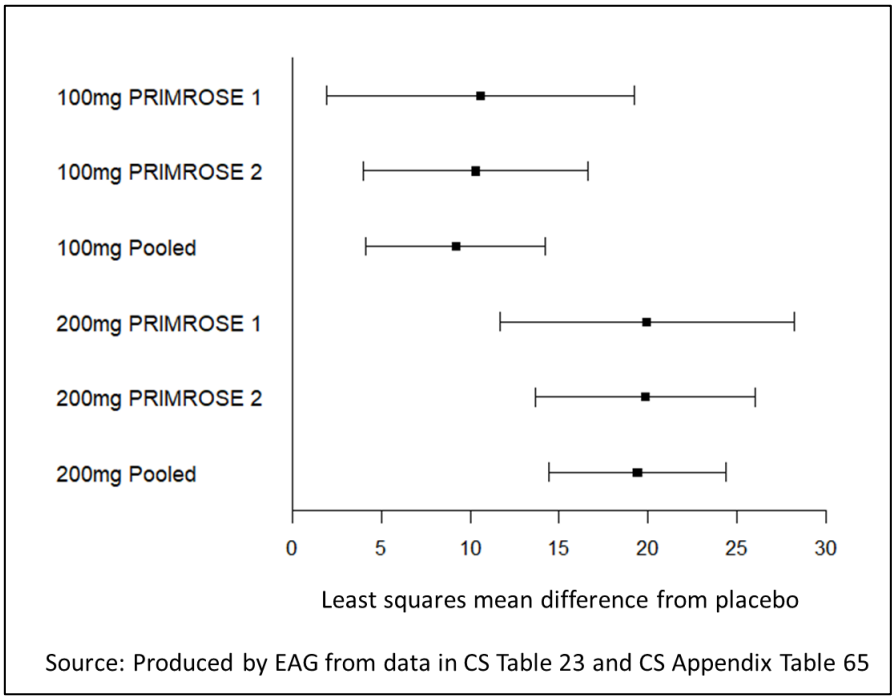


Figure 6 UFS-QoL HRQoL total score, Week 24

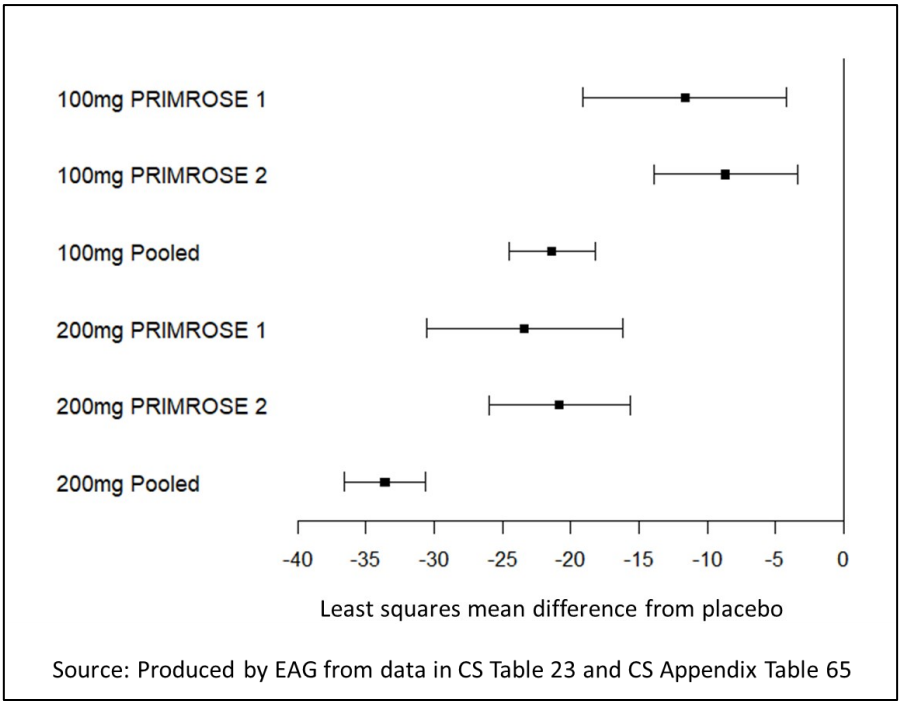


Figure 7 UFS-QoL symptom severity score, Week 24

3.2.5.3.2 EQ-5D-5L

In the pooled analysis at Week 24 all treatment groups showed similar small improvements in both index values and VAS scores, but there were no statistically significant differences for any of the linzagolix treatment groups, including the 100 mg and 200 mg linzagolix groups, compared to placebo (CS section B.2.6.2.7, CS Table 24).

Week 52 EQ-5D-5L results for the individual PRIMROSE trials appear consistent with the Week 24 results, i.e. there were no noticeable differences between treatment groups and placebo (CS Appendix Table 68).

3.2.5.4 Subgroup analyses

Subgroup analyses of the primary outcome (response, defined as a clinically meaningful reduction in HMB at Week 24) that were performed for the pooled analysis show responses across treatment groups were generally consistent for race (Black or African American; other), weight, BMI and age (CS section B.2.7; CS Appendix Figure 23); this is consistent with the individual PRIMROSE trials (CS Appendix Figure 24).

Subgroup analyses of the primary outcome for other planned subgroups were not performed for the pooled analysis, but some are reported for the individual PRIMROSE trials: excessively heavy menstrual bleeding, baseline FIGO 0, 1, or 2 in at least one fibroid (submucosal fibroids), and cycle length (≤28 days; <28 days). The results are generally

consistent but the EAG note that as the confidence intervals are wide (CS Appendix Figure 24).

A pre-specified subgroup of patients who had anaemia at baseline was included for the haemoglobin concentrations outcome which is reported above in section 3.2.5.2.3 as the subgroup is only relevant to that specific secondary ranked outcome.

EAG conclusion on the clinical efficacy outcomes

Overall, the pooled analyses for Week 24 outcomes show that linzagolix 200 mg without ABT is more effective than placebo for all reported outcomes and that linzagolix 100 mg without ABT is more effective than placebo for all reported outcomes except reduction in fibroid volume. The explanation for a placebo effect observed for the primary outcome is unclear. Caution should be exercised in interpreting results for fibroid volume (up to the 3 largest fibroids were measured, missing data) and for Hb concentrations in the subgroup who were anaemic at baseline (severely anaemic patients were excluded from the trials). The HRQoL results are ambiguous because linzagolix does not show any significant improvements compared to placebo according to the EQ-5D-5L results, yet linzagolix shows improvements in the UFS-QoL results (much greater than a 9-15 point change from baseline used in another study to indicate a clinically meaningful change).

3.2.5.5 Safety outcomes

CS section B.2.10 reports the results from the pooled Safety Analysis Set of PRIMROSE 1 and PRIMROSE 2 for Week 24 (Day 1 to Week 24) and for Week 52 (Week 24 to Week 52, i.e. not cumulative from Day 1). Safety results for the individual trials are reported in CS Appendix M.3.4. Safety results are relevant to all population groups, so this section of the report covers all trial regimens.

The pooled Safety Analysis Set included all randomised patients in the trials who received at least one dose of the study drug: Week 24 n=1,037; Week 52 n=757 (CS section B.2.4.2.1) and mean overall compliance was 98.7% and 99.3% at Weeks 24 and Week 52 respectively (CS section B.2.10.1.1).

Adverse event outcomes specifically noted in the NICE scope are: vasomotor symptoms (covered by hot flushes, below); incontinence, which was not reported for more than one patient in either treatment period (Confidential Pooled Analysis);[28] and pelvic organ prolapse which was not assessed and which the EAG's clinical expert considered inconsequential.

3.2.5.5.1 Treatment-emergent adverse events (TEAEs)

At Week 24, there were slightly more TEAEs in the linzagolix treatment groups compared to placebo, with the 200 mg group having the highest incidence at 63.3% compared to the placebo group at 49.3% (CS Table 34). However, during the second treatment period (weeks 24 to 52) fewer TEAEs were reported and there was very little difference in the incidence rate across all treatment groups (range 29.9% to 41.6%) with no apparent dose dependency (CS Table 35). Very few of these TEAEs were serious or severe, in either treatment period. There was low incidence of serious adverse events (CS section B.2.10.3). TEAEs leading to permanent treatment discontinuation were similar across all treatment groups: incidence was low at Week 24 (range 7.0% to 10.5%) with the most frequent reasons being headache (1.1%) and hot flushes (1.1%), and lower at Week 52 (range 1.3% to 8.1%) with the most frequent reason being related to bone mineral density loss (1.3%) (CS section B.2.10.2).

Incidence of hot flushes (vasomotor symptoms in the NICE scope) at Week 24 were considered dose dependent: incidence was higher in the groups treated without ABT (10.1% and 33.3% for the 100mg and 200mg groups respectively) compared to those who received ABT (5.2% and 9.6%) (CS Table 36). For the second treatment period, incidence of hot flushes decreased and was similar across all treatment groups (range 0.0% to 2.4%), with the highest incidence in the placebo/200 mg + ABT group experiencing their first 24-week exposure to linzagolix (CS Table 37). There may also have been a dose dependent response at Week 24 for the more common headache TEAE as incidence was higher in the groups without ABT (CS section B.2.10.1.3).

3.2.5.5.2 Mortality

None of the TEAEs were fatal and only one death occurred, which was accidental and unrelated to the trials.[11]

3.2.5.5.3 Bone mineral density

Decrease in BMD is a TEAE of special interest due to the mechanism of action of linzagolix, which suppresses the production of serum estradiol, and the known effects of low oestrogen levels which reduce bone mineral density. Changes in BMD from baseline are reported for the lumbar spine, femoral neck, and total hip (CS section B.2.10.6.1, and CS Tables 44 and 45).

At Week 24 dose dependent reductions in BMD were seen in all linzagolix treatment groups, although the changes are described as small and only the change for the 200 mg group is described as clinically meaningful. The EAG's clinical expert suggested that a $\geq$5% change

in BMD would be clinically meaningful, therefore, as the highest percentage change from baseline was -3.697 (2.859) (mean (SD), in the 200 mg without ABT group) we concur with the company.

At Week 52 the greatest reduction in BMD was seen in the 200 mg/200 mg + ABT group, although the addition of ABT limited the risk, and for the other treatment groups the BMD decrease appeared to stabilise because it was less rapid. There was no clinically meaningful change in BMD at Week 52. However, the EPAR noted the (slight) increase in BMD-related adverse events of musculoskeletal and connective tissue disorders (osteopenia, osteoporosis and bone loss) during this second treatment period, [25] therefore the EAG view these results cautiously.

Week 76 data, reported in Table 26 of the EPAR, show that the rate of BMD loss had generally slowed or reversed, and more so in the treatment groups that included ABT. [25] Focussing on the lumbar spine (considered to be the most sensitive), the slowest to recover group was that which did not receive ABT at all i.e. the 100mg group. Furthermore, the results from PRIMROSE 3, an off-treatment extension study reported in CS section B.2.11, appear (the evidence has several limitations) to show a continued trend for partial or complete BMD recovery, and suggests that the overall bone health of the participants is [redacted], thus implying [redacted]. The EAG consider the longer-term evidence around BMD uncertain due to small patient numbers remaining in the treatment arms in the off-treatment periods (up to Week 76 in PRIMROSE 1 and 2; PRIMROSE 3), and the increase (though small in number) in BMD-related adverse events in later treatment periods.

EAG conclusion on safety results

Linzagolix appears to be well-tolerated, with very few serious or severe adverse events, few adverse events leading to treatment discontinuation, and no associated mortality. Hot flushes were common and appeared to be dose-dependent during the first 24 weeks of treatment but were much reduced and not dose dependent afterwards. It appears that reduction in BMD was dose-dependent during the first few months of treatment, but not a clinically meaningful change. During continued treatment BMD loss was less rapid, although it is uncertain whether this pattern would be sustained in the longer term.

3.3 Critique of studies included in the indirect comparisons

3.3.1 Rationale for the network meta-analysis

Placebo-controlled trials of linzagolix (PRIMROSE) and relugolix CT (LIBERTY) are available, but no direct comparisons of linzagolix against relugolix CT exist. The company therefore conducted NMAs for each outcome, where data were available, to compare linzagolix against relugolix CT (CS section B.2.9).

3.3.2 Identification, selection and feasibility assessment of studies for ITC

3.3.2.1 Comparison of linzagolix against relugolix CT

The aim of the indirect treatment comparisons was to investigate whether linzagolix has similar clinical effectiveness and safety to relugolix CT, to provide supporting information for the cost-comparisons for Population #1 and Population #2.

The company's systematic literature review of clinical efficacy studies (CS Appendix Table 7) identified five studies of relugolix CT. These were the two LIBERTY pivotal placebo-controlled trials which had informed the relugolix CT technology appraisal (T832) and three trials conducted in Japan that compared relugolix CT against placebo (Osuga et al. 2019[21]), against leuprorelin acetate (also called leuprolide acetate) (Osuga et al. 2019[20]), or compared three doses of relugolix CT (Hoshhiai et al. 2021[22]). The company excluded non-US and non-EU trials, meaning that these Japanese trials were excluded, and they also excluded trials published more than 20 years ago.

The company did not explore potential relevance of the three excluded Japanese studies but the EAG believe that these studies were excluded appropriately. Two of them included comparisons unlikely to be connected or useful in an evidence network (relugolix CT versus placebo;[21] relugolix CT dose-ranging [22] whilst the third (relugolix CT versus leuprolide[20]) used the PBAC method for measuring MBL which is not directly comparable with the AH method used in the PRIMROSE and LIBERTY trials. Although an adjustment can sometimes be made for comparing PBAC scores against AH-derived estimates of MBL (discussed in section 3.2.3.1.1), the necessary data to derive the required coeffcients for such an adjustment were not available in the trial publications and CSR for the Osuga et al. study[20] when it was scrutinised by the company in TA832.[29]

The CS reports that NMAs were conducted on the following outcomes according to data availability: response (reduced HMB, defined as a menstrual blood loss ≤80 mL and ≥50% reduction from baseline), percentage change in MBL, improvement in pain (defined as a NRS score ≤1 for participants with an NRS score ≥4 at baseline), percentage change in

primary fibroid volume, percentage change in haemoglobin for participants with haemoglobin ≤10.5 g/dL at baseline, and improvement in HRQoL (defined as the change UFS-QoL total score). The EAG believe it unlikely that other outcomes could be included, as not all outcomes of interest were reported in the trials.

3.3.2.2 Comparison of linzagolix against other GnRH analogues

The EAG requested further evidence from the company on the relative clinical effectiveness of linzagolix compared to the other GnRH analogues that could be used in clinical practice. In their response the company provided additional NMAs, using a fixed-effects model only, based on an extended network (Clarification Response A11). The company's clarification response states that the network could include the PRIMROSE, LIBERTY and PEARL trials for the response outcome but only the PRIMROSE and PEARL trials for the changes in total fibroid volume and haemoglobin, with no other outcomes being available from more than one trial. The Clarification Response does not describe the evidence network, but we assume it was as shown in Figure 8. PEARL I is an RCT that compared ulipristal acetate (a selective progesterone receptor modulator) against placebo,[17] and PEARL II is an RCT that compared ulipristal acetate against leuprolide acetate (a GnRH agonist).[18] Both PEARL I and PEARL II had been identified in the company's systematic literature search (CS Appendix Table 7) and their study designs are summarised in section 3.2.1.3 of this report. Ulipristal acetate is only indicated for intermittent treatment when uterine fibroid embolisation or surgery are unsuitable or unsuccessful, and as noted in TA832 it is unlikely that many people with uterine fibroids needing treatment would agree to have ulipristal acetate, given the level of monitoring needed and potential risks of liver damage. According to Clarification Response A11 leuprolide acetate was the only additional relevant comparator that could be included in the extended NMA network. However, the company have not reported their study selection process for this extended evidence network. It is unclear whether a more thorough search and study selection process would identify further studies relevant for inclusion in the evidence network.

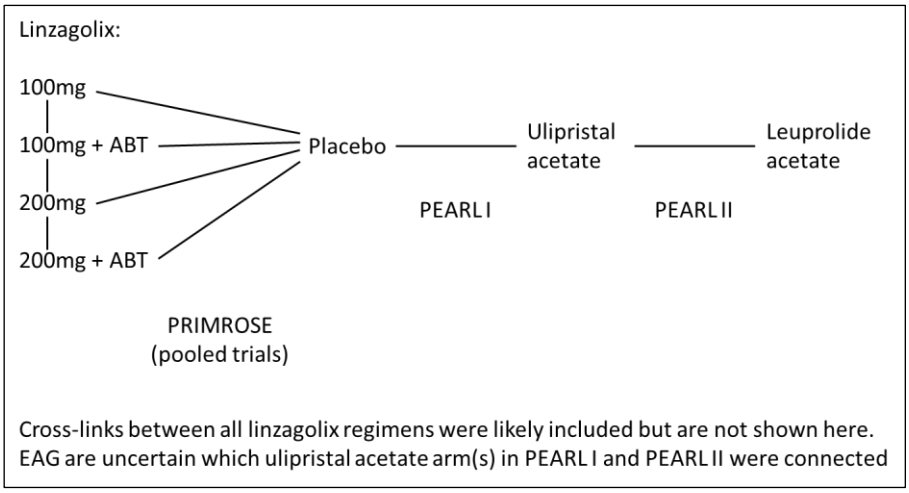


Figure 8 EAG presumed evidence network for the comparison of linzagolix against leuprolide acetate

According to the company's list of studies included in their clinical effectiveness systematic literature search (CS Appendix Table 7) and their list of studies that are available but were excluded from the systematic literature search (CS Appendix D.3.2) we believe it unlikely that other relevant studies and comparators could have been included in the NMAs.

3.3.3 Clinical heterogeneity assessment

3.3.3.1 Comparison of linzagolix against relugolix CT

Heterogeneity assessment is discussed in CS section B.2.9.4. The CS states that in general, there was good alignment between the trials; the inclusion and exclusion criteria were identical between PRIMROSE 1 and 2, as well as between LIBERTY 1 and 2; the outcomes in the PRIMROSE and LIBERTY trials were defined similarly: and pooled PRIMROSE patient-level data allowed additional comparisons to be made.

However, the CS acknowledges differences in population characteristics between the PRIMROSE and LIBERTY trials. The trials differed notably in the proportion of Black patients (approximately 63% versus 5% across arms in PRIMROSE 1 and PRIMROSE 2, respectively; and 47% and 42% across arms in LIBERTY 1 and LIBERTY 2, respectively). Other differences in baseline characteristics were in the proportion of Hispanic or Latino patients (11.8% across arms in the pooled PRIMROSE trials versus 20.7% across arms in LIBERTY 1 and 2; $p<0.001$), mean baseline MBL (207.6 across arms in the pooled PRIMROSE data versus 229.2 across arms in LIBERTY 1 and 2; $p=0.007$), uterine volume (328.2 across arms in the pooled PRIMROSE data versus 393.2 across arms in LIBERTY 1 and 2; $p<0.001$), uterine fibroid volume (98.9 across arms in the pooled PRIMROSE data versus 72.9 across arms in LIBERTY 1 and 2; $p<0.001$), and the proportion of patients with a

pain score ≥4 (77.1% across arms in the pooled PRIMROSE data versus 71.8% across arms in LIBERTY 1 and 2; p=0.029).

The company note in Clarification Response A8 that the method of accounting for missing MBL data differed between the PRIMROSE and LIBERTY trials. Missing return of menstrual products was considered 'no bleeding' in the PRIMROSE trials whereas missing data were imputed in the LIBERTY trials. The company argue that this might explain why a placebo effect exists in the PRIMROSE placebo arms but is less clear in the LIBERTY trials. The company conducted sensitivity analyses using two different methods of data imputation in the pooled PRIMROSE trials to check the robustness of the analysis to missing data and they found that the linzagolix versus placebo comparisons were not sensitive to missing data (CS section B.2.12.2.2). The company discuss how these trial differences could influence the results of NMAs that compare linzagolix against relugolix CT in CS section B.2.9.7.

The company concluded that overall, the trials appeared to be broadly comparable and an NMA was an appropriate method of indirect comparison. The company also conducted a matching adjusted indirect comparison (MAIC) as a scenario analysis to explore whether differences in baseline characteristics may have impacted comparative results from the NMA. The EAG agree with this overall approach for exploring heterogeneity, although there are caveats around the methodology of the MAIC analyses (see section 3.4.4 below).

The company elected to use the pooled PRIMROSE trials and separate LIBERTY trials for their NMAs. We assume (section 3.2.4.2) that pooling means that the trial data were added together, and then statistical analyses were run on the combined data set. Given the differences in the baseline characteristics of PRIMROSE 1 and PRIMROSE 2 noted above, the EAG requested the company to provide a NMA that included the two PRIMROSE trials separately in the network (Clarification Question A10). We compare the company's NMA results for the pooled and separate analyses of the PRIMROSE trials in section 3.5.1 below.

3.3.3.2 Comparison of linzagolix against other GnRH analogues

For their extended NMAs comparing linzagolix against leuprolide acetate (Clarification Response A11) the company did not provide a systematic comparison of the baseline characteristics of the PEARL, PRIMROSE, and LIBERTY trials. However, the clarification response highlights that the method for estimating MBL differed between the PRIMROSE and LIBERTY trials which used the alkaline haematin method (the 'gold standard'), and the PEARL trials which used the pictorial blood loss assessment chart (PBAC) method (see section 3.2.3.1.1 for a discussion of these methods and their comparability).

The EAG note there are a number of differences in the baseline characteristics of the PEARL I and PEARL II trials[17, 18] when compared to the PRIMROSE and LIBERTY trials (CS Appendix 8):

- All patients in the PEARL trials were eligible to undergo fibroid surgery at the end of the treatment period. In the PRIMROSE trials patients who would require surgery within 6 months were excluded (CS Appendix M.1).

- In PEARL I the inclusion criteria specified patients should meet a specified PBAC score and should have fibroid-related anaemia whereas these criteria were not used in the PRIMROSE and LIBERTY trials.

- PRIMROSE and LIBERTY excluded patients with fibroids of 12cm diameter or larger, whereas the PEARL trials excluded patients with fibroids of 10cm or larger.

- PEARL I did not include any Black patients but had approximately 10-15% Asian patients whereas PEARL II had approximately 9-11% Black patients and few if any Asian patients (not separated from “other”). As noted previously, the population of PRIMROSE 1 was different, with approximately 61-65% Black patients. The balance of Black and White patients in the PEARL trials aligns most closely with PRIMROSE 2.

- Total fibroid volume in PEARL I (ranging from 61.9 cm3 in the placebo arm to 100.7 cm3 in the 5mg ulipristal acetate arm) was notably larger than in the PRIMROSE trials (approximately 43-72cm3).

- BMI in both PEARL trials is similar to PRIMROSE 2 but lower than in PRIMROSE 1.

- Total fibroid volume (only measured in PEARL I) is more similar to PRIMROSE 1, being slightly higher than in PRIMROSE 2

- Uterine volume measurements in PEARL I are similar to those in PRIMROSE 1. whilst the measurements in PEARL II are similar to those in PRIMROSE 2

- UFS-QoL scores (only measured in PEARL II) correspond with PRIMROSE 2 for the symptom severity score and are better than both PRIMROSE trials for the total HRQoL score.

The company did not conduct any MAIC analyses to further explore heterogeneity in the trial population characteristics in the comparison of linzagolix against leuprolide acetate.

3.3.4 Risk of bias assessment for studies included in the NMAs

Risks of bias in the PRIMROSE, LIBERTY, and PEARL II trials are discussed in section 3.2.2 and summarised in Appendix 2. No high risks of bias were identified. We noted uncertainty in how reliable measures of fibroid volume are in the PRIMROSE trials; and uncertainty in why some outcomes had extensive missing data (summarised in Table 8) which was more frequent in PRIMROSE 1 than in PRIMROSE 2. However, there was no indication of any substantive differences in the amount of missing data between trial arms.

3.4 Critique of the indirect comparison

3.4.1 Data inputs to the NMA and MAIC analyses

The company provided the statistical code for the NMA and MAIC analyses in CS Appendix D.3.6.1 and D.3.6.2 and in Clarification Response Document Appendices 2, 4 and 5. No input data for the NMAs were provided with the code, and the NMA code does not contain sufficient detail of the data sets analysed (e.g. sample size for the input data used) for the EAG to check whether the NMAs were conducted appropriately. The EAG were not provided with the individual participant data so we could not verify the MAIC analyses.

3.4.2 Statistical methods for the NMA and MAIC analyses

The statistical methods of the NMAs are described in CS Appendix D.3.5.2, including a network diagram (CS Appendix Figure 5). The NMA was conducted in a Bayesian framework using Monte Carlo Markov Chain (MCMC). Overall, the EAG believe the methods of the NMA are appropriate, aside from the caveat noted above that we were unable to validate the analysis.

The statistical methods of the MAIC analysis are described in CS Appendix D.3.8. The MAIC statistical methods appear to have been correctly applied, with the caveat that the EAG could not verify this. The target population for weighting in the matching was the pooled LIBERTY trials, which the EAG's clinical expert agreed are broadly representative the UK clinical practice population (section 3.2.1.2.4). Matching was conducted on the proportion of Black patients, uterine volume, total fibroid volume, MBL, and haemoglobin; these were the most important variables for matching according to two internal company experts. However, the CS does not explain what the key treatment effect modifiers are (all should be included in anchored population matching) and no scenarios were conducted to investigate the influence on outcomes of different matching variables.

A comparison of trial baseline characteristics before and after weighting shows that the matching was partially successful but differences in the proportion of Hispanic / Latino patients worsened post-matching and some differences in mean pain score remained (CS Appendix Table 19). The distribution of weights (CS Appendix Figure 6) is reasonable with no very large weights used.

3.4.3 Selection of random and fixed-effects models

Fixed and random effects models were conducted in the NMAs. With only small differences observed in the deviance information criterion (DIC), the company preferred fixed effects models across all outcomes. Given the heterogeneity present and the uncertainty as to whether these differences are treatment effect modifiers, the EAG prefer the results of the random effects models (section D.3.5.3).

3.4.4 Summary of EAG critique of the NMA and MAIC analyses

In NICE technology appraisals cost-comparison analyses assume that the intervention and comparator have similar clinical efficacy and safety. Results of the company's NMA analyses are used to support inferences about the clinical similarity of linzagolix and relugolix CT but do not directly inform the company's economic models.

A challenge with interpreting NMA results to infer the similarity of linzagolix and GnRH analogue comparators is that a robust conclusion on the similarity of the treatments would require an inference of non-inferiority. However, no non-inferiority trials are available for linzagolix and so the NMA results are based on analysis of treatment differences (superiority) rather than similarity (non-inferiority). When heterogeneity is present, random-effects models produce wider credible intervals than fixed-effects models, potentially increasing the risk of falsely concluding that treatments are similar. That is, the more heterogeneity that is present, the greater the risk of falsely concluding that there is no treatment difference. The company state that "the outcomes of the NMA from the available evidence does not generally indicate any expected differences in treatment efficacy for linzagolix when compared with relugolix CT" (CS section B.2.9.8). The EAG are uncertain what is meant by "any expected differences" and we note that for most outcomes the company do not discuss whether clinical similarity (i.e. non-inferiority) of linzagolix compared to relugolix CT can be inferred from the NMA results.

The EAG were unable to verify the NMA and MAIC analyses and so the possibility of errors cannot be excluded. Results of NMAs on the company's extended evidence network, provided in Clarification Response A11 are very difficult to interpret because of lack of clarity in how the company conducted the analysis. Important limitations are:

- The PRIMROSE and PEARL II trials used in the evidence network employed different methods for estimating MBL (alkaline haematin and PBAC respectively) which in TA832 were considered incompatible without adjustment (section 3.2.3.1.1). It is unclear whether an adjustment was made to allow the different approaches to be compared in the network and, if so, how.
- The PEARL trials reported outcomes at 13 weeks whereas the timepoint of interest in the PRIMROSE trials is 24 weeks, although the PRIMROSE trials also reported some outcomes at 12 weeks. The company do not explain what timepoint their NMA results refer to (i.e. whether 12, 13 or 24 weeks) and what assumptions were applied to allow the trials' different assessment timepoints to be compared.
- The PEARL I and PEARL II trials include two ulipristal arms (5mg and 10mg) but it is unclear which of these the company included in the evidence network.
- The company do not explain in Clarification Response A11 how the trials were selected for the extended evidence network and so we are uncertain whether any relevant studies of GnRH analogues might have been missed.

3.5 Results from the NMA and MAIC analyses

Results from the NMA and MAIC analyses comparing linzagolix against relugolix CT are presented below in section 3.5.1. A summary of the results across all the outcomes and linzagolix regimens is provided in section 3.5.2.

Given the extensive limitations of the NMAs comparing linzagolix against leuprolide acetate noted above, results of these analyses are provided in Appendix 3 for reference only.

3.5.1 NMA results comparing linzagolix against relugolix CT

The results reported here are relevant to the company's cost comparison analyses for Population #1 and Population #2. For results relevant to the company's cost utility analysis (Population #3), for which the comparator is best supportive care, see section 3.2.5.

3.5.1.1 Response

3.5.1.1.1 Fixed-effects model results

Forest plots produced by the EAG from the data in company Clarification Response Table 3 (Figure 9) show [redacted] compared to those receiving r
not seen in PRIMROSE 1 it is difficult to explain. In contrast, relugolix CT is [redacted] the 100
100mg + ABT regimen. The remaining comparisons have wide credible intervals that include the null and ar
and MAIC results for PRIMROSE 2, particularly for the linzagolix 200mg dose regimen, but broad agreemen

sample size (ESS) values in the MAIC analysis for PRIMROSE 2 are very low (range [redacted] to [redacted] across the linza
ESS [redacted] for all regimens (Clarification Response Table 12), suggesting that the pooled analysis achieved r
reliable. The EAG therefore base our inferences for this outcome on the pooled trials analysis.

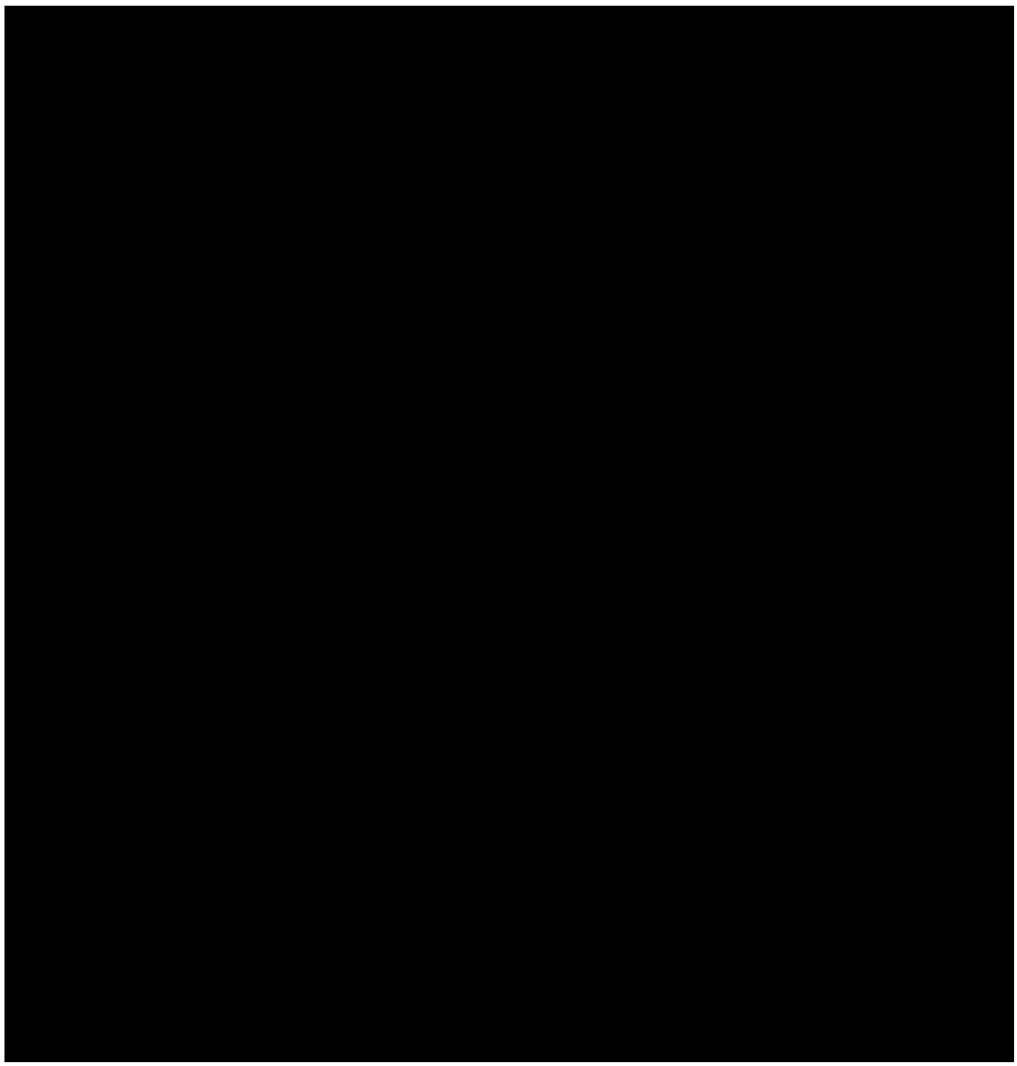


Figure 9 Linzagolix vs relugolix CT: NMA and MAIC results for response

The NMA forest plot and the posterior rank distribution probabilities for the fixed-effects pooled analysis (Cla
200mg + ABT is [redacted] relugolix CT at eliciting a response (with [redacted]% probability of being [redacted]
be driven mainly by the large effect in PRIMROSE 2 which was not seen in PRIMROSE 1. The forest plot sh
analysis the point estimates have credible intervals that lie [redacted], favouring [redacted], with a
favourable than [redacted]In conclusion, similarity of linzagolix and relugolix
[redacted]

3.5.1.1.2 Comparison with random-effects model results

The company provided random-effects model results only for the pooled analysis. As shown in Figure 10, th
is not possible to say with any certainty where the true point estimates lie. [redacted]
provide any guidance on interpretation. To be confident that one therapy is similar (i.e. non-inferior) to the ot
reasonable confidence that the point estimate lies close to the null, or that the log odds of achieving a mean
zero for that therapy. Posterior rank probabilities for the relative effectiveness of the intervention and compa
the company did not provide these for the random-effects analyses.

Figure 10 Response, pooled analysis, fixed & random effects models compared

3.5.1.2 Menstrual blood loss

3.5.1.2.1 Fixed-effects model results

Forest plots for the change in menstrual blood loss (Figure 11) show disagreement between the NMA and MAIC results for PRIMROSE 2 but broad agreement for PRIMROSE 1 and the pooled PRIMROSE trials. ESS values for MAIC analyses for PRIMROSE 2 are very low (range [redacted] to [redacted] across the linzagolix regimens) whilst the MAIC pooled analysis has the

highest ESS [redacted] for all linzagolix regimens (Clarification Response Table 13), suggesting that the pooled analysis achieved reasonably good matching of the trial populations. The EAG therefore base our inferences for this outcome on the pooled trials analysis.

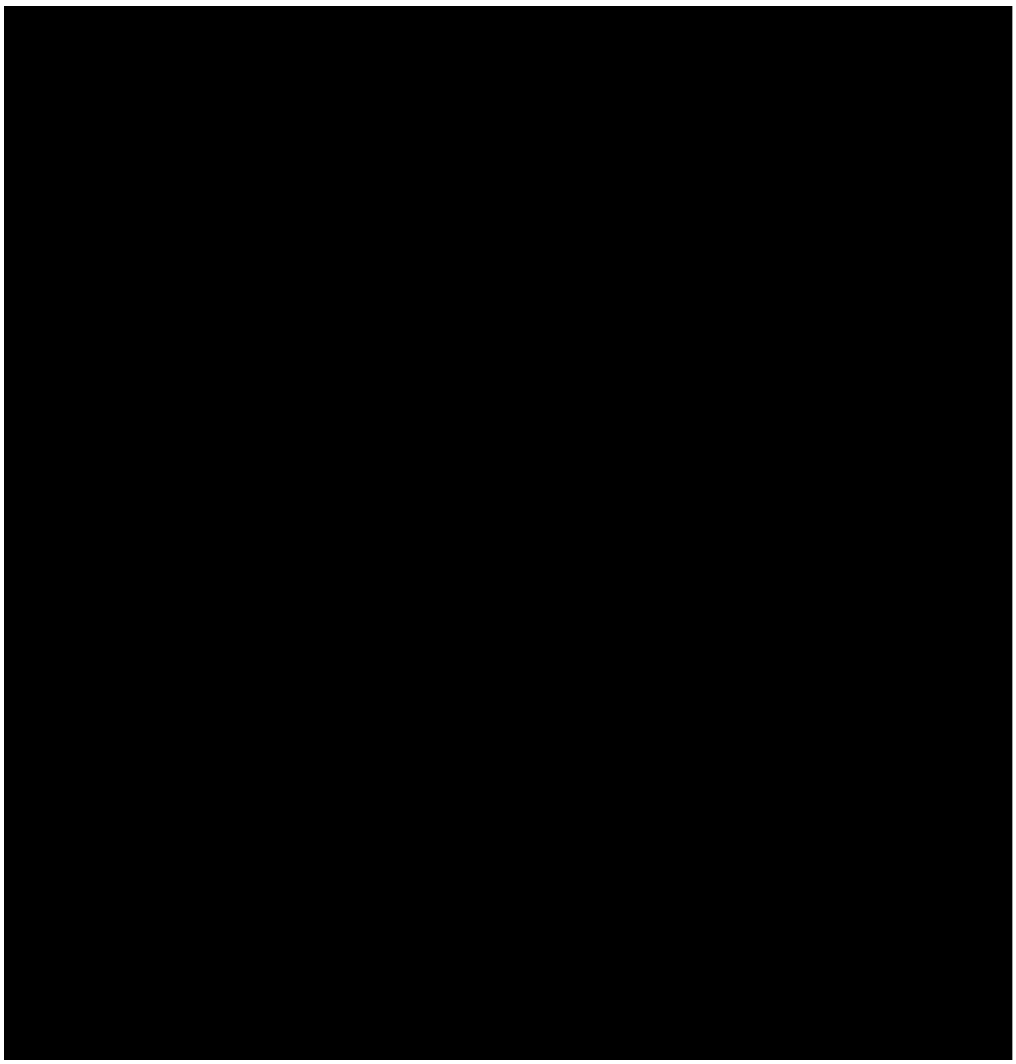


Figure 11 Linzagolix vs relugolix CT: NMA and MAIC results for menstrual blood loss

For the pooled analysis, relugolix CT is statistically superior to the 100mg, 100mg + ABT and 200mg regimens of linzagolix, so a conclusion of clinical similarity of linzagolix to relugolix CT is not supported for these regimens. The difference is non-significant for the 200mg + ABT regimen but the credible interval is wide and lies mostly above the null, suggesting relugolix CT is more likely to be superior. The posterior rank probability that relugolix CT is superior to all regimens of linzagolix and placebo is [redacted] (Clarification Response Document Appendix 1).

3.5.1.2.2 Comparison with random-effects model results

There is [redacted] between the fixed-effects and random-effects model analyses for the change in menstrual blood volume (Figure 12), with the random-effects analysis having [redacted] credible intervals. The statistical [redacted] of relugolix CT [redacted] the 100mg, 100mg + ABT and 200mg regimens of linzagolix at reducing MBL is therefore supported. Although statistically non-significant, the credible interval for the 200mg +ABT point estimate [redacted], suggesting that relugolix CT is [redacted] this linzagolix regimen. These findings [redacted] a conclusion that linzagolix is statistically similar to relugolix CT at reducing menstrual blood loss.

Figure 12 Change in MBL, pooled analysis, fixed & random effects models compared

3.5.1.3 Proportion experiencing improvement in fibroid-related pain

3.5.1.3.1 Fixed-effects model results

Forest plots for the log odds of achieving a meaningful improvement in the pain score (Figure 13) show disagreement between the NMA and MAIC results for PRIMROSE 2 but broad agreement for PRIMROSE 1 and the pooled PRIMROSE trials. The ESS values for the MAIC analysis for PRIMROSE 2 are very low (range [redacted] to [redacted] across the linzagolix regimens) whilst the MAIC pooled analysis has the highest ESS range [redacted] to [redacted] across the

linzagolix regimens, suggestive of relatively poor matching of the trial populations (Clarification Response Table 14).

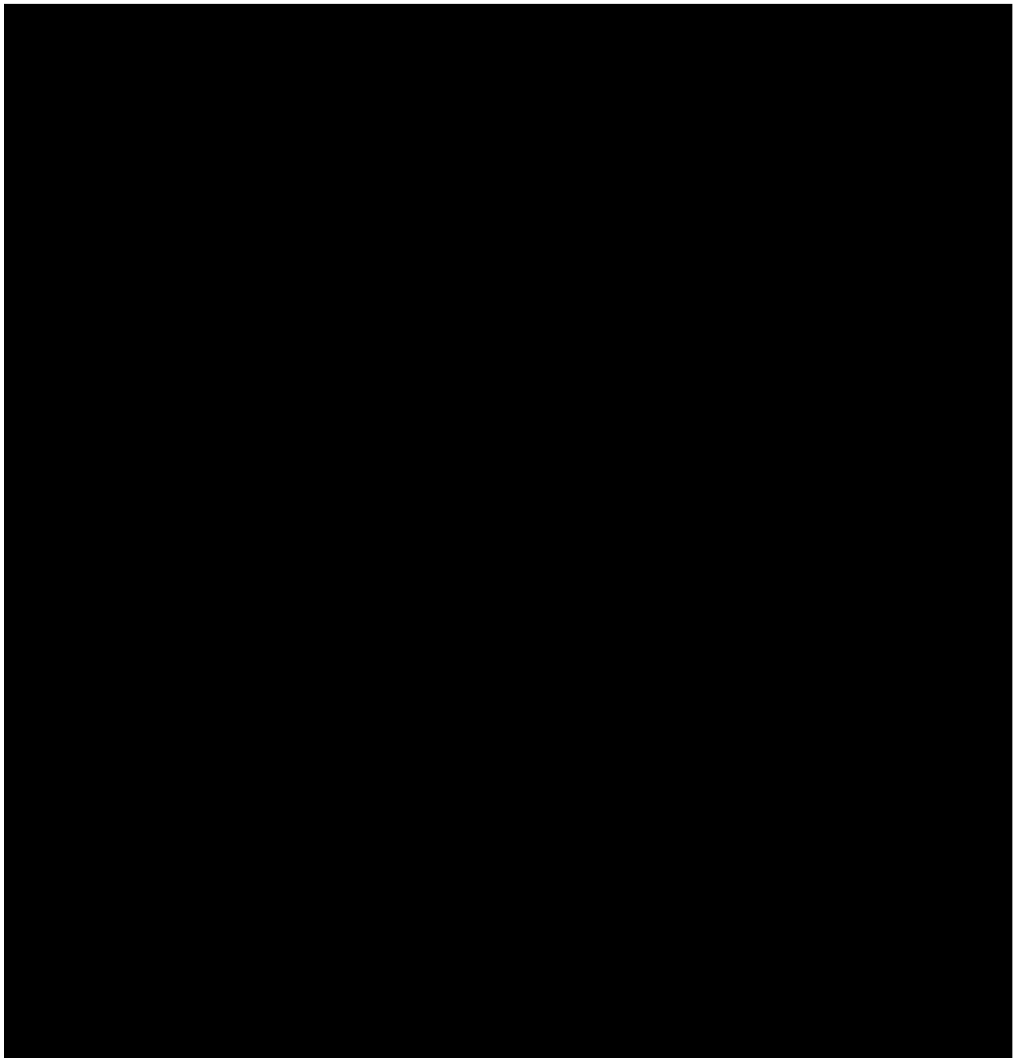


Figure 13 Linzagolix vs relugolix CT: NMA and MAIC results for the proportion achieving an improvement in pain total score

The NMA forest plot for the pooled analysis indicates [redacted] difference for the odds of improvement in the pain score between [redacted] of the linzagolix regimens and relugolix CT (all credible intervals include zero). With wide credible intervals either side of zero for the 100mg and 100mg + ABT regimens it is not possible to say with any certainty where the true point estimates lie. We are therefore unable to conclude that 100mg and 100mg + ABT linzagolix regimens are [redacted] as relugolix CT. For the linzagolix 200mg and 200mg + ABT regimens most of the credible intervals lie above zero. The posterior rank probabilities for each of these treatments (Clarification Response Document Appendix 1) suggest that there

is a [redacted] probability that the linzagolix 200mg regimen and a [redacted] probability that the linzagolix 200mg + ABT regimen are rank 1 or 2, which supports the suggestion that these linzagolix regimens may be [redacted] as relugolix CT at reducing fibroid-related pain.

3.5.1.3.2 Comparison with random-effects model results

As shown in Figure 14, the fixed-effects pooled trials analysis underestimates the heterogeneity present, with much narrower credible intervals than the random-effects analysis. The credible intervals in the random-effects analysis are so wide that is not possible to say with any certainty where the true point estimates lie.

[redacted].

Figure 14 Pain improvement, pooled analysis, fixed & random effects models compared

3.5.1.4 Primary fibroid volume

3.5.1.4.1 Fixed-effects model results

Forest plots based on fixed-effects models for the change in primary fibroid volume (Figure 15) show disagreement between the NMA and MAIC results for PRIMROSE 2 but broad agreement for PRIMROSE 1 and the pooled PRIMROSE trials. The MAIC pooled trials analysis has the highest ESS (range [redacted] to [redacted] across the linzagolix regimens) (Clarification Response Table 15) but there is also a moderate amount of missing data ([redacted]% to [redacted]%)

compared to the sample size for the response outcome. Although the pooled analysis has better matching and sample size compared to the individual trials there are uncertainties around the approach used for measuring fibroid volume (section 3.2.3.1.3), reducing confidence in the findings.

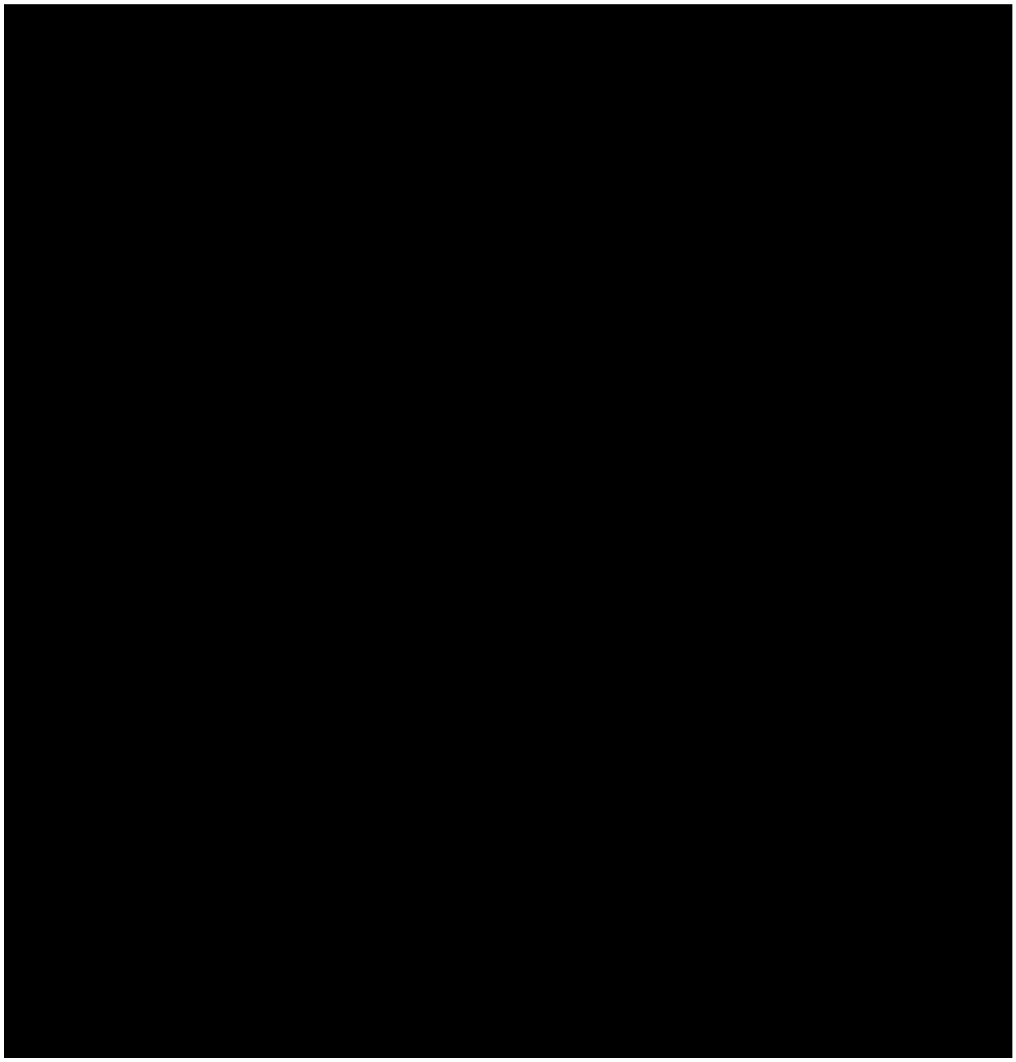


Figure 15 Linzagolix vs relugolix CT: NMA and MAIC results for primary fibroid volume

The NMA forest plot for the fixed-effects pooled analysis indicates that linzagolix 200mg is statistically [redacted] for reducing the primary fibroid volume, with [redacted]% posterior rank probability of being the most effective therapy at reducing primary fibroid volume, with the 100mg regimen having [redacted]% probability of being rank 2 (i.e. the second most effective therapy), followed by the 200mg + ABT regimen with [redacted]% probability of being rank 3 (i.e.

the third most effective therapy) (Clarification Response Document Appendix 1). However, for the linzagolix 100mg + ABT regimen the credible interval is [redacted], hindering a clear inference regarding similarity of linzagolix and relugolix CT. This regimen has a [redacted] posterior rank probability of being among the most effective therapies at reducing fibroid volume.

In summary, we conclude that, the 200mg regimen of linzagolix is [redacted] compared to relugolix CT for reducing primary fibroid volume whilst the linzagolix 100mg and 200mg + ABT regimens appear likely to be [redacted] for this outcome.

3.5.1.4.2 Comparison with random-effects model results

The random-effects analyses for the pooled trial populations generally confirm the findings of the fixed-effects analyses, demonstrating [redacted] of the linzagolix 200mg regimen compared to relugolix CT at reducing the primary fibroid volume. The credible intervals for the 100mg and 200mg + ABT linzagolix regimens remain [redacted] and largely [redacted], suggestive that linzagolix would be [redacted] relugolix CT at reducing the primary fibroid volume. A caveat, however, is that the EAG have concerns about whether the approach for selecting and measuring the primary fibroids was in the PRIMROSE trials was appropriate (section 3.2.2.1).

[redacted]

Figure 16 Change in primary fibroid volume, pooled analysis, fixed & random effects models compared

3.5.1.5 Haemoglobin, % change from baseline in patients with anaemia at baseline

3.5.1.5.1 Fixed-effects model results

Forest plots for the change in haemoglobin (Figure 17) show disagreement between the NMA and MAIC results, especially for PRIMROSE 2. However, sample sizes in the MAIC analyses are very low, with no ESS value greater than [redacted] for any of the linzagolix regimen groups, and ESS only [redacted] to [redacted] for the PRIMROSE 2 trial analyses (Clarification Response Table 16). Unsurprisingly, the credible intervals are very wide, making it difficult to determine with any certainty where the true effect estimates would lie.

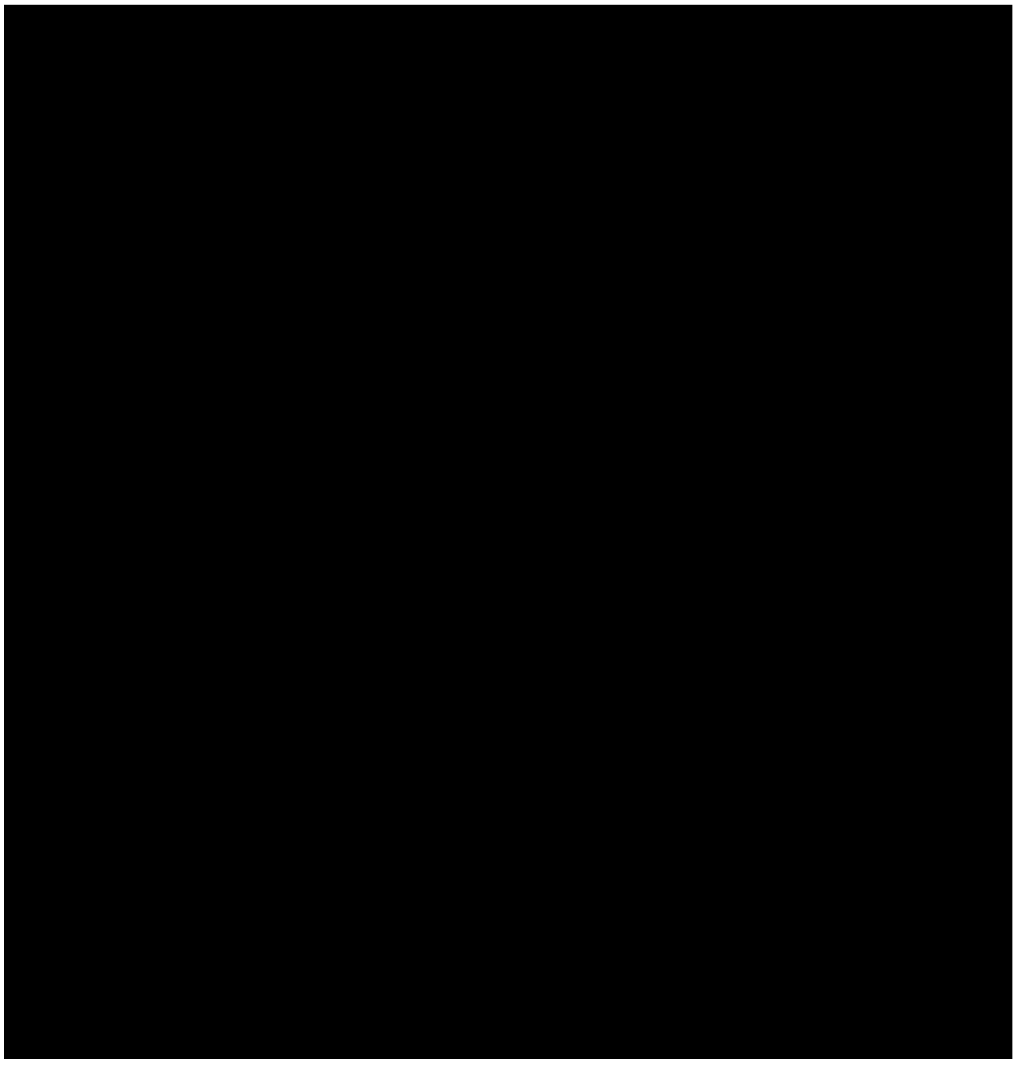


Figure 17 Linzagolix vs relugolix CT: NMA and MAIC results for % haemoglobin change (baseline anaemia subgroup)

3.5.1.5.2 Comparison with random-effects model results

The random-effects model results (Figure 18) have wider credible intervals, indicating that the fixed-effects analyses do not fully account for the statistical heterogeneity. Both the fixed- and random-effects analyses show similar distributions of the effect estimates in the forest plots, but do not resolve the uncertainty in where the true effect estimates lie. In conclusion,

[redacted]

[redacted] at improving haemoglobin levels in patients who were anaemic at baseline.

Figure 18 Change in haemoglobin (baseline anaemia subgroup), pooled analysis, fixed & random effects models compared

3.5.1.6 UFS-QoL total HRQoL score

3.5.1.6.1 Fixed-effects model results

Forest plots for the change in UFS-QoL total score (Figure 19) show disagreement between the NMA and MAIC results for PRIMROSE 2, especially for the linzagolix 200mg and 200mg + ABT regimens, but broad agreement for PRIMROSE 1 and the pooled trials analysis. The MAIC pooled trial analysis has the highest ESS (range [redacted] to [redacted] across the linzagolix regimens (Clarification Response Table 17), suggesting moderate matching of the trial populations for this outcome, albeit with [redacted]% to [redacted]% fewer data than were available for analysis of the

response outcome. The EAG therefore base our inferences for this outcome on the pooled trials analysis, acknowledging that incomplete population matching introduces uncertainty.

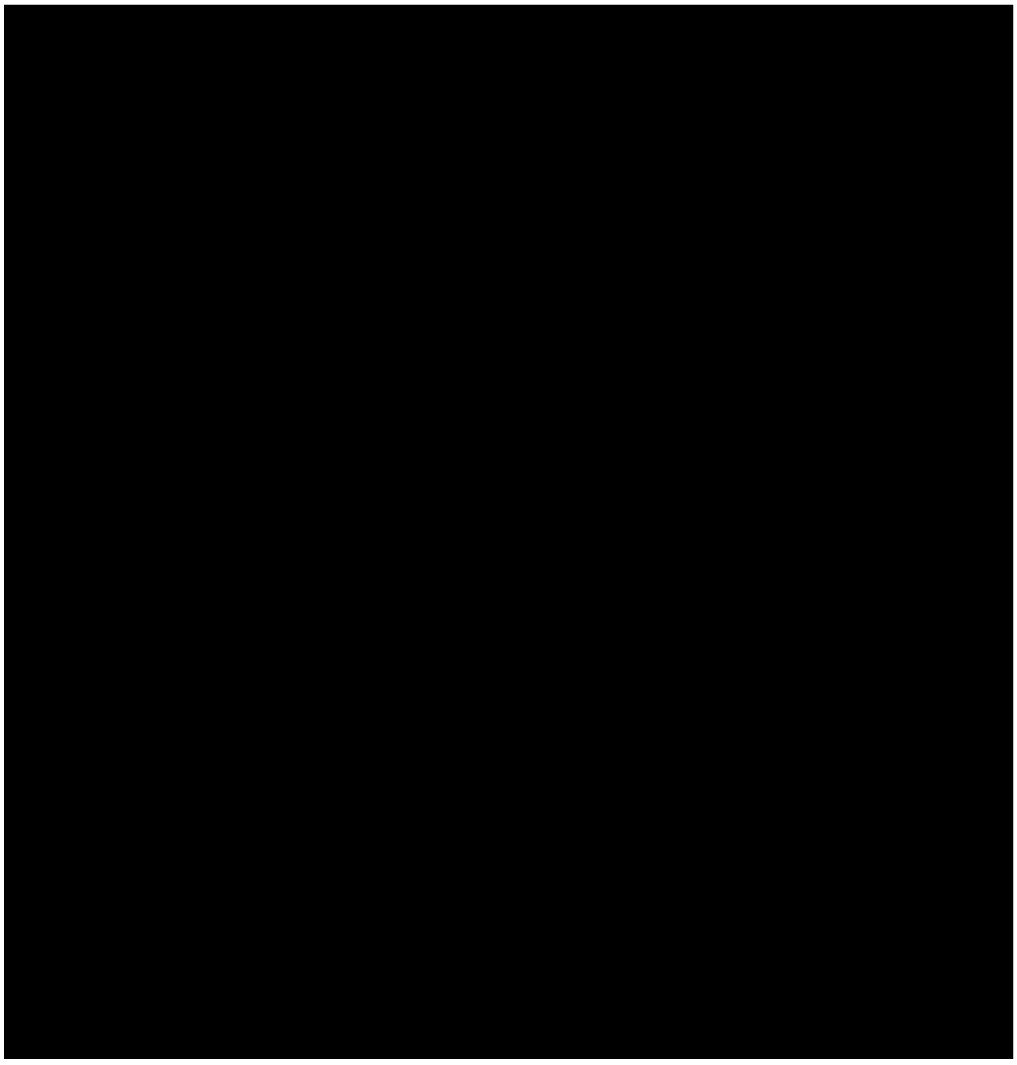


Figure 19 Linzagolix vs relugolix CT: NMA and MAIC results for UFS-QoL total score

The NMA forest plot for the pooled analysis indicates that relugolix CT is [redacted] to the 100mg and 100mg + ABT regimens of linzagolix for improving the UFS-QoL total score. Credible intervals for the 200mg and 200mg + ABT linzagolix regimens [redacted], suggesting that relugolix CT is [redacted] these linzagolix regimens. The posterior rank probability that relugolix CT is the most effective of the treatments for this outcome is [redacted]% (Clarification Response Document Appendix 1).

3.5.1.6.2 In summary, we conclude from the fixed-effects analysis that [redacted] the linzagolix regimens are conclusively [redacted] compared to relugolix CT, with relugolix CT being [redacted] to the linzagolix 100mg and 100mg + ABT regimens. Comparison with random-effects model results

The random-effects model results (Figure 20) have wider credible intervals, indicating that the fixed-effects analyses do not fully account for the statistical heterogeneity. The random-effects analyses still support the [redacted] of relugolix CT compared to 100mg linzagolix for improving fibroid-related quality of life, but the [redacted] of relugolix CT compared to linzagolix 100mg + ABT is less certain. In summary, we still conclude that [redacted] the linzagolix regimens are conclusively [redacted] compared to relugolix CT.

[redacted]

Figure 20 Change in UFS-QoL total HRQoL score, pooled analysis, fixed & random effects models compared

3.5.2 Summary of NMA results for Populations #1 and #2

Table 9 summarises the EAG's interpretation of the NMA results for the comparisons of linzagolix against relugolix CT. Despite the similar mechanisms of action of these therapies there appears to be very little evidence for the similarity or superiority of linzagolix compared to relugolix CT for most of the outcomes and dose regimens tested. This might to some extent reflect the weaknesses in the evidence synthesis methods discussed above, which

appear to have failed to cope well with heterogeneity in the clinical trials designs and populations.

Table 9 Overview of NMA results, linzagolix versus relugolix CT at Week 24

Outcome/model	Linzagolix regimen			
	100mg	100mg + ABT	200mg	200mg + ABT
Response – odds of achieving a response (meaningful reduction in MBL)				
Fixed effects Section 3.5.1.1.1	[redacted]	[redacted]	[redacted]	[redacted]
Random effects Section 3.5.1.1.2	[redacted]	[redacted]	[redacted]	[redacted]
% change in menstrual blood loss				
Fixed effects Section 3.5.1.2.1	[redacted]	[redacted]	[redacted]	[redacted]
Random eff	[redacted]	[redacted]	[redacted]	[redacted]

ects Section 3.5.1.2.2				
Pain – odds of achieving a meaningful improvement in NRS pain score				
Fixed effects Section 3.5.1.3.1	[redacted]	[redacted]	[redacted]	[redacted]
Random effects Section 3.5.1.3.2	[redacted]	[redacted]	[redacted]	[redacted]
% change in primary fibroid volume				
Fixed effects Section 3.5.1.4.1	[redacted]	[redacted]	[redacted]	[redacted]
Random effects	[redacted]	[redacted]	[redacted]	[redacted]

Section 3.5.1.4.2				
% change in haemoglobin in patients anaemic at baseline				
Fixed effects Section 3.5.1.5.1				
Random effects Section 3.5.1.5.2				
Change in UFS-QoL HRQoL score				
Fixed effects Section 3.5.1.6.1				
Random effects Section 3.5.				

1.6.2				

3.6 Clinical efficacy conclusions

3.6.1 Population #1

As noted in Table 3, Population #1 (those receiving short-term therapy prior to surgical intervention) could in theory receive any of the linzagolix regimens but the 200mg regimen without ABT is suggested by the company be the optimal regimen for achieving the fastest fibroid shrinkage prior to surgery.

The NMA results suggest that the 200mg dose of linzagolix without ABT, which we assume to be the most relevant regimen for Population #1, is [redacted] to relugolix CT for the reduction in primary fibroid volume (Table 9) but not for any of the other outcomes assessed.

Insufficient reliable evidence has been provided by the company to determine whether linzagolix 200mg would have comparable effectiveness to other GnRH analogues.

3.6.2 Population #2

The most appropriate linzagolix regimens for Population #2, who receive longer-term therapy, would be 100mg + ABT or 200mg + ABT. As shown in Table 9, the 200mg + ABT regimen of linzagolix appears to have [redacted] compared to relugolix CT for reducing primary fibroid volume. However, there is no conclusive evidence that the 100mg + ABT regimen has comparable effectiveness to relugolix CT for any of the outcomes tested.

Insufficient reliable evidence has been provided by the company to determine whether linzagolix 100mg + ABT or 200mg + ABT would have comparable effectiveness to other GnRH analogues.

3.6.3 Population #3

Evidence relevant to Population #3 (longer-term treatment without ABT, where the comparator is BSC) is summarised in section 3.2.5 of this report. Overall, the pooled analyses for Week 24 outcomes show that linzagolix 100mg without ABT and 200 mg without ABT are more effective than placebo for all reported outcomes. However, in the PRIMROSE 1 trial population, 100 mg linzagolix without ABT was not more effective than placebo for some outcomes.

Caution should be exercised in interpreting results for fibroid volume (only 3 largest fibroids were measured, missing data) and for Hb concentrations in the subgroup who were anaemic at baseline (severely anaemic patients were excluded from the trials), none of the trial participants were contraindicated for ABT, and there is a placebo effect observed for the primary outcome.

The HRQoL results are ambiguous because linzagolix does not show any significant improvements compared to placebo according to the EQ-5D-5L results, yet linzagolix shows improvements in the UFS-QoL results (much greater than a 9-15 point change from baseline used in another study to indicate a clinically meaningful change).

Safety results show linzagolix is well-tolerated, but there is some uncertainty around long-term effects on BMD.

3.7 Uncertainties in the clinical efficacy evidence

There are numerous uncertainties in the evidence base for this technology appraisal. Major uncertainties have been raised as Key Issues with the aim that further consultation might enable some of the uncertainty to be resolved (see section 1.1 of this report for details).

Key Issue 1: Uncertain clinical similarity of linzagolix to other GnRH analogues. NMAs were conducted for six outcomes but linzagolix was only clinically similar (at least as good as) relugolix CT for one of these - reducing the volume of the primary fibroids. However, results are uncertain due to challenges in interpreting clinical similarity when NMA effect estimates have wide credible intervals. Lack of methodological details about how the NMAs were conducted precludes any interpretation of whether linzagolix might have clinical similarity to leuprolide acetate.

Key Issue 2: Uncertain relevance of the PRIMROSE trials to the three sub-populations in the company Decision Problem and NICE scope. Due to the trials' eligibility criteria and short duration, few patients if any from the three population sub-groups #1 to #3 are included in the trials. We are uncertain whether those who were included could serve as a proxy for those not included, for instance whether the efficacy and safety of linzagolix without ABT would differ between people who can or cannot receive hormone therapy.

Uncertainties in the company's analysis methods. The EAG were unable to validate the company's NMA or MAIC analyses as we did not have access to the individual participant data, and the statistical code provided did not specify sufficient details of the data format. There are inconsistencies between the individual PRIMROSE trials and the pooled trials analysis that raise uncertainty in how the pooled analysis was conducted and whether it was

quality-checked. These affect the odds ratio for response, and the UFS-QoL symptom severity score, where the pooled outcome effect estimates lie outside the range of the individual trial effects. The NMAs provided for the comparison of linzagolix against leuprolide cannot be usefully interpreted because of the lack of methodological clarity; even the outcome assessment timepoint was not provided.

In the MAIC analyses the PRIMROSE 2 trial was poorly matched. Simulated treatment comparison (STC) could be explored as an alternative indirect treatment comparison approach which may be more suitable than MAIC when there is less overlap of the population characteristics. Other opportunities to further explore and perhaps reduce uncertainty could be to conduct sensitivity analyses on the NMA and MAIC analyses adjusting for different sets of covariates and to test robustness of the analyses to missing data.

4 COST EFFECTIVENESS

4.1 Company review of cost-effectiveness evidence

The company report their economic search strategy in CS section B.3.1 and CS Appendix G. They conducted searches for published economic evaluations for GnRH antagonists. Five cost-effectiveness or cost-minimization studies that assessed pharmacological treatments for uterine fibrosis and one prior NICE appraisal in moderate to severe symptoms of uterine fibrosis (TA832) were identified and summarised (CS Table 46). In TA832, a cohort-level Markov model was developed to assess the cost-effectiveness of relugolix CT compared to GnRH agonists (goserelin, triptorelin, leuprorelin) in pre-menopausal women with moderate to severe UF symptoms who have failed or are unsuitable for conventional hormonal therapy.

EAG conclusion on cost-effectiveness searches

The original searches were conducted on 21 July 2021, and update searches in March 2022 and February 2023. No grey literature sources were reported in CS Appendix G, although the company reported hand searching of published literature across several conferences. Of the identified and reported studies in the company's search, the NICE appraisal TA832 is the most pertinent to the current appraisal.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

The company's economic evaluation is discussed in relation to the NICE reference case in Table 10.

Table 10 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes

Element of health technology assessment	Reference case	EAG comment on company's submission
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Yes, for Population #3; cost-comparison for Populations #1 & #2
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes. Six months for Populations #1, 10 years for Populations #2 and #3. In the cost-effectiveness analysis for Population #3, scenarios were conducted with 30 years and 60 years (lifetime horizon). Changing the time horizon has no impact on the ICER as mortality is not affected.
Synthesis of evidence on health effects	Based on systematic review	Yes
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.	HRQoL not applied in the CCA for Populations #1 and #2. In the CEA for Population #3, trial-based disease-specific measure UFS-QoL was mapped to EQ-5D-3L in the base case and scenario was conducted using the estimates obtained from mapping the trial-based EQ-5D-5L to EQ-5D-3L.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes, HRQoL data using UFS-QoL and EQ-5D-5L were collected in the PRIMROSE trials.

Element of health technology assessment	Reference case	EAG comment on company's submission
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes (severity modifier does not apply, CS B.3.6)
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	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	No discounting in the CCA for Populations #1 and 2; same discount rate of 3.5% for costs and health effects applied in the CEA for Population #3.
Source: EAG assessment based on the company submission CCA: Cost Comparison Analysis; CEA: Cost Effectiveness Analysis		

4.2.2 Model structure

The company presented a blended approach for this appraisal, submitting two economic models for three subgroups of patients:

- A cost-comparison model for patients having short-term treatment of 6 months or less (Population #1); and those having longer-term treatment, with hormone-based therapy (Population #2)
- A cost-effectiveness model for patients having longer-term treatment, without hormone-based therapy (Population #3).

4.2.2.1 Overview of the model structure

The key features of the cost-comparison model for Population #1 and Population #2 and the cost-effectiveness model for Population #3 are presented in the following sub-sections.

4.2.2.1.1 Cost-comparison model for Populations #1 and Population #2

Key features of the model are:

- Proportion of patient estimated in four states: on-treatment, off-treatment, menopause, and death.
- For Population #2, patients are assumed to undergo no further pharmacological treatment or surgery after menopause.
- No clinical efficacy parameters were included for Population #1. For Population #2, treatment discontinuation was incorporated: a discontinuation rate of [redacted] was obtained from the PRIMROSE trials and converted to per cycle probability, and applied across all the treatment arms (discussed in Section 4.2.5.1).
- Time horizon: 6 months (Population #1); 10 years (Population #2)
- No discounting
- Perspective: National Health Service (NHS)/Personal Social Services (PSS)
- Cycle length: 28 days
- Costs included: Drug costs, administration costs, healthcare resource use costs and costs associate with surgery.

4.2.2.1.2 Cost-effectiveness model for Population #3

Key features of the model are:

- Markov model with six health states comprising:
  - Uncontrolled (defined by heavy menstrual bleeding (HMB) >80 mL MBL per cycle)
  - Controlled (defined as achieving MBL ≤ 80 mL and ≥50% reduction from baseline)
  - Surgery
  - Post surgery
  - Menopause
  - Death
- Time horizon: 10 years
- Discounting: 3.5% p.a.
- Perspective: NHS/PSS
- Cycle length: 28 days
- Half cycle correction applied.

Patients enter the model in the ‘uncontrolled’ state where they receive treatment. After this, their symptoms can remain ‘uncontrolled’ or can be ‘controlled’. Patients transition to surgery, menopause, or the death state from the ‘uncontrolled’ state. Those in the

'controlled' state may remain there or may lose response and transition to uncontrolled, surgery, menopause, or death. Surgery is assumed to last for only one cycle after which patients transition to the 'post-surgery' state and remain there till the onset of menopause. A schema of the model structure is presented in CS Figure 25.

EAG conclusion on the model structure

The company's simple modelling approach for the cost-comparison analysis is reasonable. We view the model structure for the cost-effectiveness analysis, based on symptom control (controlled, uncontrolled) as appropriate, based on clinical expert advice to the EAG and committee discussions in NICE TA832. The company explored the impact of varying model features in their scenario analyses. For further details, see section 5.2.2.

4.2.3 Population

The company specify the target population for linzagolix in CS Section B.3.2.1. Adults of reproductive age with moderate to severe symptoms of UF are divided into three subgroups:

- Population #1: People with short-term treatment of ≤6 months
- Population #2: People with longer-term treatment, with hormone-based therapy.
- Population #3: People with longer-term treatment, without hormone-based therapy.

The baseline characteristics used in the economic analyses were mean age (42.25 years) and average age of menopause (51 years). The CS assumed that all patients transitioned to the menopause state on reaching the age of 51 years, after which they did not experience any disease-related symptoms.

EAG conclusion on the model population

The patient subgroups included in the company analyses align with the final NICE scope for this appraisal. Patient characteristics in the company's analyses, based on the PRIMROSE 1 & 2 trial populations and TA832, are reflective of UK clinical practice. We note that Population #3, which includes patients who are unable to receive hormone-based therapy (shown in CS Figure 1), is inconsistent with the population in the PRIMROSE trials. The clinical trials included people who could be randomised to any trial arm, with or without hormone-based therapy, and therefore do not include a population unable to receive hormone-based therapy (see the eligibility criteria in CS Table 9). The EAG's clinical expert suggested that, in practice, very few patients would be unfit/prefer not to receive hormone-based therapy, so the unique population who could benefit from linzagolix without hormone-based therapy in clinical practice could be very small. However, this is uncertain (see section 2.2.4 above).

4.2.4 Interventions and comparators

The economic models evaluate the intervention (linzagolix) against specific comparators for each sub-population (GnRH analogues for Population #1 and Population #2; best standard of care [BSC] for Population #3). The company describe the intervention in CS section B.1.2 and we discuss the intervention and its intended use in practice earlier in Section 2.2.2 of this report. The dosing regimen for linzagolix (see CS Section B.3.2.2), that received marketing authorization, is consistent with the PRIMROSE trials.

In their cost-comparison model, the company assumed a dosage of 200mg for Population #1; and 200mg + ABT for Population #2. For Population #3 (in the cost-effectiveness model), a dosage of 200mg for 6 months followed by 100mg was assumed for their base case. Scenario analyses were conducted using different dosing regimens in both the cost-comparison analysis and cost-effectiveness analysis. These assumptions had no significant impact on the incremental costs in the cost-comparison analysis for Population #1 and Population #2. But changing the regimen in the cost-effectiveness analysis for Population #3 had significant impacts on the overall ICERs. For instance, changing to 200mg for 6 months followed by BSC or using 100mg continuously from the start, increased the company's ICER by £1,443 and £1,973, respectively.

The comparators included across the three subgroups are:

- Population #1: relugolix CT and GnRH agonists (goserelin, leuprorelin and triptorelin)
- Population #2: relugolix CT
- Population #3: BSC comprising concomitant medications for pain management (NSAIDs) and iron supplements.

EAG conclusion on the intervention and comparators

The intervention included in the economic models is consistent with the NICE scope. However, there is uncertainty with respect to the comparators used across the three populations. To elaborate, in the cost-comparison analysis for Population #1 and Population #2, relugolix CT may not be most appropriate comparator as it appears to have low market share; clinical expert advice to the EAG suggests that most of the patients (circa 90%) currently receive goserelin or leuprorelin, although the use of relugolix would likely increase over time. With respect to Population #3, our expert advice is that these patients would require protection against bone loss, which is not included within the modelled BSC. This would include prophylactic regimens of calcium

and vitamin D. We conducted scenario analyses including these regimens as part of BSC, for further details see Section 6.

4.2.5 Treatment effectiveness and extrapolation

4.2.5.1 Clinical parameters used in the cost-comparison analyses

Population #1:

- Across both the treatment arms, a similar proportion of patients (45.10%) was assumed to receive surgery.
- The distribution of types of surgery for linzagolix was assumed to be same as for relugolix CT and sourced from the TA832 company submission.
- Background mortality was not incorporated as treatment only lasts for 6 months.

Population #2:

- Treatment discontinuation for linzagolix doses were obtained from the pooled PRIMROSE trials. It was assumed to be the same as linzagolix 200mg + ABT for relugolix CT ([redacted]).
- Like Population #1, 45.10% of patients were assumed to experience surgery across both the treatment arms.
- The distribution of the types of surgery was obtained from TA832.
- Mortality due to surgery was not incorporated.

Across both the populations, the costs of surgery were applied as a one-off cost. No data from company indirect treatment comparisons was used to inform clinical efficacy. The company justified their approach citing the ITC findings (discussed above in Section 3.4), their clinical expert opinion and NICE TA832 for similar efficacy of relugolix CT with GnRH agonists.

EAG conclusion on treatment effectiveness and extrapolation

The EAG have two concerns for the cost-comparison analysis.

1. We are uncertain whether:
    a. linzagolix has similar clinical efficacy as relugolix CT and other GnRH analogues (see Key Issue 1) and
    b. relugolix-CT has an adequate market share to qualify as the selected comparator for the cost-comparison analysis (see Key Issue 2).

If the company's assumption is not supported, then cost-utility analyses would be more appropriate.

2. The company did not apply any additional risk of mortality from surgery in Population #2. Although the mortality is very low, and particularly with the short time horizon is unlikely to impact on costs, we view that it ought to be included for completeness.

4.2.5.2 Clinical parameters used in the cost-effectiveness analysis.

The company applied the following transition probabilities in their economic model for Population #3, reproduced from CS Table 54 and shown in Table 11 below. We noted an inconsistency in the transition probability from surgery to death between the CS and the economic model (Clarification Response B2) which has been corrected in the table below. We discuss and critique the derivation of these estimates in the following subsections.

Table 11 Transition probabilities used in the cost-effectiveness model.

FROM / TO	Controlled	Uncontrolled	Surgery	Post-surgery	Procedural death
Linzagolix					
Controlled	[redacted]	[redacted]	[redacted]	0.000%	0.000%
Uncontrolled	[redacted]	[redacted]	[redacted]	0.000%	0.000%
Surgery	0.000%	0.000%	0.000%	99.997%	0.003%
Post-surgery	0.000%	0.000%	0.000%	100.000%	0.000%
Procedural death	0.000%	0.000%	0.000%	0.000%	100.000%
Best Supportive Care					
Controlled	[redacted]	[redacted]	[redacted]	0.000%	0.000%
Uncontrolled	[redacted]	[redacted]	[redacted]	0.000%	0.000%
Surgery	0.000%	0.000%	0.000%	99.997%	0.003%
Post-surgery	0.000%	0.000%	0.000%	100.000%	0.000%
Procedural death	0.000%	0.000%	0.000%	0.000%	100.000%

Note: Transition matrix does not include background mortality which is applied separately within the model calculations
Source: CS Table 54 and company economic model

4.2.5.2.1 Response rate

Response rates for linzagolix and BSC arms were informed by the pooled data from the PRIMROSE 1 and 2 trials at 24 weeks (which we discuss earlier in Section 3.2.5.1). While the trials included four treatment dosing regimens for linzagolix (100mg, 100mg + ABT, 200mg, and 200mg + ABT), the cost effectiveness model included clinical effectiveness estimates for only 100mg and 200mg doses, as these are the doses indicated for Population #3. The placebo-arm of the PRIMROSE trials was assumed to be representative of the

clinical effectiveness of BSC, due to lack of active treatment options for this subgroup. This is consistent with the approach adopted in TA832.

The pooled 24-week response rate from the PRIMROSE trials, as reported in CS Table 16, determined the proportion of patients entering the 'controlled' health state (defined as MBL ≤80 mL and ≥50% reduction from baseline at 24 weeks). Those who do not have a response or achieve but subsequently lose their response enter the 'uncontrolled' health state. The company applied a standard equation (see CS Equation 1) to convert the 24-week response rate to a per cycle probability of moving from the uncontrolled to the controlled health state. These probabilities are reproduced below in column 3 of Table 12.

Table 12 Response probabilities included in the model.

Treatment	24-week response rate	Response probability per cycle	Source for response rate
Linzagolix 200mg	[redacted]	[redacted]	Pooled PRIMROSE 1 & 2 (CS Table 16)
Linzagolix 100mg	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	
Source: Company model, CS Table 50			

EAG conclusion on response

We note that the PRIMROSE trials provide a maximum duration of efficacy outcome assessments of 52 weeks, whereas the economic model used the efficacy outcomes at 24 weeks. Furthermore, the SmPC suggests linzagolix may be used for more than one year in clinical practice (subject to regular bone mineral density monitoring). In their response to Clarification Question A7, the company justified using 24-week data based on the argument that treatment effect of linzagolix is expected to be maintained over 52 weeks. They cited 2-year data from the LIBERTY randomised withdrawal study[30] for relugolix CT, where the treatment effect was maintained. They argued that given linzagolix has a similar mechanism of action to relugolix CT, its efficacy is likely to be maintained beyond 24 weeks. We are uncertain about this assumption; while the company's response is biologically plausible, there are no data to support this.

We did not identify any inconsistency in the response rate between CS Table 16 and the economic model. No error was identified in the conversion from rate to per cycle probabilities.

4.2.5.2.2 Recurrence rate

Recurrence rates of uterine fibrosis, converted to per cycle probabilities using the same formula as for response rate (i.e., CS Equation 1), were used to inform the probability of losing response and transitioning from the 'controlled' to the 'uncontrolled' state. The company state that these estimates (shown in Table 13 below) were obtained from a market research survey with UK gynaecologists (n=50). In a scenario analysis conducted by the company, these estimates are shown to have a significant impact on the cost-effectiveness results: increasing the recurrence rate during treatment with linzagolix to that used for BSC increased the base case ICER by £5,315, to £20,707.

Table 13 Recurrence rates used in the model for Population #3

Treatment	Recurrence rate	Estimated recurrence probability per cycle	Source
Linzagolix	[redacted]	[redacted]	Clinical opinion
BSC	[redacted]	[redacted]	
Source: CS Table 51 and the company's cost-effectiveness model			

EAG conclusion on recurrence rate

We conducted a targeted search of recurrence rate in patients with uterine fibrosis and found recurrence rates of 11.7% and 15.3% at 1-year post-laparoscopic myomectomy, [31, 32] and 23% at 40 months post-abdominal myomectomy[33] respectively. The EAG's clinical expert suggested that a recurrence rate of circa 23% in patients with UF may be reasonable for the linzagolix arm. For patients receiving BSC, the recurrence rate is likely to be higher as these patients are unable to receive any hormones including ABT. For completeness, we conducted a range of exploratory scenarios assuming a similar recurrence rate for linzagolix and BSC, thereby varying the rates between 10% and 25%, in Section 6.1.

4.2.5.2.3 Surgery

In the economic model, surgery is assumed to last for one model cycle. The following types of surgery were included:

- Urinary artery embolization (UAE)
- Magnetic resonance-guided focused ultrasound surgery (MRgFUS)
- Abdominal myomectomy
- Laparoscopic myomectomy
- Abdominal hysterectomy
- Laparoscopic hysterectomy

In the model, patients transition from the 'controlled' and 'uncontrolled' health states to the 'surgery' state. The surgery rate was informed by the PEARL II trial, which compared ulipristal acetate with leuprorelin acetate for the pre-operative treatment of symptomatic fibroids. Using the surgery rate from PEARL II (45.10%) and a waiting time of 18 months on average, the per cycle probability of surgery from the two health states was estimated to be 3.02%. In the base case, the probability of experiencing surgery from the two health states are assumed to be equivalent. Furthermore, the probability was assumed to be the same for linzagolix and BSC. Scenario analyses assuming lower surgery probabilities of 1% and 2% for patients in the 'controlled' state reduced the overall ICER by £4,251 and £863, respectively.

The company assume similar distributions of patients across the surgery types for both the treatment arms. The distribution for their base case, reproduced below in Table 14, were obtained from the CS of NICE TA832. Scenario analyses were conducted using the EAG estimates from the same appraisal (which had no impact on the overall cost-effectiveness results) and assuming a 10% switch from open/abdominal to laparoscopic surgery for patients in the linzagolix arm (which reduced the overall base case ICER by £2,873).

Table 14 Distribution of surgery types for the base case model

Surgery types	Patient distribution
UAE	4.8%
MRgFUS	3.0%
Open/abdominal myomectomy	25.7%
Laparoscopic myomectomy	8.2%
Open/abdominal hysterectomy	51.8%
Laparoscopic hysterectomy	6.4%

Source: CS Table 52
UAE: Urinary artery embolization; MRgFUS: Magnetic resonance-guided focused ultrasound surgery

EAG conclusion on surgery

The company's assumption that both linzagolix and BSC arms have similar distributions of surgery types is reasonable. With respect to patient distributions across the different surgery types, the EAG's clinical expert considered that some of the surgery types (e.g., laparoscopic hysterectomy and UAE are more common than others. Furthermore, patients are also likely to undergo hysteroscopic myomectomy, which is not listed in the company's analyses. Lastly, our clinical expert suggested that recovery time after

different types of surgery varies between 4 and 8 weeks. For example, the recovery time after laparoscopic surgery could be 4-6 weeks; open surgery: 6-8 weeks; UAE: 4-6 months. We have conducted scenario analyses changing the distributions across the different surgery types based on our expert's advice. While this impacts the total costs and total QALYs, the change is proportional as the distributions are similar for both the treatment arms and therefore there is no overall impact on the ICER (see Section 6).

4.2.5.2.4 Post-surgery health state

In the model, patients enter the 'post-surgery' state after undergoing surgery and remain there until the onset of menopause. We note that the choice of surgery type is dependent on a range of factors including disease characteristics and patient preferences, and therefore, the prognosis of the patients may vary depending on the type of surgery undergone. While some patients may be completely cured (e.g., those who underwent a hysterectomy), others may experience a recurrence of the symptoms post-surgery. In NICE TA832, the post-surgery state was sub-divided into two: patients who received hysterectomies and those who did not, with a proportion of the latter cohort transitioning to a second surgery state, based on re-surgery rates. Furthermore, evidence from published literature[34] indicates that although surgery has a high impact on the symptoms of the fibroids, these may recur (except after hysterectomies). Overall, we view the company's assumption that patients stay in the 'post-surgery' state until they experience menopause as simplistic and are unclear whether this is representative of the disease pathway.

EAG conclusion on the post-surgery state

The EAG are uncertain about: i) how the prognosis of different surgery types will vary; and ii) whether patients undergoing surgeries other than hysterectomies may experience a recurrence. We suggest the company could conduct scenario analyses by adding a percentage of recurrence within the post-surgery state for both the arms. Due to the uncertainties discussed above, we view further discussion with clinical experts is warranted.

4.2.5.2.5 Treatment discontinuation

In the economic model, patients could discontinue treatment either for any reasons (named as 'trial-based' treatment discontinuation by the company) or due to adverse events (named as 'modified' treatment discontinuation by the company). The discontinuation rates were obtained from the pooled PRIMROSE analysis at 24 weeks (shown below in Table 15) and converted to per cycle probabilities. These were applied throughout the time horizon for all

patients in the 'controlled' and 'uncontrolled' health states on both the treatment arms. In the base case, a constant risk of trial-based discontinuation was assumed.

The cited reasons for trial discontinuation were participant request, loss to follow-up, adverse event, lack of efficacy, pregnancy and other. Scenario analysis was conducted using the modified rates, i.e., discontinuation due to AEs only. The trial-based withdrawal rates are much higher than the modified rates, implying that fewer patients remain on treatment when the trial-based rates are applied. This has a significant impact on the ICER as it impacts the drug costs. For example, using modified rates (treatment discontinuation due to AEs) increases the ICER by £10,436, to £25,828. This is driven by a significant increase in the drug costs of linzagolix, particularly that of linzagolix 100mg as the proportion of patients receiving linzagolix 100mg post the initial 6 months is much higher due to modified discontinuation rates, compared to that of trial-based rates.

Table 15 Treatment discontinuation

Treatment	Base case (Trial based)		Scenario analysis (modified)		Source
	Withdrawal for any reason	Per cycle prob. of TTD (estimated)	Withdrawal due to AE	Per cycle prob. of TTD (estimated)	
Linzagolix 100mg	[redacted]	[redacted]	[redacted]	[redacted]	Pooled PRIMROSE analysis
Linzagolix 200mg	[redacted]	[redacted]	[redacted]	[redacted]	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	
Source: Company's cost-effectiveness analysis model TTD: Time to Treatment Discontinuation					

The company do not discuss treatment discontinuation in their CS. Like the response rates, they applied the discontinuation rates available at 24 weeks in the economic model. Data available for 24-52 weeks were not used. We view that it is appropriate to use long-term data where available. In previous NICE TA832, the company applied the discontinuation rates for relugolix-CT from the LIBERTY trials, based on clinical opinion, and from PEARL II for GnRH agonists. The TA832 committee concluded the rates used in the model as highly uncertain and that the company's model did not accurately capture the uncertainty. In the current appraisal, the discontinuation rate, whether 'trial-based' or 'modified', is important because it impacts the acquisition costs, and hence the ICER. We conducted a range of exploratory

scenarios assuming similar discontinuation rates for linzagolix 200mg, 100mg and BSC, see Section 6.

EAG conclusion on treatment discontinuation

Overall, we view the company's approach to modelling treatment discontinuation to be reasonable as the estimates are based on the PRIMROSE trials and reflect the expectation that in practice patients may discontinue due to many reasons, other than AE. However, we suggest that analysis based on 52-week data would be appropriate.

4.2.5.2.6 Adverse event rates

The economic model included treatment emergent adverse events occurring in 5% or more of patients across the treatment arms of the pooled PRIMROSE trial. These included four adverse events: anaemia, headache, hot flash, and nausea, see CS Table 55. The average duration of these adverse events was assumed to be one model cycle and the rates (in CS Table 55) were multiplied with the associated disutilities (in CS Table 64) to obtain QALY loss due to AEs. This is applied in the first model cycle.

EAG conclusion on adverse events

Overall, we agree with the company's approach. Clinical advice to the EAG suggested that anaemia should be expected to improve on treatment in patients with UF. Furthermore, allergies and intolerances to medications are common adverse events witnessed among these patients, which are not included. However, inclusion of these events is unlikely to make any significant impact on the overall cost-effectiveness results. Lastly, we are unclear if the duration of the PRIMROSE trial is sufficient to capture any detrimental effects of reduction in bone density in these patients.

4.2.5.2.7 Mortality

Age-adjusted background mortality rates obtained from the ONS data for England were incorporated in the economic model. Mortality associated with surgery related complications were also incorporated. These estimates, reproduced below in Table 16, were obtained from NICE TA832.

Table 16 Risk of procedural death

Treatment arm	Risk of death	Source
UAE	0.0200%	TA832/Zowall et al., 2008
MRgFUS	0.0000%	TA832/Gorny et al., 2011
Open/abdominal myomectomy	0.0028%	TA832/Assumption
Laparoscopic myomectomy	0.0000%	TA832/Assumption

Open/abdominal hysterectomy	0.0028%	TA832/Settnes et al 2020
Laparoscopic hysterectomy	0.0020%	TA832/Settnes et al 2020
Source: CS Table 53		

EAG conclusion on mortality

The company's approach to modelling background mortality is appropriate. We also agree with the assumption of excess mortality associated with surgical procedures. Clinical advice to the EAG indicates that there is likely to be a higher risk of mortality associated with hysterectomies and myomectomies as these are major surgeries, whereas UAE is less risky than open surgery. Considering this, we conducted a scenario analysis with a decreased mortality rate (0.0002%) associated with UAE. For further details, see Section 6.

4.2.6 Health related quality of life

The discussion and critique of the health-related quality of life (HRQoL) data in the following sub sections relate to the cost-effectiveness model developed for the Population #3, comparing linzagolix with BSC. An overview of the utility values used in the cost-effectiveness analysis is presented in Table 17. The cost-comparison analyses for Population #1 and Population #2 do not incorporate HRQoL data.

Table 17 Summary of utility values for cost-effectiveness analysis

Health state	Treatment arm	Utility value	Source	EAG discussion
Controlled	Linzagolix (200 mg)	[redacted]	PRIMROSE 1 and 2 (UFS-QoL mapped to EQ-5D)	Section 4.2.6.2.1
	BSC	[redacted]		
Uncontrolled	Linzagolix (200 mg)	[redacted]		
	BSC	[redacted]		
Surgery	Surgery and post-surgery utility values are non-treatment specific in the base case	0.677	Literature	Section 4.2.6.2.2
Post-surgery		0.846	Literature	
Source: CS Table 67				

4.2.6.1 Systematic literature review for utilities

The company conducted a systematic literature review of existing HRQoL studies in patients with uterine fibrosis and report the search and findings in CS Appendix H. In total 47 studies met their inclusion criteria. Of these, seven included patients from the UK. Most of these studies used Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QOL) (n=6) to measure HRQoL, either as the singe instrument (n=4) or in combination with other instruments (n=2). Other instruments used included SF-36, EQ-5D-3L, and the EQ-5D visual analogue scale. Of the 47 included studies, the company applied the utility values obtained

from EQ-5D-5L for two health states, controlled (0.73) and uncontrolled (0.55), from a Canadian study by Hux et al. 2015[35] in their scenario analysis (see Section 5.2.2).

In the previous NICE appraisal TA832, the company included treatment-specific utility values, which were informed by MBL from the treatment arms of the LIBERTY trials. The UFS-QoL data, obtained from the LIBERTY trials, were mapped to EQ-5D using an unpublished mapping algorithm. An ordinary least squares (OLS) model, adjusted for age and MBL, was used to predict the impact of MBL on mapped EQ-5D utilities to generate time-varying utilities. The Evidence Review Group in TA832 expressed concerns over this approach due to lack of sufficient justification for the choice of regression model. They preferred a repeated measures model to allow for exploring uncertainties and generating utility estimates closer to that of general population averages when MBL was low. The TA832 NICE committee concluded that the model was likely to underestimate the utility values to inform the QALY gains with relugolix-CT.

4.2.6.2 Study-based health related quality of life

4.2.6.2.1 Controlled and uncontrolled health states

HRQoL data from the PRIMROSE trials were used to estimate utilities for the 'controlled' and 'uncontrolled' health states in the model. PRIMROSE 1 and 2 used patient self-reported, disease specific UFS-QoL scores and the EQ-5D-5L to collect HRQoL data at baseline and at weeks 12, 24, 36 and 52. The UFS-QoL and EQ-5D-5L data from the trials were mapped onto EQ-5D-3L utility values. The company then used a linear mixed model (LMM) to predict the utility values for 'controlled' and 'uncontrolled' health states based on reduced menstrual blood loss (RMBL). The utility function is not reported in the CS: we derived this as below, based on the information in the economic model. The coefficient of the intercept (α) is the estimated utility for the 'uncontrolled' state as this reflects patients without RMBL; whereas (α + β*RMBL) gives the estimated utility for the 'controlled' state, reflecting patients with RMBL.

$$EQ\text{-}5D_{mapped} = \alpha + \beta\ RMBL + \varepsilon$$

We reproduced the coefficients of the intercept and the RMBL from the utility functions from the economic model as shown in Table 18 below.

Table 18 Coefficients from the utility function obtained from the company's model.

	Base case (EQ-5D-3L utility mapped from UFS-QoL data)	Scenario (EQ-5D-3L utility mapped from EQ-5D-5L data)
Intercept	[redacted]	[redacted]
RMBL	[redacted]	[redacted]
Source: company cost-effectiveness model		

For their base case, the company mapped UFS-QoL to EQ-5D-3L and conducted a scenario analysis with EQ-5D-5L mapped to EQ-5D-3L.

- **Base case: Mapping of UFS-QoL to EQ-5D-3L**

Following the approach adopted in TA832, the company used an unpublished algorithm reported in a paper by Rowen and Brazier 2011 and shown in CS Equation 2, to map UFS-QoL to EQ-5D-3L.[29] To account for within-patient repeated measures (a critique raised by the Evidence Review Group in TA832), a linear mixed model (LMM) was chosen to estimate the health-state utilities. It is noteworthy the UFS-QoL measure includes two scales: symptom severity and HRQoL. The directions of these scales are opposite (e.g., decrease in symptom severity indicates improvement whereas increase in HRQoL scale indicates improvement). The CS does not explicitly define which of these scales was used. CS Equation 2 is based on individual UFS-QoL questions that appear to include parts of both the symptom severity and HRQoL scales rather than focusing on HRQoL questions. The rationale for this approach is unclear.

- **Scenario analysis: Mapping of EQ-5D-5L to EQ-5D-3L**

The company state that a linear mixed model was used to map EQ-5D-5L responses in the PRIMROSE trials to EQ-5D-3L using the algorithm developed by Hernandez-Alava et al. 2017,[36] as recommended by NICE.[1] The equation was not reported in the CS. Like in their base case, LMM was used to estimate the utility values.

Table 19 Mapped utilities used in the cost-effectiveness model.

Health state	Base case	Scenario analysis
Controlled	[redacted]	[redacted]
Uncontrolled	[redacted]	[redacted]
Source: CS Tables 58 and 61		

4.2.6.2.2 Surgery and post-surgery health states

The PRIMROSE trials did not collect HRQoL data for surgery or post-surgery health states. Therefore, utility estimates for these health states were informed by published literature (CS Table 66, reproduced below in Table 20). As stated earlier in Section 4.1, the company reported a literature search of HRQoL data associated with surgical/interventional procedures in patients with uterine fibrosis. Weighted average utility values for surgery and post-surgery were obtained based on the distribution of surgery types (discussed earlier in Section 4.2.5.2.3)

Table 20 Health state utilities for surgery and post-surgery

Surgery	Health state	Value
UAE	Surgery	0.620
	Post-surgery	0.800
MRgFUS	Surgery	0.783
	Post-surgery	0.802
Open/abdominal myomectomy	Surgery	0.628
	Post-surgery	0.878
Laparoscopic Myomectomy	Surgery	0.630
	Post-surgery	0.880
Open/abdominal Hysterectomy	Surgery	0.705
	Post-surgery	0.834
Laparoscopic hysterectomy	Surgery	0.707
	Post-surgery	0.836
Source: Reproduced from CS Table 66 and the company's economic model		

4.2.6.3 Adverse events

Disutilities associated with the adverse events (see Table 21) were informed by published literature. Further details are in CS section B.3.4.4. These estimates were multiplied with the frequency of the AE of the two treatment arms obtained from PRIMROSE trials, shown in CS Table 55, and discussed earlier in Section 4.2.5.2.6, to obtain the AE QALY decrement, shown in Table 22 below. These decrements were applied as a one-off in the first model cycle.

Table 21 Adverse event disutilities

AE	Disutility

Anaemia	-0.0209
Headache	-0.0297
Hot flush/flash	-0.0600
Nausea	-0.0480
Source: CS Table 64 and the economic model	

Table 22 AE QALY decrement

Treatment arm	AE disutility
Linzagolix (200 mg, base case)	-0.002
BSC	-0.001
Source: CS Table 65 and the economic model	

4.2.6.4 Age-adjusted utilities

To account for an age-related decrease in quality of life, the company applied age-related utility decrements using a widely used algorithm published by Ara and Brazier.[37] The utility multiplier was applied in each model cycle throughout the time horizon.

EAG conclusions on HRQoL

The company adopted a similar approach as in TA832 to estimate utilities for the controlled and uncontrolled health states. An unpublished algorithm for mapping UFS-QoL to EQ-5D-3L was used, based on the previous appraisal TA832. The company did not report the mapping algorithm used for EQ-5D-5L to EQ-5D-3L. The coefficients used in the mapping algorithm were provided in the economic model; therefore, we are unable to verify if the estimates in the algorithms were implemented appropriately. Using the estimates obtained from mapping EQ-5D-5L to EQ-5D-3L has a significant impact on the ICER: the base case ICER doubles, to £30,803. This is driven by a higher increment in the total QALY gain for the BSC arm than that for linzagolix, thereby decreasing the incremental QALY gain.

We acknowledge the company's mapping in the base case is consistent with TA832. We have also noted their rationale for using a disease-specific measure in the base case (in CS Section B.3.4.5.3). Advice from our clinical expert concurs with the company's rationale for preferring disease-specific measures over generic measures. However, we note NICE's preference for trial-based EQ-5D data when it is available,[1] and question whether the TA832 committee's concerns about the availability of EQ-5D-5L data from the clinical trials apply in the current appraisal.

The company addressed one of the key uncertainties raised in TA832 associated with the choice of regression model for the utility function, by using a linear mixed model to account for repeated measures. However, they did not provide any information on the utility function used in their LMM within the CS. The intercept and the coefficient of the only covariate (RMBL) for the two LMMs (one for the base case and the other for scenario analysis) are hard coded within the model. No clarity or rationale was provided for their choice of the covariate included therefore we are unclear as to why other covariates (such as age) were excluded from the utility function. Furthermore, no sensitivity or scenario analyses were conducted to explore the impact of varying assumptions around the utility function (e.g., using alternative utility functions exploring non-linear impacts of RMBL on utility). Due to this lack of information, the EAG are uncertain about the robustness of the utility function for the LMM that was used to estimate utilities for the 'controlled' and 'uncontrolled' health states. We conducted a range of exploratory scenarios changing the coefficients by +/-10% in EAG analyses, see Section 6.

In conclusion, we view that there are uncertainties with respect to the company's approach for estimating utilities for the 'controlled' and 'uncontrolled' health states that warrant further investigation.

4.2.7 Resources and costs

We outline below the costs included in the cost-comparison and the cost-effectiveness analyses.

- Drug acquisition costs
- Administration costs
- Healthcare resource use costs
- Costs associated with surgery.

4.2.7.1 Drug acquisition and administration

CS Tables 68 and 69 report the cost of drugs used in the model. The cost reported in the model for the two doses of linzagolix (100mg and 200mg) is [redacted] using the Patient Access Scheme (PAS) discount. Within the cost-comparison model, no additional costs of ABT were applied in the comparator arms for relugolix CT and the GnRH agonists. All patients were assumed to receive concomitant medications (including ibuprofen and iron supplements) in the base case. Linzagolix is administered orally; there are no associated administration costs. However, as the GnRH agonists are administered via subcutaneous injection, the

company model assumes that a patient requires 10 minutes of a nurse's time in GP clinic, at a cost of £7.67.

4.2.7.2 Resource use

4.2.7.2.1 Health care

The health care resource use and costs used in the cost comparison and cost-effectiveness analyses are reported in CS Table 74 and CS Table 75 and summarised in Table 23 below. The costs are obtained from PSSRU 2022, and the NHS reference costs 2021/22.

Table 23 Health care resource use and costs

Resource	GnRH analogues	BSC	Cost
Gynaecologist consultation	Once only	Once only	£185.51
GP visits	None	None	£42.00
DEXA scans	One after 1 year [a]	None	£95.45
Ultrasound	Once (67% of patients)	Once (67% of patients)	£235.60
Full blood count	Once	Once	£2.96
Hysteroscopy	Once (17% of patients)	Once (17% of patients)	£286.41
MRI	Once (17% of patients)	Once (17% of patients)	£197.34

Source: Reproduced from CS Table 74 and CS Table 75
[a] Applied to 100% of patients in the first model cycle as a conservative assumption

The healthcare resource use costs for Population #3 are assumed to be equivalent to those used in TA832. The company aggregated the costs, which are applied as a one-off in the first cycle of the economic model.

4.2.7.2.2 Adverse events

Four adverse events are captured in the company model for Population #3, the costs of which are reported in CS Table 76. Headache and hot flush are assumed to incur no cost, while treatment for anaemia is assumed to be the cost of a GP surgery consultation, £42.00, as in TA832. For nausea, a cost of £0.96 is applied to cover treatment with metclopramadine, as used in TA832. CS Table 77 reports the adverse event costs which are applied in the first model cycle, obtained by combining the unit costs with the adverse event probabilities in Section 4.2.6.3 above. In the base case, a cost of £1.25 is applied for adverse events related to linzagolix 200mg treatment in the company model. The corresponding cost for BSC is £2.82. The company also implemented a scenario using linzagolix 100mg, which incurs an adverse event related cost of £4.24.

4.2.7.2.3 Surgery

For Populations #1 and #2, total costs associated with surgery are aggregated based on the proportion of patients undergoing surgery (see CS Tables 79 and 80).

For Population #3, the proportion of patients moving to the surgery state in each cycle is used to estimate the cost of surgery. The total cost of surgery is based upon a weighted average of different types of surgery. These surgery types can vary by treatment. CS Table 78 presents the costs of each type of surgery, obtained from the NHS schedule of NHS costs 2021/22, and reproduced in Table 24 below. The company assume that the distributions of surgery type are equivalent across both treatment arms in the base case, with a surgery cost of £5,278. CS Table 81 reports the surgery costs for Population #3, including the base case costs for linzagolix and BSC, and costs used in two scenario analyses with treatment-independent surgery distributions used in the TA832 Evidence Review Group report, and treatment-specific surgery distributions.

Table 24 Costs by surgery type

Surgery type	Cost
UAE	£2,786
MRgFUS	£1,131
Open/abdominal myomectomy	£4,670
Laparoscopic myomectomy	£3,496
Open/abdominal hysterectomy	£6,336
Laparoscopic hysterectomy	£5,273
Source: Reproduced from CS Table 78	

EAG conclusions on health care resource use and unit costs

The EAG have some concerns over the company's assumptions for healthcare resource use and associated unit costs applied to the economic model. Consultation with our clinical expert suggests that: i) patients receive two GP visits on average, unlike the company's assumption of no GP visits; ii) patients are likely to have two full blood count tests; and iii) they are unlikely to undergo DEXA scans or an MRI scan. With respect to unit costs for the resource use, we noted an inconsistency in the cost of gynaecologist consultation. Lastly, we view that the company may have underestimated the costs associated with MRI. We outline the EAG's assumptions (based on our expert advice) for these parameters in Table 25 and Table 26 and we conducted scenarios in the cost-effectiveness model for Population #3 (see Section 6).

Table 25 Health care resource usage

Resource	Company's assumption		EAG assumptions	
	GnRH antagonists	BSC	GnRH antagonists	BSC
GP visits	None	None	Twice	Twice
DEXA scans	One after 1 year	None	None	Same as company
Full blood count	Once	Once	Twice	Twice
MRI	Once (17% of patients)	Once (17% of patients)	None	None
Source: Company assumptions are obtained from CS Table 74				

Table 26 Unit costs for healthcare resource use

Resource	Company	EAG (source)
Gynaecologist consultation	£185.51	£181.26 (NHS Reference costs 2021/22, Gynaecologist consultation non-admitted face-to-face attendance, WF01A)
MRI	£197.34	£255.41 (NHS Reference costs 2021/22, Magnetic Resonance Imaging Scan of One Area, with Post-Contrast Only, 19 years and over, RD02A)
Source: Company assumptions are obtained from CS Table 75		

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company report the deterministic base case cost-comparison results for Population #1 and Population #2 in CS Tables 86 and 87 respectively, and the cost-effectiveness results for Population #3 in CS Table 88. These results are summarised in Table 27 and Table 28 below. Note that all results use the PAS price for linzagolix.

Table 27 Base case cost-comparison results for Populations #1 and #2 using the PAS discount

Treatment	Population #1		Population #2	
	Total costs	Incremental costs	Total costs	Incremental costs
Linzagolix	[redacted]	-	[redacted]	-
Relugolix CT	£3,411	[redacted]	£4,752	[redacted]
Leuprorelin	£3,441	[redacted]	-	-
Goserelin	£3,407	[redacted]	-	-
Triptorelin	£3,482	[redacted]	-	-

Source: Reproduced from CS Tables 86 and 87
PAS: patient access scheme

Table 28 Base case cost-effectiveness results for Population #3 using the PAS discount.

Treatment	Total			Incremental			ICER (£/QALY)
	Costs	LYG	QALYs	Costs	LYG	QALYs	
BSC	£5,107	[redacted]	[redacted]				
Linzagolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Reproduced from CS Table 88.
BSC, best supportive care; LYG, life-years gained; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PAS: patient access scheme

5.2 Company sensitivity analyses

5.2.1 Deterministic sensitivity analyses

For the Population #3 cost-effectiveness analysis the company report deterministic sensitivity analysis results for the ten most influential parameters in CS Table 90 and CS Figure 28. The ranges of variation for the input parameters were based on 95% confidence

intervals where available, or an assumption that the standard error was 10% of the mean. The company's results indicate that the assumptions regarding the BSC response rates are the main drivers of the model results, increasing the ICER to £19,035 per QALY. The proportion of patients receiving surgery and the recurrence rates for patients on BSC also have a high impact on the ICER. All ICERs remained below £20,000. No deterministic sensitivity analyses were performed in the cost-comparison analysis for Population #1 and Population #2.

5.2.2 Scenario analyses

The company report the results of 19 scenarios for Population #3 in CS Table 93. The scenarios explored included: time horizons, discount rates, transition probabilities, utility values, and dosing regimens for linzagolix. Changing the source of utility values from UFS-QoL to EQ-5D-5L mapped to 3L utility values had the largest effect on the results, increasing the ICER by £15,411 to £30,803 per QALY. Implementing the modified trial percentages (including adverse events as the reason for discontinuation) for treatment withdrawal rates produced the next-highest ICER of £25,838 per QALY, an increase of £10,436 from the base case. The greatest reduction in the ICER was obtained by using utility values from Hux et al.[35] as opposed to those from the PRIMROSE trials (£10,098 per QALY). Modifying the time horizons, source of surgery distribution to values reported in the Evidence Review Group report from TA832, and post-surgery utilities had no effect on the ICER. The results for scenario analyses performed for Population #1 and Population #2 are in CS Table 91 and CS Table 92 respectively.

5.2.3 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) with input parameter distributions as presented in CS Appendix N. The PSA was run for 1,000 iterations, and mean results reported in CS Table 89. The cost-effectiveness plane and cost-effectiveness acceptability curve are presented in CS Figure 26 and CS Figure 27 respectively. The probabilistic results were in line with the deterministic results when run by the EAG. No probabilistic sensitivity analyses were performed in cost-comparison analyses for Population #1 or Population #2.

EAG conclusion on the company's sensitivity and scenario analyses

The EAG did not find any errors in any of the company's analyses. The company included all necessary parameters in the PSA, with appropriate corresponding distributions. The EAG note a minor inconsistency in CS Table 93 reporting scenario analyses for Population #3: for concomitant medicine distribution, the company appear to have transposed the base case and scenario columns. The base case should be to

assume 100% distribution, whilst the scenario should be to assume treatment specific distributions. The results in the table are correct for the scenario.

5.3 Model validation and face validity checks

We conducted a range of checks on both the company's models (i.e., the cost-comparison model and the cost-effectiveness model) using an EAG checklist:

- Input checks: comparison of all parameter values in the model against the values stated in the company submission and cited sources.
- Output checks: replication of results reported in the company submission using the company model.
- 'White box' checks: manual checking of formulae working from the cohort-level Markov model, which includes reviewing the calculations across each cycle and working backwards to trace links to input parameters and forwards to the results.
- 'Black box' checks: working through a list of tests to assess whether changes to key model inputs or assumptions have the expected effects on the model results.
- The model is well-implemented, and no coding errors were identified.

We noted a few minor inconsistencies, such as incorrect NHS reference cost codes for laparoscopic myomectomy (the model stated MA08A and MA08B, but the correct codes are MA09A and MA09B; the corresponding unit costs applied in the model are correct) which did not impact the model results.

5.3.1 EAG corrections to the company model

Except one minor correction, the EAG did not identify any that needed to be made to either of the company models. As stated earlier in Section 4.2.7, we noted an inconsistency in the unit cost of a gynaecologist consultation. The company used an estimate of £185.51; we view the correct estimate is £181.26. This change in unit cost does not impact the overall cost effectiveness result. We incorporate this correction the EAG scenarios as well as in our preferred base case (see Section 6) within the cost-effectiveness model for Population #3. We also re-ran the cost-comparison analyses for Populations #1 and #2 with the correct unit cost (see Section 6).

5.3.2 EAG summary of key issues and additional analyses

We present a summary of the issues identified by the EAG and our additional analyses for the cost-effectiveness analysis for Population #3 in Table 29.

Table 29 Additional EAG scenarios conducted in the CEA for Population #3

Parameter	Company base case	EAG scenarios	EAG preferred	Reason for analysis
Baseline patient characteristics: mean age and age of menopause	Mean age 42.25 years, average age of menopause 51 years	+/- 10%	-	To explore the variation around the mean age.
Model time horizon	10 years	20 years Lifetime	-	Based on NICE Reference case
Medications used for BSC	NSAIDs and iron supplements	Addition of vitamin D and calcium supplements. Vit D: 10mg/day Calcium: 1500mg/day	Same as EAG scenario	Based on EAG expert opinion.
Recurrence rate	Data collected from survey completed by gynaecologists	Assume same recurrence rate of 23.8% for linzagolix and BSc Assuming 10% and 25% recurrence rate for both treatment arms	-	Exploratory analyses to illustrate the effect of using similar recurrence rates for linzagolix and BSC
Treatment discontinuation rate	Trial-based withdrawal rates: Linzagolix 100mg: [redacted] Linzagolix 200mg: [redacted] BSc: [redacted]	Assume same discontinuation rates for linzagolix 100mg, linzagolix 200mg and BSc at: [redacted]	-	Exploratory analysis

Parameter	Company base case	EAG scenarios	EAG preferred	Reason for analysis
		Assume same discontinuation rates for linzagolix 100mg, linzagolix 200mg and BSc at: [redacted]		
Surgery: procedural death	Mortality rates of UAE: 0.02%	Mortality rates: of UAE: 0.0002%	-	Based on clinical opinion
Surgery: Distribution of surgery types	UAE: 4.8% Endometrial ablation: 0.0% MRgFUS: 3.0% Abdominal myomectomy: 25.7% Laparoscopic myomectomy:8.2% Abdominal hysterectomy: 51.8% Laparoscopic hysterectomy:6.4%	UAE: 20% Endometrial ablation: 0.0% MRgFUS: 0% Abdominal myomectomy: 0% Laparoscopic myomectomy:0% Hysteroscopic myomectomy: 20% Abdominal hysterectomy: 6% Laparoscopic hysterectomy:54%	Same as EAG scenario	Based on clinical opinion
Healthcare resource use	GP visits: GnRH antagonists: none BSC: None DEXA scans GnRH antagonists: one after 1 year	GP visits: GnRH antagonists: Twice BSC: Twice DEXA scans GnRH antagonists: None BSC: None	Same as EAG scenario	Based on EAG expert opinion

Parameter	Company base case	EAG scenarios	EAG preferred	Reason for analysis
	BSC: None Full Blood Count GnRH antagonists: Once BSC: Once MRI GnRH antagonists: Once BSC: Once	 Full Blood Count GnRH antagonists: Twice BSC: Twice MRI GnRH antagonists: None BSC: None		
Unit costs	Gynaecologist: £185.51 MRI: £197.34	Gynaecologist: £181.26 MRI: £255.41	Same as EAG scenario	
Utilities	Estimates used for the EQ-5D utility function for UFS-QoL Intercept: [redacted] RMBL: [redacted]	Exploratory scenario reducing the estimates used for the EQ-5D utility function by 10%. Intercept: [redacted] RMBL: [redacted]	-	Exploratory analysis
	Estimates used for the EQ-5D utility function for UFS-QoL Intercept: [redacted] RMBL: [redacted]	Increasing the estimates used for the EQ-5D utility function for EQ-5D-5L by 10%. Intercept: [redacted]		

Parameter	Company base case	EAG scenarios	EAG preferred	Reason for analysis
		RMBL: [redacted]		
	Estimates used for the EQ-5D utility function for EQ-5D-5L Intercept: [redacted] RMBL: [redacted]	Exploratory scenario reducing the estimates used for the EQ-5D utility function by 10%. Intercept: [redacted] RMBL: [redacted]		
	Estimates used for the EQ-5D utility function for EQ-5D-5L Intercept: [redacted] RMBL: [redacted]	Increasing the estimates used for the EQ-5D utility function by 10%. Intercept: [redacted] RMBL: [redacted]		

6 EAG'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG.

6.1.1 Cost-comparison analysis for Population #1 and Population #2

For the cost-comparison analyses, we corrected the unit cost of a gynaecologist consultation as reported in Section 5.3.1, and also applied our preferred cost of an MRI at £255.41 (see Table 29) for Population #1 and Population #2. Results are reported below in Table 30 and Table 31. Changing the unit costs do not impact the incremental costs in Population #1 and Population #2 because of the proportional change in the total costs across the treatment arms. No other scenario analyses were conducted for the cost-comparison analyses on Population #1 and Population #2, due to the uncertainties surrounding the assumption of similar clinical efficacy between linzagolix and relugolix-CT and secondly, whether relugolix-CT has an adequate market share to qualify as the selected comparator for the cost-comparison analysis (discussed earlier in Section 3 and Section 4.2.5.1).

Table 30 Cost-comparison results using EAG unit cost for a gynaecologist consultation and MRI for Population #1

Treatment	Total costs	Incremental costs, linzagolix versus
Linzagolix	[redacted]	
Relugolix CT	£3,417	[redacted]
Leuprorelin	£3,446	[redacted]
Goserelin	£3,413	[redacted]
Triptorelin	£3,488	[redacted]

Table 31 Cost-comparison results using EAG unit cost for a gynaecologist consultation and MRI for Population #2

Treatment	Total costs	Incremental costs, linzagolix versus
Linzagolix	[redacted]	
Relugolix CT	£4,757	[redacted]

6.1.2 Cost-effectiveness analysis for Population #3

Results from the EAG scenario analyses (outlined in Table 29) conducted on the company's base case analysis for Population #3 are shown in Table 32 below. The ICERs vary between the range of £13,968 per QALY (Scenario: increasing the coefficients used for the EQ-5D utility function for UFS-QoL by 10%) and £34,376 per QALY (Scenario: reducing the coefficients used for the EQ-5D utility function for EQ-5D-5L by 10%).

Table 32 EAG additional scenarios applied to the company's base case for the Population #3 cost-effectiveness analysis.

Scenario	Treatment	Total Costs	Total QALYs	ICER (£/QALY)
Company base case	BSC	[redacted]	[redacted]	£15,392
	Linzagolix	[redacted]	[redacted]	
Baseline characteristics				
Patient mean age + 10%	BSC	[redacted]	[redacted]	£17,017
	Linzagolix	[redacted]	[redacted]	
Patient mean age -10%	BSC	[redacted]	[redacted]	£15,252
	Linzagolix	[redacted]	[redacted]	
Average menopause age +10%	BSC	[redacted]	[redacted]	£15,271
	Linzagolix	[redacted]	[redacted]	
Average menopause age – 10%	BSC	[redacted]	[redacted]	£17,999
	Linzagolix	[redacted]	[redacted]	
Concomitant medication				
Addition of vitamin D and calcium	BSC	[redacted]	[redacted]	£15,705
	Linzagolix	[redacted]	[redacted]	
Recurrence rate				
10% for both treatment arms	BSC	[redacted]	[redacted]	£22,137
	Linzagolix	[redacted]	[redacted]	
25% for both treatment arms	BSC	[redacted]	[redacted]	£21,108
	Linzagolix	[redacted]	[redacted]	
Treatment discontinuation				

Scenario	Treatment	Total Costs	Total QALYs	ICER (£/QALY)
[redacted] for linzagolix 100mg, linzagolix 200mg, and BSC	BSC	[redacted]	[redacted]	£14,864
	Linzagolix	[redacted]	[redacted]	
[redacted] for linzagolix 100mg, linzagolix 200mg, and BSC	BSC	[redacted]	[redacted]	£16,384
	Linzagolix	[redacted]	[redacted]	
[redacted] for linzagolix 100mg, linzagolix 200mg, and BSC	BSC	[redacted]	[redacted]	£14,930
	Linzagolix	[redacted]	[redacted]	
[redacted] for linzagolix 100mg, linzagolix 200mg, and BSC	BSC	[redacted]	[redacted]	£26,509
	Linzagolix	[redacted]	[redacted]	
[redacted] for linzagolix 100mg, linzagolix 200mg, and BSC	BSC	[redacted]	[redacted]	£23,806
	Linzagolix	[redacted]	[redacted]	
[redacted] for linzagolix 100mg, linzagolix 200mg, and BSC	BSC	[redacted]	[redacted]	£26,345
	Linzagolix	[redacted]	[redacted]	
Procedural death				
0.0002% mortality rate for UAE	BSC	[redacted]	[redacted]	£15,392
	Linzagolix	[redacted]	[redacted]	
Distribution of surgery types				
UAE: 20% Hysteroscopic myomectomy: 20% Abdominal hysterectomy: 6% Laparoscopic hysterectomy: 54%	BSC	[redacted]	[redacted]	£15,392
	Linzagolix	[redacted]	[redacted]	
Health care resource use				

Scenario	Treatment	Total Costs	Total QALYs	ICER (£/QALY)
GP visits: twice for both treatment arms DEXA scans: none for both treatment arms Full blood count: twice for both treatment arms MRI: none for both treatment arms	BSC	[redacted]	[redacted]	£14,165
	Linzagolix	[redacted]	[redacted]	
Unit costs				
Gynaecologist: £181.26 MRI: £255.41	BSC	[redacted]	[redacted]	£15,392
	Linzagolix	[redacted]	[redacted]	
Utilities				
Reducing the coefficients used for the EQ-5D utility function for EQ-5D-5L by 10%. Intercept: [redacted]; RMBL: [redacted]	BSC	[redacted]	[redacted]	£34,376
	Linzagolix	[redacted]	[redacted]	
Increasing the coefficients used for the EQ-5D utility function for EQ-5D-5L by 10%. Intercept: [redacted]; RMBL: [redacted]	BSC	[redacted]	[redacted]	£27,903
	Linzagolix	[redacted]	[redacted]	
Reducing the coefficients used for the EQ-5D utility function for UFS-QoL by 10%. Intercept: [redacted]; RMBL: [redacted]	BSC	[redacted]	[redacted]	£17,140
	Linzagolix	[redacted]	[redacted]	
Increasing the coefficients for the EQ-5D utility function for UFS-QoL by 10%. Intercept: [redacted]; RMBL: [redacted]	BSC	[redacted]	[redacted]	£13,968
	Linzagolix	[redacted]	[redacted]	

BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; UAE, uterine artery embolization; RMBL, reduced menstrual blood loss.

6.2 EAG's preferred assumptions for Population #3

The EAG's preferred base case assumptions for Population #3 are:

- Inclusion of prophylactic regimens of calcium and vitamin D in the BSC arm.
- Distribution of surgery types based on advice from our clinical expert.
- Use of healthcare resources based on advice from our clinical expert.
- Including the unit costs of gynaecological consultation and MRI as identified by the EAG.
- Using EQ-5D-5L data from the PRIMROSE trials to estimate the health state utilities.

The results are presented in Table 33 in a cumulative manner. The ICER for the EAG base case is £28,973 [redacted], an [redacted] £13,581 [redacted] from the company's base case. The ICER remains below the £30,000 [redacted] threshold.

Table 33 Cumulative EAG preferred assumptions for the Population #3 cost-effectiveness analysis

Assumption	Treatment	Total Costs	Total QALYs	ICER (£/QALY)
Company base case	BSC	[redacted]	[redacted]	£15,392
	Linzagolix	[redacted]	[redacted]	
+ Include vitamin D and calcium in BSC	BSC	[redacted]	[redacted]	£15,705
	Linzagolix	[redacted]	[redacted]	
+ EAG preferred surgery type distribution	BSC	[redacted]	[redacted]	£15,705
	Linzagolix	[redacted]	[redacted]	
+ EAG preferred health care resource use	BSC	[redacted]	[redacted]	£14,478
	Linzagolix	[redacted]	[redacted]	
+ EAG preferred unit costs (EAG preferred base case)	BSC	[redacted]	[redacted]	£14,478
	Linzagolix	[redacted]	[redacted]	
+ Utilities obtained from mapping EQ-5D-5L to EQ-5D-3L	BSC	[redacted]	[redacted]	£28,973
	Linzagolix	[redacted]	[redacted]	
EAG base case	BSC	[redacted]	[redacted]	£28,973
	Linzagolix	[redacted]	[redacted]	

BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

6.3 Scenarios conducted on the EAG base case for Population #3 cost-effectiveness analysis.

The EAG conducted further scenarios on the EAG base case economic model. Results from these scenarios are reported in Table 34 below. The ICERs ranges between £9,498 per QALY (scenario: using utility values for the 'controlled' and 'uncontrolled' health states from Hux et al.) and £49,857 per QALY (scenario: treatment discontinuation due to AEs only).

Table 34 EAG scenarios on the EAG base case model for the Population #3 cost-effectiveness analysis

Scenario	Treatment	Total Costs	Total QALYs	ICER (£/QALY)
EAG base case	BSC	[redacted]	[redacted]	£28,973
	Linzagolix	[redacted]	[redacted]	
Linzagolix dosing				
200 mg for 6 months followed by BSC	BSC	[redacted]	[redacted]	£29,325
	Linzagolix	[redacted]	[redacted]	
100 mg	BSC	[redacted]	[redacted]	£32,023
	Linzagolix	[redacted]	[redacted]	
Surgery probability from the 'controlled' health state				
1%	BSC	[redacted]	[redacted]	£17,102
	Linzagolix	[redacted]	[redacted]	
2%	BSC	[redacted]	[redacted]	£24,907
	Linzagolix	[redacted]	[redacted]	
Concomitant medication distribution				
Treatment specific	BSC	[redacted]	[redacted]	£28,711
	Linzagolix	[redacted]	[redacted]	
Treatment withdrawal rates				
Modified trial % (withdrawal due to AEs)	BSC	[redacted]	[redacted]	£49,857
	Linzagolix	[redacted]	[redacted]	
Utility for 'controlled' and 'uncontrolled' health states				
Utility mapping from UFS-QoL to EQ-5D-3L	BSC	[redacted]	[redacted]	£14,478
	Linzagolix	[redacted]	[redacted]	
Utility source 'controlled' and 'uncontrolled' health states				
Hux et al.	BSC	[redacted]	[redacted]	£9,498
	Linzagolix	[redacted]	[redacted]	
Post-surgery utility				

Scenario	Treatment	Total Costs	Total QALYs	ICER (£/QALY)
General population	BSC	[redacted]	[redacted]	£28,973
	Linzagolix	[redacted]	[redacted]	
Equal to controlled	BSC	[redacted]	[redacted]	£28,973
	Linzagolix	[redacted]	[redacted]	
Adverse event disutility				
Exclude	BSC	[redacted]	[redacted]	£27,877
	Linzagolix	[redacted]	[redacted]	
Utility age adjustment				
Exclude	BSC	[redacted]	[redacted]	£28,763
	Linzagolix	[redacted]	[redacted]	

BSC, best supportive care; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

6.4 Conclusions on the cost-comparison evidence for Population #1 and Population #2

The company developed a cost-comparison model for linzagolix compared to relugolix CT and GnRH agonists for Population #1 (people having short-term treatment of 6 months of less) and for linzagolix compared to relugolix CT for Population #2 (people having longer-term treatment with hormone-base therapy). The EAG performed validation checks on the cost-comparison model as discussed in section 5.3. No errors or inconsistencies were found, except the one discussed in section 5.3.1. We corrected this error as well as updating the company's model with the unit cost for MRI as identified by the EAG (see Table 29 Additional EAG scenarios conducted in the CEA for Population #3Table 29). These did not change the overall results (incremental costs) as shown in Table 30 and Table 31 due to the proportional change in the total costs across the treatment arms. Overall, we view the company's simple modelling approach for the cost-comparison analysis is reasonable.

The EAG did not conduct any scenario analyses for Population #1 or Population #2, as we are uncertain whether:

- linzagolix has similar clinical efficacy as relugolix CT and other GnRH analogues (see Key Issue 1) and
- relugolix-CT has an adequate market share to qualify as the selected comparator for the cost-comparison analysis (see Key Issue 2).

6.5 Conclusions on the cost-effectiveness evidence for Population #3

The company developed a model to estimate the cost-effectiveness of linzagolix compared to BSC for Population #3 (people with longer-term treatment, without hormone-based therapy). The EAG consider the overall model structure to be appropriate. The model uses clinical efficacy data from the PRIMROSE trials. The company base case produced an ICER of £15,392 per QALY gained for linzagolix compared to BSC. This ICER was obtained by applying a confidential PAS discount for linzagolix. The EAG did not identify any technical errors on checking the economic model, except a few minor inconsistencies in reporting which did not have any impact on the overall results.

The EAG disagree with some of the assumptions in the company's model. Our preferred assumptions include:

- Inclusion of prophylactic regimens of calcium and vitamin D in the BSC arm.
- Distribution of different surgery types based on clinical expert opinion.
- Inclusion of healthcare resource use based on clinical expert opinion.
- Using a unit cost of £181.26 for gynaecologist consultation (WF01A) and £255.41 for an MRI scan (RD02A), respectively, obtained from NHS Reference Costs 2021/22.
- Using the utility estimates derived from EQ-5D-5L data collected in the PRIMROSE trials.

The EAG preferred assumptions increase the ICER to £28,973 per QALY gained for linzagolix compared to BSC. In addition to the above issues addressed by the EAG, there are other key uncertainties in the company's assumptions. These include:

- Population #3, which includes patients unable to receive hormone-based therapy, is inconsistent with the population in the PRIMROSE trials where people who could receive hormone-based therapy were randomised. Our expert advice received was that very few patients would be unfit/prefer not to receive hormone-based therapy, so the unique population that linzagolix without hormone-based therapy could benefit in clinical practice could be very small. However, as we noted in section 2.2.4 above, the size of this sub-population is uncertain, and we have suggested further clarification would be helpful (see Key Issue 3).

- There is uncertainty regarding the company's assumption that treatment efficacy (response rate) of linzagolix will be maintained in the long run, over 52 weeks. This assumption is based on the evidence from 2-year data from the LIBERTY randomised withdrawal study for relugolix CT. While maintaining the response rate may be biologically plausible, there are no data to confirm this.

- We have concerns whether patients staying in the 'post-surgery' state until they experience menopause is reflective of the disease prognosis. While some patients may be cured, others may experience a recurrence of the symptoms post-surgery. This would benefit from further clarification (see Key Issue 4).

- There are also uncertainties about the reporting of the utility function. The company did not define or justify the specification for the linear mixed model regression of utility data. It is not clear why they chose to include a single independent variable (RMBL), or whether additional co-variates would have improved the model fit. Furthermore, no sensitivity or scenario analyses were reported for alternative specifications of the utility function (see Key Issue 5).

- There are uncertainties in the company's assumptions regarding healthcare resource. Their assumptions that patients would not have any GP visits, have full blood count and MRI scan once each, and people in the linzagolix arm receive one DEXA scan after 1 year may not reflect clinical practice. Based on the advice of our clinical expert, we conducted scenario analysis assuming that on average, patients visit GPs and have the full blood count, twice each. They are unlikely to undergo DEXA scans or MRI scans. We note that wider consultation with further clinical experts might help to better understand the heterogeneity in resource use across hospitals and resolve the uncertainty.

7 REFERENCES

1. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual.
2. Theramex. Data on File: Uterine Fibroids Market Research Survey for Yselty (Linzagolix) Full Report (Confidential). 2022 2022.
3. Marsh EE, Al-Hendy A, Kappus D, Galitsky A, Stewart EA, Kerolous M. Burden, Prevalence, and Treatment of Uterine Fibroids: A Survey of U.S. Women. J Womens Health. 2018;27(11):1359-67.
4. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. International Journal of Gynecology & Obstetrics. 2020;149(1):3-9.
5. Hunsche E, Rakov V, Scippa K, Witherspoon B, McKain L. The Burden of Uterine Fibroids from the Perspective of US Women Participating in Open-Ended Interviews. Women's Health Reports. 2022;3(1):286-96.
6. Soliman AM, Margolis MK, Castelli-Haley J, Fuldeore MJ, Owens CD, Coyne KS. Impact of uterine fibroid symptoms on health-related quality of life of US women: evidence from a cross-sectional survey. Current Medical Research and Opinion. 2017;33(11):1971-8.
7. European Medicines Agency (EMA). Yselty (linzagolix) Summary of Product Characteristics. EMA; 2023.
8. National Institute for Health and Care Excellence. NG88. Heavy menstrual bleeding: assessment and management. 2018.
9. Theramex. Data on File: Linzagolix for treating moderate to severe symptoms of uterine fibroids: an indirect treatment comparison. 2023 2023/06/09/.
10. National Institute for Health and Care Excellence. Fast track appraisals - guiding notes for ERGs. NICE; 2017.
11. Donnez J, Taylor HS, Stewart EA, Bradley L, Marsh E, Archer D, et al. Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. The Lancet. 2022;400(10356):896-907.
12. Kissei Pharmaceutical Co. Ltd. Data on File: PRIMROSE 3 CSR. 2023 2023/03/09/.
13. Al-Hendy A, Venturella R, Arjona Ferreira JC, Li Y, Soulban G, Wagman RB, et al. LIBERTY randomized withdrawal study: relugolix combination therapy for heavy menstrual bleeding associated with uterine fibroids. American Journal of Obstetrics and Gynecology. 2023.
14. de Lange ME, Semmler A, Clark TJ, Mol BWJ, Bet PM, Huirne JAF, et al. Considerations on implementation of the newest treatment for symptomatic uterine

fibroids: Oral GnRH antagonists. British Journal of Clinical Pharmacology. 2023;n/a(n/a).

15. Al-Hendy A, Lukes AS, Poindexter AN, Venturella R, Villarroel C, Critchley HOD, et al. Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy. The New England Journal of Medicine. 2021;384(7):630-42.
16. Stewart EA, Lukes AS, Venturella R, Arjona Ferreira J-C, Li Y, Hunsche E, et al. Relugolix Combination Therapy for Uterine Leiomyoma–Associated Pain in the LIBERTY Randomized Trials. Obstetrics & Gynecology. 2022;139(6):1070-81.
17. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. The New England Journal of Medicine. 2012;366(5):409-20.
18. Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, et al. Ulipristal acetate versus leuprolide acetate for uterine fibroids. The New England Journal of Medicine. 2012;366(5):421-32.
19. Magnay JL OBS, Gerlinger C, Seitz C. A systematic review of methods to measure menstrual blood loss. BMC Womens Health. 2018;18(1):1-13.
20. Osuga Y KE, Kudou K, Tanimoto M, Hoshiai H. Oral gonadotropin-releasing hormone antagonist relugolix compared with leuprorelin injections for uterine leiomyomas: a randomized controlled trial. Obstetrics and Gynecology. 2019;133(3):423-33.
21. Osuga Y KE, Kudou K, Hoshiai H. 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. Fertility and Sterility 2019;112(5):922-9.e2.
22. Hoshhiai H, Seki Y, Kusumoto T, Kudou K, Tanimoto M. Relugolix for oral treatment of uterine leiomyomas: a dose-finding, randomized, controlled trial. BMC Women's Health. 2021;21:375 (11pp).
23. Anchan RM SJ, Zhang S, Wojdyla D, Bortoletto P, Terry K, et al. Long-term health-related quality of life and symptom severity following hysterectomy, myomectomy, or uterine artery embolization for the treatment of symptomatic uterine fibroids. American Journal of Obstetrics and Gynecology. 2023;275:275.e1-.e17.
24. Harding G, Coyne KS, Thompson CL, Spies JB. The responsiveness of the uterine fibroid symptom and health-related quality of life questionnaire (UFS-QOL). Health and Quality of Life Outcomes. 2008;6(1):99.
25. European Medicines Agency (EMA). Yselty (linzagolix) European Public Assessment Report (EPAR). 2022 2022/07/01/.
26. ObsEva S.A. Data on File: PRIMROSE 1 CSR Week 24, v2.0. 2021 2021/06/22/.

27. ObsEva S.A. Data on File: PRIMROSE 2 CSR Week 52, v2.0. 2021 2021/05/26/.
28. ObsEva S.A. Data on file: PRIMROSE 1 and 2 Pooled Analysis, 16-OBE2109-008_and_16-OBE2109-009_Combined. 21-09-08. 2021 2021.
29. National Institute for Health and Care Excellence. Relugolix-estradiol-norethisterone acetate for treating moderate to severe symptoms of uterine fibroids (TA832). Available at: https://www.nice.org.uk/guidance/ta832 (Last accessed: 8 Nov 2023). 2022.
30. Al-Hendy A, Venturella R, Ferreira JCA, Li Y, Wagman R, Lukes AS. LIBERTY RANDOMIZED WITHDRAWAL STUDY: 2-YEAR EFFICACY AND SAFETY OF RELUGOLIX COMBINATION THERAPY IN WOMEN WITH HEAVY MENSTRUAL BLEEDING ASSOCIATED WITH UTERINE FIBROIDS. Fertility and Sterility. 2021;116(3):e2.
31. Yoo E-H, Lee PI, Huh C-Y, Kim D-H, Lee B-S, Lee J-K, et al. Predictors of leiomyoma recurrence after laparoscopic myomectomy. Journal of Minimally Invasive Gynecology. 2007;14(6):690-7.
32. Shiota M, Kotani Y, Umemoto M, Tobiume T, Hoshiai H. Recurrence of uterine myoma after laparoscopic myomectomy: What are the risk factors? Gynecology and Minimally Invasive Therapy. 2012;1(1):34-6.
33. Rossetti A, Sizzi O, Soranna L, Cucinelli F, Mancuso S, Lanzone A. Long-term results of laparoscopic myomectomy: recurrence rate in comparison with abdominal myomectomy. Human Reproduction. 2001;16(4):770-4.
34. Radosa MP, Owsianowski Z, Mothes A, Weisheit A, Vorwergk J, Asskaryar FA, et al. Long-term risk of fibroid recurrence after laparoscopic myomectomy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014;180:35-9.
35. Hux M, Ng C, Ortega GL, Ferrazzi S, Goeree R. Utility values for pre-menopausal women suffering from symptomatic uterine fibroids. Expert Review of Pharmacoeconomics & Outcomes Research. 2015;15(1):181-9.
36. Hernández-Alava M, Pudney S. Econometric modelling of multiple self-reports of health states: The switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. Journal of Health Economics. 2017;55:139-52.
37. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research. 2010;13(5):509-18.

8 APPENDICES

Appendix 1 Systematic review critique

Table 35 – APPENDIX 1 – EAG appraisal of systematic review methods of the clinical effectiveness review

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Was the review question clearly defined using the PICO framework or an alternative?	Yes	PICO criteria are in CS Appendix Tables 5 and 6, and the searches were structured accordingly.
Were appropriate sources of literature searched?	Yes	Core healthcare and medical databases were searched alongside handsearching of multiple conferences (CS Appendix D.1.1).
What time period did the searches span and was this appropriate?	Partly	An initial search and two update searches covered the period from database inception to 7th February 2023 (conferences since 2019). Although searches were 6 months old when the CS was received by the EAG, no studies are thought to have been missed because the EAG's background search on 4th September 2023 only found six further conference abstracts for results from the same studies already identified by the company (i.e. not listed in the complete reference lists for included studies in CS Appendix Table 7). We did not find additional studies.
Were appropriate search terms used and combined correctly?	Yes	Search strategies are reported in CS Appendix D.1.1.
Were inclusion and exclusion criteria specified? If so, were these criteria appropriate and	Probably	Eligibility criteria are reported in CS Appendix Tables 5 and 6. Eligibility criteria for the first update search differs

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
relevant to the decision problem?		from the original search in that it omits treatments such as radiofrequency ablation, hysterectomy, and watchful waiting, which are not in scope. It is not clear how watchful waiting might be different from BSC in this appraisal without looking at the studies it applies to. Watchful waiting does not involve any therapy whereas BSC in this appraisal includes NSAIDs and/or iron supplements (and tranexamic acid according to NG88). The eligibility criteria for the second update search reverted to that of the original search. Further eligibility criteria were applied for suitability for the NMA, e.g. excluding non-USA and non-EU studies. Whilst this would exclude Asian participants, it was appropriate to exclude those trials due to other limitations.
Were study selection criteria applied by two or more reviewers independently?	Yes	Both citation screening and full-text screening were done by two independent reviewers, with discrepancies reconciled by a third independent reviewer (CS Appendix D.1.2).
Was data extraction performed by two or more reviewers independently?	Yes	Data was extracted by two independent reviewers and any discrepancies were reconciled by a third independent reviewer (CS Appendix D.1.4).
Was a risk of bias assessment or a quality assessment of the included studies undertaken? If so, which tool was used?	Yes	A critical appraisal of PRIMROSE 1 and PRIMROSE 2 combined, using the NICE checklist for RCTs, is reported in CS section B.2.5. An earlier assessment was

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
		carried out for the NMA in CS Appendix D.3.7 for PRIMROSE 1 and 2 and for LIBERTY 1 and 2, but the critical appraisal tool and sources are not reported. .
Was risk of bias assessment (or other study quality assessment) conducted by two or more reviewers independently?	Unclear	The methods for conducting the risk of bias assessments are not reported.
Is sufficient detail on the individual studies presented?	Yes	Study details for PRIMROSE 1 and PRIMROSE 2 are reported in CS sections B.2.3 to B.2.4, and in CS Appendices D and M. Additionally the CSRs, SAPs, and study publications provided necessary details. Study details for LIBERTY 1 and LIBERTY 2 are reported in CS Appendix D.3.3.2 and various study publications. Study details for PEARL I and PEARL II are reported in CS Appendix D.3.3.3 and D.3.3.4 and the study publications.
If statistical evidence synthesis was undertaken (e.g. pairwise meta-analysis, ITC, NMA) was undertaken, were appropriate methods used?	Yes	An NMA was undertaken to demonstrate equivalence of efficacy and safety of linzagolix with relugolix CT. Further analyses were provided by the company in Clarification Responses A10 and A12. The methods were generally appropriate although the EAG was unable to validate the results. The methods are critiqued in section 3.4 of this report.

Systematic review components and processes	EAG response (Yes, No, Unclear)	EAG comments
Abbreviations: CSR: clinical study report; ITC: indirect treatment comparison; NMA: network meta-analysis; PICO population, intervention, comparator, outcome; SAP: statistical analysis plan.		

Appendix 2 Risk of bias assessments

Table 36 – APPENDIX 2.1 – Risk of bias assessment for PRIMROSE 1 and PRIMROSE 2

Questions	PRIMROSE 1	PRIMROSE 2	EAG Comments
Was randomisation carried out appropriately?	Yes. Patients were randomised using a computer-generated randomisation list using the random allocation of treatment according to a permuted block randomisation stratified by race (Black or African American vs. Other)		Agree. Low risk of bias.
Was the concealment of treatment allocation adequate?	Yes. The patients were randomised to treatment groups by IWRS		Agree, the interactive web response system should ensure concealment of treatment allocation. Low risk of bias.
Were the groups similar at the outset of the trial in terms of prognostic factors?	Yes. As the prevalence of fibroids is higher and symptoms are more severe in Black women, randomisation was stratified to ensure equal distribution of Black patients among treatment groups. In the PRIMROSE 1 trial, patients had a higher mean BMI, a higher number of Black patients and a higher percentage of patients who were anaemic at baseline (Hb <12 g/dL) compared the PRIMROSE 2 trial		Stratification of randomisation by race is important and there is low risk of bias in that respect. The company consider race, BMI, and anaemia; however, fibroid characteristics such as FIGO type, size, number, and location are not reported or accounted for. Fibroid characteristics are important as they can influence which symptoms are experienced and to what extent. There is lack of clarity around whether the total fibroid volume could be measured consistently across all

Questions	PRIMROSE 1	PRIMROSE 2	EAG Comments
			groups (report section 3.2.3.1.3). Unclear risk of bias.
Were the care providers, patients and outcome assessors blind to treatment allocation?	Yes. Masked treatment kits were sent to each site and kept in controlled conditions. Masking was achieved by using tablets with an identical appearance between the linzagolix treatments and corresponding placebo and over-encapsulation of the ABT and corresponding placebo. All patients took two tablets and one capsule daily. The operational teams were masked to group allocation until unmasking after the database was locked; patients and investigation teams at each site remained blinded.		Agree. Clarification Response A5 states that investigators and subjects in both trials were blinded until the trials were complete, and the unmasking of PRIMROSE 1 at week 24 described in Donnez et al. 2022 only refers to the study Sponsor. Key endpoints were assessed by central laboratory. Low risk of bias
Were there any unexpected imbalances in dropouts between groups?	No. In order to consider all randomised and treated patients in the analysis, the assessment of the primary endpoint for patients who discontinued prior to Week 24 for a reason other than lack of efficacy, AEs, or operative or radiological interventions for UF was based on the results from the 28 days prior to the last eDiary entry in order to use as many data as possible up to Week 24 after the start of treatment, irrespective of actual treatment taken. Patients who had less than 28 days of data were considered as non-responders. The secondary endpoint of amenorrhea was assessed in a similar way		Patient flow, including discontinuations, are reported in the CONSORT diagrams in CS Appendix M.2. The CSRs report the randomised set numbers. For each individual trial the numbers were similar across groups except for weeks 24-52 (the second treatment period) where more patients discontinued in the 200mg/200mg+ABT group in both trials. Comparing the two trials, about twice as many patients discontinued during weeks 1-24 in

Questions	PRIMROSE 1	PRIMROSE 2	EAG Comments
			PRIMROSE 1 than in PRIMROSE 2 in each group. The amount of missing data varied by outcome and was almost 50% for some outcomes (Table 8). Unclear risk of bias.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No		All outcomes are reported in CS section B and CS Appendix M.3.3.3. FIGO classification of fibroid type was assessed (reported in summary in the SmPC and as evidenced by the existence of the FIGO 0, 1, 2 at baseline subgroup) but not reported in the patient baseline characteristics. Unclear risk of bias.
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. A sensitivity analysis was conducted on the primary efficacy endpoint to check the robustness of the analysis results under alternative assumptions with regards to missing data. Results of the sensitivity analyses imputing missing data and results in the PP Set were consistent with those of the main analysis. Missing values for continuous efficacy endpoints were handled within the analysis itself via mixed model repeated measures, with the assumption that the model specification was correct, and that the data were missing at random. All data recorded in the eCRF were included in data listings.		The CS reports a modified ITT analysis, the Full Analysis Set (FAS) which includes all randomised patients who received at least one dose of the study drug. The number of discontinuations varies between trials (n=48 PRIMROSE 1; n=21 PRIMROSE 2) and between treatment groups (randomized sets for each treatment group are reported in the CSRs) the

Questions	PRIMROSE 1	PRIMROSE 2	EAG Comments
			linzagolix 100 mg group had the most discontinuations. However the baseline characteristics do not show imbalances, nor did the study lose statistical power. The FAS also excludes patients who met exclusion criteria for liver function or BMD based on results of pre-treatment baseline assessments reported after Day 1 (CS Appendix M.3.1) which is appropriate (Clarification Response A9). Probably low risk of bias.
Was there good quality assurance for this trial?	Yes the trial was conducted in accordance with ICH GCP guidelines and regulatory requirements. The study monitor reviewed eCRFs and other study documents, and conducted source data verification, to verify that these and the trial protocol were followed.		No impact on risk of bias.

Source: reproduced from CS Table 15 with added EAG comments.
Abbreviations: ABT: add-back therapy; AE: adverse event; BMD: bone mineral density; BMI: body mass index; CONSORT: CONsolidated Standards Of Reporting Trials; eCRF: electronic case report form; FIGO: International Federation of Gynecology and Obstetrics; ICH GCP: International Council for Harmonisation Good Clinical Practice; ITT: intention to treat; IWRS: interactive web response system; PP per protocol.

37 – APPENDIX 2.2 – Risk of bias assessment for LIBERTY 1 and LIBERTY 2

The name of the critical appraisal tool used is not reported although it covers the main areas of bias, except reporting bias. The company sometimes made different assessments for LIBERTY 1 and LIBERTY 2 in answer to the same question for which the Al-Hendy et al. 2021 paper could answer as it covers both trials – described as "replicate".[15] We have used the NICE checklist below for our own assessment.

Questions	EAG comments based on Al-Hendy et al. 2021[15]		EAG assessment
	LIBERTY 1	LIBERTY 2	
Was randomisation carried out appropriately?	The randomisation method is not reported. Stratification is not reported.		Unclear risk of bias
Was the concealment of treatment allocation adequate?	Yes. Allocation was performed using an interactive website.		Low risk of bias
Were the groups similar at the outset of the trial in terms of prognostic factors?	"Within each trial, the demographic and clinical characteristics of the participants as baseline were similar across the trial groups (Tables 1 and S4)" - Al-Hendy et al. 2021. However, FIGO type, location, and number are not reported, and these are important prognostic factors.		Unclear risk of bias
Were the care providers, patients and outcome assessors blind to treatment allocation?	The trials are described as "double-blind", however, blinding/unmasking methods and policies are not reported.		Probably low risk of bias
Were there any unexpected imbalances in dropouts between groups?	Figure S4, Al-Hendy et al. 2021 reports patient disposition. Dropouts ranged between 17.2% and 21.9% for each group, fairly high, but similar numbers. With regard to reasons for discontinuation, proportions were similar across groups.		Low risk of bias
Is there any evidence to suggest that the authors measured more	The reported outcomes in the study publication, Al-Hendy et al. 2021, match the primary and key secondary outcomes in the statistical analysis plan (Table S2 of study publication) which although		Low risk of bias

Questions	EAG comments based on Al-Hendy et al. 2021[15]		EAG assessment
	LIBERTY 1	LIBERTY 2	
outcomes than they reported?	different from the protocol was finalised prior to database lock and unblinding.		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	A modified ITT analysis was performed on all participants who underwent randomisation and received at least one dose of relugolix or placebo. Any missing data was imputed and used in a mixed methods model (Al-Hendy et al. 2021 supplement).		Low risk of bias
Was there good quality assurance for this trial?	"The trials were conducted in accordance with the guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. All the participants provided written informed consent." – Al-Hendy et al. 2021.		No impact on risk of bias.

Abbreviations: FIGO: International Federation of Obstetrics and Gynecology; ITT: intention-to-treat.

38 – APPENDIX 2.3 – Risk of bias assessment for PEARL I

Questions	EAG comments based on Donnez et al. 2012[17]	EAG assessment
	PEARL I	
Was randomisation carried out appropriately?	Yes. Patients were randomly assigned in a 2:2:1 ratio which was stratified according to the haematocrit level at screening (≤28% or >28%) and race (black or other).	Low risk of bias
Was the concealment of treatment allocation adequate?	Yes. Patients were assigned to study group using a Web-integrated interactive voice-response system.	Low risk of bias

Questions	EAG comments based on Donnez et al. 2012[17]	EAG assessment
	PEARL I	
Were the groups similar at the outset of the trial in terms of prognostic factors?	Patients were stratified by race: black or other; but baseline characteristics for race are reported for White and Asian – with similar proportions across groups. Patients in the ulipristal acetate 10 mg arm had slightly more subserosal fibroids than patients in the other study arms (study publication Table 1). Study publication states there were no significant differences between the ulipristal acetate and placebo groups.	Low risk of bias
Were the care providers, patients and outcome assessors blind to treatment allocation?	Yes. Double-blind trial. Study materials and medication packaging were identical for all three groups. MRI results were assessed centrally by a radiologist unaware of study-group assignments.	Low risk of bias
Were there any unexpected imbalances in dropouts between groups?	There were very few dropouts: 1 in the placebo group, 5 in the 5mg group and 6 in the 10 mg group.	Low risk of bias
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All assessments for outcomes in the protocol (available online with the study publication) are reported in the study publication and/or its supplement, except for ferritin. Ferritin levels help understand iron deficiency, but anaemia is defined by haemoglobin levels which are reported, therefore the EAG have no concern.	Low risk of bias
Did the analysis include an intention-to-treat analysis?	Yes. A modified ITT analysis was carried out. Only 1 patient in the 5 mg group (withdrawn prior to receiving study drug) and 4 patients in the 10 mg group (no efficacy data available) were excluded	Low risk of bias

Questions	EAG comments based on Donnez et al. 2012[17]	EAG assessment
	PEARL I	
If so, was this appropriate and were appropriate methods used to account for missing data?	from the primary analysis. Due to comparing two doses of ulipristal acetate with placebo, a Bonferroni correction was used (all p-values doubled). Missing values were imputed using the last available post-baseline value. A sensitivity analysis included the 4 patients in the 10 mg group who were excluded due to having no efficacy data by using baseline data carried forward.	
Was there good quality assurance for this trial?	The study was approved by the independent ethics committee at each study site and conducted in accordance with the principles of the International Conference on Harmonization – Good Clinical Practice guidelines. The original protocol, amendments, and statistical analysis plan are available with the full text article.	No impact on risk of bias

Abbreviations: ITT: intention-to-treat; MRI: magnetic resonance imaging.

39– APPENDIX 2.4 – Risk of bias assessment for PEARL II

Questions	EAG comments based on Donnez et al. 2012[18]	EAG assessment
	PEARL II	
Was randomisation carried out appropriately?	Yes. “The randomization list followed a stratification process for avoiding imbalance with respect to race or ethnic group among the three study groups”	Low risk of bias
Was the concealment of treatment allocation adequate?	Yes. “A Web-integrated voice-response system transmitted the randomization to the packaging organization, which delivered the medications to the treatment centers”	Low risk of bias

Questions	EAG comments based on Donnez et al. 2012[18]	EAG assessment
	PEARL II	
Were the groups similar at the outset of the trial in terms of prognostic factors?	Patient baseline characteristics are reported in study publication Table 1. They are similar, except that the 5 mg ulipristal treatment group had a much larger median uterine fibroid volume than the other two treatment groups, although the ranges were similar, and they had a pain score of 9 whereas the other two groups had a pain score of 7. Similar to other trials of uterine fibroids, the FIGO classification for the characteristics of the fibroids, which can indicate type and severity of symptoms, is not reported.	Unclear risk of bias
Were the care providers, patients and outcome assessors blind to treatment allocation?	The study was double-blind. “Data were collected by an independent contract research organization (ICON Clinical Research) and handled and analyzed by an independent data-management organization (MDSL International).”	Low risk of bias
Were there any unexpected imbalances in dropouts between groups?	Study publication Figure 1 describes patient flow. There were very few dropouts: 4 excluded between randomisation and receiving treatment; and a further 2, 3 and 6 patients were withdrawn from each treatment group; 2 patients from the ulipristal treatment groups (1 each) did not receive the study drug.	Low risk of bias
Is there any evidence to suggest that the authors measured more	No. Outcomes reported in the study publication match the primary and secondary endpoints outlined in the study protocol.	Low risk of bias

Questions	EAG comments based on Donnez et al. 2012[18] PEARL II	EAG assessment
outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	There were two analyses: a modified ITT analysis that excluded 5 patients – two who never received the study drug and three with missing efficacy data after baseline – and a per-protocol population – the ITT population with the exclusion of patients with major protocol deviations and a compliance rate of <80%. The per-protocol population was favoured as the most conservative analysis, with the modified ITT population used for sensitivity analysis of missing data by using the baseline data carried forward.	Low risk of bias
Was there good quality assurance for this trial?	The study was approved by the independent ethics committee at each study site and conducted in accordance with the principles of the International Conference on Harmonization – Good Clinical Practice guidelines. The original protocol, amendments, and statistical analysis plan are available with the full text article.	No impact on risk of bias

Abbreviations: FIGO: International Federation of Obstetrics and Gynecology; ITT: intention-to-treat.

Appendix 3 NMA results: linzagolix versus leuprolide acetate

As noted above, the NMAs for the comparison of linzagolix against GnRH analogues suffer from serious methodological limitations and were based only on fixed-effects models. According to the company, only leuprolide acetate could be included in the evidence network and only three outcomes could be assessed: odds of response, % change in total fibroid volume, and % change in haemoglobin (Clarification Response A11). Results of these analyses are provided here for illustrative purposes and should be interpreted with caution. The assessment timepoint for the outcomes was not reported, so it is unclear whether these results refer to Week 12 or Week 24 assessments.

Figure 21 – APPENDIX 3.1 – Linzagolix vs leuprolide acetate: NMA results for odds of achieving a response

Figure 22 – APPENDIX 3.2 – Linzagolix vs leuprolide acetate: NMA results for the percentage change in total fibroid volume (fixed-effects model)

Figure 23 – APPENDIX 3.3 – Linzagolix vs leuprolide acetate: NMA results for % change in haemoglobin in patients who were anaemic at baseline (fixed-effects model)

CONFIDENTIAL UNTIL PUBLISHED

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Linzagolix for treating moderate to severe symptoms of uterine fibroids

EAG REPORT ERRATUM

8th January 2024

This erratum provides corrected versions for Figure 2 and Figure 7 in the EAG report.

Figure 2 inadvertently reproduced incorrect odds ratios that are reported in both the CS and the Lancet trial publication. Figure 7 contained an error in data extraction by the EAG for which we apologise, as well as a minor discrepancy in the company's data, both of which have been corrected. The amended Figures provided here do not change the direction of treatment effects or alter the interpretation of results presented in the EAG report.

Correction to EAG report Figure 2 (response outcome in the PRIMROSE trials)

Rationale for the correction:

- The odds ratios and their confidence intervals as reported in the Donnez et al. Lancet paper and CS Appendix Figure 35 for the individual PRIMROSE trials are incorrectly inflated by a factor of 10. We have used the correct data from PRIMROSE 1 CSR Table 9 and PRIMROSE 2 CSR Table 11.

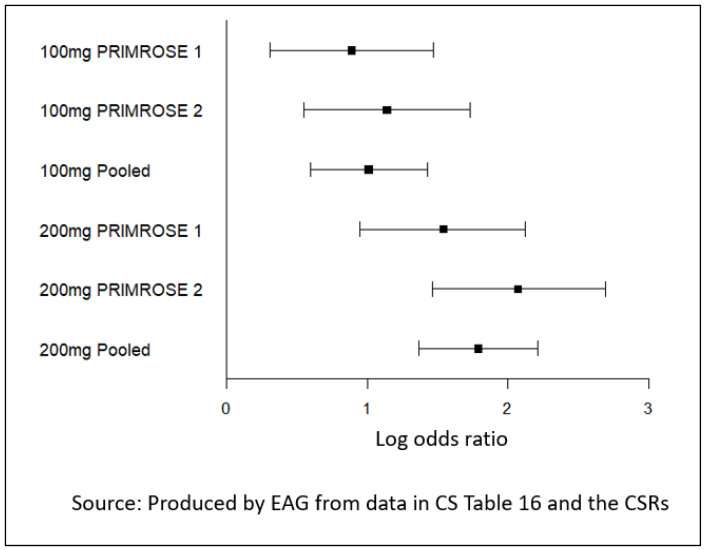


Figure 1 Proportion achieving response: linzagolix versus placebo, Week 24

Correction to EAG report Figure 7 (UFS-QoL severity score outcome in the PRIMROSE trials)

Rationale for the correction:

- The EAG incorrectly extracted the pooled trial data from CS Table 23. We have rectified this.
- Data for PRIMROSE 2 in CS Appendix Table 65 and the Donnez et al. 2022 Lancet publication differ slightly from the data in Table 35 of the PRIMROSE 2 CSR. We have used the CSR data.

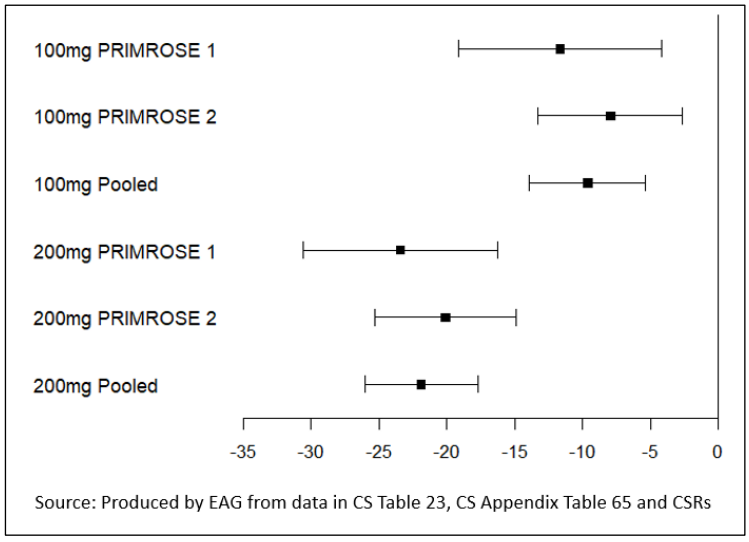


Figure 2 UFS-QoL symptom severity score, Week 24

Single Technology Appraisal

Linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG 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 Monday 20 November 2023** 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 information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as [redacted]' in pink.

Issue 1 Incorrect information about NICE's methods and processes

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response** (page numbers refer to track changes version of EAG report)
Page ii–iii *"Commercial in confidence (CIC) information in blue* *Academic in confidence (AIC) information in yellow"*	*"Confidential information in blue"*	Confidentiality marking stated is not as currently stipulated by NICE Methods. The report should be updated throughout to be consistent with the latest guidance on redaction	Thank you for highlighting this inconsistency. We have updated the terminology relating to confidential information on report page iii.
Section 1.3; page 13 *"An important assumption of cost-comparison analysis in NICE technology appraisals is that the intervention and comparator have similar clinical efficacy, i.e. linzagolix should be at least as efficacious as relugolix CT."*	*"An important assumption of cost-comparison analysis in NICE technology appraisals is that the intervention and comparator have similar clinical efficacy, i.e. linzagolix should provide similar or greater efficacy than relugolix CT."*	A revised is requested to match the wording in the NICE Methods guide:[1] *"4.2.13 A cost-comparison analysis is for technologies that are likely to provide similar or greater health benefits at similar or lower cost than the relevant comparator(s)."* The NICE Methods guide does not specify that therapies should be "at least as efficacious…"	Thank you for highlighting this inconsistency (not a factual inaccuracy). The EAG had paraphrased NICE's Methods Guide but on reflection we agree that precisely quoting the NICE methods is more appropriate. We have amended the text in the table for Key Issue 1 in report section 1.3 (page 13).

Issue 2 Missing or incorrect information

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response** (page numbers refer to track changes version of EAG report)
Section 1.2; page 12 *"Switching the surgery types, from myomectomy to hysterectomy, which is associated with an improved quality of life."*	*"Switching the surgery types, from open/abdominal to laparoscopic, which is associated with an improved quality of life."*	In the company base case, equal surgery type distributions are assumed between treatment arms. In scenario analysis, a higher proportion of linzagolix patients receiving laparoscopic compared with open/abdominal surgery was tested.	Thank you for highlighting this discrepancy. We have made the proposed amendment on page 12 of the EAG report.
Section 1.3; page 15 *"Population #1: Patients included in the trials were not eligible to receive surgery for their fibroids."*	*"Population #1: Patients included in the trials were not eligible to receive surgery for their fibroids within 6 months regardless of the treatment provided."* Please note that this distinction should be made clear throughout the report	It is incorrect to state that patients were not eligible for surgery, as they could potentially receive surgery in the future. Appendix M, Table 50, states the PRIMROSE exclusion criterion as: *"The patient's condition was so severe that she would require surgery within 6 months regardless of the treatment provided."*	Thank you for highlighting this inaccuracy in the wording. We have amended the text in the table for Key Issue 3 in report section 1.3 (page 15).
Section 1.3; page 15	*"Population #3: People for whom hormonal therapy (add-back therapy; ABT) is*	The current wording does not fully reflect the exclusion criterion, which states that patients who	Thank you for highlighting this inaccuracy in the wording. We have amended the text in the table

"Population #3: People who are unable to receive hormonal therapy (add-back therapy; ABT) were excluded from the PRIMROSE trials."	*contraindicated were excluded from the PRIMROSE trials."*	were contraindicated to hormonal therapy should be excluded from the PRIMROSE studies.	for Key Issue 3 in report section 1.3 (page 16).
Section 1.3; page 16 *"The company do not provide a rationale for this assumption or provide reasons why patients would not be able to receive hormonal ABT, and the EAG are uncertain whether the assumption is valid."*	Please delete the struckthrough text below. *"The company do not provide a rationale for this assumption ~~or provide reasons why patients would not be able to receive hormonal ABT~~, and the EAG are uncertain whether the assumption is valid."*	The current wording does not reflect the reasons provided in the company submission that support the validity of this assumption, specifically: *"…hormonal ABT may not be appropriate for some patients for reasons including contraindications, elevated risk of side effects associated with hormone replacement therapy (HRT) (e.g. in women who smoke or are obese), personal preference and in those who prefer not to take hormonal treatments for other reasons (e.g. transgender men)"* – CS, page 13 *"…are contraindicated to ABT — obesity, hypertension, and dyslipidaemia are ABT contraindications associated with higher risks of thrombosis, stroke and cardiac events, which disproportionately affect Black women…"* – CS, page 34	Thank you for highlighting this inaccuracy in the wording. We have amended the text in the table for Key Issue 3 in report section 1.3 (page 16).

Section 2.2.1.1; page 21 *"The exact cause is not known but they have been linked to oestrogen, occur in people of reproductive age…"*	*"The exact cause is not known but they have been linked to oestrogen <u>and progesterone</u>, occur in people of reproductive age…"*	The connection between progesterone and fibroids is missing, but should be included as it is relevant to the mechanism of action of linzagolix.[3, 4]	Thank you for highlighting this. The text is as stated in the NICE TA382 recommendations, but we have made the amendment in report section 2.2.1.1 (page 21), as suggested, to improve accuracy.
Section 2.2.1.1; page 21 *"Uterine fibroids affect around 1 in 3 women"*	*"Uterine fibroids affect around <u>2</u> in 3 women"*	The statistic used is incorrect; 1 in 3 patients typically experience symptoms, but around 2 in 3 women are affected by uterine fibroids.[5]	Thank you for highlighting this typographic error. We have corrected this in report section 2.2.1.1 (page 21).
Section 2.2.1.1; page 21 *"Each type of fibroid may or may not have a stalk (pedunculate fibroids) and some fibroids may encompass more than one uterine location."*	*"Submucosal and subseroral fibroids may or may not have a stalk (pedunculate fibroids) and some fibroids may encompass more than one uterine location.*	Intramural fibroids do not have stalks (are not pedunculated).	Thank you for highlighting this inaccuracy. We have corrected this in report section 2.2.1.1 (page 21).
Section 2.2.1.3; page 22	*"Symptoms that are often considered moderate or severe include heavy menstrual bleeding <u>– which</u>*	Women can have moderate or severe heavy menstrual bleeding without anaemia. Infertility is a moderate or severe symptom of	This is not strictly a factual inaccuracy, but we appreciate the opportunity to improve completeness of the list, thank

"Symptoms that are often considered moderate or severe include heavy menstrual bleeding leading to anaemia…"	*can lead ~~leading~~ to anaemia – bladder or bowel pressure, infertility or pain.*	fibroids and therefore should be included here.	you. We have amended the text in report section 2.1.1.3 on page 22.
Section 2.2.3; page 24 *"NB this implies that whilst the 100mg dose without ABT can achieve symptom control, its aim is not to control uterine or fibroid volume, although it is not stated explicitly in the CS."*	*"NB this implies that whilst the 100 mg dose without ABT can achieve symptom control, it does not provide the same magnitude of ~~its aim is not to control~~ uterine or fibroid volume reduction as the 200mg dose, ~~although it is not stated explicitly in the CS~~.*	The 100 mg without ABT dose does reduce uterine and fibroid volume, but the 200 mg without ABT dose is superior.	This is not strictly a factual inaccuracy but we agree with the company's suggestion and have amended the text in report section 2.2.3 on page 24.
Section 2.2.3; page 25 *"…patients able to tolerate long-term hormone-based therapy (referred to as Population #2); and patients who are unable to receive*	*"…people having longer-term treatment, with hormone-based therapy (referred to as Population #2); and people having longer-term treatment, without hormone-based therapy (referred to as Population #3)."*	The current wording does not match the CSR, and includes additional statements about tolerating therapy (Population #2) or which might not include individuals who might choose not to have hormone-based therapy (Population #3). The Company requests these are amended to	Thank you for highlighting this discrepancy. We have amended the text in section 2.2.3 on page 25.

hormone-based therapy (referred to as Population #3).”	This is a global change throughout the EAR, as the text as written does not accurately reflect the description in the company submission	match the company submission, in order to provide clarity.	

Section 2.2.4; page 27 *"…unable to take ABT, although…"*	*"…unable or would prefer to avoid hormone therapies, although…"*	To correct inaccurate wording.	Thank you for highlighting this potential ambiguity. We have amended the text, as suggested, in report section 2.2.4 on page 27.
Section 3.2.5.1; page 61 *"The company argue that because of the high response rate in the placebo group the relative efficacy of linzagolix may be underestimated."*	*"The company argue that because of the high response rate, low patient numbers and potential compliance issues in the placebo group, the relative efficacy of linzagolix may be underestimated."*	The high response rate was not the only reason for the underestimation of the relative efficacy of linzagolix vs. placebo (see CS B.3.7 and response to the clarification questions; response A8).	Not a factual inaccuracy. The company's assertion about non-compliance is a potential explanation for the placebo effect, not an additional factor to the placebo effect, and is discussed in the next sentence in the EAG report. None of the cited CS sections or Clarification Response A8 mention low patient numbers. No change made.

Section 3.2.5.1; page 61 *"Despite the higher response rate in the placebo group, the difference between placebo and each of the linzagolix treatment groups for the pooled PRIMROSE trials is statistically significant (p<0.001) (CS Appendix Figure 35). However, the linzagolix 100 mg treatment group in PRIMROSE 1 did not have a statistically significant response rate compared to placebo."*	*"Despite the higher response rate in the placebo group, the difference between placebo and each of the linzagolix treatment groups for the pooled PRIMROSE trials is statistically significant (p~~<0.001~~ ≤0.003 for all doses) (CS Appendix Figure 35). ~~However, the linzagolix 100 mg treatment group in PRIMROSE 1 did not have a statistically significant response rate compared to placebo.~~"*	The p value for the linzagolix 100 mg treatment group was 0.003. As p=0·0125 was considered significant, then the linzagolix 100 mg treatment group did show a statistically significant response rate vs. placebo in PRIMROSE 1 (Appendix Figure 35).	Thank you for highlighting this discrepancy. We have amended the text in report section 3.2.5.2 (page 61) to make this correction to the p-value. We have also updated the cross-references so that CS Table 16 and CS Appendix Figure 35 are correctly cited for the pooled and individual trial analyses respectively.

Section 3.2.5.2.1; page 62 *"…Compared to placebo, only the result for the 200 mg linzagolix dose was statistically significant : p=0.002 100 mg linzagolix compared to placebo and p=<0.001 200 mg linzagolix compared to placebo (CS Table 17)."*	*Compared to placebo, ~~only~~ the result<u>s</u> for the <u>100 mg and</u> 200 mg linzagolix dose<u>s</u> ~~was~~ <u>were nominally</u> statistically significant: p=0.00<u>1</u>2 100 mg linzagolix compared to placebo and p=<0.001 200 mg linzagolix compared to placebo (CS Table 17).*	P value for 100 mg dose is incorrect (p=0.012) and is nominally statistically significant (CS Table 17). Each active treatment group is compared versus placebo at the 0.0125 level of significance.	Thank you for highlighting this typographic error (some text is missing from the EAG's statement). We have amended the text in report section 3.2.5.2.1 to correct this (page 62).
Section 3.2.5.2.3; page 63 *"…(Pooled Analysis Data on file Table 2.7.3.6.5.2)."*	*"…(Pooled Analysis Data on file Table 2.7.3.6.5.2, <u>and Table 2.7.3.6.5.1</u>)."*	The data cited by the EAG appear in two tables. The second table should therefore be cited too.	Thank you for highlighting this missing table cross reference. We have corrected this in report section 3.2.5.2.3 on page 64. We also deleted some unnecessary text here to clarify the meaning.

Section 3.2.5.2.3; page 64 *"Haemoglobin concentrations in patients anaemic at baseline (Hb <12 g/dL) (pooled analysis) were significantly improved in all linzagolix treatment groups, except linzagolix 100 mg, compared to placebo at week 24."*	"Haemoglobin concentrations in patients anaemic at baseline (Hb <12 g/dL) (pooled analysis) were significantly improved in all linzagolix treatment groups~~,~~ ~~except linzagolix 100 mg,~~ ~~compared to placebo~~ at week 24.	The p value for the 100 mg dose is 0.002 and is statistically significant. Each active treatment group is compared versus placebo at the 0.0125 level of significance.	Thank you for highlighting this discrepancy We have deleted the text, as suggested, in report section 3.2.5.2.3 on page 65. We also deleted 3 further words to improve clarity and added a missing cross-reference to Table 2.7.3.6.6.2.

Section 3.2.5.2.3; page 65 *"The CS argues that these results support a meaningful reduction in HMB for all linzagolix treatment groups. However, in PRIMROSE 1 where ranking of these outcomes was applied to the statistical analysis, time to reduced HMB was not statistically significant for the 100 mg linzagolix treatment group and therefore none of the other bleeding-related outcomes were statistically significant in for the 100 mg group in PRIMROSE 1 (CS Appendix M.3.3.3.1 to M.3.3.3.2)."*	*"The CS argues that these results support a meaningful reduction in HMB for all linzagolix treatment groups. ~~However, in PRIMROSE 1 where ranking of these outcomes was applied to the statistical analysis, time to reduced HMB was not statistically significant for the 100 mg linzagolix treatment group and therefore none of the other bleeding-related outcomes were statistically significant in for the 100 mg group in PRIMROSE 1~~ (CS Appendix M.3.3.3.1 to M.3.3.3.2).*	This incorrect. The p value for the 100 mg dose in PRIMROSE 1 is 0.002 and is statistically significant. Each active treatment group is compared versus placebo at the 0.0125 level of significance.	Thank you for highlighting this inaccuracy. We have made the suggested amendment in report section 3.2.5.2.3 on page 65.

Section 3.3.3.1; page 74 *"The company note in Clarification Response A8 that the method of accounting for missing MBL data differed between the PRIMROSE and LIBERTY trials….The company do not discuss whether these trial differences could influence the results of NMAs that compare linzagolix against relugolix CT."*	*"The company note in Clarification Response A8 that the method of accounting for missing MBL data differed between the PRIMROSE and LIBERTY trials….The company ~~do not~~ discuss ~~whether~~ how these trial differences could influence the results of NMAs that compare linzagolix against relugolix CT in Section B.2.9.7 of the CS."*	To correct inaccurate wording.	Thank you for highlighting this discrepancy. We have amended the text, as suggested, in report section 3.3.3.1 on page 75.

Section 3.4.2; page 77 *"The company provided the effective sample sizes (ESS) for the MAIC analyses (Clarification Response Document Tables 12 to 17) but these are inconsistent between the individual and pooled trials, raising questions around the reliability of the results."* **Section 3.4.4; page 77** *"For instance, it is unclear why in the MAIC results the ESS values are inconsistent between the individual trials and the pooled analysis."*	Text should be removed.	This text suggests that the ESS for the pooled MAIC should equal the sum of the ESSs for the individual MAICs. This is not the case. ESS is a non-linear function based on the inverse of the sum of the squared weights. As such, generally the ESS cannot be decomposed in this way.	Thank you for highlighting this misinterpretation. We agree that this is incorrect and have deleted the text, as suggested, in report sections 3.4.2 and 3.4.4 on pages 78 and 79 respectively.

Section 3.4.4; page 77 *"The company do not discuss their approach to interpreting the NMA results and appear to interpret non-significant treatment effects as indicating that the treatments are similar"*	*"When interpreting the NMA results, the company conclude that the available evidence does not generally indicate any expected difference in efficacy between the linzagolix regimens and relugolix CT and that overall there is no strong indication that one treatment option is better than another."*	To correct inaccurate wording.	Not a factual inaccuracy. The CS provides a brief conclusion on the NMAs based on superiority analysis but does not discuss whether or how clinical similarity can be inferred. In the interests of transparency, we have added text quoting CS section B.2.9.8 and added a sentence to link this to the EAG's interpretation in report section 3.4.4 on page 78.

Section 3.5.1.1.2; page 80 *"As shown in Figure 10, the fixed-effects analysis considerably underestimates the heterogeneity present, with much narrower credible intervals than the random-effects analysis, despite the company claiming good model fit. The credible intervals in the random-effects analysis are so wide that is not possible to say with any certainty where the true point estimates lie."*	Please delete the struckthrough text below. *"As shown in Figure 10, the ~~fixed-effects analysis considerably underestimates the heterogeneity present, with much narrower credible intervals than the random-effects analysis, despite the company claiming good model fit. The~~ credible intervals in the random-effects analysis are so wide that is not possible to say with any certainty where the true point estimates lie."*	It is incorrect to state that *"the fixed-effects analysis considerably underestimates the heterogeneity"* as this assumes the random-effects model to be correct. With such a small network, the estimation of variance in the random-effects model will be largely driven by the prior, which may suggest that the random-effects model overestimates the heterogeneity. Model fit statistics such as the DIC and residual deviance suggest that there is little difference between the fixed- and random-effects models in terms of model fit.	Thank you for highlighting the potential for misinterpretation here. We have amended the text in report section 3.5.1.1.2 on page 82 as suggested. We have also updated the text in section 3.5.1.3.2 on page 91 for consistency. We are not assuming the random-effects model to be correct, but it does attempt to capture some of the uncertainty that is due to heterogeneity. The fixed-effects model would underestimate uncertainty in the presence of heterogeneity. The presentation of both fixed-effects and random-effects model results is therefore informative.

Section 3.5.1.3.1; page 83 *"However, there is also a substantial amount of missing data for the pooled analysis (40% to 48%) when compared to the number of data available for the response outcome (Clarification Response Table 14)."*	Text should be removed.	The comparative analysis of fibroid-related pain was performed using a subgroup of patients that had an NRS score ≥ 4 at baseline, in line with the LIBERTY studies. Therefore, the number of patients included in this analysis cannot be directly compared to the number of patients included in the comparison of response.	Thank you for highlighting this misinterpretation. We agree that this is incorrect and have deleted the text as suggested in report section 3.5.1.3.1 on page 85.

Section 3.5.1.3.1; page 84 *"Although most of the credible intervals for the linzagolix 200mg and 200mg + ABT regimens lie above zero, the posterior rank probabilities for each of the treatments (Clarification Response Document Appendix 1) do not give a clear signal that any of the intervention or comparators are favoured."*	*"~~Although~~ In addition to most of the credible intervals for the linzagolix 200mg and 200mg + ABT regimens ~~lie~~ lying above zero, the posterior rank probabilities for each of the treatments (Clarification Response Document Appendix 1) ~~do not give a clear signal that any of the intervention or comparators are favoured,~~ suggest [redacted] there is a [redacted] and a [redacted] probability that the linzagolix 200mg and 200mg + ABT regimens, respectively, are rank 1 or 2, which supports the suggestion that the linzagolix 200mg and 200mg + ABT regimens may be [redacted] as relugolix CT at reducing fibroid-related pain."*	To correct inaccurate wording.	Thank you for highlighting this inconsistency. We have amended the text as suggested for the 200mg and 200mg + ABT regimens in report section 3.5.1.3.1 on pages 86-87. We have also updated the text for the 100mg and 100mg + ABT regimens in this paragraph so that the text across the paragraph is consistent. Additionally, we have updated the text in section 3.5.1.3.2 on page 87 to clarify that the interpretation from fixed-effects and random-effects is different, as this was inconsistent following the amendment to section 3.5.1.3.1.

Section 3.5.1.4.1; page 86 *"…with the 100mg regimen having 62.3% probability of being the next-best therapy, followed by the 200mg + ABT regimen with 56.0% probability (Clarification Response Document Appendix 1)."*	*"…with the 100mg regimen having* [redacted] *probability of being rank 2, ~~next-best therapy, followed by the~~ and the 200mg + ABT regimen ~~with~~ having* [redacted] *probability of being rank 3 (Clarification Response Document Appendix 1)."*	To correct inaccurate wording.	Thank you for highlighting the ambiguity of the wording. We have amended the text in report section 3.5.1.4.1 on page 88 to improve clarity and accuracy.
Section 3.5.1.5.1; page 87 *"However, sample sizes in the MAIC analyses are very low, with 71% to 74% fewer data than were available for the analysis of the response outcome, no ESS value greater than 36 for any of the linzagolix regimen groups…"*	Please delete the struck-through text below. *"However, sample sizes in the MAIC analyses are very low, with ~~71% to 74% fewer data than were available for the analysis of the response outcome,~~ no ESS value greater than 36 for any of the linzagolix regimen groups…"*	The comparative analysis of haemoglobin was performed using a subgroup of patients that were anaemic at baseline, in line with LIBERTY studies. Therefore, the number of patients included in this analysis cannot be directly compared to the number of patients included in the comparison of response.	Thank you for highlighting this misinterpretation. We agree that the EAG statement is incorrect and have deleted the text as suggested in report section 3.5.1.5.1 on page 90.

Section 3.6.3; page 95 *"Overall, the pooled analyses for Week 24 outcomes show that linzagolix 200 mg without ABT is more effective than placebo for all reported outcomes and that linzagolix 100 mg without ABT is more effective than placebo for all reported outcomes except reduction in fibroid volume . However, in the PRIMROSE 1 trial population, 100 mg linzagolix without ABT was not more effective than placebo for most outcomes."*	*"Overall, the pooled analyses for Week 24 outcomes show that linzagolix 200 mg without ABT is more effective than placebo for all reported outcomes and that linzagolix 100 mg without ABT is more effective than placebo for all reported outcomes ~~except reduction in fibroid volume~~ . However, in the PRIMROSE 1 trial population, 100 mg linzagolix without ABT was not more effective than placebo for <u>some</u> ~~most~~ outcomes."*	Each active treatment group is compared versus placebo at the 0.0125 level of significance.	Thank you for highlighting this discrepancy. We have amended the summary text as suggested in report section 3.6.3 on page 96. Whilst reviewing this update we noticed that the secondary and additional outcomes were inadvertently included together in report section 3.2.5.2. We have made minor amendments to the following subheadings within this section to clarify which outcomes are secondary and which are additional: 3.2.5.2 (secondary and additional efficacy outcomes) 3.2.5.2.1 (additional outcome) 3.2.5.2.2 (additional outcome) 3.2.5.2.3 (secondary outcomes; we have also added "in the following rank order" after the heading to clarify that these outcomes are listed in rank order) 3.2.5.2.4 (additional outcome)

Section 3.7; page 95 *"There are inconsistencies between the individual PRIMROSE trials and the pooled trials analysis that raise uncertainty in how the pooled analysis was conducted and whether it was quality-checked. These affect ESS values of the MAIC analyses , the odds ratio for response, and the UFS-QoL symptom severity score, where the pooled outcome effect estimates lie outside the range of the individual trial effects."*	Please delete the struckthrough text below. *"There are inconsistencies between the individual PRIMROSE trials and the pooled trials analysis that raise uncertainty in how the pooled analysis was conducted and whether it was quality-checked. These affect ~~ESS values of the MAIC analyses ,~~ the odds ratio for response, and the UFS-QoL symptom severity score, where the pooled outcome effect estimates lie outside the range of the individual trial effects."*	This text suggests that the ESS for the pooled MAIC should equal the sum of the ESSs for the individual MAICs. This is not the case. ESS is a non-linear function based on the inverse of the sum of the squared weights. As such, generally the ESS cannot be decomposed in this way.	Thank you for highlighting this misinterpretation. We agree that the EAG statement is incorrect and have deleted the text as suggested in report section 3.7 on page 98.

Section 4.1; page 96 *"…the cost-effectiveness of relugolix CT compared to goserelin"*	*"…the cost-effectiveness of relugolix CT compared to GnRH agonists (goserelin, triptorelin, leuprorelin)"*	In TA832, the committee concluded that GnRH agonists were the most appropriate comparators for relugolix CT.	Thank you for highlighting this discrepancy. We have amended the sentence in EAG Report page 99 as suggested.
Section 4.2.5.1; page 102 *"…same as linzagolix 200mg + ABT for relugolix CT and GnRH agonists…"*	*"…same as linzagolix 200mg + ABT for relugolix CT…"*	The cost-comparison analysis for Population #2 compares linzagolix with relugolix CT.	Thank you for highlighting this discrepancy. The sentence has been corrected in the EAG Report page 105.
Section 4.2.5.1; page 102 *"• Background mortality rates, obtained from ONS life tables 2018-20, were incorporated"*	Suggest deletion of bullet point.	Background mortality rates were excluded from the cost-comparison analysis for Population #2 in the base case, as a simplifying assumption, as they do not impact results.	Thank you for highlighting this discrepancy. We have removed the bullet point for Population #2 from Page 105 of the EAG report.
Section 4.2.5.2.4; page 107 *"…, with the latter cohort transitioning to a second surgery state."*	*"…, with a proportion of the latter cohort transitioning to a second surgery state, based on re-surgery rates."*	The existing text implies that 100% of patients in TA832 who did not receive a hysterectomy received multiple surgeries. In TA832 there was an annual risk of re-surgery for myomectomy (3.5%), UAE (11%) and MRgFUS (6.1%).	Not a factual error. However, to improve clarity, we agree with the proposed amendment and have modified the sentence as suggested in the EAG Report page 110.

Section 4.2.5.2.5; page 108 *"The company do not discuss treatment discontinuation in their CS."*	Suggest deletion of sentence.	Treatment discontinuation is discussed in Section B.5.1.1 (treatment discontinuation rates) of the CS.	Not a factual error. Although treatment discontinuation is included in the economic model, the company do not include any discussion of treatment discontinuation in their company submission. The treatment discontinuation section reported by the company in this FAC (Section B.5.1.1) does not exist in the CS Document B. No change made.
Section 4.2.6.2.1; page 112 *"The CS does not explicitly define which of these scales was used. We assume the UFS-QoL HRQoL scale was used for the mapping."*	*"The CS does not explicitly define which of these scales was used. However, the mapping algorithm presented in CS Equation 2 is based on individual UFS-QoL questions rather than a specific scale."*	Potential misinterpretation of the approach taken.	We have added text in report section 4.2.6.2.1 on page 115 to clarify that CS Equation 2 appears to combine individual UFS-QoL questions on symptom severity and HRQoL, but the rationale for this is unclear and there is uncertainty in the utility mapping approach used.

Section 6.4; page 132 *"The company developed a cost-comparison model for linzagolix compared to relugolix CT for Population #1 (people having short-term treatment of 6 months of less) and Population #2 (people having longer-term treatment with hormone-base therapy)."*	*"The company developed a cost-comparison model for linzagolix compared to relugolix CT <u>and GnRH agonists</u> for Population #1 (people having short-term treatment of 6 months of less) and <u>for linzagolix compared to relugolix CT for</u> Population #2 (people having longer-term treatment with hormone-base therapy)."*	GnRH agonists were included in supporting analysis for Population #1.	Thank you for highlighting this. We have made the proposed amendments to the sentence in EAG report page 135.
Section 6.4; page 134 *"…, and uncertainty over the regression coefficients was not included in the probabilistic sensitivity analysis…"*	Suggest deletion of text.	The utility regression parameters in the cost-effectiveness model for Population #3 were included in probabilistic sensitivity analysis, using the variance-covariance matrix to account for joint parameter uncertainty.	Thank you for highlighting this inconsistency. We have deleted the text from report section 6.4 on page 137 of the EAG report as suggested.

Issue 3 Requests to clarify ambiguous wording

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response** (page numbers refer to track changes version of EAG report)
Section 1.3; page 13 *"…and those receiving linzagolix for longer-term treatment (Population #2)."* **Section 1.3; page 15** *"• Population #2: Patients having longer-term treatment with hormone-based therapy (cost-comparison analysis)"* *"• Population #3: Patients having longer-term treatment without hormone-based therapy (cost-utility analysis)."* *"These patients, taking longer-term therapy, are not fully represented…"*	Throughout the report, please clarify the length of treatment meant by 'longer term' (i.e. >6 months) and 'short term' (i.e. ≤6 months).	The Company feels the existing text could be clearer regarding the duration considered "long-term" by the EAG. This is important when considering the length of follow-up in the PRIMROSE studies.	Not a factual inaccuracy. The boundaries of "longer-term" therapy are not defined for linzagolix or the comparators in the CS. For instance, CS Figure 4 does not define what "longer term pharmacological therapy" means. It is unclear how flexible the timescales implied in CS Figure 4 are. For example, patients awaiting surgery might experience waiting times that exceed the 6-month cut-off and it is unclear whether it would be reasonable to define a therapy duration of, say, 7 or 8 months as "short-term" or "long-term". The maximum duration for which linzagolix could be used in clinical practice is also unclear in the CS. No changes made.

Section 2.2.2; page 23 *"Long-term use of GnRH analogues therefore requires…"* **Section 2.2.3; page 26; Table 3** *"…having longer-term treatment, with hormone-based therapy"* **Section 2.2.3; page 27; Table 3** *"*…having longer-term treatment, without hormone-based therapy*"* **Section 2.2.4; page 27** *"The proposed position of linzagolix in the treatment pathway is either for short term use…or for longer-term use…"* **Section 3.2.1; page 38**			

"…relevant to Population #3 (long-term treatment without ABT)…relevant to Population #1 (short-term treatment with or without ABT) and Population #2 (long-term therapy with ABT)." **Section 3.2.1.1.5.3; page 42** *"Exclusion of patients receiving long-term therapy (Population #2)"* **Section 3.2.1.3.3; page 48** *"…those who would receive long-term treatment (Population #2)…"* **Section 3.2.5; page 59** *"…Population #3, people receiving*			

longer-term treatment…" **Section 3.6.2; page 93** *"…for Population #2, who receive longer-term therapy…"* **Section 3.6.3; page 94** *"Evidence relevant to Population #3 (longer-term treatment without ABT…"* **Section 6.5; page 133** *"…compared to BSC for Population #3 (people with longer-term treatment…"*			
Section 1.6; page 19 *"There are no data to support the company's assumption that the treatment effect (i.e., response) of linzagolix is maintained in the long term, although it*	Please clarify the specific duration of time referred to as 'long term'. *"There are no data to support the company's assumption that the treatment effect (i.e., response) of linzagolix is maintained beyond one year,*	It is unclear whether the reference to a lack of long-term data takes into account the response to the clarification questions (response A7) that discusses the mechanism of action of linzagolix and refers to 2-year efficacy data for relugolix CT (which has a similar	We agree with the company that the suggested amendment improves clarity, so we have amended the text in report section 1.6 on page 19 as suggested.

may be biologically plausible."	*although it may be biologically plausible."*	mechanism of action) from the LIBERTY trial.[2] There is no biological rationale why the linzagolix treatment effect should decrease over time, as treatment effect is maintained over 52 weeks and dose-dependent E2 suppression is expected to continue as long as treatment is maintained. Efficacy is expected to be durable throughout long-term treatment with linzagolix, continual GnRH suppression.	
Section 2.2.2; page 23 *In contrast, the more recently-developed GnRH antagonists, which include linzagolix and its potential comparator, relugolix CT,…"*	*In contrast, the more recently-developed GnRH antagonists, which include linzagolix and ~~its potential comparator,~~ relugolix ~~CT~~,…"*	Relugolix is the GnRH antagonist; relugolix CT is the comparator – so we would like to suggest this amendment to remove ambiguity.	Think you for highlighting this potential ambiguity (although we note this also occurs in CS Figure 4 so is not a factual inaccuracy). We have amended the text as suggested in report section 2.2.2 on page 23.

Section 3.5.1.4.1; page 85 *"Although the pooled analysis has better matching and sample size compared to the individual trials the analysis is weak, reducing confidence in the findings."*	This statement should be removed or expanded upon to give justification for the claim that the *"analysis is weak"*.	It is unclear why the EAG believe that *"the analysis is weak".*	We have clarified that there are uncertainties around the approach used for measuring fibroids (section 3.2.3.1.3) – the text has been amended in report section 3.5.1.4.1 on page 88.

Issue 4 Typographical errors

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response** (page numbers refer to track changes version of EAG report)
Section 1.2; page 12 *"● The modelling assumptions that have the greatest effect on the ICER are:"*	Remove bullet point. *"The modelling assumptions that have the greatest effect on the ICER are:"*	Please amend for clarity of reporting	Thank you for highlighting this typographical error in report section 1.2 – this has been corrected on page 12.
Section 2.2.1.2; page 22 *"The risk of developing uterine fibroids is also increased in women who obesity, early menarche, age more than 5 years since last birth, and hypertension, as well as exposure to oestrogen-like chemicals (e.g. phytoestrogens in soy milk)"*	*"Other risk factors for developing uterine fibroids include obesity, early menarche (first menstrual period), time since last birth ≥5 years, hypertension, and exposure to oestrogen-like chemicals (e.g. phytoestrogens in soy milk)"*	To improve sentence clarity.	Thank you for highlighting these potential ambiguities in report section 2.21.2 – the text has been amended on page 22 as suggested.

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response** (page numbers refer to track changes version of EAG report)
Section 2.2.2; page 23 *"(brand name Yselty)"*	Please include a registered symbol. *"(brand name Yselty®)"*	This is the name of a registered brand.	Added on page 23 as requested.
Section 2.2.2; page 23 *"The effect of linzagolix on the production of LS and FSH causes immediate dose-dependent suppression of ovarian progesterone and estradiol secretion with the changes in hormone levels quickly reversible on stopping the therapy."*	*The effect of linzagolix on the production of ~~LS~~ LH and FSH causes immediate dose-dependent suppression of ovarian ~~progesterone and~~ estradiol secretion and subsequent progesterone secretion, with the changes in hormone levels quickly reversible on stopping the therapy*	Typographical error (the abbreviation is LH not LS). Progesterone is produced after ovulation and is independent from LH/FSH stimulation. Suppressing estradiol will lead to anovulation which subsequently will prevent progesterone production.	Thank you for highlighting these inaccuracies in report section 2.2.2 – these have been corrected on page 23.
Section 3.2.1.1.2; page 38; Table 5	*"95 sites in USA and 8 European countries (no UK sites)"*	The current text inaccurately states the number of USA sites. Please see Table 9 in the Company Submission.	Thank you for highlighting this typographical error – this has been corrected in report Table 5

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response** (page numbers refer to track changes version of EAG report)
"85 sites in USA and 8 European countries (no UK sites)"			

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response** (page numbers refer to track changes version of EAG report)
Section 3.2.1.1.5.4; page 43 *"…Asian women not receiving HRT therapy have greater risk…"*	*"…Asian women not receiving HRT have greater risk…"*	To correct a typographical error.	Thank you for highlighting this typographical error in report section 3.2.1.1.5.4 – this has been corrected on page 44.
Section 3.5.1.3.1; page 83 *"…(range 5 to 9 across the linzagolix regimens)…"*	*"…(range 4 to 9 across the linzagolix regimens)…"*	To correct a typographical error.	Thank you for highlighting this typographical error in report section 3.5.1.3.1 – this has been corrected on page 85.
Section 3.5.1.5.1; page 87 *"…no ESS value greater than 36 for any of the linzagolix regimen groups…"*	*"…no ESS value greater than 32 for any of the linzagolix regimen groups…"*	To correct a typographical error.	Thank you for highlighting this typographical error in report section 3.5.1.5.1 – this has been corrected on page 90.
Section 4.2.2.1.1; page 99 "28 days weeks"	*"28 days"*	To correct a typographical error.	Thank you for highlighting this, we have corrected the typographical error in EAG report page 102.

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response** (page numbers refer to track changes version of EAG report)
Section 4.2.6.2.2; page 113 **Table 20, UAE, Post-surgery utility** *"0.801"*	*"0.800"*	To correct a typographical error.	We have corrected this utility value in Table 20 of the EAG report to match the value provided in the economic model. However, the EAG would like to note that there are two post-surgery utility values in CS Table 66 for UAE, citing both 0.800 and 0.801.
Section 4.2.7.2.1; page 116 **Table 23, table heading** "GnRH antagonists"	*"GnRH analogues"*	To correct a typographical error (the resource use reflects both GnRH antagonists and agonists).	Thank you for highlighting this discrepancy. We have corrected the typographical error in Table 23, page 119 of the EAG report.

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response** (page numbers refer to track changes version of EAG report)
Section 7; page 135 *"2. Marsh EE, Al-Hendy A, Kappus D, Galitsky A, Stewart EA, Kerolous M. Burden, Prevalence, and Treatment of Uterine Fibroids: A Survey of U.S. Women. Journal of Women's Health (2002). 2018;27(11):1359-67."*	Please correct the date of the reference to 2018.	The reference currently has two publication dates.	Thank you for highlighting this error (which occurs in the CS reference list and was inadvertently copied into the EAG report when we imported the CS references RIS file). We have corrected this.
Appendix 1; page 139; Table 35 *"Although searches were 6 months old en the CS…"*	*"Although searches were 6 months old <u>wh</u>en the CS…"*	To correct a typographical error.	Thank you for highlighting this typographical error in Appendix 1 – this has been corrected on page 141.
Appendix 1; page 141; Table 35 *"…reported in CS Appendix D.3.3.3 and D/3/3/4…"*	*"…reported in CS Appendix D.3.3.3 and <u>D.3.3.4</u>…"*	To correct a typographical error.	Thank you for highlighting this typographical error in Appendix 1 – this has been corrected on page 143.

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response** (page numbers refer to track changes version of EAG report)
Appendix 1; page 141; Table 35 *"The methods are critiqued in section* ***Error! Reference source not found.*** *of this report."*	*"The methods are critiqued in section 3.4 of this report."*	To correct a typographical error.	Thank you for highlighting this typographical error in Appendix 1 – this has been corrected on page 143.

Issue 5 Confidential markup

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response** (page numbers refer to track changes version of EAG report)
ID6190 Linzagolix Final EAR v0.2 **Section 3.2.5.2.3; page 64**	None of the data in this section are confidential and none need redaction.	AIC yellow highlighting not required.	We have removed the confidentiality markup from section 3.2.5.2.3 on pages 64 and 65
ID6190 Linzagolix Final EAR v0.2 **Section 3.5.2; page 92–93; Table 9**	The information in Table 9 is confidential and should be marked for redaction.	Please mark up all content in Table 9.	We have added confidentiality markup to Table 9
ID6190 Linzagolix Final EAR v0.2 **Section 4.2.2.1.1; page 99**	Time to treatment discontinuation data are confidential (to prevent the calculation of confidential patient access scheme discount and costs).	Please mark up the value.	Thank you for highlighting this. We have marked the data as confidential on page 102 of the EAG report.

ID6190 Linzagolix Final EAR v0.2 **Section 1; page 18-20** **Section 5 and 6; page 119-134**	For Population #3 (cost-effectiveness analysis), per request from NICE, an updated version of the company submission was provided which unredacted ICERs and instead redacted BSC total costs.	Mark up BSC total costs for Population #3 results. Unmark ICERs for Population #3 results.	Thank you for highlighting this; we were unaware of this change in the confidential marking. We have marked the total cost results for BSC for Population #3 as confidential and have removed the confidentiality marking on the ICERs for Population #3 in the following sections and/or tables: • Issue 5 Page 19 • Table 2 Page 20 • Section 4.2.4 • Section 4.2.5.2.2 • Section 4.2.5.2.3 • Section 4.2.5.2.5 • Section 4.2.6.4 • Section 5.2.1 • Section 5.2.2 • Section 6.1.2 • Table 32 Page 129-131 • Section 6.2 • Table 33 Page 132 • Section 6.3 • Table 34 Page 133-134 • Section 6.5

References:

1. NICE. PMG36 - NICE health technology evaluations: the manual. Available at: https://www.nice.org.uk/process/pmg36/ [last accessed: 16/11/2023]. 2022.
2. Al-Hendy A, Venturella R, Ferreira JCA, Li Y, Wagman RB, Lukes AS. LIBERTY RANDOMIZED WITHDRAWAL STUDY: 2-YEAR EFFICACY AND SAFETY OF RELUGOLIX COMBINATION THERAPY IN WOMEN WITH HEAVY MENSTRUAL BLEEDING ASSOCIATED WITH UTERINE FIBROIDS. *Fertil Steril*. 2021;116(3):e2. https://doi.org/10.1016/j.fertnstert.2021.07.014.
3. Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. *BMC Womens Health*. 2012;12(1):6. https://doi.org/10.1186/1472-6874-12-6.
4. Williams ARW. Uterine fibroids – what's new? *F1000Research*. 2017;6:2109. https://doi.org/10.12688/f1000research.12172.1.
5. Fibroids. *nhs.uk*. 10/19/2017. Last accessed: 09/13/2022. https://www.nhs.uk/conditions/fibroids/.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190]

Clinical expert statement

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 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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Wednesday 3 January 2024.** 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, 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 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 moderate to severe symptoms of 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	Funlayo Odejinmi
2. Name of organisation	Whipps Cross University Hospital Barts Health NHS Trust London
3. Job title or position	Consultant gynaecologist and obstetrician
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.	No disclosures

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 primary aim of treatment of uterine fibroids is to alleviate symptoms and improve quality of life of people who have symptoms related to uterine fibroids. Additional aims would include: 1.Timely intervention, as this is crucial to prevent long-term health issues, such as severe anaemia or fertility problems, which may arise from delayed treatment 2. to prevent complications from surgical and non-surgical interventions 3. to prevent recurrence of fibroids following intervention 4. to individualise the care of people with fibroids
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)	The primary significant clinical response would be: 1. Amelioration of patient symptoms and 2. Improvement of quality of life. For most women this would be a reduction in Heavy Menstrual bleeding as a result of the presence of fibroids. In some cases, this would include: 1. Decrease in the size of the fibroids. 2. Prevention of regrowth of fibroids
10. In your view, is there an unmet need for patients and healthcare professionals in uterine fibroids?	Most women with fibroids would want interventions that provide the maximum returns in terms of alleviation of symptoms with the least morbidity and invasiveness overall most important unmet need for women with uterine fibroids is the provision of information and education about interventions and outcomes of these interventions for the treatment of fibroids. Closing the knowledge gap between interventions available for management of fibroids in order to individualise care This is exemplified by the UK government All party parliamentary group for womens health of 2018 on informed choice (ref APPG 2018). Women want 1. improved research 2. decrease in disparity of access to care

	3. expansion of awareness and education 4. individualisation of care and shared decision making 5. interventions with minimal intervention but maximum returns a reference for this is: (Aninye IO, Laitner MH, Society for Women's Health Research Uterine Fibroids Working Group. Uterine fibroids: assessing unmet needs from bench to bedside. Journal of Women's Health. 2021 Aug 1;30(8):1060-7.) Thus the use of therapies with good effect on symptoms with minimal side effects taking into consideration patients preferences and possible future reproductive needs For clinicians the unmet need is providing treatments that women require as stated above as well as resources to keep up with ever changing medical literature around the treatment of people with uterine fibroids in order to keep up with emerging technologies
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?	In the NHS people present with symptoms to GP symptoms usually include: 1. Heavy menstrual bleeding, 2. Pressure symptoms of frequency of micturition or constipation, or 3. Problems with fertility. 4. Some women have painful periods and painful intercourse. 5. Some women present with Anaemia secondary to heavy menstrual bleeding After a history and physical examination they would have investigations in primary care these usually include 1. FBC 2. Pelvic ultrasound scan

	Ideally they are then managed on the basis of their symptoms in line with NICE guideline (https://www.nice.org.uk/guidance/ng88). Interventions for fibroids then depend on the number site and size of the fibroids and the woman's desire for pregnancy (immediate or in the future). The expectation is that most women with severe symptoms would be referred to secondary care where further investigations are performed commonly an MRI for fibroid mapping. They would then have a detailed discussion with clinicians around available options depending on their individual circumstance. In the UK national guidelines and pathways or Royal college of obstetricians and gynaecologist green top guidelines do not exist. Thus pathways for treatment are based on NICE NG88. Guidelines do however exist in other European countries and USA (ACOG) however a recent systematic review of international guidelines showed that most of the international guidelines that do exist are not based on grade A evidence: (Amoah A, Joseph N, Reap S, Quinn SD. Appraisal of national and international uterine fibroid management guidelines: a systematic review. BJOG: An International Journal of Obstetrics & Gynaecology. 2022 Feb;129(3):356-64.). For the above stated reasons there are differences in opinion and access to fibroid care in the UK and differences in outcomes. This stems mainly from education of patients and doctors who care for patients with fibroids and geographical location of patients within the UK. There is also heterogeneity in presentation of women with fibroids and where they are in terms of fertility. If fertility is not an immediate concern then Hormonal preparations can be used for symptoms and fibroid size reduction. For women who require

	immediate fertility alternative options are available depending on the number site and size of fibroids. **Impact of Current Technology:** As women seek interventions that avoid surgery with minimal side effects the current technology in question; Linzagolix will help relieve symptoms prevent fibroid growth and allow for women to be treated before more invasive procedures become necessary 1. Can be used in women to improve symptoms relating to heavy menstrual bleeding 2. Help improve quality of life 3. Limit the growth of fibroids (depending on the dosage and the use of addback therapy) 4. Help women who have contraindications to other interventions. 5. Help women in whom other interventions have failed 6. Help women who may be waiting for surgery and are anaemic 7. Help reduce the size of fibroids so women can have minimal access approach (key hole) to surgery and its inherent benefits rather than open surgery 8. Women close to the menopause who are wanting to avoid surgery or interventions 9. Could hypothetically be used to decrease the size of fibroids for women who are seeking future fertility treatment (ref: Donnez J, Dolmans MM. Hormone therapy for intramural myoma-related infertility from ulipristal acetate to GnRH antagonist: A review. Reproductive biomedicine online. 2020 Sep 1;41(3):431-42.)

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 a similar way to existing gonadotrophin releasing hormone antagonist therapy (newly introduced Relugolix) However in view of its multi dosage has the potential to be used in a different way by modulating the dosage and preparation depending on treatment response with or without addback therapy, thus has the ability to individualise care. There is also the potential to be used in a different way when compared to GnRH analogues: (eg prostap or zoladex) currently used for: 1. women who are awaiting surgery who either need for their fibroids to decrease in size to allow for better outcomes for example to allow for minimal access surgery for myomectomy or hysterectomy instead of open surgery. or 2. for women who are anaemic who need optimisation before surgery. 3. Can also be used on an outpatient basis for women who need hysteroscopic resection of submucous fibroids (FIGO type 0-2) In the above patient groups current GnRH analogues are given in secondary care parenterally by injection usually be a nurse specialist or clinician either at monthly or 3 monthly intervals. This is at cost to the hospitals and travel times for the patients impacting on quality of life. . As (Linzagolix) can be given orally patients can be given a monthly prescription of medication, monitored for side effects and efficacy of the medication remotely and prescriptions repeated virtually without the need for repeated visits to secondary care. For patients who are on active waiting lists on the NHS since COVID-19 pandemic there has been a 66% increase in the length of waiting lists and the number of weeks women wait for their procedures (ref: https://www.rcog.org.uk/about-us/campaigning-and-opinions/left-for-too-long-understanding-the-scale-and-impact-of-gynaecology-waiting-lists/)

	There is also a recognised social and psychological impact for women who had to wait for surgery during the pandemic (ref: Strong SM, Magama Z, Mallick R, Sideris M, Odejinmi F. Waiting for myomectomy during the COVID-19 pandemic: the vicious cycle of psychological and physical trauma associated with increased wait times. Int J Gynaecol Obstet. 2020 Nov 1;151(2):303-5.) For anaemic patients or patients who require shrinkage of fibroids current therapy is usually GnRH analogues eg Zoladex these however can only be given for 6 months and are often limited by side effects. Though they are sometimes given for more than 6 month off license. As Linzagolix comes in variable doses with or without addback it could be used in women on these waiting lists who would benefit from control of symptoms and or surgical optimisation. **Location of Care of Patients** Once introduced the medication would be used in different ways depending on drawn up pathways. With lessons learned from the introduction of previous molecules which needed to be withdrawn because of side-effects (eg Ulipristal acetate) and is now subject to limited use. Linzagolix would initially be used in secondary care and specialist clinics however monitoring of patients would be virtual and thus reduce the need for repeated clinic appointments Once follow up is assured and after initial monitoring shared care arrangements would be put in place and most patients managed in primary care with arrangements for monitoring.

	No Additional investment required No investment will be needed for the introduction of the medication. It would reduce the number of times patients need to physically visit the hospitals and has the potential to free up slots in secondary care that could be used for other purposes.
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 expect the technology to provide clinically meaningful benefits compared to current care. As explained above 1. Better care than GnRH agonists that can only be given for a limited period of time 6 months and needs injections monthly or 3 monthly. 2. Ability to titrate the dose of Linzagolix with or without addback therapy depending on the desired effect and response to therapy by the patient. I do not expect the technology to increase the length of life compared to current care however is one extrapolates and compared medication to current surgical interventions, though mortality is rare it still occurs. There was no reported mortality in the PRIMROSE TRIALS related to the use of relagolix. Yes I expect the technology to increase health related quality of life more than what is currently available particularly when compared to medications that existed before the advent of gonadotrophin releasing hormone antagonists of which Linzagolix is one. Quality of life will probably be the same as for Relugolix but better than GnRH analogues that are given parenterally.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In general the technology Linzagolix would be beneficial for the majority of patients who suffer from fibroid related symptoms. However for 1. patients who do not wish to have addback therapy it would be more beneficial than existing therapy 2. patients who have contraindications to the use of hormone therapy Maybe less beneficial in women with larger fibroids as exclusion criteria in the studies was fibroid greater than 12cm and uterine size of more than 20 weeks

	Comparing PRIMROSE 1 and Primrose 2 due to the population differences and smaller fibroids lower BMI and less of an ethnic mix in primrose 1, it is possible to extrapolate that response would be better in symptomatic with smaller fibroids.
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)	The medication will not be more difficult to use for patients that currently available modalities of treatment that are oral preparations. The medication will be easier to use when compared to current GnRH analogues like prostap that require visiting secondary or primary care for monthly injections. As most patients would have a scan and blood tests before initiation of management of fibroids irrespective of modality of intervention there would be no increased need for additional tests. Bone mineral density tests would be required for patients after 52 weeks of use, the same as would be required for patients who continue to use GnRH analogues off license after a year of treatment. Bone mineral density scans may also be needed for at risk patients before starting the medication
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	When starting to use the drug women may be required to monitor symptoms for side effects mostly in secondary care Once it is ascertained that women have benefit from the medication and are free from symptoms with no side effects then the medication will be continue according to predefined protocols There would be a shared care arrangement for further prescriptions and monitoring of symptoms between primary and secondary care

	No further testing will be required if used within current timeframe, and treatment parameters demonstrated in the primrose trials and long term use data. After a year a bone mineral density scan may be required if real world data shows the benefits of long term use beyond current trial parameters. Stopping or starting the medication will depend on symptoms or side effects and generally would not require additional tests.
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	Yes the use of the technology will result in substantial health related benefits and quality of life A commonly used quality of life questionnaire is the UFS-QoL which was used along with other instruments to measure quality of life Current instruments used fully capture the quality-of-life calculations as included in the primrose trial data. The treatment is designed as an oral preparation so could have added benefits over parenteral medications such as included in the group of GnRH analogues.
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 the technology is innovative as it meets the unmet needs of women with fibroids in terms of provision of a long term use medication that addresses the issues of side effects when compared to GnRH analogues and also addresses the issues of side effects mainly the potential for menopausal symptoms including effects on bone. In addition there is a titratable dosage regime that address the issue of side effects and the ability to administer the medication in different clinical scenarios depending on the needs of the patient. The medication thus represents a step change in the provision of care for women with symptoms of fibroids
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 main side effects relate to the effect on the downregulation of the ovaries. These include somatic(vasomotor)/physical symptoms and the possibility of the development of osteoporosis. The addition of addback therapy to the treatment regime and the provision of a possible multi dose regimen act to negate the

	negative side effects on the patients quality of life in a dose vs side-effects titration fashion.
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 clinical trials reflect current UK practice but add a new dimension with the use of GNRH antagonists that can be administered with addback for women who have fibroids. Without the need for parenteral administration thus reducing the need for multiple hospital visits. The most important issues are the 1. Amelioration of symptoms of fibroids 2. Improvement in heavy menstrual bleeding 3. Improvement in anaemia (patients with severe anaemia were excluded from the trials this would be expected as different management is required for patients with severe anaemia) 4. Improvement in quality of life as well as 5. Improvement of pain symptoms. These outcomes were measured in the Trials All the primary and secondary outcomes in the trials reflect expectations for long term clinical outcomes up to the 52 weeks in the primrose trials The outcome measure studies were sufficient to identify primary objectives within the trials however the use of core outcome sets for the management of heavy menstrual may have been beneficial in retrospect. Notably these were not developed at the time of the trials There have only been recently studies published on core outcome sets in the management of women with heavy menstrual bleeding

	(ref: Cooper NA, Rivas C, Munro MG, Critchley HO, Clark TJ, Matteson KA, Papadantonaki R, Yorke S, Tan A, Bofill Rodriguez M, Bongers M. Standardising outcome reporting for clinical trials of interventions for heavy menstrual bleeding: Development of a core outcome set. BJOG: An International Journal of Obstetrics & Gynaecology. 2023 Oct;130(11):1337-45.) Though these core outcome sets are not specific for women with fibroids, the use of core outcome sets in future studies will help identify this and what is actually important to clinicians and patients as outcome measures for the management of heavy menstrual bleeding and fibroids. In real life data studies. No adverse events have come to light subsequently
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 such evidence
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA832]?	Since the publication of guidance TA832 in October 2022, there is the long term 2 year data published in the American journal of obstetrics and gynaecology Showing no new adverse events and maintenance of efficacy through 104 weeks for Relugolix Ref: Al-Hendy A, Venturella R, Ferreira JC, Li Y, Soulban G, Wagman RB, Lukes AS. LIBERTY randomized withdrawal study: relugolix combination therapy for heavy menstrual bleeding associated with uterine fibroids. American Journal of Obstetrics and Gynecology. 2023 Dec 1;229(6):662-e1.
23. How do data on real-world experience compare with the trial data?	Real world data can actually differ from data from clinical trials particularly for the management of women with fibroids because of the heterogeneity of fibroids themselves and different symptoms women with fibroids can present with. However using the example of ulitpristal acetate. Molecules introduced for the management of symptomatic women with fibroids, do in the real world what happened in the clinical trials before approved for general use. Shah and

	colleagues published on real world data after implementation of ulipristal acetate. They showed that it did improve symptoms and reduce the size of fibroids as in the Trials. (ref: Shah N, Egbase E, Sideris M, Odejinmi F. What happens after randomised controlled trials? Uterine fibroids and ulipristal acetate: systematic review and meta-analysis of" real-world" data. Archives of Gynecology and Obstetrics. 2021 May;303:1121-30.) There is to date no real world experience data on GnRh antagonists and the management of uterine fibroids to date outside of the randomised trials.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. 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 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 evaluation 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	Fibroids are more common in Black and Ethnic minority women. These women tend to present earlier with symptoms and have a greater burden of disease in terms of number and size of fibroids and severity of symptoms. Black women also suffer from lack of equity of access and outcomes when it comes to certain managements for uterine fibroids. And because of socio-economic factors also have limited access to education and awareness of different interventions for the management of fibroids. In the Linzagolix trials this was taken into account in the primrose 1 trial that included more than 60% black women in the study population The study populations in the Primrose 1 and 2 Trials represent study populations and real life populations that suffer from uterine fibroids Implementation of this medication will not lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population or lead to recommendations that have an adverse impact on disabled people

• 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.	

Key issues to consider

Key issue 1 – Uncertainty around whether linzagolix is clinically similar to relugolix and GnRH analogues In your clinical opinion is linzagolix likely to be clinically similar to relugolix or GnRH analogues? *See section 3.4 and 3.5 of the EAG report (EAR) for details*	Linzagolix is different from GnRH analogues such as zoladex and prostap in that it is an antagonist rather than an analogue thus it binds receptors directly leading to downregulation of the ovaries and inducing a hypo estrogenic state without the flare up that is seen with GnRH analogues. GnRH analogues used in general clinical practice for the management of fibroids are given enterally rather than orally. Linzagolix is similar to Relugolix as they are in the same class of GnRH antagonists They are different in that Relugolix is single dose and only comes in one dosage regimen with Addback Linzagolix has the same mode of action but is difference in its possible multidose approach to management based on Barbieri principle of oestrogen threshold (ref: Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. American journal of obstetrics and gynecology. 1992 Feb 1;166(2):740-5.) where there is a balance between complete shut down of the ovaries as opposed to partial shut down leading to an effect of the medication without compromise on mode of action or increase in side effects. Thus unlike Relugolix in low doses Linzagolix can be given with or without addback therapy depending on the desired clinical effects balanced against side effects.

	The Data analysis using the Network meta-analysis appears sound taking into account the critique by the AER the end points for Relugolix and Linzagolix are similar and by extrapolation using Relugolix comparison to GnRH analogues in the Liberty trials one could infer that it is similar to GnRH analogues but with a better mode of action and a better side effect profile
Key issue 2 – Uncertain market share of relugolix CT In your experience or clinical opinion what proportion of people with moderate to severe symptoms of uterine fibroids have relugolix for: a) short term use of less than 6 months (e.g before or while waiting for surgery) b) longer term use *See section 2.3 of EAR for details.*	Clinical use of Relugolix is limited because it has just been introduced to clinical practice however All patients who present with anaemia and heavy menstrual bleeding waiting for surgery will have Relugolix about 10-20% of patients on waiting lists for hysterectomy or myomectomy. For longer term use patients who do not respond to first line treatment Probably another 20% of patients One would expect the use of GnRH antagonists to expand depending on the response noted in real world data studies. At the present moment however due to the newness of Relugolix it is impossible to estimate its current market share for the 3 populations included in the company analysis and that of the AER
Key issue 3 – Uncertainty around the relevance of the PRIMROSE trials to the decision problem	

Would you expect any of the following groups of people to have a different clinical response to linzagolix compared to the population of the PRIMROSE trials? A) People awaiting surgery for uterine fibroids B) People having linzagolix for longer term use (over 52 weeks) C) People who cannot or would not have hormone add back therapy *See pages 15-16 of EAR for details*.	a) I would expect people waiting for surgery for uterine fibroids to respond as outlined in the primrose trials Even though patients waiting for surgery were excluded from the trials. In retrospect these patients should have been included to estimate how many of these patients would have not eventually had surgery. However with the methodology used in the primrose trials the key would be patient optimisation prior to surgery in terms of symptoms and quality of life. Whether patients go on to avoid surgery if put on GnRH antagonists would be a future real-life study similar to a study carried out for the use of ulipristal acetate after introduction (ref: Fernandez H, Schmidt T, Powell M, Costa AP, Arriagada P, Thaler C. Real world data of 1473 patients treated with ulipristal acetate for uterine fibroids: Premya study results. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017 Jan 1;208:91-6.) b) I would expect people who have Linzagolix for over 52 weeks to respond as in the primrose trials (primrose 3) c) I would expect people in this group who would not have hormone add back therapy to respond as in the primrose trials Though the group of patients were excluded from the trials and the results of Linzagolix without the use of ABT were used as proxys the response could be extrapolated by using the group of patients within the trial. In current clinical practice there are a few patients that fall into this group of patient because medication to treat this group does not currently exist other than GnRH agonists which are limited by side effects. An example would be women who have current DVT who have to have therapy for pressure symptoms. At the current time such patients would have to have

	GnRH analogues without add back with the inherent side effects with the inability to flex the dose because of the parenteral nature of administration. As more women become aware that they can have GnRH antagonists without addback with bone preservation with lower doses they may opt for this method of treatment. These therapy issues will become evident in real world studies
Key issue 4 – Uncertainty around post-surgery recurrence Is it plausible to expect zero recurrence of symptoms of uterine fibroids after surgery? If not, could you comment on whether recurrence was more likely with some types of surgeries than others? *See P17 of the EAR for details*	It is not possible to expect zero recurrence after surgery for uterine fibroids As long as the womb is retained there is a chance of recurrence of fibroids as fibroids develop from single muscle fibres within the uterus with every fibre having the potential to become a fibroid. The recurrence of fibroids and symptoms after interventions is rather complex Recurrence depends on 1. the surgical approach 2. the number of fibroids present 3. the sizes of the fibroid removed 4. the expertise of the surgeon undertaking the procedure 5. the characteristics of the patient selected for the surgery. As a general rule recurrence is commoner after laparoscopic than open surgery and least for hysteroscopic surgery.

	One would expect that some women who require surgery for uterine fibroids to have a hysteroscopic approach some of these patients will have submucous fibroids (fibroids within the cavity of the womb (FIGO classification types 0-2). As stated above depending on the size of the fibroids some of these women are treated with GnRH analogues to improve patient outcomes and reduce surgical complications. The quoted figures are usually 5-10% of women who have interventions for fibroids will need reintervention within 5-10 years of the index procedure. The recovery times used by the EAG are probably overstated as most women recover from minimal access approach to surgery in 2-4 weeks abdominal surgery after 6-8 weeks Most people recover from UAE after 2 weeks As stated by the EAG only patients who have hysterectomy will have no risk of recurrence of symptoms and analysis should take place for both groups of patients. The only assumption would be that the older the patient after surgery the more unlikely it is that they would have recurrence of symptoms. It is probably that the cost effectiveness would be maintained even with the analysis for different groups of patients dependent on age.
Key issue 5 – Uncertainty surrounding the utility function	Both of the methods used for the utility function are based on complex statistical analysis informed by published literature Used in context both methods would be applicable

Do you consider the company (base case) or EAG preferred (scenario analysis) estimates of utility in Table 19 of the EAR to be most reflective of clinical practice? *See P18 and section 4.2.6 of the EAR for details*	The 2 methods of analysis should be considered in different aspects of the analysis As the company's use of methodology similar to TA832 for utility estimates who also used published literature data for quality of life Both methods (company and EAR calculations) are based on assumptions But disease based specific quality of life is used in most studies so would be more appropriate for technology such as Linzagolix and thus more reflective of clinical practice as suggested by the company.

Other issues to consider

Other issue 1 – Components of best-supportive care. Do you consider Vitamin D and Calcium to be part of best supportive care for treatment of symptoms of uterine fibroids? *See section 4.2.4 of EAR for details.*	There is emerging literature on the case for vit D as supportive treatment for the management of fibroids reported to limit size of fibroids as well as growth with or without the use of green tree extracts. This at the moment is not widely used in clinical practice and numbers in clinical literature are small. And would not currently be regarded as best supportive care for the treatment of symptoms of fibroids.
Other issue 2 – **Proportions of different surgery types.** Do you consider the company or EAG preferred distribution of surgery types in Table 29 to be more reflective of clinical practice? *See section and Table 29 of the EAR for details.*	the company the numbers used for the distribution of surgery types are reflective of clinical practice in general However there is published literature that differs from both the company submission and the EAG Though the numbers for abdominal hysterectomy may be different as publications in medical literature point to a decline in open hysterectomy and an increasing trend to

	laparoscopic hysterectomy for women who require hysterectomy in the united kingdom (ref: Madhvani K, Curnow T, Carpenter T. Route of hysterectomy: a retrospective, cohort study in English NHS Hospitals from 2011 to 2017. BJOG: An International Journal of Obstetrics & Gynaecology. 2019 May;126(6):795-802.) Laparoscopic Myomectomy rates average about 18-22%% in the UK depending on the region (ref: Aref-Adib M, Strong S, Ojukwu O, Zeltser H, Cooper NA, Mcdougall A, Odejinmi F. 10512 Why and Where Are Interventions Performed: A Retrospective Analysis of Myomectomy for Uterine Fibroids in England (2018-2019). Journal of Minimally Invasive Gynecology. 2023 Nov 1;30(11):S126.)
Other issue 3 – **Numbers of healthcare appointments modelled.** Do you consider the company or EAG preferred estimates of healthcare resource use in Table 29 to be more reflective of clinical practice? *See Table 29 of the EAR for details.*	Both Scenarios would be appropriate depending on how Linzagolix is introduced. There are currently 2 approaches to the use of Relugolix Hospital only prescriptions and shared care with GP In both scenarios patients visit the practitioner once have a questionnaire filled in and monitored for side effects after this they are then reviewed virtually (telephone consultations) and prescriptions repeated. To date in the UK there are no one year follow up of GnRH antagonists It is unlikely that the patients on GnRH antagonists will need 2 visits unlike currently with GnRH analogues. Thus leading to a decrease in healthcare resource use.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Linzagolix a new molecule for the treatment of people with moderate to severe heavy menstrual bleeding has effects comparable to other GnRH antagonists available based on the literature provided and to GnRH analogues with the added benefit of variable doses with or without Addback therapy and can be used long term for the management of symptoms.

GnRH antagonists do provide for an unmet need for people who have uterine fibroids and provide good quality of life when appropriate clinical pathways are applied to care. As people with uterine fibroids prefer less invasive interventions with minimal side effects

With lengthening waiting lists in the United Kingdom Linzagolix will allow for alleviation of symptoms in the short and longer time whilst women are awaiting surgery and will allow for optimisation before surgery without multiple visits to hospital for parenteral administration as is currently available with GnRH analogues.

Though the populations in the PRIMROSE studies did not include as many ethnic minority women as the LIBERTY studies and did not include people from the UK, the combination of primrose 1 and 2 is reflective of people who suffer from severe symptoms related to fibroids in the UK. Future studies will also be needed to reflect people who were excluded from the PRIMROSE trials to see if they respond as people in the trials (future real life data studies)

Because of the multidose possibilities with Linzagolix it does offer choice to administer medication to people on an individualised basis depending on clinical scenario as well as response to treatment titrated against possible side effects. It is thus an innovation above what current therapy exists at the moment.

Though there remains some ambiguity around the # 3 population of patients who cannot or will not use addback therapy there would no doubt be gained quality of life which will probably come to light in real life data studies in the future.

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.