

Single Technology Appraisal

Linzagolix for treating symptoms of endometriosis [ID6357]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Linzagolix for treating symptoms of endometriosis [ID6357]

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**
 - a. Company response
 - b. Addendum to company response
 - c. Response to A13c
 - d. Response to B24, B25, B28
- 3. Patient group, professional group, and NHS organisation submission from:**
 - a. Endometriosis UK
- 4. Expert personal perspectives from:**
 - a. Dr Togobo – clinical expert, nominated by the Cochrane Gynaecology and Fertility Group
- 5. External Assessment Report prepared by Kleijnen Systematic Reviews**
- 6. External Assessment Group response to factual accuracy check of EAR**

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 symptoms of
endometriosis**

[ID6357]

Document B

Company evidence submission

October 2024

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Abbreviations

ABT	Add-back therapy
AE	Adverse event
AFS	American Fertility Society
ANCOVA	Analysis of covariance
AI	Aromatase inhibitor
AIC	Akaike Information Criterion
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BIC	Bayesian information Criterion
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
BSGE	British Society for Gynaecological Endoscopy
CC	Complications and comorbidities
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CHC	Combined hormonal contraceptive
CHMP	Committee for Medicinal Products for Human Use
COC	Combined oral contraceptive
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
DMPA	Depot-medroxyprogesterone acetate
DNG	Dienogest
DXA	Dual X-ray absorptiometry
E2	Oestradiol
EAG	Evidence assessment group
EAP	Endometriosis-associated pain
EAPP	Endometriosis-associated pelvic pain
eCRF	electronic case report form
eDiary	Electronic diary
EHP-30	Endometriosis health profile-30
EMA	European Medicines Agency
EQ-5D	EuroQoL 5-Dimension
EQ-5D-3L	EuroQoL 5-Dimension 3-Level
EQ-5D-5L	EuroQoL 5-Dimension 5-Level
ESAF	Extension safety analysis set
ESHRE	European Society of Human Reproduction and Embryology
ExFU	Extension follow-up
FAS	Full analysis set
FU EAS	Follow-up extension analysis set
FSH	Follicle-stimulating hormone
GDP	Gross domestic product
GGT	Gamma-glutamyl transpeptidase
GnRH	Gonadotropin-releasing hormone
GP	General Practitioner
HCP	Healthcare professional
HRQoL	Health-related quality of life
HRU	Healthcare resource use
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison

ITT	Intention-to-treat
KM	Kaplan–Meier
KT	Kazakhstani Tenge
LARC	Long-acting reversible contraception/contraceptive
LDL	Low-density lipoprotein
LGX	Linzagolix
LH	lutinising hormone
LNG-IUS	Levonorgestrel-releasing intrauterine system
LSM	Least squares mean
LYG	Life years gained
MAR	Missing at random
MCM	Markov chain model
MCT	Meaningful change threshold
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NHS	National Health Service
NMB	Net marginal benefit
NMPP	Non-menstrual pelvic pain
NR	Not reported
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
OC	Oral contraceptive
OPP	Overall pelvic pain
OR	Odds ratio
PCS	Physical component summary
PICOS	Population, intervention, outcomes, study design
PP	Per-protocol
PP EAS	Per-protocol extension analysis set
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSIQ	Physician Surgery Intention Question
Q	Quartile
QALY	Quality-adjusted life year
QD	Once daily
OWSA	One-way deterministic sensitivity analysis
QoL	Quality of life
rASRM	revised American Society for Reproductive Medicine
RCT	Randomised controlled trial
Relugolix CT	Relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)
RoB 2	Risk-of-bias tool 2
SAF	Safety analysis set
SAP	Statistical analysis plan
SARC	Short-acting reversible contraception/contraceptive
SD	Standard deviation
SF-36	36-Item Short Form Survey
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SSIQ	Subject Surgery Intention Question
STA	Single technology appraisal

TEAE	Treatment-emergent adverse event
TEAS	Treatment extension analysis set
TS	Treatment sequence(s)
ULN	Upper limit of normal
VAS	Visual analogue scale
VAT	Value added tax
VRS	Verbal rating scale
WERF	World Endometriosis Research Foundation
WTP	Willingness to pay

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

SUMMARY

- Endometriosis is an oestrogen-dependent gynaecological condition, where endometrium-like tissue grows outside the uterus
- Endometriosis is estimated to affect approximately 10% of women of reproductive age.^{1,2}
- The main clinical consequences of endometriosis are chronic pelvic pain (cyclical and non-cyclical), dysmenorrhoea (painful menstruation) and impaired fertility²
- Symptoms of endometriosis can significantly impact the person's quality of life (QoL), their physical and psychosocial functioning, including social life, absenteeism from school or work, intimacy and intimate partnerships, as well as mental health and emotional wellbeing³
- Delays in diagnosis, where UK patients wait on average 9 years for a diagnosis,⁴ as well as the ongoing management of this chronic condition, which often involves multiple invasive surgeries, places an additional burden on patients with endometriosis
- The economic impact of endometriosis is substantial, and its direct and indirect healthcare costs are comparable to those for other chronic conditions such as type 2 diabetes, rheumatoid arthritis and Crohn's disease⁵
- There is no known way to prevent endometriosis nor guaranteed cure⁶
- Treatment options for endometriosis-associated pain (EAP) are diverse and consist of analgesic therapies, hormonal therapies, conservative or minimally invasive surgery, or a combination of these
- Treatment decisions are dependent on both the impact of symptoms and patient's priorities regarding pain management and fertility. As such, a personalised, interdisciplinary treatment approach is required
- There is still a significant need for better options for the treatment of endometriosis: approximately 30% of patients with endometriosis develop chronic pelvic pain that is unresponsive to conventional treatments, including surgery⁷
- In patients not responding to conventional treatments, effective pharmacological therapies are required to reduce pain and improve QoL
- Gonadotropin-releasing hormone (GnRH) agonists may be used as a second-line treatment option but have numerous limitations, including side effects associated with suppression of oestradiol (E2) to post-menopausal levels and unpredictable reversibility of treatment with injectable depot forms.⁸ In addition, currently available GnRH agonists are administered mainly by intramuscular or subcutaneous injections (every 1 to 3 months) that require healthcare professional (HCP) administration
- GnRH antagonists, including linzagolix, are an effective new treatment option for symptoms of endometriosis that provide immediate suppression of follicle-stimulating hormone (FSH) and luteinising hormone (LH) secretion with rapid reversibility. As GnRH antagonists are administered orally, this can be done at home without HCP supervision
- Based on clinical expert opinion in the UK, and in line with European clinical guidelines, GnRH antagonists (including linzagolix) will be used as second-line hormonal treatment options, as an alternative to GnRH agonists⁹

B.1.1 Decision problem

Linzagolix 200 mg plus add-back hormone-replacement therapy (ABT) is currently under consideration by the UK Medicines and Healthcare products Regulatory Agency (MHRA) for the symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis. This submission covers the technology's intended 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
Population	Adults with symptoms of endometriosis	Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis	The submission is aligned with the intended indication for linzagolix in women with endometriosis
Intervention	Linzagolix 200 mg plus ABT	Linzagolix 200 mg plus ABT	Linzagolix 200 mg plus ABT
Comparator(s)	Where hormone-based therapy is suitable Established clinical management without linzagolix, including: - analgesics or NSAID alone or in combination - neuromodulators - relugolix-oestradiol-norethisterone acetate (relugolix CT; subject to NICE evaluation) - other hormonal treatment such as combined hormonal contraception (off-label for some combined hormonal contraceptives), oral progestogens, GnRH agonists - surgery such as excision/ablation with or without hysterectomy Where hormone-based therapy is not suitable Established clinical management without linzagolix, including: - analgesics or NSAID alone or in combination - neuromodulators - surgery such as excision/ablation with or without hysterectomy	- Leuprorelin, as a representative of all GnRH agonists - Surgery - specific surgical procedure(s) to be explored as relevant comparators based on UK clinical practice and types of surgeries undertaken in second line	As linzagolix would be expected to be used as a second-line treatment (in accordance with the indication), the comparators are based on those potentially used at the same point of the treatment pathway. Relugolix CT has not yet been approved by NICE.
Outcomes	- Pain - Opioid use - Analgesic use - Recurrence, progression and regression of endometriosis	- Pain - Opioid use - Analgesic use - Adverse effects of treatment - Health-related quality of life	The Company provided comments on the draft scope, proposing that the following outcomes should be excluded from the scope: - Admission to hospital - Recurrence of endometriosis

Company evidence submission for linzagolix for treating pain caused by endometriosis

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	• Admission to hospital • Subsequent surgical treatment • Fertility • Adverse effects of treatment • Complications of treatment • Health-related quality of life		• Subsequent surgical treatment • Fertility • Complications of treatment The exclusion of 'admission to hospital' is due to an absence of relevant outcome data from the pivotal trials. In the EDELWEISS 3 and 6 studies, fewer than 2% of patients required hospitalisation at any time, or in any treatment arm. The other excluded outcomes were not collected in the key studies and, therefore, cannot be included in the analysis for this evaluation.
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.	A cost-effectiveness analysis of linzagolix versus leuporelin and relevant surgical procedures, from an NHS and Personal Social Services perspective. Cost-effectiveness is expressed in terms of incremental cost per quality-adjusted life year.	Not applicable
Subgroups to be considered	If the evidence allows the following subgroups will be considered:	Subgroups have not been considered in the submission. In this indication, linzagolix will always be administered with concomitant ABT.	The submission is aligned with the intended indication for linzagolix in women with endometriosis which

	• people having short-term treatment of 6 months or less, with hormone-based therapy • people having short-term treatment of 6 months or less, without hormone-based therapy • people having longer-term treatment, with hormone-based therapy • people having longer-term treatment, without hormone-based therapy	There is no set time duration (specified course) for this treatment and treatment may continue for as long as patients continue to benefit. If the risks of BMD decrease exceed the potential benefit of treatment with linzagolix, treatment should be discontinued.	does not include the use of linzagolix without hormone-based therapy.

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; GnRH, gonadotropin-releasing hormone; NHS, National Health Service; NSAID, non-steroidal anti-inflammatory drug; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)

B.1.2 Description of the technology being appraised

A description of linzagolix is presented in Table 2. The Summary of Product Characteristics (SmPC) submitted to the European Medicines Agency relating to the addition of the endometriosis indication is provided in Appendix C. The European and UK Public Assessment Reports are not yet available.

Table 2: Technology being evaluated

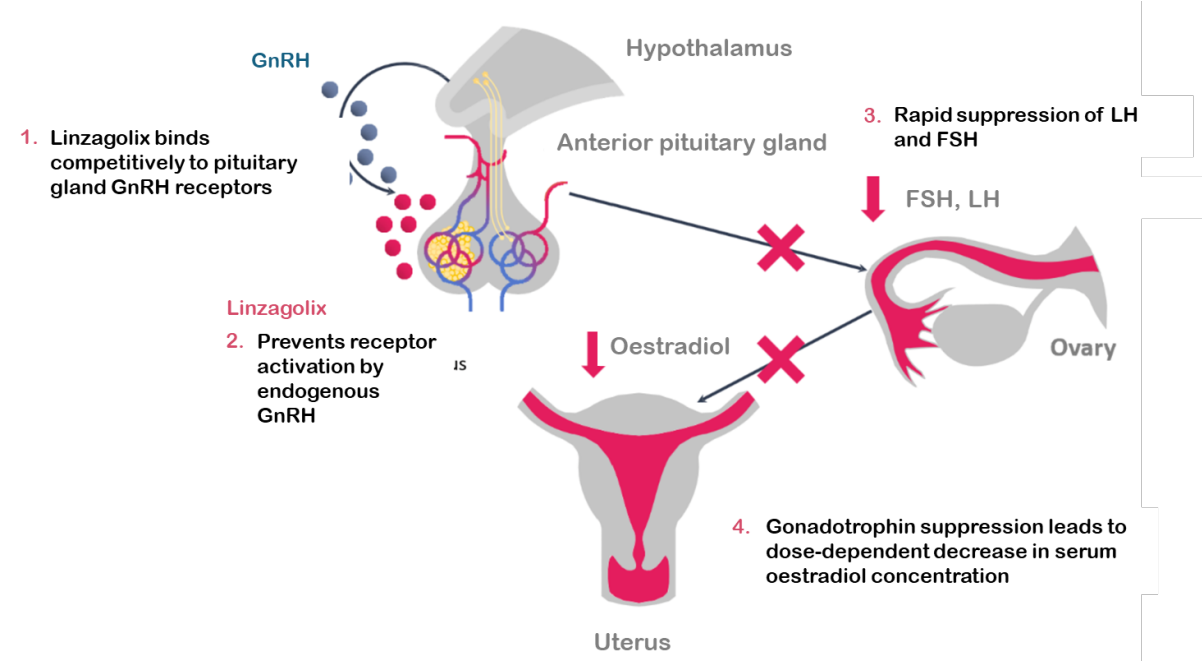
UK approved name and brand name	Linzagolix, Yselyt [®]
Mechanism of action	Linzagolix is a selective, non-peptide GnRH receptor antagonist that inhibits endogenous GnRH signalling by binding competitively to GnRH receptors in the pituitary gland, thereby modulating the hypothalamic-pituitary-gonadal axis. 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 E2 and progesterone, without the initial stimulation (flare effect) of the receptors that occurs with GnRH agonists. ^{10–12}
Marketing authorisation/CE mark status	Linzagolix will be assessed via the MHRA Reliance Procedure following assessment by the EMA. On 17 October 2024 the CHMP adopted a positive opinion on inclusion of the new indication for treatment of patients with endometriosis. The anticipated date of UK marketing authorisation is [REDACTED]
Indications and any restriction(s) as described in the SmPC	Linzagolix is anticipated to be indicated for [REDACTED] [REDACTED] Linzagolix is currently indicated for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. ¹²
Method of administration and dosage	Linzagolix is administered as an oral tablet (200mg), once daily with or without food. ¹² The anticipated dose for symptoms of endometriosis is 200 mg once daily with concomitant hormonal ABT.
Additional tests or investigations	Pregnancy must be ruled out prior to initiating treatment. In patients with risk factors for osteoporosis or bone loss, a DXA scan is recommended prior to starting treatment. ¹² A DXA scan is recommended after 1 year of treatment for all women, and there is a need for continued BMD monitoring thereafter [REDACTED] [REDACTED]
List price and average cost of a course of treatment	• Cost per 28-pack of 200 mg tablets: £80 • Hormonal ABT (oestradiol/norethisterone) indicative price: Cost per 84-pack of 1 mg/0.5 mg tablets: £13.20 (£15.84 with VAT) Linzagolix can be taken without interruption. There is no set time duration (specified course) for this treatment. If the risks of BMD decrease exceed the potential benefit of treatment with linzagolix, treatment should be discontinued.

Patient access scheme	Not applicable.

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; CHMP, Committee for Medicinal Products for Human Use; DXA, dual X-ray absorptiometry; E2, oestradiol; EMA, European Medicines Agency; GnRH, gonadotropin-releasing hormone; MHRA, Medicines and Healthcare products Regulatory Agency; VAT, value added tax

The mechanism of action of linzagolix is summarised in Figure 1.

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)¹⁴

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

Endometriosis is an oestrogen-dependent gynaecological condition, where endometrium-like tissue grows outside the uterus. It causes a chronic inflammatory reaction that may result in the formation of scar tissue (adhesions, fibrosis) within the pelvis and other parts of the body.² Several lesion types have been described:

- Superficial peritoneal endometriosis: endometrial tissue attachment to the peritoneum. This is the most common type of endometriosis
- Endometriomas: dark, fluid-filled cysts, also known as chocolate cysts
- Deeply infiltrating endometriosis: endometrial tissue invasion of organs either within or outside the pelvic cavity
- Abdominal wall endometriosis: endometrial tissue growth on the abdominal wall

Establishment and growth of such endometriotic tissue is oestrogen-dependent, thus the condition is predominantly found in women in their reproductive years and usually regresses after menopause, although a small proportion of women (~2–5%) experience post-menopausal endometriosis.¹⁵

Whilst several classification systems exist, to date, there is no gold standard for the classification of endometriosis.¹⁶ The revised American Society for Reproductive Medicine (rASRM) classification is the most widely used, and divides endometriosis severity into 4 stages: stage I (mild) to IV (severe) according to the size of the endometriotic lesions in the ovaries, peritoneum, and fallopian tubes, and the severity of adhesion at each of the sites. The staging system is useful for physicians and surgeons to explain the severity of endometriosis in simple terms to the patients, however severity of pain is not correlated with the rASRM stage.¹⁶

Endometriosis can cause severe pain in the pelvis and infertility.² Patients experience a variety of symptoms including dysmenorrhoea (painful menstrual periods), dyspareunia (painful intercourse), chronic non-menstrual pelvic pain (NMPP), painful urination and dyschezia (painful or difficult bowel movements).^{17,18}

Symptoms of endometriosis can have a significant impact on the woman's QoL, her physical and psychosocial functioning, including social life, absenteeism from school or work, intimacy and intimate partnerships, as well as mental health and emotional wellbeing.³

The exact cause of endometriosis is unknown. Reflux of endometrial tissue fragments/cells and protein rich fluid through the fallopian tubes into the pelvis during

menstruation is considered the most likely explanation for formation of endometriotic lesions within the peritoneal cavity, although this mechanism is not sufficient as nearly all women experience retrograde menstruation.⁷ Additional postulated origins include metaplasia and lymphatic and vascular metastasis.⁷ It remains unclear how endometriosis causes pain; suggested mechanisms include stimulation of neural pathways and inflammation.⁷

There is no known way to prevent endometriosis, and there is no guaranteed cure.⁶ Current treatments involve a mixture of medical and surgical interventions, with substantial limitations (Section B.1.3.4).

B.1.3.1.2 Epidemiology

Globally, endometriosis is estimated to affect approximately 10% of women of reproductive age.^{1,2} The number of affected women may be even higher, with a recent survey estimating that 25% will have endometriosis in their lifetime.¹⁹ Most commonly, endometriosis is diagnosed in women between the ages of 25 and 45 years old, and the average age at diagnosis is 28 years old.²⁰

A serious clinical consequence of endometriosis includes infertility; the prevalence of endometriosis among women with infertility is estimated at 50%.²¹

Data from The Health Improvement Network have been used to estimate the incidence of endometriosis reported by primary care physicians in the UK. The incidence of endometriosis was found to be 1.02 per 1000 person-years, which increased to 1.46 per 1000 person-years after case validation. The incidence of endometriosis increased with age, peaking in the 30–34 years age group. Prevalence was estimated as 2%, with the highest prevalence (3.32%) in women aged 40–44 years.²²

B.1.3.2 Burden of endometriosis

B.1.3.2.1 Clinical burden

The main clinical consequences of endometriosis are chronic pelvic pain (cyclical and non-cyclical), dysmenorrhoea (painful menstruation) and impaired fertility.

Dyspareunia (painful intercourse) may affect 30%–50% of patients and, together with infertility, has a tremendous impact on sexual life and reproductive plans.²⁰ In

addition to dysmenorrhoea, patients may experience a range of painful cyclical symptoms including dyschezia (painful or difficult defecation), dysuria (painful urination) and shoulder pain, as well as intestinal complaints; haematuria (presence of blood in the urine) and rectal bleeding.²³

Symptom severity can range from mild to debilitating. Some patients have no symptoms, others have episodic pelvic pain, and still others experience constant pain in multiple body regions. In a European market research survey,¹⁹ it was estimated that over 50% of women with endometriosis in the UK experience moderate to severe symptoms. Some progress from episodic and localised pain to that which is chronic, complex, and more challenging to treat.⁷ It should be noted that patients with a disease that is anatomically “severe” can have minimal symptoms, and patients with “minimal” evidence of endometriosis can have severe, life-affecting symptoms.⁷

Endometriosis is a multisystem condition, and although pelvic pain is the most common symptom of possible endometriosis, patients with endometriosis also have a high risk of co-occurring or evolving multisite pain such as fibromyalgia and migraines.⁷ Patients with endometriosis have a greater risk of presenting with other non-malignant gynaecologic diseases, including uterine fibroids and adenomyosis.⁷ They are also at greater risk of a subsequent diagnosis of malignancies, autoimmune diseases, early natural menopause, ovarian cysts, bowel conditions and cerebrovascular and cardiovascular conditions.^{6,7}

While women without endometriosis have a 10%–20% chance of getting pregnant each month, this is reduced to only a 1%–10% chance for patients with endometriosis.²⁴ Incidence of infertility and the time to conceive have been reported to increase with the stage of disease: reported as 53% and 3.4 years for those with stage 1 (minimal) endometriosis, increasing to 96% and 6.1 years for those with stage 4 (severe) endometriosis, respectively.²⁵

Delays in diagnosis and the ongoing management of this chronic condition place an additional burden on patients with endometriosis. The route to an accurate diagnosis of endometriosis is often circuitous and lengthy. A delay in diagnosis is a significant issue as it can lead to prolonged suffering, ill health and risks to fertility. A study by

Endometriosis UK that used data from 4,371 UK participants reported that, in 2023, time to diagnosis was nearly 9 years and had increased from 2020 when the delay was 8 years.⁴ Reasons for delayed diagnosis included the length of waiting lists and clinicians' lack of awareness and training on endometriosis.⁴ The severity of symptoms experienced prior to diagnosis was reflected in patients's attempts to seek treatment: almost half of all respondents (47%) had visited their general practitioner (GP) 10 or more times, while 52% had visited an accident and emergency department at least once.⁴

Patients with endometriosis often require multiple invasive surgeries. In the UK, 75% of women with endometriosis will undergo at least one surgery, and over 60% will have multiple surgical procedures.^{19,26} In addition, waiting times for surgery can be lengthy: the average time to waiting time for surgery in the UK is estimated to be 19 months.¹⁹

B.1.3.2.2 Patient burden

In addition to endometriosis-specific symptoms, broader effects include depression, feelings of isolation, fatigue and lack of energy, along with an adverse impact on physical, mental and social wellbeing.²⁷ Endometriosis may have a significant, sometimes devastating impact on all aspects of life, including education, career, relationships, sexual relationships, fertility and QoL.⁴

In a questionnaire-based study (World Endometriosis Research Foundation [WERF] EndoCost study) with more than 900 respondents, 56% reported problems with pain/discomfort, 29% reported problems with usual activities, 29% reported being unable to work due to endometriosis, 16% of women reported (some or major) problems with mobility and 3% reported problems with self-care.²⁸ Similarly, in a US study where 40 women with moderate-to-severe endometriosis were interviewed, participants reported significant impacts of their symptoms on daily activities and work or school commitments, as well as social interactions, sleep and emotional well-being:²⁹ 95% of women described that endometriosis symptoms made it difficult to exercise or complete leisure activities; 92.5% were unable to attend social events or had cancelled pre-existing plans due to endometriosis symptoms; >80% described impairments in sleep; 80% felt they could not cope with signs/symptoms of

endometriosis; and more than half of women (55.0%) highlighted that endometriosis symptoms had caused them to miss work or school.

Many women with endometriosis experience depression, the prevalence of which positively correlates with the beginning of dyspareunia and severity of pain.²⁵ In the WERF EndoCost study 36% of women reported problems with anxiety/depression, and respondents to the UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) survey also widely reported being diagnosed with depression (44%) and anxiety (49%).⁶

Endometriosis impairs work productivity. Women with endometriosis lose an average of 10.8 hours of work weekly, and loss of work productivity was associated with pelvic pain and disease severity.³⁰

Endometriosis has a negative effect on health-related quality of life (HRQoL). The burden of endometriosis is predominantly captured using the generic 36-Item Short Form Survey (SF-36) and disease-specific Endometriosis Health Profile-30 (EHP-30) in addition to the EuroQol 5D (EQ-5D) and Endometriosis Health Profile-5.²⁷ Routine assessment of HRQoL in women with endometriosis is essential for informing treatment decisions and assessing outcomes following treatment.⁶ In the UK additional tools may be used in clinical practice, including the British Society for Gynaecological Endoscopy (BSGE) pelvic pain questionnaire and simple numerical rating /visual analogue scales.⁹

In the WERF Endocost study, endometriosis-associated symptoms generated an average of 0.809 quality-adjusted life-years (QALYs) per woman annually, representing a QoL reduction of 19% compared with a person with the best possible health state.²⁸ In a further large study (the Global Study of Women's Health),³⁰ the effect of endometriosis on physical (but not mental) HRQoL of women was substantial, with SF-36v2 physical component summary (PCS) scores similar to those reported in women with cancer. The effect was less if women were employed and free of pelvic pain, and worse with severe pelvic pain and advanced disease. PCS scores were significantly reduced in those with moderate/severe compared with minimal/mild disease.

B.1.3.2.3 Economic and societal burden

The economic impact of endometriosis is substantial. As well as indirect costs encompassing reduced work performance and lost productivity, the condition incurs direct costs which include healthcare expenditures for diagnosis and endometriosis treatment (i.e. expenses associated with consultations, surgeries and hormonal therapies). Taken together, these costs contribute to the overall financial strain on healthcare systems, and its direct and indirect healthcare costs are comparable to those for other chronic conditions such as type 2 diabetes, rheumatoid arthritis and Crohn's disease.⁵

There are approximately 1.5 million women in the UK with endometriosis, of which 75% will undergo at least one surgery.^{1,19} Endometriosis is estimated to cost the UK economy around £8.2 billion every year in healthcare costs, loss of work and treatment.⁴

In the WERF EndoCost study, average total annual costs amounted to €9,579 per woman (95% CI: €8,559–€10,599), equating to €12,064 when inflated to the year 2022.^{28,31} Total costs were dominated by indirect costs of productivity loss (66% of total costs). Direct costs were made up of healthcare costs (95% of direct costs) and non-healthcare costs (5% of direct costs). The most important healthcare cost components were surgery (29% of healthcare costs), monitoring tests (19%), hospitalisation (18%) and physician visits (16%). Medication accounted for 10% of healthcare costs.²⁸

The economic burden of endometriosis escalates with increasing disease severity. As the frequency of hospitalisations and complexity of surgeries relate to the severity of the condition, the greater the disease severity, the greater the economic burden. Costs are greater with increasing severity of endometriosis, presence of pelvic pain, presence of infertility and a higher number of years since diagnosis.²⁸

B.1.3.3 Current treatment pathway

The principal objective in treating endometriosis is symptom-relief management. Treatment options for patients with EAP are diverse and consist of analgesic therapies, hormonal therapies, conservative or minimally invasive surgery, or a combination of these (Section B.1.3.4; B.1.3.5).¹⁷

Endometriosis-associated symptoms progress and recede over the life course, and EAP affects women in different ways during their lives. As such, a personalised, interdisciplinary treatment approach is required. Treatment decisions are made in consultation with the patient and depend on patient preference, the current impact of their endometriosis-related symptoms on their QoL, and priorities concerning family planning.⁹ For example, clinical experts stated that women who wish to conceive immediately would be prioritised for surgical treatment, while those not currently planning a family may try hormonal therapies to manage their symptoms before considering surgery.⁹

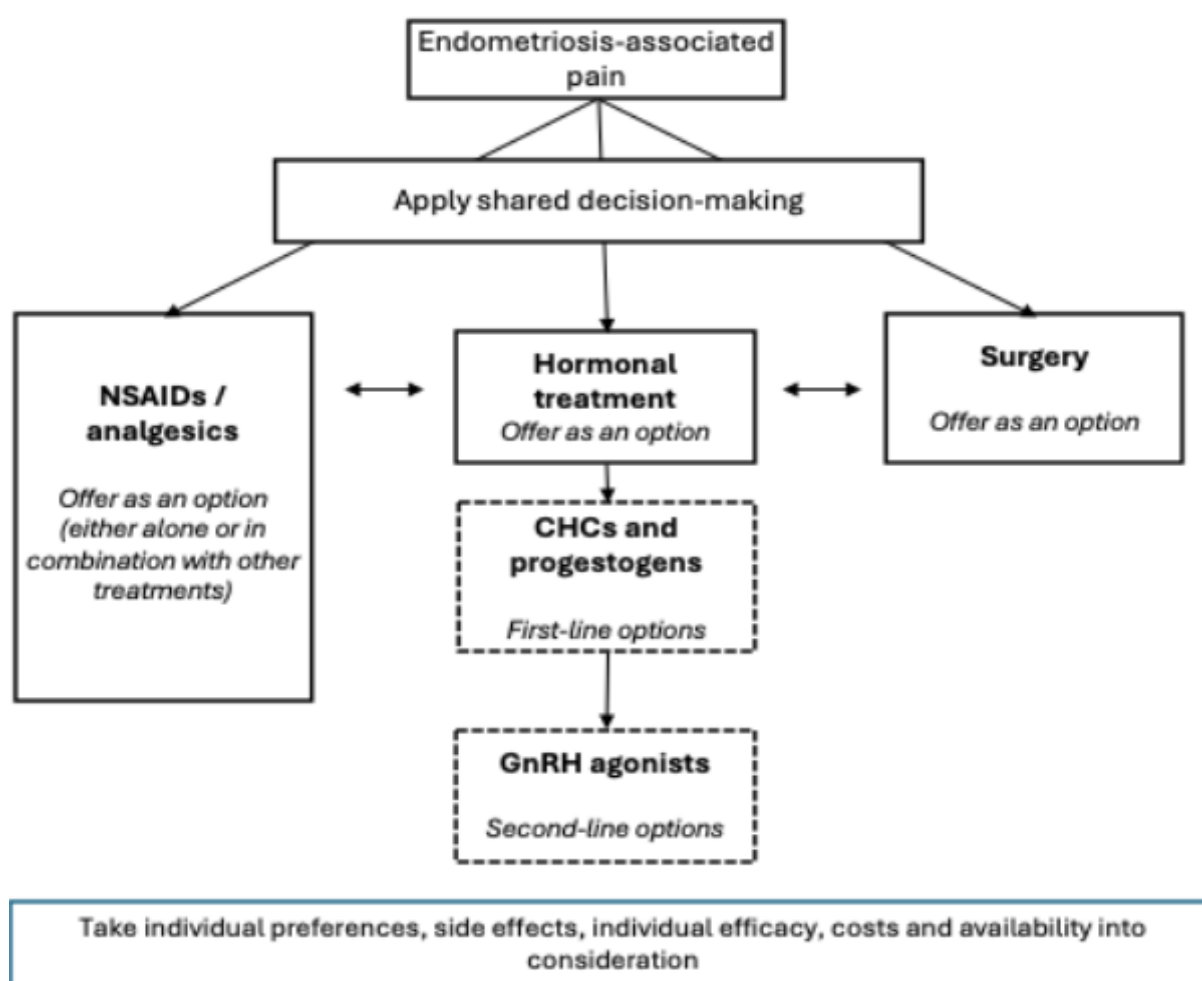
Severe endometriosis should be treated in specialist centres accredited by the BSGE, of which there are 79 in England and Wales.^{32–35} The requirements to be an Accredited Endometriosis Centre are:

- A dedicated consultant-led endometriosis service within a specialist outpatient clinic
- Sufficient workload to maintain surgical skills for the most complex cases
- A named colorectal surgeon and other supporting clinicians, including urologists and pain management specialists, (to provide broader specialist support as needed) and an endometriosis specialist nurse
- Annual submission of an exemplar video of surgery for laparoscopic excision of severe recto-vaginal endometriosis that required dissection of the pararectal space.

B.1.3.4 Treatment options for management of EAP

An overview of the current treatment pathway for EAP, based on guidelines from NICE and the European Society of Human Reproduction and Embryology (ESHRE^{36,37}), and verified by UK clinical experts, is shown in Figure 2.

Figure 2: Treatment pathway for endometriosis and EAP in the UK



Abbreviations: CHC: combined hormonal contraceptives, EAP, endometriosis-associated pain, GnRH: gonadotropin-releasing hormone, NSAID: non-steroid anti-inflammatory drug.

B.1.3.4.1 Analgesics

Both NICE and the ESHRE guidance recommend analgesics for the initial management of EAP. However, there is scarce evidence to support the use of simple analgesics, such as paracetamol and NSAIDs, for this.³⁷

Neuromodulators (e.g. anti-depressants, selective serotonin reuptake inhibitors or anticonvulsants), may also be used to manage pain, however, they have not been shown to be superior to placebo and are associated with dose-limiting side effects.⁶

UK experts advise that the experience of pain is very patient-dependent. For patients with well-managed endometriosis, regular analgesia should not be required but may

be used as necessary mid-cycle and/or during menstruation. It is unusual for patients to require neuromodulators, with <5% of patients prescribed such treatments.⁹

B.1.3.4.2 Hormonal therapies

Hormone therapy can be offered both pre- and post-surgery and often prior to confirmation by laparoscopy where endometriosis is suspected. In the NCEPOD study, 60.5% of patients received hormonal therapy in secondary care, most commonly levonorgestrel-releasing intrauterine systems (40.6%), combined oral contraceptives (COCs); 31.8%), GnRH agonists (30.8%) or oral progestogen (30.5%). In women not receiving hormonal treatments, the most common recorded reason was that they were trying to conceive (40.6%).⁶

First-line hormonal therapies such as COCs and progestins can be effective for the treatment of EAP.³⁸ However, in the UK NCEPOD study, only 53% of respondents experienced any improvement in symptoms when their GP first prescribed medications.⁶ Over time, many patients on COCs no longer have adequate pain relief and require additional medical therapy.³⁹ Only one randomised placebo-controlled clinical trial of COCs has been published, demonstrating a statistically significant, though modest, 50% reduction in dysmenorrhoea but no beneficial effect on NMPP or dyspareunia.⁴⁰ Progestin monotherapy can be efficacious for the reduction of EAP, but is often associated with breakthrough bleeding, alterations in mood, weight gain and breast tenderness.⁴¹ In addition, progestins are not always effective, and progestin resistance occurs in 30%–50% of patients using progestin-based therapies for endometriosis.^{14,42}

GnRH agonists are reserved as second-line hormonal treatment. Although shown to relieve EAP, their use is often limited due to undesirable side effects.³⁷ For example, depot GnRH agonists – available only as intramuscular or subcutaneous injections – stimulate the receptor leading to a flare in LH and FSH which increases E2 secretion, causing a temporary worsening of endometriosis symptoms before the therapeutic effect is achieved.⁸ In practice, patients are counselled to expect the flare, and this does not affect their treatment.⁹ However, eventually, they lead to desensitisation of the GnRH receptor, reduced LH and FSH output and ultimately, suppression of ovulation and a significant reduction in serum oestrogen; thus, their use is associated with hypo-oestrogenic side effects. Short-term side effects include

menopausal symptoms such as hot flushes, vaginal dryness, loss of libido and emotional lability, and their long-term use is limited by substantial bone mineral density (BMD) reduction.⁴³

To minimise or prevent the hypo-oestrogenic side effects of GnRH agonists, ABT (oestrogen or progestin or a combination of both) is recommended in ESHRE guidelines and frequently used in practice since it prevents loss of BMD without affecting the efficacy of the GnRH agonist treatment.³⁷ Patients prescribed a short-term trial of GnRH agonist, i.e. ≤6 months, may not receive concomitant ABT; however, in those on treatment for more extended periods, i.e. >6 months, ABT is universally prescribed.⁹

GnRH agonists such as leuprorelin, goserelin and triptorelin need to be given via injection, which can be uncomfortable and can result in injection site reactions.⁴⁴ Injectable GnRH agonists also need to be given under the supervision of a HCP, increasing the burden on healthcare systems and placing a time burden on patients.⁴⁴ Other GnRH agonists are administered via a nasal spray, risking inconsistent absorption, inaccurate dosing, damage to nasal mucosa and local irritation, however their use is minimal in the UK.⁴⁵ In addition, reversibility of GnRH agonist treatment is unpredictable, and it can take months for ovarian function to return to normal.⁴⁶ The following GnRH agonists are indicated for the treatment of endometriosis: goserelin (depot injection), leuprorelin (depot injection), nafarelin (nasal spray), buserelin (nasal spray), and triptorelin (depot injection). Although treatment duration may be extended in clinical practice with concomitant ABT, it should be noted that all available preparations have a licensed maximum treatment duration of 6 months, after which symptoms may return, requiring further alternative treatment.^{47–49}

GnRH antagonists are recommended in the ESHRE guideline as second-line therapies (for example, if hormonal contraceptives or progestogens have been ineffective) due to their side-effect profile. They are effective in relieving EAP and benefit from oral administration.³⁷ No specific GnRH antagonist is recommended over another in relieving EAP.³⁷

Relugolix in a fixed dose combination with ABT (relugolix combination therapy [relugolix-oestradiol-norethisterone acetate] [relugolix CT]) is a GnRH antagonist indicated for the symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis, and is also currently undergoing assessment by NICE.^{50,51}

Aromatase inhibitors (AIs) are reserved for women with EAP refractory to other medical or surgical treatment, and may be prescribed in combination with other hormone treatments.³⁷ In practice, the proportion of patients prescribed AIs is negligible compared with the overall population undergoing medical treatment.⁹

B.1.3.4.3 Surgical treatment

Surgery is recommended as a treatment option to reduce EAP.^{34,37}

Laparoscopic elimination of endometriosis via excision (most common), ablation/vapourisation or diathermy is central to treatment. Laparoscopic excision and/or ablation of endometrial tissue accounts for 50% of first surgical procedures, and over 60% of women diagnosed with endometriosis undergo multiple surgical procedures.^{19,26,52} Where management of endometriosis-associated symptoms has not been successful, more invasive methods may be indicated, involving either partial or complete removal of the uterus. Hysterectomy (with or without oophorectomy) with removal of all visible endometriosis lesions should be reserved for women who no longer wish to conceive and either have coexisting adenomyosis or have not responded to more conservative management.^{7,34}

Surgical treatment during laparoscopy is not always successful; a recent Cochrane review considered that it was uncertain whether laparoscopic surgery reduced overall pain associated with endometriosis.⁵³ Following surgical treatments, the reported recurrence rate of painful symptoms attributed to endometriosis is high, estimated as 21.5% at two years and 40–50% at 5 years.⁷ Surgical treatments are invasive and carry risks of long-term complications. Specifically for deep infiltrating endometriosis, surgery can cause serious lifetime complications including abdominal abscess, rectovaginal or urinary fistulas, intestinal obstruction, or stenosis, all of which can negatively influence patients' QoL.⁵⁴ While hysterectomy can provide symptomatic relief in patients with endometriosis, it can result in a range of short-

and long-term complications ranging from blood clots and infections to urinary incontinence and early menopause. Nearly 4% of patients undergoing hysterectomy for endometriosis are likely to experience major morbidity.⁵⁵ In addition, there is a complete loss of fertility, a severe limitation in pre-menopausal women who wish to preserve fertility.

B.1.3.5 Current treatment guidelines

Clinical guidelines from NICE (NG73³⁴ [Figure 3 and Figure 4] and QS172³⁵) and ESHRE³⁷ are generally aligned on the diagnosis and management of endometriosis. Both recommend clinical examination and imaging as initial investigations for symptomatic women, although NICE recommends against using pelvic magnetic resonance imaging (MRI) as the primary investigation for diagnosis.³⁴ NICE recommends that diagnostic laparoscopy be considered if clinical suspicion remains, even if initial investigations appear normal, although ESHRE acknowledges that the invasiveness of the procedure should be considered and initial hormonal treatment (e.g. COCs or progestogens) may be preferred.^{34,37} However, treatment choices must consider whether fertility is a current or upcoming priority.

Some initial treatment (e.g. excision or ablation) may be given during a diagnostic laparoscopy if appropriate.³⁴ A short trial (e.g. 3 months) of analgesics such as paracetamol and/or an NSAID should be considered for the first-line management of EAP. However, other forms of pain management and referral for further assessment should be considered where these simple analgesics do not provide adequate pain relief.³⁴ Women not currently planning a pregnancy may opt for a COC initially, although NICE recommends referral to a gynaecology service if initial hormonal treatment is not effective, not tolerated or is contraindicated.³⁵ Hormonal treatment may also be used after laparoscopic surgery to further manage symptoms. Patients with suspected or confirmed deep endometriosis involving the bowel, bladder or ureter should be referred to a specialist endometriosis service (Section B.1.3.3).³⁵ Three months of GnRH agonist treatment should be considered before surgery as an adjunct to surgery for deep endometriosis involving the bowel, bladder or ureter. Ultimately, a hysterectomy (with or without oophorectomy) may be indicated, although the benefits and risks of this surgery need to be considered, taking into account the loss of fertility, possible need for further surgery if endometriosis recurs,

and the benefits and risks of hormone replacement therapy after hysterectomy with oophorectomy.³⁴

GnRH agonists and antagonists are recommended as second-line treatment options in the ESHRE guidelines, but are not currently included in the NICE guidelines (GnRH agonists are included in the NICE guidelines as adjunct to surgery only).^{34,37} NICE does not make a recommendation about AIs; however, due to the severe side effects (vaginal dryness, hot flushes, diminished BMD), the ESHRE guidelines recommend AIs are reserved for women with EAP refractory to other medical or surgical treatment.

Figure 3: NICE NG73 algorithm for diagnosing and managing endometriosis (page 1)³⁴

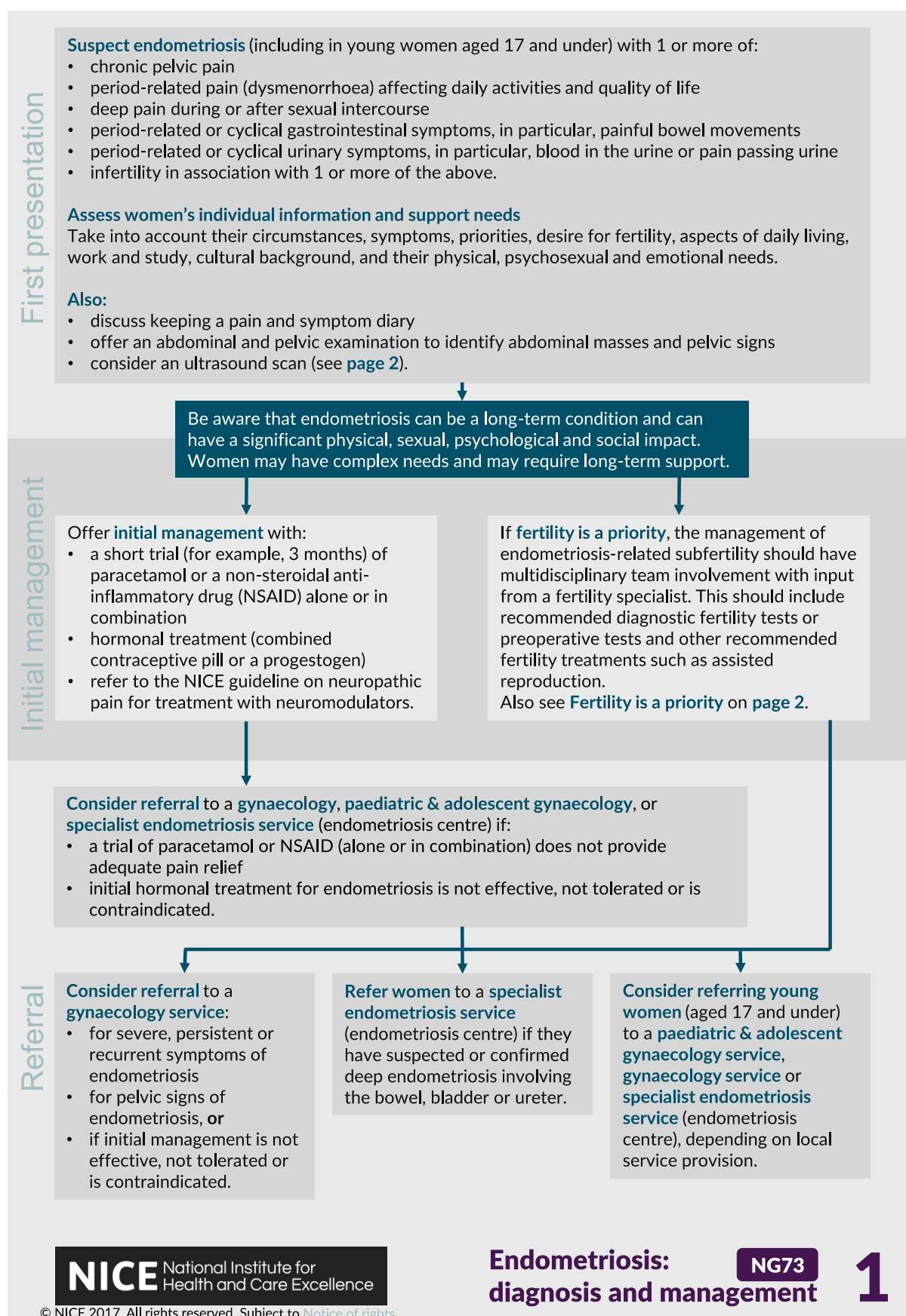


Figure 4: NICE NG73 algorithm for diagnosing and managing endometriosis (page 2)³⁴



B.1.3.5.1 Unmet need

Endometriosis is a chronic condition with no cure. There is a significant and growing unmet need with regard to timely diagnosis, as well as a need for improvement in ongoing holistic care.⁶ Despite available treatment modalities, there is still a major need for better options for the treatment of endometriosis: approximately 30% of women with endometriosis develop chronic pelvic pain that is unresponsive to conventional treatments, including surgery.⁷

In patients not responding to conventional treatments, effective pharmacological therapies are required to reduce pain and improve QoL. GnRH agonists are effective at treating endometriosis symptoms but have numerous limitations, including a delayed therapeutic impact because of the flare-up effect, suppression of E2 to less than 20 pg/mL, and unpredictable reversibility of treatment when injectable depot forms of GnRH agonists are used.⁸

In addition, currently available GnRH agonists are mostly administered by intramuscular or subcutaneous injections (every 1 to 3 months) that require HCP administration. The administration of GnRH agonists can be offered as an enhanced service in primary care; practices that provide this service are paid according to a locally agreed-upon price.⁵⁶ The use of an orally administered GnRH antagonist would negate the need for HCP administration, vastly reducing the treatment burden for HCPs and patients, and would remove the potential for injection-site reactions.

Availability of additional effective and well-tolerated hormonal therapies would:

- 1) provide symptomatic relief whilst patients are waiting for surgery
- 2) help reduce the risk of symptom recurrence post-surgery, and
- 3) delay or prevent surgery in patients preferring medical therapy.¹⁹

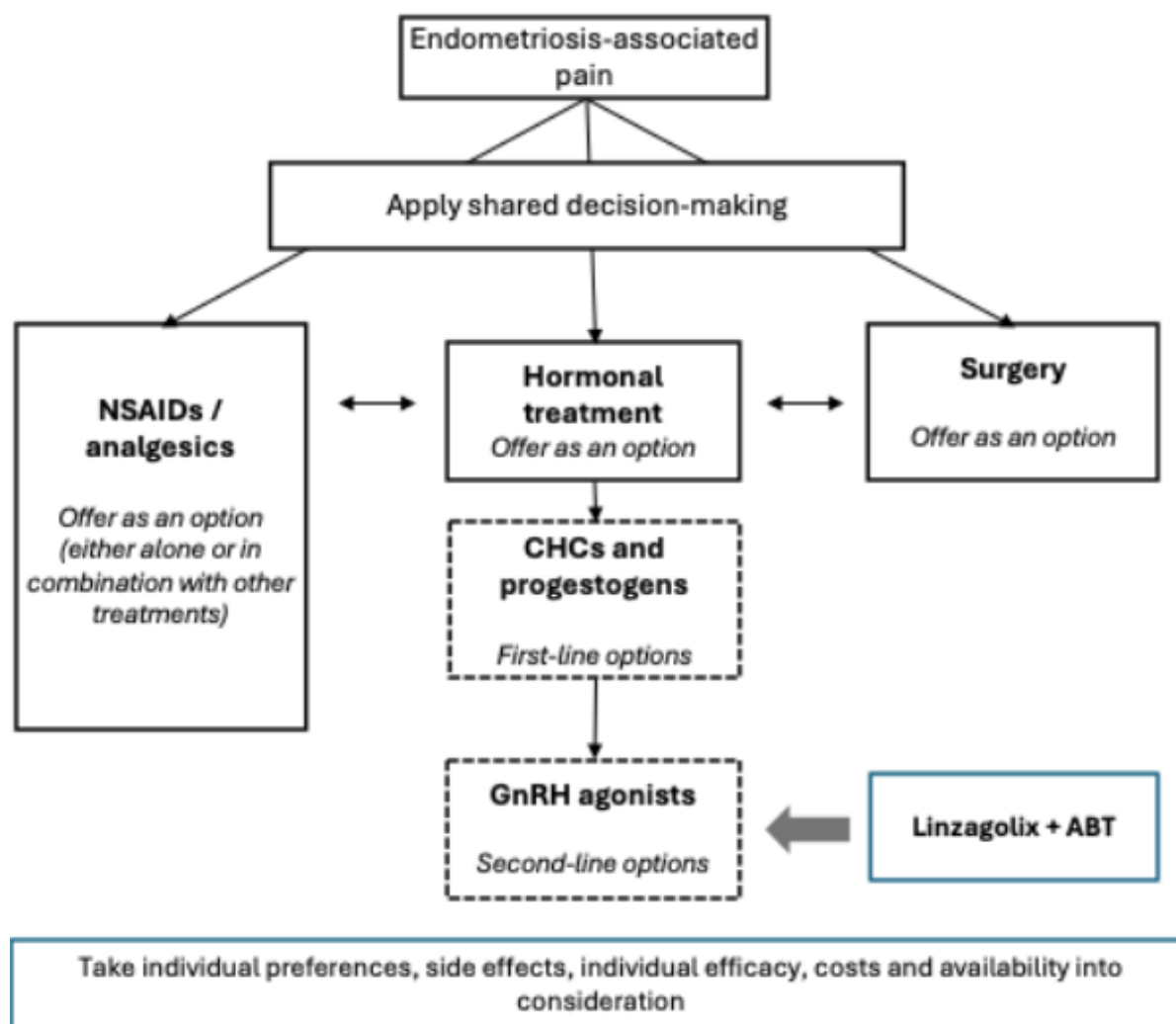
B.1.3.5.2 Proposed place of linzagolix in the current treatment pathway

GnRH antagonists, including linzagolix, are an effective new treatment option for symptoms of endometriosis that result in immediate suppression of FSH and LH secretion, with no flare-up, rapid reversibility and recovery of hormone secretion after stopping treatment. GnRH antagonists may be administered orally at home without physician supervision:⁸

Based on clinical expert opinion in the UK, and in line with European clinical guidelines, GnRH antagonists (including linzagolix) will be used as second-line hormonal treatment options, as an alternative to GnRH agonists (Figure 5). Due to the convenience of oral administration, clinicians may initiate treatment earlier than they otherwise would with GnRH agonists.^{9,37}

Clinical experts stated that, based on the administration and adverse effect profiles, GnRH antagonists may be considered preferentially over GnRH agonists in the treatment pathway.^{9,37} Unlike linzagolix, relugolix is a fixed dose combination tablet, which, whilst convenient, does not allow for choice of the ABT, if required for management of menopausal symptoms.⁹

Figure 5: Proposed place of linzagolix in treatment pathway for EAP in the UK



Abbreviations: ABT: add-back therapy, CHC: combined hormonal contraceptive, EAP, endometriosis-associated pain; GnRH: gonadotropin-releasing hormone, NSAID: non-steroid anti-inflammatory drug.

B.1.4 Equality considerations

Although linzagolix 200 mg plus ABT is expected to be indicated for the symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis, this should not prevent the use of linzagolix by people with endometriosis who do not identify as a woman.

B.2 Clinical effectiveness

SUMMARY

- Results from the Phase 3 EDELWEISS 3 study (N=484) and its extension study EDELWEISS 6 (N=353 for the treatment extension analysis set / 356 in the extension safety analysis set) demonstrated the efficacy and safety of linzagolix 200 mg plus ABT for the treatment of moderate-to-severe EAP in women of reproductive age
- The daily dose of linzagolix 200 mg plus ABT met the primary endpoint of EDELWEISS 3, demonstrating clinically meaningful and statistically significant reductions in dysmenorrhoea ($p<0.001$) and NMPP ($p=0.007$) at month 3 versus placebo, with stable or reduced use of analgesics. Significant reductions versus placebo were also observed at month 6
- This was accompanied by statistically significant improvements at month 6 in the ranked secondary endpoints of dyschezia ($p=0.012$), overall pelvic pain (OPP) ($p<0.001$) and ability to participate in daily activities (based on the EHP-30 pain dimension; $p<0.001$) for linzagolix 200 mg plus ABT versus placebo
- The clinically meaningful improvements observed at month 6 (end of EDELWEISS 3 treatment period) generally improved further at month 12 in the EDELWEISS 6 extension study
- Reductions in EAP resulted in a reduced intention for surgery after 6 months in EDELWEISS 3 based on both the Physician Surgery Intention Question (PSIQ) and Subject Surgery Intention (SSIQ) in patients who received linzagolix versus placebo; the reduction from baseline to month 6 on the PSIQ became more pronounced at month 12 in EDELWEISS 6
- Reductions in EAP were also accompanied by improved HRQoL as shown by improved scores for the EHP-30 and EuroQoL 5-Dimension 5-Level (EQ-5D-5L) Index and visual analogue scale (VAS)
- An indirect treatment comparison (ITC) showed that there is no significant difference between linzagolix and leuporelin in terms of efficacy and safety
- The safety profile for linzagolix for women with EAP was consistent with that observed previously for women with uterine fibroids
- Linzagolix showed good overall tolerability, with treatment-emergent adverse events (TEAEs) being similar to placebo; the incidence of severe TEAEs was low and comparable between groups, and no fatal or suicide-related TEAEs were reported
- The most common TEAEs with linzagolix 200 mg plus ABT were headaches (10.5% at month 6 in EDELWEISS 3), hot flushes (6.8%), and fatigue (6.8%)
- Serum E2 levels were maintained within a therapeutic range (20–60 pg/mL) throughout the treatment period in patients receiving linzagolix
- BMD was largely unaffected by linzagolix treatment at month 6 (EDELWEISS 3) and month 12 (EDELWEISS 6), with most patients having either an increase, no change, or $\leq 3\%$ decrease in BMD at months 6 and 12 in the lumbar spine, femoral neck and total hip. Some BMD increases were noted at 6 months after the end of treatment (EDELWEISS 6, month 6 extension follow-up), indicating partial recovery
- Menses resumed within a median time of approximately one month after the end of treatment in EDELWEISS 3 and EDELWEISS 6

B.2.1 Identification and selection of relevant trials

A systematic literature review (SLR) was conducted to identify clinical evidence regarding the safety and efficacy of linzagolix 200 mg (the intervention) and other therapies (comparators) for the treatment of endometriosis. Searches for the clinical SLR were conducted in September 2024. Following assessment for eligibility using the population, intervention, comparison, outcomes and study design (PICOS) criteria, four records for two trials were identified for the intervention (the phase 2b dose-ranging EDELWEISS trial⁵⁷ [which included a dose of linzagolix 200 mg alone (without ABT) for 12 weeks] and the phase 3 EDELWEISS 3 trial^{58–60} [linzagolix 200 mg plus ABT or linzagolix 75 mg versus placebo for up to 24 weeks]) and 18 records for 20 trials were identified for comparators. Full details of the SLR methodology, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram and included and excluded studies of the SLR are provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified one phase 3 study (EDELWEISS 3^{58,59}) (Table 3) that provides evidence of the efficacy and safety of linzagolix 200mg plus ABT for treating women of reproductive age with moderate to severe EAP. Data are also included from the EDELWEISS 3 extension study (EDELWEISS 6^{61,62}); data from EDELWEISS 3 and EDELWEISS 6 were reported in the Summary of Product Characteristics (SmPC) submitted to the European Medicines Agency.¹³ However, the data from EDELWEISS 6 are not yet published. Although the EDELWEISS 3 and EDELWEISS 6 trials evaluated both linzagolix 200 mg plus ABT and linzagolix 75 mg versus placebo, the linzagolix 200 mg plus ABT dose met the co-primary efficacy endpoints and is the dose for symptomatic treatment of endometriosis stated in the SmPC. This submission, therefore, focuses on the evidence for linzagolix 200 mg plus ABT in women with EAP requiring symptomatic treatment.

Adverse event data from another phase 3 study, EDELWEISS 2, were also included in the SmPC and are presented in this submission. The EDELWEISS 2 trial (NCT03986944; 18-OBE2109-002) and its extension (EDELWEISS 5; NCT04372121; 19-OBE2109-005) were planned (to take place in the US and Canada) as replicate pivotal trials to EDELWEISS 3 and 6, but were discontinued

early due to challenges in patient screening and recruitment affected by the coronavirus disease 2019 (COVID-19) pandemic; no efficacy analyses were therefore performed for these studies due to insufficient numbers of randomised patients.^{46,63,64}

Table 3: Clinical effectiveness evidence

Study	EDELWEISS 3	EDELWEISS 6
Study design	Randomised, double-blind, placebo-controlled, multicentre phase 3 trial (NCT03992846)	Extension study of patients who completed the 6-month treatment period of EDELWEISS 3 (NCT04335591)
Study geography	91 centres across Europe (65 centres [Austria (5), Bulgaria (8), Czech Republic (5), France (6), Hungary (6), Poland (12), Romania (6), Spain (6), Ukraine (11)]) and the US (26 centres) There were no UK trial centres.	45 centres across Europe (36 centres [Austria (1), Bulgaria (4), Czech Republic (2), Poland (11), Romania (6), Spain (1), Ukraine (11)]) and the US (9 centres) There were no UK trial centres.
Population	Women of reproductive age with moderate to severe EAP	Women of reproductive age with moderate to severe EAP who completed the 6-month treatment period of EDELWEISS 3
Intervention(s)	Once daily linzagolix 75 mg (plus ABT placebo) Once daily linzagolix 200 mg plus ABT	Once daily linzagolix 75 mg (plus ABT placebo) Once daily linzagolix 200 mg plus ABT (Patients who received placebo in EDELWEISS 3 were randomised to linzagolix 75 mg [plus ABT placebo] or linzagolix 200 mg plus ABT. Patients who received active treatment in EDELWEISS 3 continued with the same treatment).
Comparator(s)	Placebo	None
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes

Study	EDELWEISS 3	EDELWEISS 6
Rationale if study not used in model	N/A	N/A
Reported outcomes specified in the decision problem	• Pain • Opioid use • Analgesic use • Adverse effects of treatment (only grade 3/4 TEAEs) • Health-related quality of life	• Pain • Opioid use • Analgesic use • Adverse effects of treatment • Health-related quality of life
All other reported outcomes	• Dyschezia • Intention for surgery • Number of days in hospital • Time to post-treatment menses	• Dyschezia • Intention for surgery • Number of days in hospital • Time to post-treatment menses
Key publications/data sources	Donnez et al 2024 ⁵⁸ EDELWEISS 3 CSR (data on file) ⁵⁹	Dolmans et al 2024 ⁶² EDELWEISS 6 CSR (data on file) ⁶¹

Abbreviations: ABT, add-back therapy; CSR, clinical study report; EAP, endometriosis-associated pain; TEAE, treatment-emergent adverse event

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

B.2.3.1 Phase 3 trial design

B.2.3.1.1 EDELWEISS 3

EDELWEISS 3 (NCT03992846; 18-OBE2109-003) was a randomised, double-blind, placebo-controlled, multicentre phase 3 trial of linzagolix in women of reproductive age with moderate to severe EAP⁵⁸ (Figure 6; Table 4). The trial was conducted in 91 centres (65 in Europe and 26 in the US) and comprised a 3-month screening period, a 6-month treatment period and a 6-month drug-free follow-up period, although patients who completed the 6-month treatment period were invited to enter the EDELWEISS 6 extension study (Section B.2.3.1.2) for a further 6 months of treatment before entering the 6-month off-treatment follow-up period.^{58,59}

The trial included women of reproductive age with surgically confirmed pelvic endometriosis in the past 10 years. Prior to screening, patients had to exhibit moderate-to-severe EAP, defined as scores of ≥ 2 for both dysmenorrhoea and NMPP over the previous month according to the modified Biberoglu and Behrman scale.⁶⁵ During the screening period, patients had to show a mean OPP score of ≥ 4 (based on a numeric rating scale [NRS] of 0–10) for 5 days over two full menstrual cycles, and ≥ 2 days of moderate-to-severe pelvic pain (based on a verbal rating

scale [VRS] of 0–3) on bleeding and non-bleeding days. All participants of childbearing potential were required to use one of the specified birth control methods during the entire study treatment period and for 3 months after the end of treatment.^{58,59}

The main exclusion criteria were liver enzyme anomalies, osteoporosis or other metabolic bone disease, and the use of certain medications (e.g. combined oral contraceptives, GnRH agonists or systemic glucocorticoids) within a specified wash-out period.

Patients were randomised 1:1:1 to receive placebo, linzagolix 75 mg alone or linzagolix 200 mg plus ABT for a period of 6 months, followed by a 6-month off-treatment follow-up (or entry into the EDELWEISS 6 extension study followed by a 6-month off-treatment follow up [Section B.2.3.1.2]).

The co-primary efficacy endpoints were a clinically meaningful reduction from baseline of dysmenorrhoea (reduction of ≥ 1.10 points on the VRS) and NMPP (reduction of ≥ 0.8 points on the VRS) to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP. Ranked secondary endpoints were changes from baseline to month 6 in dysmenorrhoea, NMPP, dyschezia, overall pelvic pain, interference of pain with the ability to perform daily activities (using the EHP-30 pain dimension) and dyspareunia, and no analgesic / no opiate use for EAP during the preceding 4-week period at month 6.

Other secondary endpoints included analgesic and opioid use for EAP, number of days in hospital, PSIQ/SSIQ and HRQoL.

Safety analyses included incidence and severity of TEAEs, changes in laboratory data, change from baseline in BMD at the lumbar spine, femoral neck and total hip, time to post-treatment menses, and pathological alterations in the endometrium.

B.2.3.1.2 EDELWEISS 6

Patients who completed the 6-month treatment period in the EDELWEISS 3 study (Section B.2.3.1.1) were invited to enter the EDELWEISS 6 extension study (NCT04335591; 19-OBE2109-006; Figure 6).^{61,62} The primary objective of

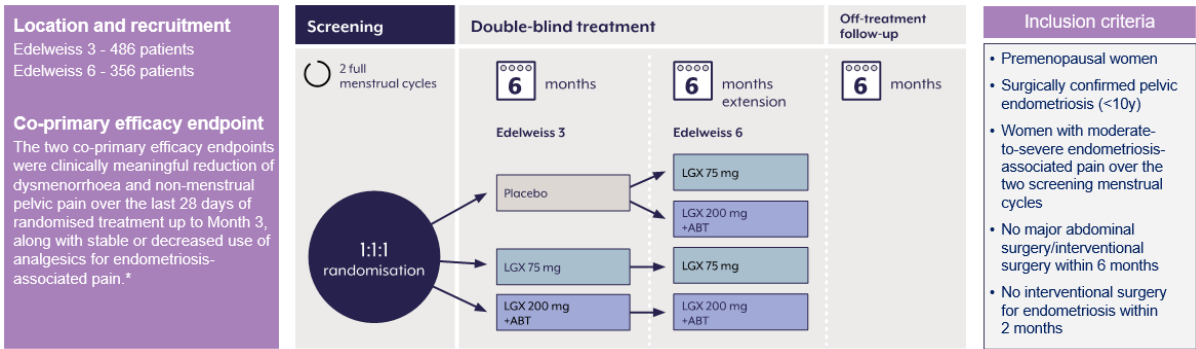
EDELWEISS 6 was to assess the maintenance of efficacy of linzagolix for up to an additional 6 months (up to 12 months of treatment in total) in women who had already completed 6 months of linzagolix treatment at a dose of 75 mg alone or 200 mg plus ABT in EDELWEISS 3.⁶¹

In EDELWEISS 6, patients who received placebo in EDELWEISS 3 were randomised 1:1 to linzagolix 75 mg or linzagolix 200 mg plus ABT. Patients who received active treatment in EDELWEISS 3 continued with the same treatment.

In line with EDELWEISS 3, the co-primary endpoints of EDELWEISS 6 were clinically meaningful reduction of dysmenorrhoea (reduction of ≥ 1.10 points on the VRS) and NMPP (reduction of ≥ 0.8 points on the VRS) from baseline to the last 28 days preceding the month 12 visit, along with stable or decreased use of analgesics for EAP.

Secondary endpoints of EDELWEISS 6 included changes from baseline to month 12 in dysmenorrhoea, NMPP, dyschezia, OPP, interference of pain with the ability to perform daily activities (using the EHP-30 pain dimension) and dyspareunia. Other secondary endpoints included analgesic and opioid use for EAP, number of days in hospital, PSIQ/SSIQ and HRQoL.

Figure 6: EDELWEISS 3 (NCT03992846) and EDELWEISS 6 (NCT04335591) trial design



Abbreviation(s): ABT, add-back therapy; LGX, linzagolix; NMPP, non-menstrual pelvic pain; VRS, verbal rating scale

ABT comprised oestradiol (E2) 1 mg/norethisterone acetate 0.5 mg

*The clinically meaningful reduction thresholds for the primary analysis of dysmenorrhoea and NMPP were based on blinded month 3 data using appropriate anchors and were defined as a reduction of ≥ 1.10 and ≥ 0.8 points from baseline on the VRS for dysmenorrhoea and NMPP, respectively, as measured using an electronic diary (eDiary)

Sources: Donnez et al 2024;⁵⁸ EDELWEISS 3 CSR (data on file);⁵⁹ Dolmans et al 2024;⁶² EDELWEISS 6 CSR (data on file)⁶¹

Table 4: EDELWEISS 3 and EDELWEISS 6 | Summary of trial methodology

Trial name/number	EDELWEISS 3 (NCT03992846)	EDELWEISS 6 (NCT04335591)
Trial design	Randomised, double-blind, placebo-controlled, multicentre phase 3 trial	Extension study of patients who completed the 6-month treatment period of the EDELWEISS 3 trial
Duration of trial	6 months treatment plus 6 months off-treatment follow up (or entry into EDELWEISS 6 at month 6)	6 months treatment plus 6 months off-treatment follow up
Settings and locations where data were collected	91 centres across Europe (65 centres [Austria (5), Bulgaria (8), Czech Republic (5), France (6), Hungary (6), Poland (12), Romania (6), Spain (6), Ukraine (11)]) and the US (26 centres)	45 centres across Europe (36 centres [Austria (1), Bulgaria (4), Czech Republic (2), Poland (11), Romania (6), Spain (1), Ukraine (11)]) and the US (9 centres)
Patient eligibility criteria	Key inclusion criteria • Women of reproductive age with surgically confirmed endometriosis in the past 10 years • Moderate to severe EAP over the month prior to screening and over two menstrual cycles during screening • Body mass index ≥ 18 kg/m² • Practice birth control if of childbearing potential	Key inclusion criteria • Patients who completed the 6-month treatment period in EDELWEISS 3
	Key exclusion criteria • Liver enzyme anomalies • Osteoporosis or other metabolic bone disease • Use of certain medications (e.g. COC, GnRH agonists or systemic glucocorticoids) within a specified wash-out period	Key exclusion criteria • Liver enzyme anomalies reaching discontinuation levels • BMD decrease of $>8\%$ from EDELWEISS 3 baseline or a Z-score ≤ 2.5 at either the femoral neck, hip or spine at EDELWEISS 3 month 6
Trial drugs	• Interventions • Once daily linzagolix 75 mg (plus ABT placebo) • Once daily linzagolix 200 mg plus ABT • Placebo	• Interventions • Once daily linzagolix 75 mg (plus ABT placebo) • Once daily linzagolix 200 mg plus ABT (Patients who received placebo in EDELWEISS 3 were randomised to linzagolix 75 mg [plus ABT placebo] or linzagolix 200 mg plus ABT. Patients who received active treatment in EDELWEISS 3 continued with the same treatment).
Concomitant medication	Permitted concomitant medication: • Analgesics provided/prescribed by the sponsor (ibuprofen and locally permitted opioids)	Permitted concomitant medication: • Analgesics provided/prescribed by the sponsor (ibuprofen and locally permitted opioids)

	- Patients received daily calcium (500–1000 mg) and vitamin D (400 IU) supplementation to prevent or minimise BMD loss Prohibited concomitant medication: - Other analgesics, prophylactic analgesics - Certain medications (e.g. COC, GnRH agonists or systemic glucocorticoids) within a specified wash-out period - Cannabinoids	- Patients received daily calcium (500–1000 mg) and vitamin D (400 IU) supplementation to prevent or minimise BMD loss Prohibited concomitant medication: - Other analgesics, prophylactic analgesics - Certain medications (e.g. COC, GnRH agonists or systemic glucocorticoids) - Cannabinoids
Primary endpoint	Co-primary efficacy endpoints: Clinically meaningful reduction of dysmenorrhoea (reduction of ≥ 1.10 points on the VRS) and NMPP (reduction of ≥ 0.8 points on the VRS) from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP.	Co-primary efficacy endpoints: Clinically meaningful reduction of dysmenorrhoea (reduction of ≥ 1.10 points on the VRS) and NMPP (reduction of ≥ 0.8 points on the VRS) from EDELWEISS 3 baseline to the last 28 days preceding the month 12 visit, along with stable or decreased use of analgesics for EAP.
Other endpoints used in the model/specified in scope	Ranked secondary endpoints: Changes from baseline to month 6 in dysmenorrhoea, NMPP, dyschezia, OPP, interference of pain with the ability to perform daily activities (using the EHP-30 pain dimension), dyspareunia, and no analgesic / no opiate use for EAP during the preceding 4-week period at month 6. Other secondary endpoints included analgesic and opioid use for EAP and HRQoL. Safety, BMD	Secondary endpoints included: Changes from baseline to month 12 in dysmenorrhoea, NMPP, dyschezia, OPP, interference of pain with the ability to perform daily activities (using the EHP-30 pain dimension) and dyspareunia. Other secondary endpoints included analgesic and opioid use for EAP and HRQoL. Safety, BMD
Other outcomes of interest	Number of days in hospital, intention for surgery (PSIQ/SSIQ), time to post-treatment menses	Number of days in hospital, intention for surgery (PSIQ/SSIQ), time to post-treatment menses
Pre-planned subgroups	Subgroup analyses were performed for each co-primary endpoint and BMD. Subgroups included: - Race (black or African American, other) - Ethnicity (Hispanic or Latino, not Hispanic or Latino) - Age group 1 ($<$ or $\geq$ median value at baseline; based on FAS population) - Age group 2 (<25, ≥ 25 to <35, ≥ 35 to <45, ≥ 45 years)	Secondary endpoint of dyspareunia for patients with a mean dyspareunia score >1 at baseline

	• Weight (< or ≥ median value at baseline; based on FAS population) • BMI group 1 (< or ≥ median value at baseline; based on FAS population) • BMI group 2 (<20, ≥20 to <25, ≥25 to <30, ≥30 kg/m²) • Baseline analgesic use (patients who took no rescue medication for EAP at baseline, patients who took any NSAIDs and narcotics at baseline) • Baseline pain VRS scores for dysmenorrhoea, NMPP and dyspareunia (< or ≥ median value at baseline; based on FAS population) • Time since endometriosis diagnosis (<2, ≥2 to <5, >5 years) • History of pregnancy at baseline (yes, no) Secondary endpoint of dyspareunia for patients with a mean dyspareunia score >1 at baseline.	

Outcomes listed in bold are included in the economic model.

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; BMI, body mass index; COC, combined oral contraceptives; EAP, endometriosis-associated pain; EHP-30, Endometriosis Health Profile-30; FAS, full analysis set; GnRH, gonadotrophin-releasing hormone; HRQoL, health-related quality of life; NMPP, non-menstrual pelvic pain; NSAID, non-steroidal anti-inflammatory drug; OPP, overall pelvic pain; PSIQ/SSIQ, Physician/Subject Surgery Intention Question; VRS, verbal rating scale

Source: Donnez et al 2024;⁵⁸ EDELWEISS 3 CSR (data on file);⁵⁹ EDELWEISS 3 SAP (data on file);⁶⁶ EDELWEISS 6 CSR (data on file);⁶¹ EDELWEISS 6 protocol (data on file);⁶⁷ EDELWEISS 6 SAP (data on file)⁶⁸

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 the EDELWEISS 3 and 6 trials are summarised in Table 5.

Table 5: Clinical effectiveness studies | Summary of statistical analyses

	EDELWEISS 3	EDELWEISS 6
Trial name/number	NCT03992846	NCT04335591
Hypothesis objective	The primary objective was to demonstrate the efficacy and safety of once daily linzagolix at a dose of 75 mg alone or 200 mg with ABT, versus placebo, in the management of moderate-to-severe EAP in women with surgically confirmed endometriosis.	The primary objective was to assess the maintenance of efficacy of once daily linzagolix for up to an additional 6 months (for up to 12 months of treatment in total) in women who had already completed 6 months of linzagolix treatment (in EDELWEISS 3) at a dose of 75 mg alone or of 200 mg plus ABT in the management of moderate to severe EAP in women with surgically confirmed endometriosis.
Statistical analysis	Statistical analyses were performed using SAS statistical software. Efficacy analyses were performed using the FAS (primary analysis) and PP populations. Responder threshold analyses for co-primary endpoints and ranked secondary endpoints were performed based on MCTs estimated from blinded data using anchor-based methods. Co-primary endpoints: Analysed using a logistic regression model, with the treatment group as the main effect (three values) and the baseline pain score as a covariate. Estimated proportions of responders were reported based on the overall mean baseline pain score and differences between the linzagolix groups versus placebo were reported using Bonferroni-corrected p-values. Ranked secondary endpoints: A fixed-sequence testing strategy within individual groups was used for ranked secondary endpoints, to maintain the family-wise type I error rate. Comparisons for each	Statistical analyses were performed using SAS statistical software. Efficacy analyses were performed using the TEAS (primary analysis), the FU EAS and the PP EAS. Efficacy endpoints were derived in the same way as for EDELWEISS 3 although results were summarised using descriptive statistics.

	linzagolix group versus placebo for each ranked endpoint only reached a statistically significant difference if the doubled raw p-value was ≤ 0.05 for that particular endpoint and all preceding endpoints for that linzagolix dose versus placebo. Changes from baseline in dysmenorrhoea, NMPP, dyschezia, OPP, EHP-30 pain dimensions and dyspareunia were analysed using ANCOVA, with treatment group as the main effect and baseline and pain scores as covariates. Other secondary endpoints Other secondary endpoint analyses used Bonferroni correction for p-values of comparison of treatment groups. The analyses did not form part of the fixed-sequence strategy being used for the co-primary and ranked secondary endpoints and were not fully controlled for an overall type I error rate.	
Sample size, power calculation	The planned sample size was 150 patients per treatment group (450 patients in total). This considered the hierarchical, fixed sequence testing of the ranked secondary endpoints as well as the co-primary endpoints. The assumptions used for the sample size calculations were informed by response rates from the Phase 2b EDELWEISS study (NCT02778399).^{46,57} The inclusion of 150 patients per treatment group provided a power >95% to reject the null hypothesis for both co-primary endpoints for either treatment group, assuming (based on EDELWEISS study results), a placebo response rate of 14.6% and an active treatment response rate of 48.6% (75 mg) or 64.7% (200 mg) for dysmenorrhoea, and a placebo response rate of 18.8% and an active treatment response rate of 42.1% (75 mg) for NMPP; the response rate for 200 mg in EDELWEISS was lower but was inconsistent with the other doses and other timepoints for the same dose so was not used for NMPP.	With 150 subjects in each of the three treatment groups in the main study (450 patients in total), the power was >95% to reject the null hypothesis for both co-primary endpoints and 85% to reject all the null hypotheses for the ranked secondary endpoints. All patients who had completed the full 6-month treatment period in the main study and who met the inclusion criteria were invited to enter the extension study. It was estimated that up to 288 subjects would enter the extension study, assuming that 80% of the patients randomised in the main study would complete the study (namely 360 subjects) and that up to 80% of these would enter the extension study.

	Including 150 patients per treatment group also provided 85% power to reject the null hypotheses for all the ranked secondary endpoints based on the observed results from the placebo and 200 mg treatment group in the EDELWEISS study. The values used for the sample size calculations assumed that these response rates are what would be seen on average when on treatment including taking into account any possible early withdrawals; therefore no further adjustment for dropouts was needed.	
Data management, patient withdrawals	Summary statistics were based primarily on non-missing values. The planned statistical analyses aimed to estimate the efficacy of linzagolix versus placebo while under randomised treatment and therefore lack of data after treatment discontinuation were not considered as missing for these analyses. Patients whose response could not be assessed for the co-primary efficacy endpoints, e.g. due to lack of on treatment pain data (i.e. subjects who received less than 28 days of treatment), were considered as non-responders (and assigned a change from baseline of zero). For any missing data during the screening or treatment periods (e.g. missed days of completing the eDiary), the primary analyses used observed data only in such cases where a minimum number of completed daily eDiary entries were available. This effectively assumed that the individual values such as daily eDiary assessments (observed or not) were independent of being missing. Patients with less than the minimum number of days available were excluded from the analysis. This is valid under the assumption that such data were MAR, conditional on the baseline value. Imputation of missing adverse event and concomitant medication data was only done to identify TEAEs.	Summary statistics were based primarily on non-missing values. As the planned analyses aimed to estimate the efficacy of linzagolix versus placebo while under randomised treatment, lack of data after treatment discontinuation were not considered as missing for these analyses. For any missing data (e.g. missed days of completing the eDiary) during the screening period (from EDELWEISS 3) and treatment periods, the primary analyses used observed data only in such cases that a minimum number of completed daily eDiary entries were available. This effectively assumed that the individual values such as daily eDiary assessments (observed or not) were independent of being missing. Imputation of missing adverse event and concomitant medication data was only done to identify TEAEs.
Statistical analysis timepoints	The co-primary endpoint analyses were based on the 28 days preceding the month 3 visit. Ranked secondary endpoint analyses were	The co-primary endpoint and main secondary endpoint analyses were based on the 28 days preceding the month 12 visit.

	based on the 28 days preceding the month 6 visit.	

Abbreviations: ANCOVA, analysis of covariance; EAP, endometriosis-associated pain; EHP-30, Endometriosis Health Profile-30; FAS, full analysis set; FU EAS, follow-up extension analysis set; MAR, missing at random; MCT, meaningful change threshold; NMPP, non-menstrual pelvic pain; OPP, overall pelvic pain; PP EAS, per-protocol extension analysis set; OR, odds ratio; PP, per-protocol; TEAE, treatment-emergent adverse event; TEAS, treatment extension analysis set

Sources: Donnez et al 2024;⁵⁸ EDELWEISS 3 SAP (data on file);⁶⁶ EDELWEISS 3 CSR (data on file);⁵⁹ EDELWEISS 6 SAP (data on file);⁶⁸ EDELWEISS 6 CSR (data on file)⁶¹

B.2.4.2 Analysis sets

Main patient data sets analysed in EDELWEISS 3 and 6 are described in Table 6 and Table 7.

Table 6: EDELWEISS 3 | Analysis sets

Analysis set	Definition	EDELWEISS 3			
		Number of patients			
		Linzagolix 75 mg	Linzagolix 200 mg plus ABT	Placebo	Total
Full analysis set	All randomised patients who received ≥ 1 dose of study drug, irrespective of the treatment received. Patients were analysed according to randomised treatment.	160	162	162	484
Per-protocol	All randomised patients who completed the 6 months of treatment, excluding those with major protocol deviations that could potentially affect efficacy assessments up to month 6. Patients were analysed according to randomised treatment.	134	139	133	406
Safety analysis set	All randomised patients who received ≥ 1 dose of study drug, irrespective of the treatment received. Patients were analysed according to the treatment received.	160	162	162	484

Abbreviations: ABT, add-back therapy

Sources: Donnez et al 2024;⁵⁸ EDELWEISS 3 CSR (data on file)⁵⁹

Table 7: EDELWEISS 6 | Analysis sets

Analysis set	Definition	EDELWEISS 6				
		Number of patients				
		Placebo/ linzagolix 75 mg	Placebo/ linzagolix 200 mg plus ABT	Linzagolix 75 mg	Linzagolix 200 mg plus ABT	Total
Treatment extension analysis set	All patients from the EDELWEISS 3 study who entered the EDELWEISS 6 extension study and received ≥ 1 dose of study drug, with the exception of patients whose month 6 assessments subsequently met any of the protocol discontinuation criteria. Patients were analysed according to randomised treatment.	57	57	118	121	353
Follow-up extension analysis set	All patients from the main study who entered the extension study and received ≥ 1 dose of study drug, with the exception of patients whose month 6 assessment subsequently met any of the discontinuation criteria, and who entered the post-treatment follow-up period. Patients were analysed according to randomised treatment.	53	50	111	112	326
Per-protocol extension analysis set	All patients from the treatment extension analysis set, excluding those with major protocol deviations that could potentially affect efficacy assessments up to month 12. Patients were analysed according to randomised treatment.	54	55	112	115	336
Extension safety analysis set	All patients randomised into the extension study who received ≥ 1 dose of study drug irrespective of the treatment received. Patients were analysed according to treatment received.	58	57	119	122	356
Follow-up safety analysis set	All subjects randomised into the extension study who received ≥ 1 dose of study drug irrespective of the treatment received, and who entered the post-treatment	54	50	112	113	329

Analysis set	Definition	EDELWEISS 6				
		Number of patients				
		Placebo/ linzagolix 75 mg	Placebo/ linzagolix 200 mg plus ABT	Linzagolix 75 mg	Linzagolix 200 mg plus ABT	Total
	follow-up period. Patients were analysed according to treatment received.					

Abbreviations: ABT, add-back therapy

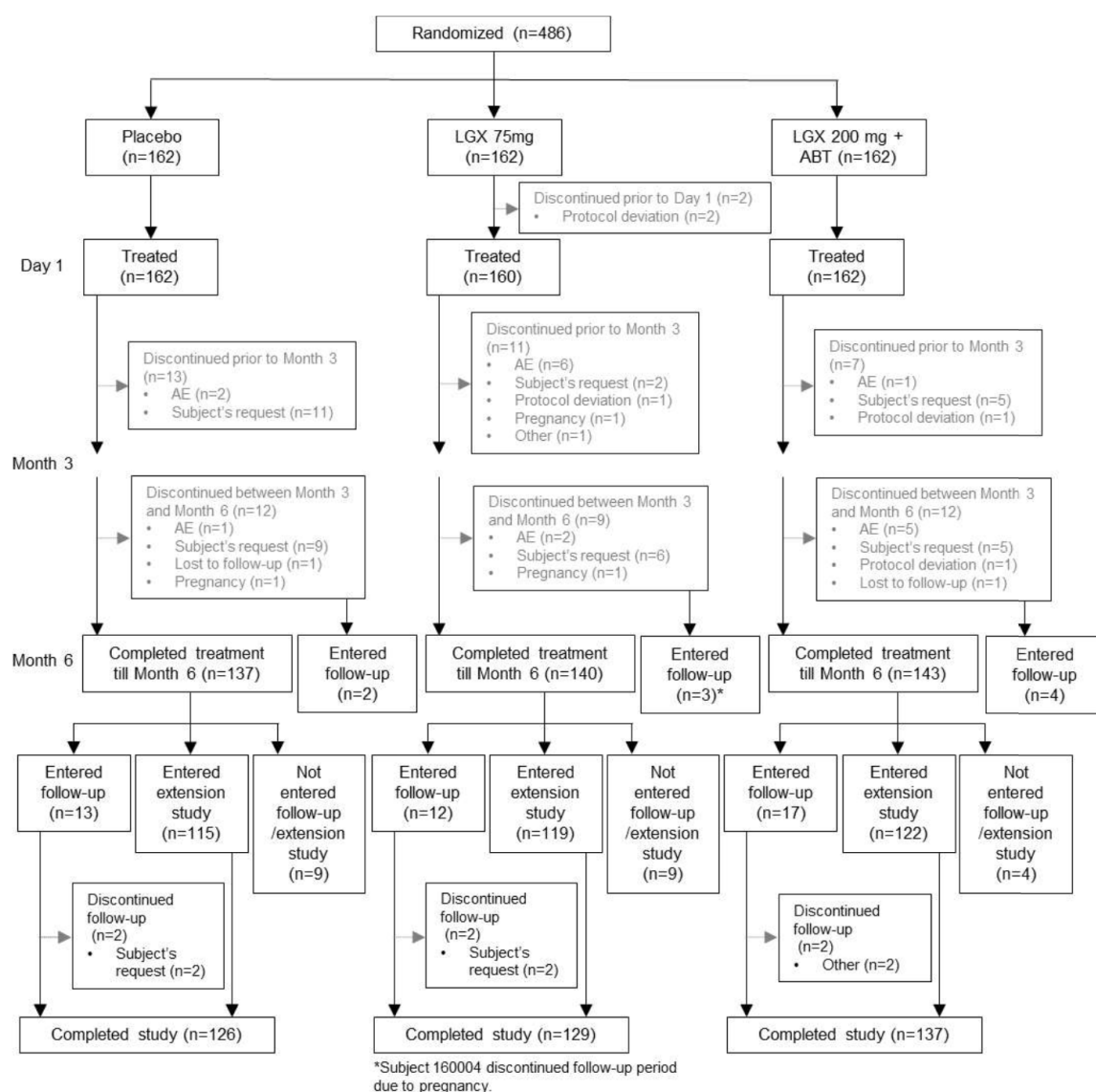
Sources: EDELWEISS 6 CSR (data on file)⁶¹

B.2.4.3 Patient flow

Overall, 484 women were included in the full analysis set (FAS) in EDELWEISS 3; patient disposition up to month 6 is summarised in Figure 7.

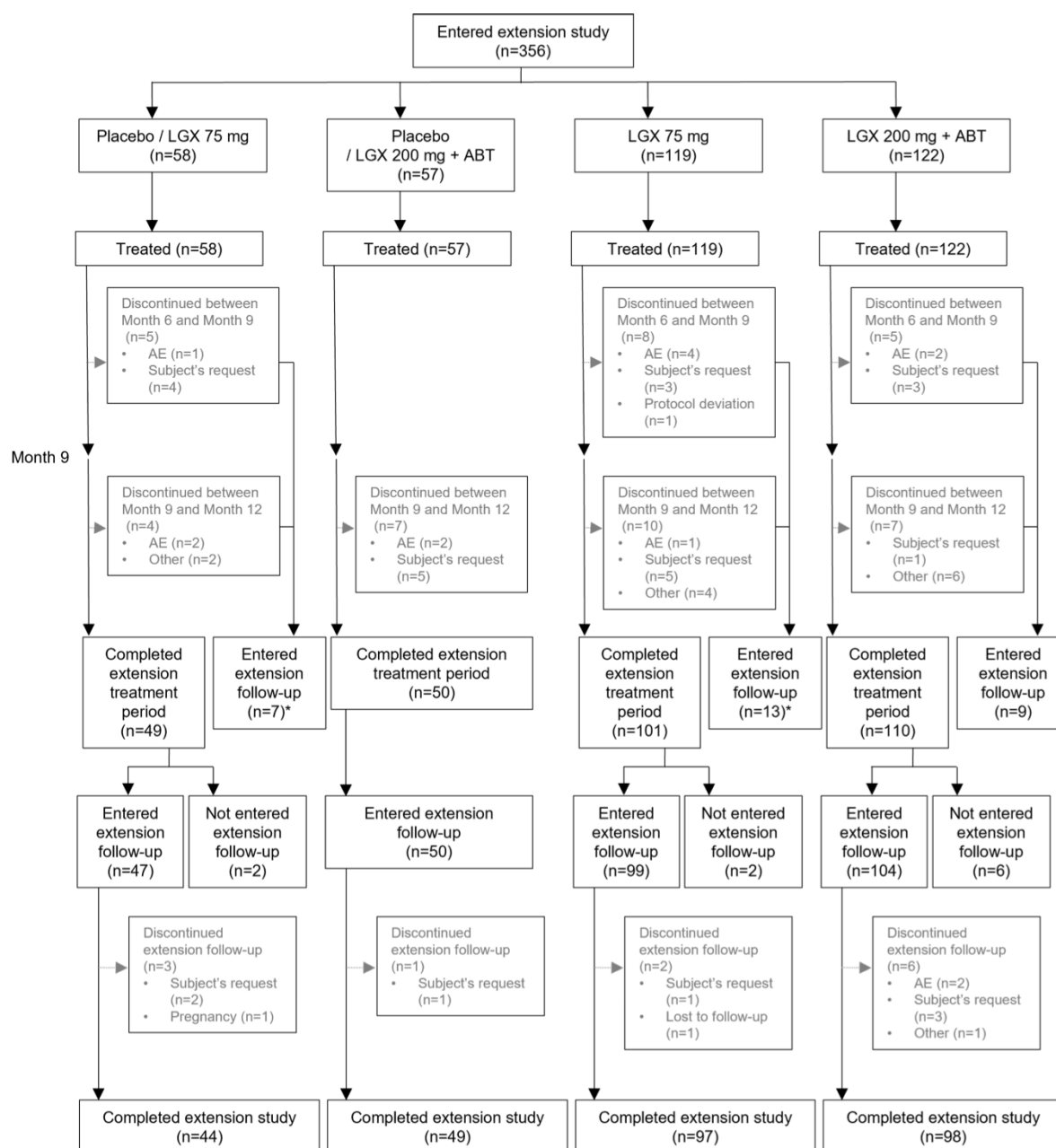
A total of 356 subjects who completed the 6-month treatment period in the EDELWEISS 3 study entered the EDELWEISS 6 extension study and were treated. Three patients discontinued the treatment period prematurely due to discontinuation criteria met at month 6 of BMD loss >8% or Z-score ≤-2.5 (one patient in each of the placebo/linzagolix 75 mg, linzagolix 75 mg and linzagolix 200 mg plus ABT groups). The treatment extension analysis set (TEAS) therefore included 353 patients.⁶¹ Patient disposition in EDELWEISS 6 is summarised in Figure 8.

Figure 7: EDELWEISS 3 | Patient disposition



Source: EDELWEISS 3 CSR (data on file)⁵⁹

Figure 8: EDELWEISS 6 | Patient disposition^a



^aThree patients discontinued the treatment period prematurely due to discontinuation criteria met at month 6 of BMD loss >8% or Z-score ≤-2.5 (one patient in each of the placebo/linzagolix 75 mg, linzagolix 75 mg and linzagolix 200 mg plus ABT groups).

*Three patients in the placebo/linzagolix 75 mg group and one patient in the linzagolix 75 mg group discontinued the follow-up period due to the patient's requests

Abbreviations: ABT, add-back therapy; AE, adverse event; BMD, bone mineral density; LGX, linzagolix

Source: EDELWEISS 6 CSR (data on file)⁶¹

B.2.4.4 Patient baseline characteristics

Demographic and baseline characteristics were generally well balanced among treatment groups in both the EDELWEISS 3 (Table 8)⁵⁸ and EDELWEISS 6 (Table 9)⁶¹ studies.

Women in EDELWEISS 3 had an overall mean (standard deviation [SD]) age of 34.9 (6.6) years and were mostly white (98.6%).⁵⁹ The mean (SD) weight was 66.42 (13.77) kg and mean (SD) body mass index (BMI) was 24.27 (4.95) kg/m².⁵⁹

Women who entered EDELWEISS 6 had a mean (SD) age of 34.8 (6.7) years and most (98.6%) were white. The mean (SD) weight was 66.61 (13.87) kg and mean (SD) BMI was 24.25 (4.94) kg/m².⁶¹

Table 8: EDELWEISS 3 | Baseline characteristics (FAS)

Characteristics	EDELWEISS 3			
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Total (N=484)
Age, years, mean (SD)	34.9 (6.8)	35.1 (6.4)	34.6 (6.8)	34.9 (6.6)
Race, n (%)				
White	160 (98.8)	158 (98.8)	159 (98.1)	477 (98.6)
Black or African-American	2 (1.2)	1 (0.6)	1 (0.6)	4 (0.8)
Asian	0	1 (0.6)	0	1 (0.2)
American Indian or Alaska Native	0	0	1 (0.6)	1 (0.2)
Multiple	0	0	1 (0.6)	1 (0.2)
BMI, kg/m ² , mean (SD)	24.14 (4.44)	24.60 (5.23)	24.09 (5.17)	24.27 (4.95)
Weight, kg, mean (SD)	65.81 (11.96)	67.73 (14.45)	65.75 (14.75)	66.42 (13.77)
Time since seeking medical diagnosis/treatment, years, mean (SD)	4.94 (4.51)	5.15 (4.38)	5.50 (4.74)	5.20 (4.54)
Baseline pain scores, mean (SD)				
Overall pelvic pain VRS ^a	1.90 (0.40)	1.87 (0.41)	1.92 (0.42)	1.90 (0.41)
NMPP VRS ^a	1.78 (0.44)	1.73 (0.46)	1.80 (0.46)	1.77 (0.45)
Dysmenorrhoea VRS ^a	2.29 (0.43)	2.25 (0.40)	2.29 (0.43)	2.28 (0.42)
Overall pelvic pain NRS	6.18 (1.51)	5.84 (1.65)	6.12 (1.60)	6.05 (1.59)
Dyspareunia VRS	1.95 (0.87)	1.92 (0.86)	2.09 (0.84)	1.99 (0.86)
EHP-30 pain dimension	51.77 (14.43)	51.46 (14.28)	52.37 (15.14)	51.87 (14.60)

Characteristics	EDELWEISS 3			
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Total (N=484)
Baseline analgesic use on bleeding days ^a , pill count/day, mean (SD)	1.65 (1.45)	1.88 (1.69)	2.01 (1.95)	1.85 (1.71)
Baseline analgesic use on non-bleeding days ^a , pill count/day, mean (SD)	0.78 (0.98)	1.00 (1.23)	1.08 (1.26)	0.95 (1.17)
Baseline dyschezia NRS, mean (SD)	4.46 (2.51)	3.73 (2.60)	4.07 (2.79)	4.09 (2.65)
Baseline lipids and BMD data [SAF]	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Total (N=484)
Baseline lipid levels, mg/dL, mean (SD) [SAF]				
LDL cholesterol	114.3 (31.8)	117.4 (39.4)	115.4 (32.1)	115.7 (34.5)
Triglycerides	91.9 (46.8)	92.0 (48.5)	90.0 (43.2)	91.3 (46.2)
Baseline BMD, g/cm ² , mean (SD) [SAF]				
Femoral neck	1.002 (0.132)	0.995 (0.141)	0.980 (0.144)	0.992 (0.139)
Lumbar spine	1.214 (0.140)	1.197 (0.150)	1.169 (0.134)	1.193 (0.143)
Total hip	1.031 (0.116)	1.026 (0.127)	1.015 (0.125)	1.024 (0.123)
Baseline BMD, Z-scores, mean (SD) [SAF]				
Femoral neck	0.25 (0.88)	0.35 (0.96)	0.14 (0.93)	0.25 (0.93)
Lumbar spine	0.49 (1.01)	0.51 (1.15)	0.25 (0.93)	0.41 (1.04)
Total hip	0.40 (0.90)	0.44 (0.99)	0.30 (0.97)	0.38 (0.96)

^aBased on the two selected screening menstrual cycles.

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; BMI, body mass index; EHP-30, endometriosis health profile-30; FAS, full analysis set; LDL, low-density lipoprotein; NMPP, non-menstrual pelvic pain; NRS, numeric rating scale; SAF, safety analysis set; SD, standard deviation; VRS, verbal rating scale.

Source: Donnez et al 2024;⁵⁸ EDELWEISS 3 CSR (data on file)⁵⁹

Table 9: EDELWEISS 6 | Baseline characteristics (TEAS)

Characteristics	EDELWEISS 6				
	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)	Total (N=353)
Age, years, mean (SD)	34.2 (6.6)	35.0 (7.7)	35.0 (6.3)	34.9 (6.8)	34.8 (6.7)
Race, n (%)					
White	57 (100.0)	56 (98.2)	116 (98.3)	119 (98.3)	348 (98.6)
Black or African-American	0	1 (1.8)	1 (0.8)	1 (0.8)	3 (0.9)
Asian	0	0	1 (0.8)	0	1 (0.3)

Characteristics		EDELWEISS 6				Total (N=353)
		Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)	
Multiple		0	0	0	1 (0.8)	1 (0.3)
BMI, kg/m ² , mean (SD)		23.41 (4.04)	24.77 (5.06)	24.83 (5.55)	23.83 (4.59)	24.25 (4.94)
Weight, kg, mean (SD)		63.93 (11.19)	68.03 (13.83)	65.59 (15.13)	65.26 (13.55)	66.61 (13.87)
Time since seeking medical diagnosis/treatment, years, mean (SD)		5.76 (5.20)	4.56 (4.22)	5.13 (4.49)	5.36 (3.99)	5.22 (4.40)
Baseline pain scores, mean (SD)						
Overall pelvic pain VRS ^a		1.84 (0.41)	1.93 (0.41)	1.90 (0.40)	1.90 (0.39)	1.89 (0.40)
NMPP VRS ^a		1.70 (0.45)	1.82 (0.47)	1.76 (0.45)	1.77 (0.43)	1.76 (0.45)
Dysmenorrhoea VRS ^a		2.27 (0.41)	2.30 (0.45)	2.27 (0.39)	2.28 (0.40)	2.28 (0.41)
Overall pelvic pain NRS		5.97 (1.53)	6.37 (1.60)	6.00 (1.62)	6.16 (1.53)	6.11 (1.57)
Dyspareunia VRS		1.93 (0.87)	2.00 (0.83)	1.94 (0.87)	2.12 (0.84)	2.01 (0.86)
EHP-30 pain dimension		50.56 (15.40)	52.92 (13.45)	51.83 (14.30)	52.08 (15.00)	51.88 (14.55)
Baseline analgesic use on bleeding days ^a , pill count/day, mean (SD)		1.80 (1.49)	1.36 (1.17)	1.96 (1.83)	2.11 (1.79)	1.89 (1.68)
Baseline analgesic use on non-bleeding days ^a , pill count/day, mean (SD)		0.85 (1.03)	0.60 (0.74)	1.05 (1.27)	1.11 (1.12)	0.97 (1.12)
Baseline dyschezia NRS, mean (SD)		4.38 (2.22)	4.57 (2.76)	3.78 (2.70)	3.94 (2.75)	4.06 (2.66)
Baseline lipids and BMD data [ESAF]	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)	Total (N=356)	
Baseline lipid levels, mg/dL, mean (SD) [ESAF]						
LDL cholesterol		110.6 (33.3)	116.7 (32.6)	115.5 (33.5)	116.4 (31.9)	115.2 (32.7)
Triglycerides		88.3 (39.2)	93.0 (51.5)	97.3 (53.9)	90.6 (42.2)	92.9 (47.4)
Baseline BMD, g/cm ² , mean (SD) [ESAF]						

Characteristics	EDELWEISS 6				
	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)	Total (N=353)
Femoral neck	1.000 (0.121)	1.002 (0.148)	1.009 (0.141)	0.987 (0.143)	0.999 (0.139)
Lumbar spine	1.224 (0.135)	1.194 (0.140)	1.210 (0.153)	1.179 (0.128)	1.199 (0.140)
Total hip	1.034 (0.106)	1.029 (0.121)	1.041 (0.127)	1.022 (0.124)	1.031 (0.122)
Baseline BMD, Z-scores, mean (SD) [ESAF]					
Femoral neck	0.245 (0.831)	0.251 (0.930)	0.437 (1.008)	0.195 (0.920)	0.293 (0.940)
Lumbar spine	0.600 (0.973)	0.313 (0.987)	0.576 (1.153)	0.257 (0.911)	0.428 (1.027)
Total hip	0.430 (0.854)	0.379 (0.904)	0.529 (1.025)	0.347 (0.973)	0.427 (0.962)

^aBased on the two selected screening menstrual cycles.

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; BMI, body mass index; EHP-30, endometriosis health profile-30; ESAF, extension safety analysis set; LDL, low-density lipoprotein; NRS, numeric rating scale; SD, standard deviation; TEAS, treatment extension analysis set; VRS, verbal rating scale.

Source: EDELWEISS 6 CSR (data on file);⁶¹ Dolmans et al 2024⁶²

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of the studies included in the SLR was completed using the NICE single technology assessment: User guide for company evidence submission template, adapted from Systematic reviews: Centre for Reviews and Dissemination's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination) and is provided in Appendix D.

Quality assessment of EDELWEISS 3 is provided in Table 10.

Table 10: EDELWEISS 3 | Quality assessment results

Questions	EDELWEISS 3
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes

Were there any unexpected imbalances in drop-outs between groups?	No
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?	No. Full analysis and per protocol analysis.
If ITT analysis was included, was this appropriate and were appropriate methods used to account for missing data?	N/A

Abbreviations: ITT, intention-to-treat; N/A, not applicable

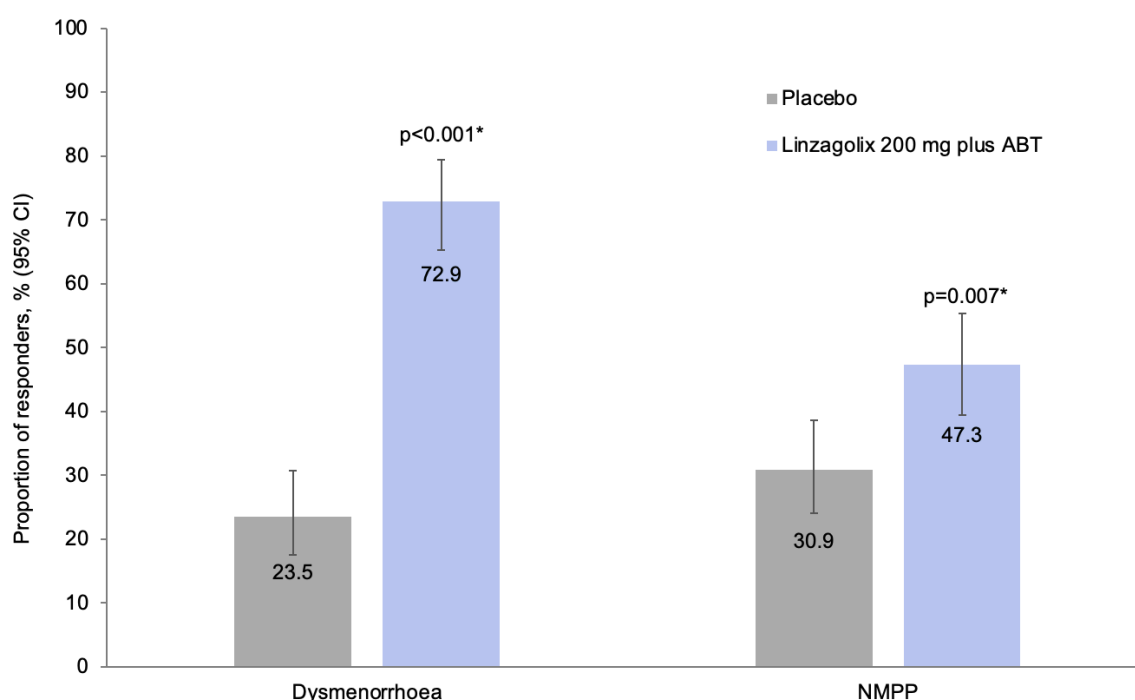
B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 EDELWEISS 3 and EDELWEISS 6 | Co-primary endpoints

The daily dose of linzagolix 200 mg plus ABT met the co-primary endpoint of the EDELWEISS 3 study, demonstrating clinically meaningful and statistically significant reductions in dysmenorrhoea and NMPP (reductions of ≥ 1.10 and ≥ 0.8 points on the verbal rating scale for dysmenorrhoea and NMPP, respectively) from baseline to the last 28 days of randomised treatment up to month 3, with stable or reduced use of analgesics⁵⁸ (Figure 9). At month 3, the estimated percentage of responders for dysmenorrhoea was 72.9% (95% confidence interval [CI]: 65.3–79.4) in the linzagolix 200 mg plus ABT group versus 23.5% (95% CI: 17.5–30.7) in the placebo group (odds ratio [OR] 8.80 [97.5% CI: 4.86–15.91]; $p < 0.001$). Respective proportions for NMPP were 47.3% (95% CI: 39.5–55.3) with linzagolix 200 mg plus ABT versus 30.9% (95% CI: 24.1–38.6) with placebo (OR 2.01 [97.5% CI: 1.18–3.42]; $p = 0.007$).

The linzagolix 75 mg alone dose demonstrated a clinically meaningful and statistically significant reduction in dysmenorrhoea versus placebo at month 3, but the reduction in NMPP at month 3 versus placebo was not statistically significant. Linzagolix 200 mg plus ABT is, therefore, the dose for EAP stated in the SmPC, and this submission focuses on the evidence for linzagolix 200 mg plus ABT.

Figure 9: EDELWEISS 3 | Pain and analgesia | Dysmenorrhoea and NMPP responders at month 3 (co-primary endpoints; FAS)



Responders for the co-primary endpoint were defined as patients who met the clinically meaningful reduction thresholds for the primary analysis of dysmenorrhoea and NMPP as a reduction of ≥ 1.10 and ≥ 0.8 points on the VRS for dysmenorrhoea and NMPP, respectively, from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for endometriosis-associated pain.

Data represent the estimated proportions of responders according to logistic regression analyses (based on the overall baseline pain score). *Clinically significant value.

Abbreviations: ABT, add-back therapy; CI, confidence interval; FAS, full analysis set; NMPP, non-menstrual pelvic pain; VRS, verbal rating scale

Source: Donnez et al 2024⁵⁸

Further improvements were observed at month 12 in EDELWEISS 6 in the linzagolix 200 mg plus ABT group.^{61,62} At month 12, the estimated percentage of responders (EDELWEISS 6 co-primary endpoint) in the linzagolix 200 mg plus ABT group was 91.0% for dysmenorrhoea and 67.6% for NMPP (Table 11).

Table 11: EDELWEISS 6 | Pain and analgesia co-primary endpoint | Dysmenorrhoea and NMPP responders at month 12 (TEAS)

Endpoint	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
Proportion of responders for	32 (56.1)	43 (78.2)	62 (55.9)	101 (91.0)

dysmenorrhoea, n (%)				
Proportion of responders for non-menstrual pelvic pain, n (%)	34 (59.6)	27 (49.1)	66 (59.5)	75 (67.6)

Abbreviations: ABT, add-back therapy; NMPP, non-menstrual pelvic pain; TEAS, Treatment Extension Analysis Set; VRS, verbal rating scale

Responders at month 12 were defined as patients who met the clinically meaningful reduction thresholds of a reduction of ≥ 1.10 and ≥ 0.8 points on the VRS for dysmenorrhoea and NMPP, respectively, from EDELWEISS 3 baseline to the last 28 days of randomised treatment up to month 12, along with stable or decreased use of analgesics for endometriosis-associated pain.

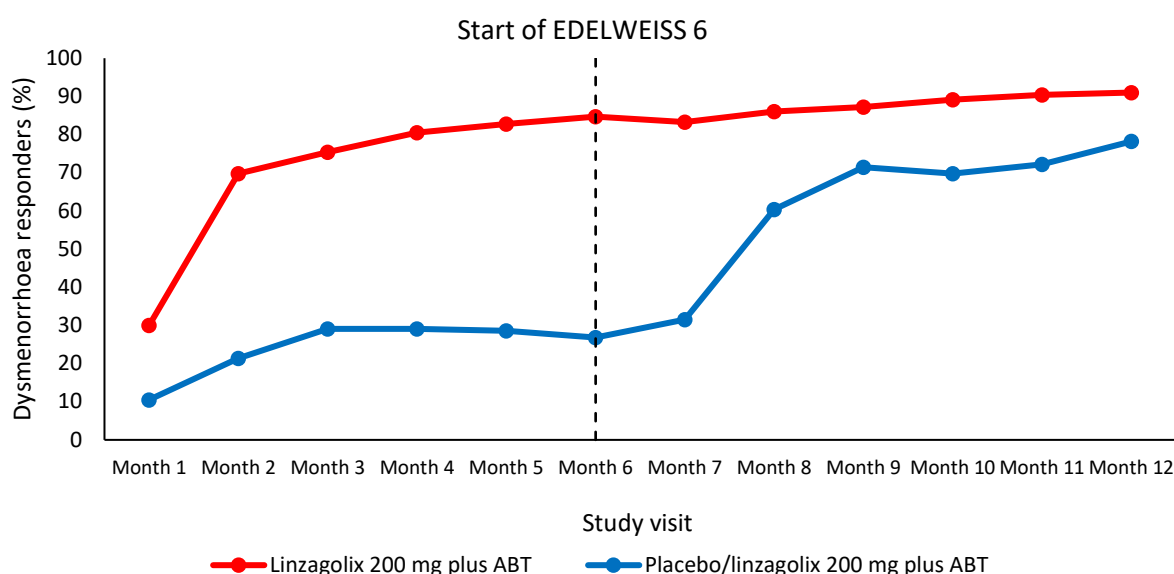
Scores were computed as means of daily assessments on the last 28 days prior to Month 12 or discontinuation. Patients with <43% of daily diary data completed were excluded.

Source: EDELWEISS 6 CSR (data on file);⁶¹ Dolmans et al 2024⁶²

A reduction in dysmenorrhoea was observed from month 1 (during EDELWEISS 3) (Figure 10). In the linzagolix 200 mg plus ABT group, the proportion of responders for dysmenorrhoea rose sharply until month 2 and continued to rise steadily until the end of treatment at month 12.

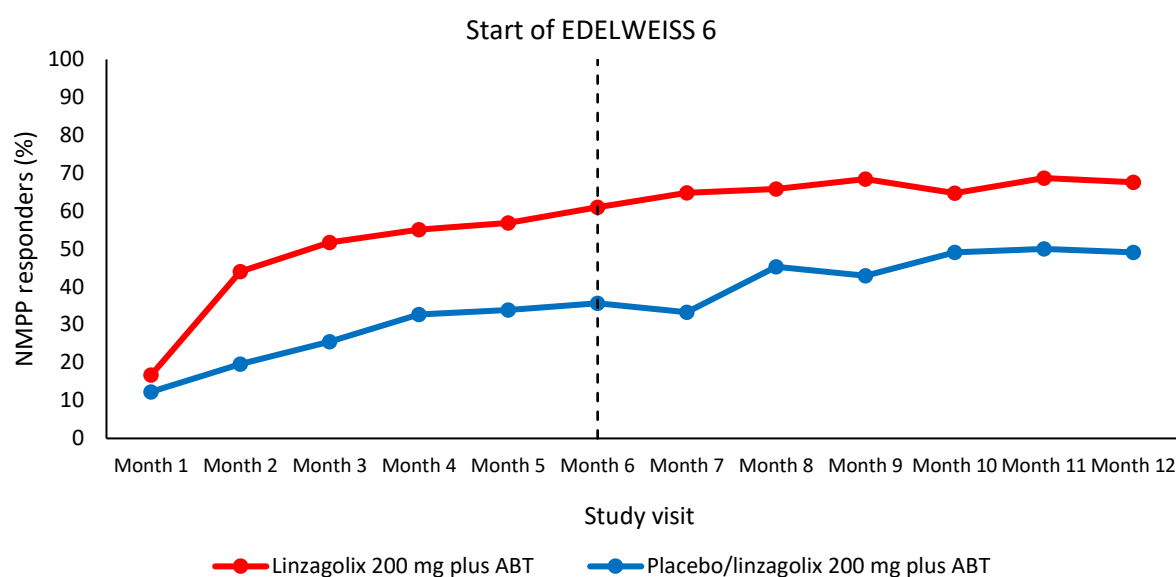
The proportion of responders for NMPP rose gradually from month 1 until month 6 (during EDELWEISS 3) in the linzagolix 200 mg plus ABT group, then remained relatively stable until the end of treatment at month 12 (with a slight decrease at Month 10) (Figure 11).

Figure 10: EDELWEISS 6 | Pain and analgesia co-primary endpoint | Dysmenorrhoea responders up to month 12 (TEAS)



Abbreviations: ABT, add-back therapy; TEAS, treatment extension analysis set; VRS, verbal rating scale
 Patients with <43% of daily diary data completed were excluded.
 Patients who received placebo for 6 months in EDELWEISS 3 were then randomised to receive either linzagolix 75 mg or linzagolix 200 mg ABT for 6 months in EDELWEISS 6.
 Dysmenorrhoea responders were defined as patients who met the clinically meaningful reduction threshold of a reduction of ≥ 1.10 on the VRS for dysmenorrhoea from EDELWEISS 3 baseline to the last 28 days of randomised treatment, along with stable or decreased use of analgesics for endometriosis-associated pain.
 Source: EDELWEISS 6 CSR (data on file)⁶¹

Figure 11: EDELWEISS 6 | Pain and analgesia co-primary endpoint | NMPP responders up to month 12 (TEAS)



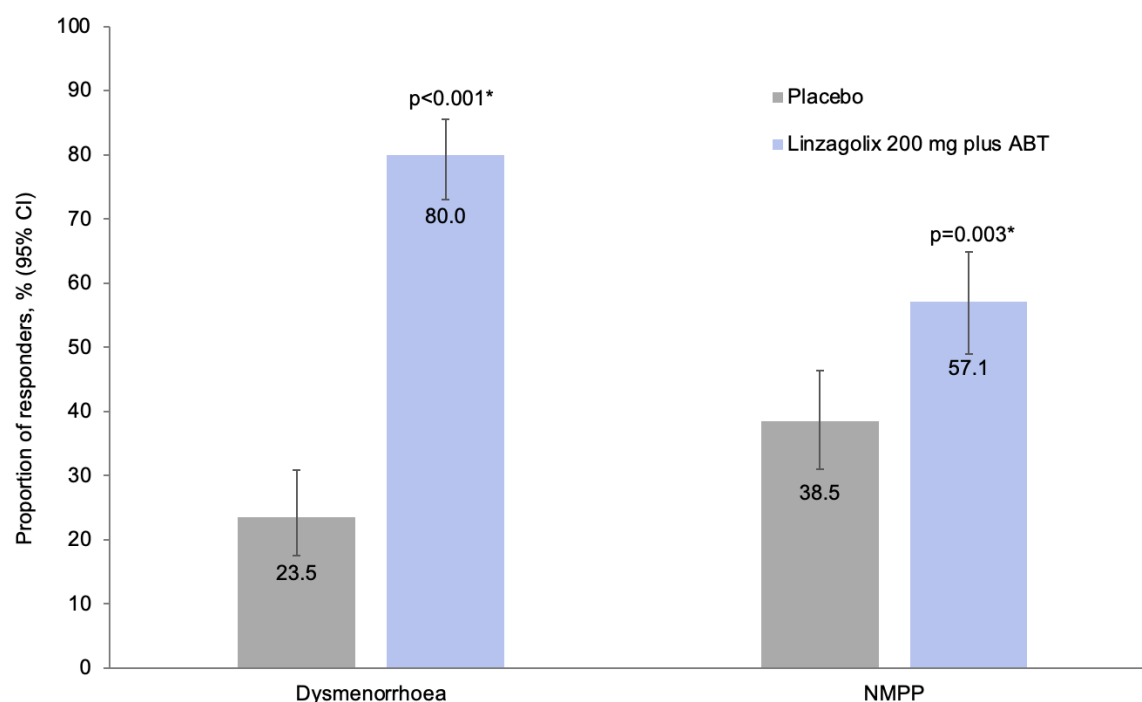
Abbreviations: ABT, add-back therapy; NMPP, non-menstrual pelvic pain; TEAS, treatment extension analysis set; VRS, verbal rating scale
 Patients with <43% of daily diary data completed were excluded.
 Patients who received placebo for 6 months in EDELWEISS 3 were then randomised to receive either linzagolix 75 mg or linzagolix 200 mg ABT for 6 months in EDELWEISS 6.
 NMPP responders were defined as patients who met the clinically meaningful reduction thresholds of a reduction of ≥ 0.8 points on the VRS for NMPP from EDELWEISS 3 baseline to the last 28 days of randomised treatment, along with stable or decreased use of analgesics for endometriosis-associated pain.
 Source: EDELWEISS 6 CSR (data on file)⁶¹

B.2.6.2 EDELWEISS 3 and EDELWEISS 6 | Secondary endpoints

B.2.6.2.1 EDELWEISS 3 and EDELWEISS 6 | Secondary endpoints | Pain and analgesia

At EDELWEISS 3 month 6 (secondary endpoint), the proportions of responders for both dysmenorrhoea and NMPP were significantly greater for linzagolix 200 mg plus ABT than placebo (Figure 12).

Figure 12: EDELWEISS 3 | Pain and analgesia | Dysmenorrhoea and NMPP responders at month 6 (secondary endpoints; FAS)



Responders at month 6 were defined as patients who met the clinically meaningful reduction thresholds of a reduction of ≥ 1.10 and ≥ 0.8 points on the VRS for dysmenorrhoea and NMPP, respectively, from baseline to the last 28 days of randomised treatment up to month 6, along with stable or decreased use of analgesics for endometriosis-associated pain.

Data represent the estimated proportions of responders according to logistic regression analyses (based on the overall baseline pain score). *Clinically significant value.

Abbreviations: ABT, add-back therapy; CI, confidence interval; FAS, full analysis set; NMPP, non-menstrual pelvic pain; VRS, verbal rating scale

Source: Donnez et al 2024⁵⁸

Ranked secondary endpoints showing statistically significant and clinically meaningful improvements from baseline to month 6 with linzagolix 200 mg plus ABT versus placebo were dysmenorrhoea, NMPP, dyschezia, OPP and ability to participate in daily activities (based on pain dimensions listed in the EHP-30) (Table 12). The statistical analysis hierarchy was interrupted as the change from baseline to month 6 in dyspareunia with linzagolix did not differ significantly from that observed with placebo. Therefore, statistical significance cannot be confirmed for the numerically higher proportions of patients reporting no use of analgesia in the 4 weeks to month 6 with linzagolix versus placebo (Table 12). The proportion of patients reporting opiate use in the 4 weeks before month 6 was minimal (<10%) for all groups (Table 12).

These main analyses of linzagolix 200 mg plus ABT versus placebo from the FAS were confirmed from analyses based on the per-protocol (PP) set and sensitivity analyses.

Table 12: EDELWEISS 3 | Ranked secondary endpoints at month 6 (FAS)

Endpoint	EDELWEISS 3						
	Placebo (N=162)	Linzagolix 75 mg (N=160)			Linzagolix 200 mg plus ABT (N=162)		
Change from baseline to month 6 in:							
	LSM (95% CI)	LSM (95% CI)	Difference versus placebo (97.5% CI)	p-value ^a	LSM (95% CI)	Difference versus placebo (97.5% CI)	p-value ^a
Dysmenorrhoea (VRS)	−0.66 (−0.79, −0.53)	−1.10 (−1.23, −0.97)	−0.44 (−0.65, −0.23)	<0.001	−1.83 (−1.96, −1.70)	−1.17 (−1.38, −0.97)	<0.001
NMPP (VRS)	−0.66 (−0.79, −0.56)	−0.84 (−0.95, −0.73)	−0.17 (−0.35, 0.00)	0.048	−0.92 (−1.03, −0.82)	−0.26 (−0.43, −0.09)	0.002
Dyschezia (NRS)	−1.41 (−1.71, −1.12)	−1.98 (−2.28, −1.69)	−0.57 (−1.05, −0.09)	0.015	−1.99 (−2.29, −1.70)	−0.58 (−1.05, −0.11)	0.012
OPP (NRS)	−2.19 (−2.55, −1.84)	−2.84 (−3.20, −2.48)	−0.65 (−1.23, −0.07)	0.024	−3.39 (−3.74, −3.03)	−1.19 (−1.77, −0.62)	<0.001
EHP-30 Pain dimension	−19.47 (−22.66, −16.28)	−27.37 (−30.50, −24.25)	−7.90 (−13.01, −2.79)	0.001	−35.60 (−38.73, −32.48)	−16.13 (−21.24, −11.02)	<0.001
Dyspareunia (VRS)	−0.82 (−0.97, −0.66)	−1.04 (−1.21, −0.88)	−0.23 (−0.49, 0.03)	0.100	−1.01 (−1.18, −0.85)	−0.20 (−0.46, 0.07)	0.184
No analgesic/opiate use for EAP during the preceding 4-week period at month 6							
	% of responders (95% CI)	% of responders (95% CI)	OR ^{b,c} (97.5% CI)	p-value ^{a,c}	% of responders (95% CI)	OR ^{b,c} (97.5% CI)	p-value ^{a,c}
No analgesic use for EAP	13.2 (8.9, 19.2)	30.9 (23.8, 39.1)	2.95 (1.58, 5.50)	<0.001	44.5 (36.3, 52.9)	5.27 (2.83, 9.82)	<0.001
No opiate use for EAP	97.0 (92.5, 98.9)	93.8 (88.5, 96.8)	0.47 (0.12, 1.82)	0.420	97.0 (92.7, 98.8)	0.99 (0.22, 4.51)	1.000

Abbreviations: ABT, add-back therapy; CI, confidence interval; EAP, endometriosis-associated pain; EHP-30, Endometriosis Health Profile-30; FAS, full analysis set; LSM, least squares mean; NMPP, non-menstrual pelvic pain; NRS, numeric rating scale; OPP, overall pelvic pain; OR, odds ratio; VRS, verbal rating scale.

Scores were computed as means of daily assessments on the last 28 days prior to month 6 or discontinuation.

Analysis of covariance with change from baseline as response variable, and baseline value, treatment as covariates.

EHP-30 Pain Score at month 6 or discontinuation was computed as the sum of each pain question score/(number of items × 4) × 100; scores range ranged from 0 (best possible health status) to 100 (worst possible health status).

For dyspareunia, subjects not sexually active for other reasons than endometriosis have missing values.

Analgesic and opiate use for EAP data are as collected in eDiary and Concomitant Medication page on the last 28 days prior to month 6 or discontinuation.

^aBonferroni-corrected p-value. A fixed-sequence testing strategy was used to account for multiplicity. The linzagolix 200 mg plus ABT group demonstrated statistically significant differences versus placebo for both co-primary endpoints. The linzagolix 75 mg group was not statistically significantly different from placebo for the non-menstrual pelvic pain co-primary endpoint.

^bORs and 97.5% CIs were estimated using a logistic regression model with no analgesic use/no opiate use in the last 28 days on treatment prior to Month 6 as the response variable, treatment group as the main effect and including the baseline analgesic use/opiate use as a covariate.

Patients with <43% of daily diary data completion were excluded.

^cThe statistical analysis hierarchy was interrupted as the change from baseline to month 6 in dyspareunia with linzagolix did not differ significantly from that observed with placebo. Therefore, statistical significance cannot be confirmed for the proportions of patients reporting no analgesic use in the 4 weeks to month 6 with linzagolix versus placebo.

Sources: Donnez et al 2024;⁵⁸ EDELWEISS 3 CSR⁵⁹

EDELWEISS 6 month 12 data for key secondary endpoints are presented in Table 13. Steady improvements were observed with linzagolix 200 mg plus ABT throughout the treatment period.

Table 13: EDELWEISS 6 | Pain and analgesia secondary endpoints at month 12 (TEAS)

Endpoint	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
Mean (SD) change from baseline to month 12 in:				
Dysmenorrhoea (VRS)	-1.26 (0.93)	-1.79 (0.93)	-1.32 (0.90)	-2.02 (0.71)
NMPP (VRS)	-0.85 (0.62)	-0.96 (0.81)	-1.03 (0.72)	-1.16 (0.64)
Dyschezia (NRS)	-2.52 (2.26)	-2.47 (2.50)	-2.11 (2.43)	-2.72 (2.36)
OPP (NRS)	-3.44 (2.14)	-3.56 (2.42)	-3.46 (2.37)	-4.35 (2.14)
EHP-30 Pain dimension	-29.68 (20.91)	-33.04 (21.69)	-31.65 (22.88)	-41.89 (20.21)
Dyspareunia (VRS)	-0.99 (1.05)	-1.00 (1.11)	-1.24 (1.04)	-1.29 (1.07)
No analgesic/opiate use for EAP during the preceding 4-week period at month 12, n (%)				
No analgesic use for EAP	19 (33.3)	27 (48.2)	52 (45.2)	62 (56.1)
No opiate use for EAP	54 (94.7)	54 (98.2)	107 (95.5)	109 (98.2)

Abbreviations: ABT, add-back therapy; EAP, endometriosis-associated pain; EHP-30, Endometriosis Health Profile-30; NMPP, non-menstrual pelvic pain; NRS, numeric rating scale; OPP, overall pelvic pain; SD, standard deviation; TEAS, Treatment Extension Analysis Set; VRS, verbal rating scale.

Scores were computed as means of daily assessments on the last 28 days prior to month 12 or discontinuation. Patients with <43% of daily diary data completed were excluded.

Source: EDELWEISS 6 CSR (data on file)⁶¹

These main analyses from the TEAS were confirmed based on analyses from the PP extension analysis set and sensitivity analyses.

After the end of treatment, patients in the EDELWEISS 6 follow-up extension analysis set were still experiencing lingering treatment benefits, although the proportion of responders for dysmenorrhoea (with stable or reduced use of analgesics) decreased after the end of treatment. The proportions of responders for NMPP (with stable or reduced use of analgesics) remained relatively stable after the end of the treatment period (Table 14).

Table 14: EDELWEISS 6 | Pain and analgesia | Dysmenorrhoea and NMPP responders at month 12 (end of treatment) and at month 6 after the end of treatment (FU EAS)

Endpoint	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=53)	Placebo/ linzagolix 200 mg plus ABT (N=50)	Linzagolix 75 mg (N=111)	Linzagolix 200 mg plus ABT (N=112)
Proportion of responders for dysmenorrhoea, n (%)				
Month 12 (end of treatment)	29 (54.7)	39 (79.6)	59 (56.2)	94 (90.4)
Month 6 extension follow-up (month 6 after end of treatment)	18 (41.9)	15 (35.7)	36 (40.9)	51 (54.3)
Proportion of responders for NMPP, n (%)				
Month 12 (end of treatment)	32 (60.4)	24 (49.0)	61 (58.1)	68 (65.4)
Month 6 extension follow-up (month 6 after end of treatment)	17 (39.5)	18 (42.9)	49 (55.7)	63 (67.0)

Abbreviations: ABT, add-back therapy; FU EAS, Follow-up Extension Analysis Set; NMPP, non-menstrual pelvic pain; VRS, verbal rating scale

Scores were computed as means of daily assessments on the last 28 days prior to month 12 or discontinuation. Patients with <43% of daily diary data completed were excluded.

Responders were defined as patients who met the clinically meaningful reduction thresholds of a reduction of ≥ 1.10 and ≥ 0.8 points on the VRS for dysmenorrhoea and NMPP, respectively, from baseline to the last 28 days of randomised treatment up to month 12 (month 12 analysis) or 28 days prior to month 6 post-treatment follow-up (month 6 extension follow-up analysis), along with stable or decreased use of analgesics for endometriosis-associated pain.

Source: EDELWEISS 6 CSR (data on file)⁶¹

B.2.6.2.2 EDELWEISS 3 and EDELWEISS 6 | Secondary endpoints | Number of days in hospital

Hospitalisations were infrequent throughout the EDELWEISS 3 and EDELWEISS 6 studies, with <2% of patients hospitalised at any measured time point (and most time points having 0% hospitalisation). For this reason, it was not deemed necessary to incorporate into the economic modelling.

B.2.6.2.3 EDELWEISS 3 and EDELWEISS 6 | Secondary endpoints | Physician/Subject Surgery Intention Question

The reductions in EAP resulted in a reduced intention for surgery after 6 months in EDELWEISS 3 based on both the PSIQ and SSIQ with linzagolix versus placebo (Table 15).

Table 15: EDELWEISS 3 | Change from baseline in intention for surgery: analysis of covariance (FAS)

	EDELWEISS 3		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)
PSIQ			
Baseline, mean (SD)	4.1 (2.7)	4.0 (2.8)	4.4 (2.7)
Month 6			
LSM (95% CI)	-0.8 (-1.2, -0.5)	-1.5 (-1.8, -1.1)	-1.5 (-1.9, -1.2)
LSM difference vs placebo (97.5% CI)		-0.6 (-1.2, 0.0) p=0.037 ^a	-0.7 (-1.3, -0.1) p=0.017 ^a
SSIQ			
Baseline, mean (SD)	5.2 (3.2)	5.2 (3.1)	5.5 (3.3)
Month 6			
LSM (95% CI)	-0.7 (-1.1, 0.3)	-1.5 (-1.9, -1.1)	-1.6 (-2.1, -1.2)
LSM difference vs placebo (97.5% CI)		-0.8 (-1.5, -0.1) p=0.022 ^a	-0.9 (-1.6, -0.2) p=0.005 ^a

Abbreviations: ABT, add-back therapy; CI, confidence interval; FAS, full analysis set; LSM, least squares mean; PSIQ, Physician Surgery Intention Question; SD, standard deviation; SSIIQ, Subject Surgery Intention Question. Answers ranged from 0-Not at all to 10-Very likely.

Analysis of covariance at each timepoint or discontinuation with change from baseline as response variable, baseline value and treatment as covariates.

^aBonferroni-corrected p-value.

Source: EDELWEISS 3 CSR (data on file)⁵⁹

The reduction from baseline to EDELWEISS 3, month 6, on the PSIQ in the linzagolix 200 mg plus ABT group became more pronounced at EDELWEISS 6, month 12, while the previous reduction on the SSIIQ remained stable (Table 16), i.e. the longer patients received linzagolix, the lower the desire of physicians to recommend surgery. For patients themselves, the desire for surgery was reduced at month 6 after introducing linzagolix but this did not change further at month 12.

Table 16: EDELWEISS 6 | Change from baseline in intention for surgery (TEAS)

	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
PSIQ				
Baseline, mean (SD)	4.5 (2.4)	4.0 (2.6)	4.0 (2.7)	4.6 (2.7)
Mean (SD) change from baseline				
Month 6	-1.1 (3.0)	-0.7 (2.4)	-1.5 (2.1)	-2.0 (2.8)

Month 12	-1.5 (2.8)	-1.6 (2.8)	-1.8 (2.6)	-2.7 (2.8)
SSIQ				
Baseline, mean (SD)	5.7 (2.9)	5.1 (3.1)	5.4 (3.0)	5.5 (3.2)
Mean (SD) change from baseline				
Month 6	-1.0 (2.9)	-0.6 (2.8)	-1.4 (2.7)	-1.9 (3.4)
Month 12	-2.1 (3.0)	-1.7 (3.7)	-1.6 (3.5)	-1.9 (3.7)

Abbreviations: ABT, add-back therapy; PSIQ, Physician Surgery Intention Question; SD, standard deviation; SSIQ, Subject Surgery Intention Question; TEAS, Treatment Extension Analysis Set.

Answers ranged from 0-Not at all to 10-Very likely.

Source: EDELWEISS 6 CSR (data on file)⁶¹

B.2.6.2.4 EDELWEISS 3 and EDELWEISS 6 | Secondary endpoints | Health-related quality of life

In parallel with the observed reductions in EAP and the ability to perform daily activities based on EHP-30 pain scores (as reported with other ranked secondary endpoints in Table 12) with linzagolix 200 mg plus ABT versus placebo in EDELWEISS 3, there were improvements in broader HRQoL aspects (Table 17).⁵⁹ The EHP-30 dimensions of 'control and powerlessness', 'emotional wellbeing', 'social support' and 'self-image' also showed statistically significant improvements (score reductions) from baseline to month 6 in the linzagolix 200 mg plus ABT group versus placebo, although improvement in the 'modular sexual relationship' dimension was not statistically significant versus placebo (Table 17). The improvement (increase) in EQ-5D-5L Index and VAS scores from baseline to month 6 was also significantly greater with linzagolix 200 mg plus ABT versus placebo.

Table 17: EDELWEISS 3 | Change from baseline in health-related quality of life (FAS)

	EDELWEISS 3		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)
EHP-30 Pain^a			
Baseline, mean (SD)	51.77 (14.43)	51.46 (14.28)	52.37 (15.14)
Change from baseline to month 6			
LSM (95% CI)	-19.47 (-22.66; -16.28)	-27.37 (-30.50, -24.25)	-35.60 (-38.73, -32.48)
LSM difference vs placebo (97.5% CI)		-7.90 (-13.01, -2.79) p=0.001 ^b	-16.13 (-21.24, -11.02) p<0.001 ^b
EHP-30 Control and powerlessness^a			
Baseline, mean (SD)	58.36 (19.47)	55.53 (20.92)	60.65 (19.93)
Change from baseline to month 6			

LSM (95% CI)	-21.75 (-25.63, -17.88)	-28.12 (-31.93, -24.31)	-37.38 (-41.19, -33.58)
LSM difference vs placebo (97.5% CI)		-6.36 (-12.59, -0.14) p=0.044 ^b	-15.63 (-21.84, -9.42) p<0.001 ^b
EHP-30 Emotional wellbeing^a			
Baseline, mean (SD)	46.18 (19.51)	46.50 (20.32)	47.27 (20.58)
Change from baseline to month 6			
LSM (95% CI)	-12.57 (-16.13, -9.01)	-19.04 (-22.52, -15.57)	-22.03 (-25.52, -18.54)
LSM difference vs placebo (97.5% CI)		-6.47 (-12.17, -0.78) p=0.022 ^b	-9.46 (-15.17, -3.76) p<0.001 ^b
EHP-30 Social support^a			
Baseline, mean (SD)	45.21 (25.10)	44.79 (25.33)	47.05 (25.42)
Change from baseline to month 6			
LSM (95% CI)	-13.82 (-17.69, -9.95)	-18.48 (-22.25, -14.70)	-25.89 (-29.68, -22.10)
LSM difference vs placebo (97.5% CI)		-4.65 (-10.85, 1.54) p=0.183 ^b	-12.07 (-18.27, -5.87) p<0.001 ^b
EHP-30 Self-image^a			
Baseline, mean (SD)	41.56 (25.76)	42.57 (23.96)	43.97 (25.79)
Change from baseline to month 6			
LSM (95% CI)	-9.57 (-13.31, -5.84)	-16.43 (-20.07, -12.78)	-20.69 (-24.34, -17.03)
LSM difference vs placebo (97.5% CI)		-6.86 (-12.83, -0.88) p=0.020 ^b	-11.11 (-17.10, -5.13) p<0.001
EHP-30 Modular sexual relationship^a			
Baseline, mean (SD)	56.90 (25.08)	53.63 (24.86)	59.96 (23.43)
Change from baseline to month 6			
LSM (95% CI)	-20.55 (-24.96, -16.14)	-22.59 (-27.00, -18.18)	-26.79 (-31.14, -22.44)
LSM difference vs placebo (97.5% CI)		-2.04 (-9.18, 5.10) p=1.000 ^b	-6.24 (-13.33, 0.86) p=0.097 ^b
EQ-5D-5L Index value^c			
Baseline, mean (SD)	0.72 (0.16)	0.74 (0.16)	0.74 (0.15)
Change from baseline to month 6			
LSM (95% CI)	0.08 (0.06, 0.10)	0.11 (0.08, 0.13)	0.12 (0.10, 0.15)

LSM difference vs placebo (97.5% CI)		0.03 (-0.01, 0.06) p=0.190 ^b	0.05 (0.01, 0.08) p=0.009 ^b
EQ-5D-5L VAS score^d			
Baseline, mean (SD)	61.9 (19.6)	63.8 (19.7)	62.0 (19.8)
Change from baseline to month 6			
LSM (95% CI)	5.4 (1.9, 8.8)	9.4 (6.0, 12.7)	14.6 (11.2, 18.0)
LSM difference vs placebo (97.5% CI)		4.0 (-1.5, 9.5) p=0.209 ^b	9.2 (3.7, 14.7) p<0.001 ^b

Abbreviations: ABT, add-back therapy; CI, confidence interval, EHP-30, Endometriosis Health Profile-30; EQ-5D-5L: EuroQoL 5-Dimension 5-Level; FAS, full analysis set; SD, standard deviation; VAS, visual analogue scale.

^aEHP-30 Scale Score was computed as the sum of each scale question score/(number of items*4)*100 and ranges from 0 (best possible health status) to 100 (worst possible health status).

^bBonferroni-corrected p-value.

^cThe index score ranges from -0.109 to 1. A higher Index value indicates a better quality of life.

^dThe VAS Score ranges from 0 to 100. A higher VAS score indicates a better quality of life.

Scores were computed as mean of daily assessments on the last 28 days prior to each visit or discontinuation.

Analysis of covariance at each timepoint with change from baseline as response variable, baseline value and treatment as covariates.

Subjects with less than 43% of daily diary data completed were excluded.

Source: EDELWEISS 3 CSR (data on file)⁵⁹

Improvements from baseline in the EHP-30 dimensions of pain, control and powerlessness, emotional wellbeing, social support, self-image and sexual relationship and EQ-5D-5L Index and VAS scores continued to be observed with linzagolix 200 mg plus ABT up to month 12 in EDELWEISS 6.⁶¹

B.2.6.3 Efficacy conclusions

The efficacy of up to 12 months of treatment with linzagolix 200 mg plus ABT for moderate-to-severe EAP in women of reproductive age was confirmed in the Phase 3 EDELWEISS 3 study and its extension study EDELWEISS 6.

The daily dose of linzagolix 200 mg plus ABT met the primary endpoint of EDELWEISS 3, demonstrating clinically meaningful and statistically significant reductions in dysmenorrhoea and NMPP at month 3 versus placebo, with stable or reduced use of analgesics. At month 3, the estimated percentage of responders for dysmenorrhoea was 72.9% (95% CI: 65.3–79.4) in the linzagolix 200 mg plus ABT group versus 23.5% (95% CI: 17.5–30.7) in the placebo group (OR 8.80 [97.5% CI: 4.86–15.91]; p<0.001). Respective proportions for NMPP were 47.3% (95% CI:

39.5–55.3) with linzagolix 200 mg plus ABT versus 30.9% (95% CI: 24.1–38.6) with placebo (OR 2.01 [97.5% CI: 1.18–3.42]; p=0.007).

Significant reductions in dysmenorrhoea and NMPP were observed at month 6 for linzagolix 200 mg plus ABT versus placebo. This was accompanied by statistically significant improvements in the ranked secondary endpoints of dyschezia, OPP and ability to participate in daily activities (based on pain dimensions listed in the EHP-30).

The clinically meaningful improvements observed at month 6 (end of EDELWEISS 3 treatment period) generally improved further at month 12 in the EDELWEISS 6 extension study. Reductions in EAP resulted in a reduced intention for surgery after 6 months in EDELWEISS 3 based on both the PSIQ and SSIQ in patients who received linzagolix versus placebo; the reduction from baseline to month 6 on the PSIQ became more pronounced at month 12 in EDELWEISS 6.

Reductions in EAP were also accompanied by improved HRQoL as shown by improved scores for the EHP-30 and EQ-5D-5L Index and VAS.

B.2.7 Subgroup analyses

Pre-planned subgroup analyses for EDELWEISS 3 are listed in Section B.2.3 (Table 4), although some planned analyses (based on race, ethnicity, history of pregnancy) were not performed due to small patient numbers.⁵⁹ Subgroup analyses for the co-primary endpoints for EDELWEISS 3 showed consistent results across analysed pre-planned subgroups.⁵⁹ Forest plots for subgroup analyses of the co-primary endpoints are presented in Appendix E.

Dyspareunia for patients with a mean dyspareunia score >1 at baseline was the only pre-planned subgroup analysis for EDELWEISS 6. Data for dyspareunia for patients with a mean dyspareunia score >1 at baseline were consistent with those in the main analyses for both EDELWEISS 3 and EDELWEISS 6.

EDELWEISS 3 subgroup analyses for BMD showed more bone loss in all sites in patients aged ≥ 35 years, those weighing < 63 kg and those with a BMI < 23 kg/m² (Appendix E).^{58,59}

B.2.8 Meta-analysis

A network meta-analysis was not performed as there was only one randomised controlled trial for linzagolix 200 mg plus ABT (EDELWEISS 3^{58,59} and its extension study EDELWEISS 6⁶¹).

B.2.9 Indirect and mixed treatment comparisons

In the absence of head-to-head data, an ITC was performed using the Bucher analysis method to compare the efficacy and safety of linzagolix 200 mg plus ABT with leuprorelin, the pharmacological comparator of relevance to the decision problem using published evidence from the clinical SLR (see Section B.2.1 and Appendix D). The efficacy outcomes analysed in the ITC were based on those specified in the final scope issued by NICE and the availability of data reported in the literature.

Table 18: Outcomes assessed in the ITC

Outcome	Analyses	Output statistics
Efficacy outcomes: - Dysmenorrhoea - NMPP - OPP - EHP-30 (pain dimension) - Dyspareunia Safety outcomes: - BMD at lumbar spine - TEAEs	Logistic regression	Risk difference, mean difference or odds ratios with 95% CIs

Abbreviations: BMD, bone mineral density; CI, confidence interval; EHP-30, Endometriosis Health Profile-30; ITC, indirect treatment comparison; NMPP, non-menstrual pelvic pain; OPP, overall pelvic pain; TEAE, treatment-emergent adverse event.

Various surgical techniques are recommended in guidelines for the treatment of EAP, however due to the invasiveness of these procedures they may be considered following initial hormonal treatment (see Section B.1.3.4).^{34,37} An SLR was conducted to identify relevant evidence and assess the feasibility of a comparison of

efficacy and safety of minimally invasive surgical procedures versus linzagolix in combination with ABT. Full details of the SLR and feasibility assessment are provided in Appendix M.

Four relevant publications reporting outcomes following surgical procedures were identified for further comprehensive analysis (Table 19). The studies are highly heterogeneous, with considerable differences that precluded an ITC with linzagolix plus ABT:

- definitions of endometriosis severity varied in the trials, with some studies lacking the specific severity measure altogether;
- the diagnostic processes in the studies on surgeries were inconsistent with the diagnostic process in the EDELWEISS 3 trial;
- limited baseline characteristics suitable for comparison were available in the publications of interest;
- the publications identified for surgery were published ≥ 20 years ago. Since then, multiple improvements and modifications have been made regarding the training of professionals and the approach to the perioperative care;
- in some cases, a lack of a common comparator was a considerable limitation;
- outcomes were defined and measured differently. Adjusting of the identified results for surgeries to match the results for linzagolix is unfeasible or highly limited.

Considering the aforementioned factors, conducting an ITC between linzagolix and the currently recommended minimally invasive surgical treatments for endometriosis is not feasible.

Table 19. Summary of inconsistencies across the identified trials that were potentially eligible to use in an ITC

PICOS	Potentially relevant studies and the reasons for ineligibility for an ITC			
	<i>Abbott 2004</i> ⁶⁹	<i>Johnson 2004</i> ⁷⁰	<i>Sutton 1994</i> ⁷¹	<i>Zullo 2003</i> ⁷²
Population	- The severity of endometriosis was not specified; - Diagnosis of endometriosis confirmed at the time of surgery in the trial instead of prior to enrolling to the trial; - Baseline characteristics were limited compared with those in the EDELWEISS 3 trial	- The severity of endometriosis was not specified; - Diagnosis of endometriosis confirmed at the time of surgery in the trial instead of prior to enrolling to the trial; - Baseline characteristics were limited compared with those in the EDELWEISS 3 trial	- Patients with endometriosis of different severity compared to EDELWEISS 3 trial were included (i.e., defined based on the AFS scale); - The timing of the definitive diagnosis of endometriosis not specified; - Baseline characteristics were limited compared with those in the EDELWEISS 3 trial	- Narrower population compared to EDELWEISS 3 trial (i.e., patients with severe dysmenorrhoea were included); - Diagnosis of endometriosis was not histological/laparoscopic; - Baseline characteristics were limited compared with those in the EDELWEISS 3 trial
Intervention	The trials were published 20 or more years ago. Since the publication of the studies, changes to the surgical training programme were implemented and NICE's guideline (24) establishing specific standards and recommendations for perioperative care was introduced			
Comparator	No limitations	Lack of common comparator	No limitations	Lack of common comparator
Outcomes	- Data presented on VAS scale instead of VRS and NRS; - Data related to pain gathered differently compared with EDELWEISS 3 trial; - Mean (SD) values at timepoint reported for pain instead of required values (i.e., mean [SD] change from baseline); - The proportion of responders defined differently compared with EDELWEISS 3 trial; - No safety analysis provided	- Data presented on VAS scale instead of VRS and NRS; - The proportion of responders defined differently compared with EDELWEISS 3 trial; - Safety analysis focused on surgery-related complications	- Data presented on VAS scale instead of VRS and NRS; - Data related to pain gathered differently compared with EDELWEISS 3 trial; - Median value for pain reported instead of required values (i.e., mean [SD] change from baseline); - The proportion of responders defined differently compared with EDELWEISS 3 trial; - Safety analysis focused on surgery-related complications	- Data presented on VAS scale instead of VRS and NRS; - Data related to pain gathered differently compared with EDELWEISS 3 trial; - Mean (SD) values at timepoint reported for pain instead of required values (i.e., mean [SD] change from baseline); - The proportion of responders defined differently compared with EDELWEISS 3 trial; - Safety analysis focused on surgery-related complications

Abbreviations: AFS, American Fertility Society; ITC, indirect treatment comparison; NRS, numerical rating scale; PICOS, Population, intervention, outcomes, study design; SD, standard deviation; VAS, visual analogue scale; VRS, verbal rating scale

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

As described in Section B.2.1 and Appendix D, an SLR was conducted in September 2024. Of the 22 studies identified for the intervention (n=2) and comparators (n=20), only two studies relating to linzagolix and leuporelin were eligible according to the scope for this submission. The PICOS criteria used for the ITC are presented in Appendix D.

B.2.9.2 Risk of bias

The methodological quality of each trial was assessed independently by two reviewers using the Cochrane Collaboration's revised risk-of-bias tool for randomised trials (RoB 2).⁷³ Disagreements were resolved by consensus. The risk of bias was defined as low for all the trials included in the Bucher analysis. Further details can be found in Appendix D.

B.2.9.3 Overview of the selected studies

The SLR identified the EDELWEISS⁵⁷ and EDELWEISS 3⁵⁸ studies for linzagolix in EAP and 20 comparator trials (described in 18 publications) The studies considered to be suitable for inclusion in the ITC Bucher analysis are presented in (Table 20).

The SLR for the comparators searched for trials that could be compared with the trials found in the review for the intervention (linzagolix 200 mg plus ABT). Therefore, only studies with 12 or 24 weeks of follow-up were included in the ITC for the efficacy analysis. Safety was assessed using the longest available follow-up period of 24 weeks.

Although two linzagolix studies (EDELWEISS 3, EDELWEISS) were identified from the SLR, only the EDELWEISS 3 trial was included in the ITC. The EDELWEISS study was a dose-ranging phase 2b study that included a dose of linzagolix 200 mg alone (without ABT) and was not included in the ITC for the efficacy analysis due to a lack of alignment of clinically relevant endpoints for inclusion in the treatment

comparison. In addition, safety in the EDELWEISS study was only assessed for 12 weeks, so this study could not be included in the ITC for the safety analysis.

Reasons for exclusion of other studies from the ITC included: comparator therapy not relevant to the scope of this submission; no placebo group for comparison with the intervention arm; data displayed only graphically, without detailed breakdown for analysis; outcomes data did not include standard deviation/standard error; lack of clarity of scale used. Further details regarding the rationale for inclusion/exclusion of individual comparator trials on the basis of heterogeneity can be found in Appendix D.

Table 20: Trials included in the Bucher analysis

Study name	Intervention	N	Phase	Study design
EDELWEISS 3 (Donnex et al 2024) ⁵⁸	Linzagolix 200 mg plus ABT Placebo	162 162	3	RCT, double-blind, placebo-controlled, parallel-group, multi-centre, multinational study
Osuga et al 2021a/Osuga et al 2021b ^{74,74,75}	Leuprorelin 3.75 mg Relugolix 10 ,20 or 40 mg ^a Placebo	69 77	2	RCT and open-label ^b , multi-centre, parallel-group, long-term extension

^aThe relugolix arm was not included in the analysis as it was administered with add-back therapy

^bThis study was designed as an open-label study but randomisation information for the study drug was not broken until the last patient in the study was assessed and observed at week 24

Abbreviations: ABT, add-back therapy; RCT, randomised controlled trial

B.2.9.4 Heterogeneity assessment of trials included

Consistently reported inclusion/exclusion criteria were age, diagnosis of endometriosis, menstrual cycle, presence of dysmenorrhoea and pelvic pain, history of surgery, and need for treatment.

No trials were excluded from the Bucher analysis because of their inclusion/exclusion criteria. The effect of different inclusion/exclusion criteria was assessed by reviewing the baseline characteristics. The included trials used similar inclusion criteria for age, endometriosis diagnosis and interval between menstrual cycles. Although the trials all included adult premenopausal women with moderate to severe EAP as measured by dysmenorrhoea and NMPP, the scales used to measure dysmenorrhoea and NMPP scores differed between trials. The heterogeneity assessment confirmed the feasibility of an ITC between linzagolix

versus leuprorelin. Further details regarding heterogeneity are presented in Appendix D.

B.2.9.5 Methods

An ITC was conducted using the Bucher method performed in R version 4.3.2. The Bucher method can only be applied to two-arm trials. The main assumption is that the relative efficacy of a treatment is the same in all trials included in the ITC to allow the indirect comparison of A versus C when direct evidence of A versus B and B versus C is available.

The results of the included trials were analysed to determine whether it was possible to construct a network of relationships between the different arms of the trials. The methodology of each study and patient baseline characteristics were also analysed to identify differences between the trials that might have an impact on the health outcomes. Non-inferiority was defined based on p-values of >0.05 for the ITC, indicating no statistically significant difference between the treatments.

Detailed methods for the ITC are presented in Appendix D.

B.2.9.6 ITC results

B.2.9.6.1 Efficacy of linzagolix versus leuprorelin

The ITC revealed no significant difference between linzagolix and leuprorelin (Table 21) for efficacy at 12 and 24 weeks.

Table 21: Bucher ITC for the efficacy of linzagolix versus leuporelin at week 12 and week 24

Outcome	Linzagolix 200 mg plus ABT versus placebo	Leuporelin 3.75 mg versus placebo	Indirect comparison	
	Mean difference (95% CI)		Mean difference (95% CI)	p-value
Week 12				
Dysmenorrhoea (VRS)	-1.06 (-1.25, -0.87)	-1 (-1.15, -0.85)	-0.06 (-0.30, 0.18)	0.63
NMPP (VRS)	-0.24 (-0.38, -0.1)	-0.2 (-0.32, -0.08)	-0.04 (-0.22, 0.14)	0.67
Week 24				
Dysmenorrhoea (VRS)	-1.22 (-1.41, -1.03)	-1 (-1.17, -0.83)	-0.22 (-0.47, 0.03)	0.09
NMPP (VRS)	-0.27 (-0.43, -0.11)	-0.3 (-0.44, -0.16)	0.03 (-0.18, 0.24)	0.78
EHP-30 pain dimension	-16.93 (-21.9, -11.96)	-21 (-27.72, -14.28)	4.07 (-4.29, 12.43)	0.34
Dyspareunia (VRS)	-0.26 (-0.52, 0.0013)	-0.2 (-0.55, 0.15)	-0.06 (-0.50, 0.38)	0.79

Abbreviations: ABT, add-back therapy; CI, confidence interval; EHP-30, endometriosis health profile-30; ITC, indirect treatment comparison; VRS, verbal rating scale
All outcomes showed no statistically significant difference between linzagolix versus leuporelin ($p > 0.05$).

B.2.9.6.2 Safety of linzagolix versus leuporelin

The safety of linzagolix was comparable to leuporelin (Table 22), although some statistically significant differences between these treatments are discussed in this section.

Linzagolix demonstrated a statistically significantly reduced impact on lumbar spine BMD (possibly due to the use of ABT with linzagolix) and lower incidence of hot flushes versus leuporelin, although the incidence of serious TEAEs was statistically significantly higher with linzagolix versus leuporelin (Table 22). However, the incidence of serious TEAEs was similar for both treatments (1.2% for linzagolix⁵⁸, 0.0% for leuporelin⁷⁴) and the significant difference was likely driven by the relatively high incidence of serious TEAEs in the placebo group of the Osuga et al study (5.2%) versus the EDELWEISS 3 study (0.0%).

Table 22: Bucher ITC for the safety of linzagolix versus leuporelin at week 24

Outcome	Linzagolix 200 mg plus ABT versus placebo	Leuporelin 3.75 mg versus placebo	Indirect comparison	
	Mean difference (95% CI)		Mean difference (95% CI)	p-value
Lumbar spine BMD	-0.02 (-0.03, -0.01)	-4.2 (-4.82, -3.58)	4.18 (3.56; 4.80)	<0.001*
	Risk difference (95% CI)		Risk difference (95% CI)	p-value
TEAEs	0.1 (-0.01, 0.21)	0.16 (0.08, 0.25)	-0.06 (-0.20, 0.08)	0.40
Severe TEAEs	0.01 (-0.02, 0.03)	-0.02 (-0.06, 0.01)	0.03 (-0.01, 0.07)	0.17
Serious TEAEs	0.01 (-0.01, 0.03)	-0.05 (-0.1, -0.003)	0.06 (0.01, 0.11)	p=0.03*
TEAEs leading to permanent discontinuation of study drug	0.01 (-0.03, 0.04)	0.05 (-0.03, 0.13)	-0.04 (-0.13, 0.05)	0.37
Incidence of hot flushes	0.04 (-0.002, 0.09)	0.38 (0.26, 0.5)	-0.34 (-0.47, -0.21)	<0.001*
Incidence of headaches	0.02 (-0.04, 0.09)	0.03 (-0.06, 0.13)	-0.01 (-0.13, 0.11)	0.86

*Lumbar spine BMD loss and the incidence of hot flushes was statistically significantly lower with linzagolix versus leuporelin; the incidence of serious TEAEs was statistically significantly higher with linzagolix versus leuporelin; all other outcomes showed no statistically significant difference between treatments ($p>0.05$). Abbreviations: ABT, add-back therapy; BMD, bone mineral density; CI, confidence interval; ITC, indirect treatment comparison; TEAE, treatment-emergent adverse event

B.2.9.7 ITC conclusions

The ITC using the Bucher method, suggests that there is no significant difference in terms of efficacy between linzagolix 200 mg plus ABT and leuporelin at both week 12 and week 24. Furthermore, linzagolix appeared to have comparable safety to leuporelin at week 24 in terms of any TEAE, severe TEAE, TEAE leading to permanent discontinuation of study drug and headache. In addition, linzagolix showed significantly lower incidence of hot flushes than leuporelin monotherapy.

B.2.10 Adverse reactions

Key safety evidence from EDELWEISS 3 and 6 is presented in this section; this is supported by adverse event data from the terminated EDELWEISS 2 study (see Section B.2.2). The safety profile for linzagolix in women with EAP was consistent with that observed previously for women with uterine fibroids.^{10,76} Linzagolix showed good overall tolerability, with TEAEs similar to placebo.

B.2.10.1 Treatment compliance and exposure

B.2.10.1.1 EDELWEISS 3 and EDELWEISS 2 | Treatment compliance and exposure up to month 6

The median treatment duration in EDELWEISS 3 was 24 weeks for each group, with ≥50% of patients remaining on treatment for between 23.6 and 24.2 weeks (Table 23).^{58,59}

In EDELWEISS 2, the median treatment duration and time on study were longer for patients in the linzagolix groups versus the placebo group (Table 23), which aligned with higher dropout rates from approximately month 2 in the placebo versus linzagolix groups.⁶³

Treatment compliance was high in EDELWEISS 3 and EDELWEISS 2, with a median in all treatment groups of 100% in EDELWEISS 3 and >90% in EDELWEISS 2.^{59,63} Approximately 75% of patients in EDELWEISS 3 had a compliance of ≥98%.⁵⁹

Table 23: EDELWEISS 3 and EDELWEISS 2 | Exposure to study treatment (EDELWEISS 3 FAS; EDELWEISS 2 SAF)

	EDELWEISS 3			EDELWEISS 2		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Placebo (N=27)	Linzagolix 75 mg (N=28)	Linzagolix 200 mg plus ABT (N=29)
Treatment duration, weeks^a						
Mean (SD)	22.22 (4.93)	22.18 (5.32)	22.72 (4.24)	14.50 (9.30)	18.34 (7.64)	15.76 (8.93)
Median (Q1, Q3)	24.00 (23.57, 24.14)	24.00 (23.57, 24.21)	24.00 (23.71, 24.14)	14.57 (4.29, 24.14)	23.64 (12.21, 24.07)	18.14 (8.00, 24.14)
Range	1.1–25.9	0.1–26.1	1.6–27.9	0.1–25.0	1.4–25.3	0.1–25.0
Time on study, weeks^b						
Mean (SD)	25.68 (11.66)	25.13 (10.35)	26.41 (9.84)	18.51 (11.90)	20.43 (8.66)	17.46 (8.39)
Median (Q1, Q3)	24.00 (23.71, 24.57)	24.00 (23.71, 24.29)	24.00 (23.86, 24.57)	14.86 (9.71, 24.84)	23.86 (14.50, 24.29)	19.86 (10.14, 24.29)
Range	1.4–84.3	0.1–78.0	1.7–72.1	3.1–50.9	4.1–46.4	0.1–29.0

Abbreviations: ABT, add-back therapy; eCRF, electronic case report form; FAS, full analysis set; Q, quartile; SAF, safety analysis set; SD, standard deviation

^aDuration of treatment (weeks) was defined as: [(date of last treatment administration) - (date of first administration as collected in the eCRF) +1] / 7;

^bThe time on study (weeks) was defined as: [(end of study date) – (date of first dose) +1]/7.

Source: EDELWEISS 3 CSR (data on file);⁵⁹ EDELWEISS 2 CSR (data on file)⁶³

B.2.10.1.2 EDELWEISS 6 | Treatment compliance and exposure up to month 12

In the extension study period (EDELWEISS 6), the median treatment duration for each treatment group was 24 weeks and the median time on study was 49 weeks. In the overall study period (EDELWEISS 3 and EDELWEISS 6) the median treatment duration was 48 weeks and the median time on study was 73 weeks (Table 24).⁶¹ Treatment compliance was high, with a median of 100% in all groups. Approximately 75% of patients had compliance of around $\geq 99\%$.

Table 24: EDELWEISS 6 | Exposure to study treatment (TEAS)

	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
Treatment duration in extension study, weeks^a				
Mean (SD)	22.29 (5.20)	23.12 (2.89)	22.41 (4.65)	23.02 (3.53)
Median (Q1, Q3)	24.00 (23.71, 24.29)	24.00 (23.86, 24.29)	24.00 (23.71, 24.14)	24.00 (23.71, 24.14)
Range	4.0–24.9	9.3–25.4	3.3–27.1	4.0–27.0
Treatment duration overall, weeks^b				
Mean (SD)	46.43 (4.92)	47.37 (2.45)	46.49 (4.51)	47.17 (3.39)
Median (Q1, Q3)	48.00 (47.71, 48.29)	48.00 (47.86, 48.43)	48.00 (47.57, 48.29)	48.00 (47.86, 48.29)
Range	28.3–49.3	39.0–49.9	27.6–50.9	31.9–51.4
Time on extension study, weeks^c				
Mean (SD)	47.55 (13.38)	48.21 (12.78)	49.32 (13.40)	50.47 (13.27)
Median (Q1, Q3)	48.43 (47.29, 50.29)	48.86 (47.71, 50.29)	48.79 (47.29, 51.29)	49.14 (47.86, 52.43)
Range	4.3–75.1	5.0–78.4	4.0–82.4	4.1–82.0
Time on study overall, weeks^d				
Mean (SD)	71.69 (13.18)	72.46 (12.53)	73.40 (13.31)	74.62 (13.16)
Median (Q1, Q3)	72.86 (71.29, 74.14)	72.46 (71.71, 74.57)	72.57 (71.43, 75.14)	73.29 (71.71, 77.00)
Range	28.4–99.3	34.7–103.4	27.9–106.6	32.0–105.4

Abbreviations: ABT, add-back therapy; eCRF, electronic case report form; Q, quartile; SD, standard deviation; TEAS, treatment extension analysis set

^aDuration of treatment in extension (weeks) was defined as: [(date of last treatment administration in extension) - (date of first administration in extension as collected in the eCRF) + 1] / 7; ^bDuration of treatment overall (weeks) was defined as: [(date of last treatment administration in extension) - (date of first administration in EDELWEISS 3 as collected in the eCRF) + 1] / 7; ^cThe time on study in extension (weeks) was defined as: [(end of extension study date) - (date of first dose in extension) + 1] / 7; ^dThe time on study overall (weeks) was defined as: [(end of extension study date) - (date of first dose in EDELWEISS 3) + 1] / 7.

Source: EDELWEISS 6 CSR (data on file)⁶¹

B.2.10.2 Summary of treatment-emergent adverse events

B.2.10.2.1 EDELWEISS 3 and EDELWEISS 2 | Summary of treatment-emergent adverse events up to month 6

Linzagolix was well tolerated, with similar percentages of patients reporting TEAEs in the linzagolix 75 mg and placebo groups (46.9% in each group) during the 6-month treatment period in EDELWEISS 3; slightly higher rates of TEAEs were observed in the linzagolix 200 mg plus ABT group (56.8%; Table 25). In EDELWEISS 2, the percentages of patients reporting TEAEs were similar between placebo and linzagolix groups. In both studies, most TEAEs were mild or moderate in intensity, and the incidence of severe TEAEs was low and comparable between groups. No fatal or suicide-related TEAEs were reported.

Table 25: EDELWEISS 3 and EDELWEISS 2 | Summary of adverse events up to month 6 (SAF)

TEAEs, n (%)	EDELWEISS 3			EDELWEISS 2		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Placebo (N=27)	Linzagolix 75 mg (N=28)	Linzagolix 200 mg plus ABT (N=29)
Any TEAE	76 (46.9)	75 (46.9)	92 (56.8)	14 (51.9)	14 (50.0)	15 (51.7)
Severe TEAEs	2 (1.2)	5 (3.1)	3 (1.9)	2 (7.4)	0	0
TEAEs related to linzagolix	40 (24.7)	45 (28.1)	56 (34.6)	4 (14.8)	4 (14.3)	7 (24.1)
TEAEs related to ABT	33 (20.4)	33 (20.6)	45 (27.8)	4 (14.8)	4 (14.3)	5 (17.2)
Serious adverse events	0	2 (1.3)	2 (1.2)	0	0	0
Serious TEAEs	0	1 (0.6)	2 (1.2)	0	0	0
Serious TEAEs related to linzagolix	0	0	0	0	0	0
Serious TEAEs related to ABT	0	0	0	0	0	0
TEAEs leading to permanent discontinuation of study drug	4 (2.5)	9 (5.6)	5 (3.1)	2 (7.4)	1 (3.6)	2 (6.9)
Fatal TEAEs	0	0	0	0	0	0

Abbreviations: ABT, add-back therapy; SAF, safety analysis set; TEAE, treatment-emergent adverse event
Source: Donnez et al 2024,⁵⁸ EDELWEISS 3 CSR (data on file);⁵⁹ EDELWEISS 2 CSR (data on file)⁶³

B.2.10.2.2 EDELWEISS 6 | Summary of treatment-emergent adverse events from month 6 to month 12

Linzagolix continued to be well tolerated during EDELWEISS 6, with no additional safety signals observed during the extension study treatment period or post-treatment follow-up period (follow-up safety analysis set [FU SAF]).⁶¹ More than 40% of patients reported TEAEs between month 6 and the end of the treatment period at month 12. The percentage of patients reporting ≥ 1 TEAE was comparable across treatment groups (Table 26). Most TEAEs (approximately 99% overall) were mild or moderate in intensity. No fatal or suicide-related TEAEs were reported.

Table 26: EDELWEISS 6 | Summary of adverse events from month 6 to month 12 (ESAF)

TEAEs, n (%)	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)
Any TEAE	27 (46.6)	27 (47.4)	53 (44.5)	49 (40.2)
Severe TEAEs	1 (1.7)	2 (3.5)	1 (0.8)	1 (0.8)
TEAEs related to linzagolix	13 (22.4)	14 (24.6)	19 (16.0)	23 (18.9)
TEAEs related to ABT	10 (17.2)	8 (14.0)	14 (11.8)	13 (10.7)
Serious TEAEs	0	1 (1.8)	3 (2.5)	0
Serious TEAEs related to linzagolix	0	0	0	0
Serious TEAEs related to ABT	0	0	1 (0.8)	0
TEAEs leading to permanent discontinuation of study drug	2 (3.4)	2 (3.5)	3 (2.5)	2 (1.6)
Fatal TEAEs	0	0	0	0

Abbreviations: ABT, add-back therapy; ESAF, extension safety analysis set; TEAE, treatment-emergent adverse event

Source: EDELWEISS 6 CSR (data on file)⁶¹

B.2.10.3 Most common treatment-emergent adverse events

B.2.10.3.1 EDELWEISS 3 and EDELWEISS 2 | Most common treatment-emergent adverse events up to month 6

The most common TEAEs were headaches, which were reported for similar proportions of patients in each group.⁵⁸ Hot flushes were more common in the linzagolix groups than the placebo group in EDELWEISS 3. Rates of fatigue were similar in the linzagolix 75 mg and placebo groups, but slightly higher in the linzagolix 200 mg plus ABT group in EDELWEISS 3 (Table 27). Data from EDELWEISS 2 were generally in line with those from EDELWEISS 3, but interpretability was limited by the low patient numbers.

Table 27: EDELWEISS 3 and EDELWEISS 2 | TEAEs reported up to month 6 by ≥5% of patients in any group in EDELWEISS 3 (SAF)

TEAEs, n (%)	EDELWEISS 3			EDELWEISS 2		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Placebo (N=27)	Linzagolix 75 mg (N=28)	Linzagolix 200 mg plus ABT (N=29)
Headache	13 (8.0)	13 (8.1)	17 (10.5)	2 (7.4)	2 (7.1)	2 (6.9)
Hot flush	4 (2.5)	12 (7.5)	11 (6.8)	1 (3.7)	1 (3.6)	1 (3.4)
Fatigue	4 (2.5)	6 (3.8)	11 (6.8)	1 (3.7)	2 (7.1)	0
Anaemia	10 (6.2)	5 (3.1)	4 (2.5)	0	0	0
Mood swings	3 (1.9)	8 (5.0)	5 (3.1)	1 (3.7)	0	0
Arthralgia	2 (1.2)	8 (5.0)	3 (1.9)	0	0	0

Abbreviations: ABT, add-back therapy; MedDRA, Medical Dictionary for Regulatory Activities; SAF, safety analysis set; TEAE, treatment-emergent adverse event

Coded by MedDRA Version 23.0

Source: Donnez et al 2024;⁵⁸ EDELWEISS 3 CSR (data on file);⁵⁹ EDELWEISS 2 CSR (data on file)⁶³

B.2.10.3.2 EDELWEISS 6 | Most common treatment-emergent adverse events from month 6 to month 12

Headache and hot flushes were also among the most commonly reported TEAEs from month 6 to month 12 in EDELWEISS 6, along with COVID-19 and anaemia (Table 28).

Hot flushes were not reported for any patients in the placebo/linzagolix 200 mg plus ABT group and anaemia was not reported in the linzagolix 200 mg plus ABT group (Table 28).

Table 28: EDELWEISS 6 | TEAEs reported from month 6 to month 12 by ≥5% of patients in any group (ESAF)

TEAEs, n (%)	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)
COVID-19	1 (1.7)	2 (3.5)	6 (5.0)	6 (4.9)
Headache	3 (5.2)	3 (5.3)	5 (4.2)	3 (2.5)
Hot flush	4 (6.9)	0	4 (3.4)	5 (4.1)
Anaemia	3 (5.2)	2 (3.5)	7 (5.9)	0
Vaginal haemorrhage	1 (1.7)	3 (5.3)	3 (2.5)	3 (2.5)

Abbreviations: ABT, add-back therapy; COVID-19, coronavirus disease 2019; ESAF, extension safety analysis set; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event
Coded by MedDRA Version 23.0.

Source: EDELWEISS 6 CSR (data on file)⁶¹

B.2.10.4 Most common treatment-related adverse events

B.2.10.4.1 EDELWEISS 3 and EDELWEISS 2 | Most common treatment-related adverse events up to month 6

B.2.10.4.1.1 EDELWEISS 3 and EDELWEISS 2 | Most common linzagolix-related adverse events up to month 6

The most common TEAEs related to linzagolix treatment were hot flushes and headache (Table 29).

Table 29: EDELWEISS 3 and EDELWEISS 2 | TEAEs related to linzagolix treatment reported up to month 6 by ≥5% of patients in any group in EDELWEISS 3 (SAF)

TEAEs, n (%)	EDELWEISS 3			EDELWEISS 2		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Placebo (N=27)	Linzagolix 75 mg (N=28)	Linzagolix 200 mg plus ABT (N=29)
Headache	6 (3.7)	12 (7.5)	10 (6.2)	0	1 (3.6)	1 (3.4)
Hot flush	4 (2.5)	12 (7.5)	11 (6.8)	1 (3.7)	1 (3.6)	1 (3.4)
Mood swings	2 (1.2)	8 (5.0)	4 (2.5)	1 (3.7)	0	0

Abbreviations: ABT, add-back therapy; MedDRA, Medical Dictionary for Regulatory Activities; SAF, safety analysis set; TEAE, treatment-emergent adverse event

Coded by MedDRA Version 23.0

Source: EDELWEISS 3 CSR (data on file);⁵⁹ EDELWEISS 2 CSR (data on file)⁶³

B.2.10.4.1.2 EDELWEISS 3 and EDELWEISS 2 | Most common ABT-related adverse events up to month 6

Overall, 22.9% of patients in the EDELWEISS 3 safety analysis set reported TEAEs considered related to ABT.⁵⁹ The percentage of patients reporting TEAEs related to ABT was similar in the placebo (20.4%) and linzagolix 75mg (20.6%) groups and slightly higher in the linzagolix 200 mg ABT group (27.8%). The most common ABT-related TEAEs included headache (5.8%), fatigue (2.9%), nausea (2.9%), and hot flushes (2.7%). Nausea was observed with similar frequency in the placebo and linzagolix groups. Headache, fatigue and hot flushes were reported more frequently in the linzagolix groups compared with placebo.

In EDELWEISS 2, the number of patients reporting ABT-related TEAEs was similar between the placebo (n=4 patients), linzagolix 75 mg (n=4) and linzagolix 200 mg plus ABT (n=5) groups. In the placebo group, nausea, headache, chest discomfort, anxiety, and pain in extremities were reported by one patient each. In the linzagolix 75 mg group, nausea, abdominal distension, vomiting, headache, breast tenderness and non-cardiac chest pain were reported by one patient each. In the linzagolix 200 mg plus ABT group, two patients reported dizziness; nausea, upper abdominal pain, diarrhoea, headache, menstrual disorder, vaginal haemorrhage, nervousness and dyspnoea were reported by one patient each.

B.2.10.4.2 EDELWEISS 6 | Most common treatment-related adverse events from month 6 to month 12

B.2.10.4.2.1 EDELWEISS 6 | Most common linzagolix-related adverse events from month 6 to month 12

Most TEAEs related to linzagolix were reported by 1 to 2 patients in any treatment group with no discernible pattern.⁶¹ The most common linzagolix-related TEAEs included decreased bone density, hot flush and mood swings (Table 30).

Table 30: EDELWEISS 6 | TEAEs related to linzagolix treatment reported from month 6 to month 12 by ≥2% of patients in any group (ESAF)

TEAEs, n (%)	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)

Bone density decreased	2 (3.4)	2 (3.5)	5 (4.2)	2 (1.6)
Hot flush	3 (5.2)	0	4 (3.4)	4 (3.3)
Mood swings	2 (3.4)	1 (1.8)	1 (0.8)	3 (2.5)
Headache	1 (1.7)	2 (3.5)	1 (0.8)	1 (0.8)
Nausea	2 (3.4)	2 (3.5)	1 (0.8)	1 (0.8)
Vaginal haemorrhage	0	2 (3.5)	1 (0.8)	1 (0.8)
Vulvovaginal dryness	0	2 (3.5)	0	1 (0.8)
Increased appetite	0	2 (3.5)	0	1 (0.8)
Alopecia	2 (3.4)	0	0	0

Abbreviations: ABT, add-back therapy; ESAF, extension safety analysis set; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event
Coded by MedDRA Version 23.0.
Source: EDELWEISS 6 CSR (data on file)⁶¹

B.2.10.4.2.2 EDELWEISS 6 | Most common ABT-related adverse events from month 6 to month 12

Overall, 12.6% of patients in the ESAF reported TEAEs considered to be related to ABT from month 6 to month 12. The percentage of patients reporting ABT-related TEAEs was slightly higher in the placebo/linzagolix 75 mg group (17.2%, compared with placebo/linzagolix 200 mg plus ABT: 14.0%; linzagolix 75 mg: 11.8%; linzagolix 200 mg plus ABT: 10.7%). Most ABT-related TEAEs were reported by 1 to 2 patients in any treatment group with no discernible pattern. The most common (i.e., in at least 1% of the ESAF overall) ABT-related TEAEs included vaginal haemorrhage (1.7%), hot flush (1.4%) and nausea (1.4%).⁶¹

B.2.10.5 Treatment discontinuation due to adverse events

B.2.10.5.1 EDELWEISS 3 and EDELWEISS 2 | Treatment discontinuation due to adverse events up to month 6

In EDELWEISS 3, the treatment discontinuation rate due to TEAEs in the linzagolix 200 mg plus ABT group (3.1%) was similar to that for the placebo group (2.5%), although the rate was slightly higher for the linzagolix 75 mg group (5.6%; Table 25).^{58,59} There was no pattern to the TEAEs leading to treatment discontinuations. Other than nausea (n=3 patients), headache (n=3), and mood swings (n=2), all other TEAEs leading to treatment discontinuation were reported in one patient each. Nausea led to treatment discontinuation in both the placebo (n=1)

and linzagolix 200 mg plus ABT (n=2) groups, while headache and mood swings led to discontinuation only in the linzagolix groups (headache: n=3 in linzagolix 75 mg group, n=0 in linzagolix 200 mg plus ABT group; mood swings: n=1 each in the linzagolix 75 mg and linzagolix 200 mg plus ABT groups).

In EDELWEISS 2, treatment discontinuation rates due to TEAEs were comparable between the placebo and linzagolix groups (Table 25).⁶³ Two patients in the linzagolix 200 mg plus ABT group discontinued due to vaginal haemorrhage, one patient in the linzagolix 75 mg group discontinued due to headache and two patients in the placebo group discontinued due to COVID-19 (n=1) or chest discomfort (n=1).

B.2.10.5.2 EDELWEISS 6 | Treatment discontinuation due to adverse events from month 6 to month 12

Overall, nine patients discontinued treatment due to TEAEs from month 6 to month 12 (Table 26),⁶¹ with rates comparable across treatment groups (placebo/linzagolix 75 mg: 3.4%; placebo/linzagolix 200 mg plus ABT: 3.5%; linzagolix 75 mg: 2.5%; linzagolix 200 mg plus ABT: 1.6%). Four patients in total discontinued treatment between month 6 and month 12 due to decreased bone density (n=1 in the placebo/linzagolix 75 mg group; n=3 in the linzagolix 75 mg group). All other TEAEs leading to treatment discontinuation were reported in one patient each.

B.2.10.6 Serious adverse events

B.2.10.6.1 EDELWEISS 3 and EDELWEISS 2 | Serious adverse events up to month 6

The incidence of serious adverse events was similar for all three groups in EDELWEISS 3 (Section B.2.10.2.1; Table 25), with no serious adverse events in EDELWEISS 2, further supporting good tolerability for linzagolix.^{58,59,63} Serious TEAEs in EDELWEISS 3 were pneumonia and abdominal pain (n=1 patient each) in the linzagolix 200 mg group and peritonitis and endometriosis (both in the same patient) in the linzagolix 75 mg group. None of these serious TEAEs were related to treatment.

B.2.10.6.2 EDELWEISS 6 | Serious adverse events from month 6 to month 12

Four patients experienced serious TEAEs from month 6 to month 12, none of which were related to linzagolix (Section B.2.10.2.2; Table 26).⁶¹ Serious TEAEs between month 6 and month 12 were bleeding from the genital tract (n=1, placebo/linzagolix 200 mg plus ABT), exacerbation of cholelithiasis (n=1 placebo/linzagolix 75 mg), acute anxiety attack (n=1, linzagolix 75 mg) and vaginal bleeding (n=1, linzagolix 75 mg). The vaginal bleeding serious TEAE was considered to be related to ABT, although this patient was in the linzagolix 75 mg group which received an ABT placebo.

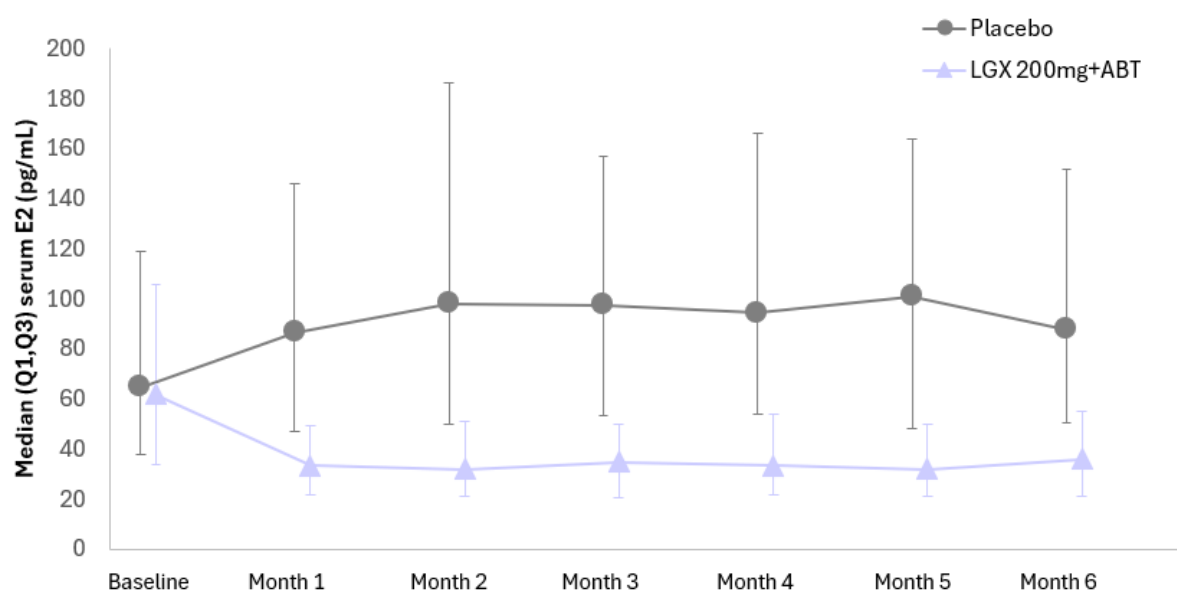
B.2.10.7 Clinical laboratory evaluations

B.2.10.7.1 EDELWEISS 3 | Clinical laboratory evaluations up to month 6

B.2.10.7.1.1 EDELWEISS 3 | Serum E2 levels

In EDELWEISS 3, E2 levels were maintained within a therapeutic range (between 20 and 60 pg/mL), similar to that naturally observed during the early follicular phase, throughout the treatment period in both linzagolix treatment groups (Figure 13).⁵⁸ This is considered the ideal range to manage endometriosis symptoms while reducing oestrogen-deprivation side effects such as hot flushes and BMD loss,⁷⁷ although the optimal E2 level may vary from patient to patient. E2 levels of >60 pg/mL were observed for most patients in the placebo group.

Figure 13: EDELWEISS 3 | Median E2 levels during the early follicular phase (SAF)



Abbreviations: ABT, add-back therapy; E2, oestradiol; LGX, linzagolix; Q, quartile; SAF, safety analysis set
Source: Donnez et al 2024⁵⁸

B.2.10.7.1.2 EDELWEISS 3 | liver enzymes and triglycerides

Elevated liver enzyme parameters that were considered clinically significant by the investigator were reported for 12 patients during treatment (placebo: n=3, 1.9%; linzagolix 75 mg: n=6, 3.2%; linzagolix 200 mg plus ABT: n=3, 1.9%, including one patient with alanine transaminase [ALT]/aspartate aminotransferase [AST] ≥ 3 times upper limit of normal [ULN]).⁵⁸ Elevated liver enzymes were transient and reversible. One patient had an isolated AST increase with concomitant creatine kinase increase due to excessive physical training, which was rapidly reversed, and one patient in the linzagolix 200 mg plus ABT group showed gamma-glutamyl transpeptidase (GGT) $\geq 3 \times \text{ULN}$. All other transaminase increases were $< 3 \times \text{ULN}$.

Two patients had clinically significantly elevated triglyceride levels.⁵⁸ In the placebo group, a patient with grade 1 elevation (187 mg/dL) at baseline had high triglyceride levels at month 4 (428 mg/dL; grade 2), month 5 (392 mg/dL; Grade 2) and month 6 (327 mg/dL; grade 2), but values normalised when she switched to linzagolix 75 mg during the extension study. In the linzagolix 75 mg group, one patient had a single increased triglyceride level at month 3 (637 mg/dL; grade 3) that returned to normal under continued treatment.

B.2.10.7.2 EDELWEISS 6 | Clinical laboratory evaluations up to month 12

Clinically significant changes in laboratory values, including increases in liver enzymes, were infrequent in all groups. There were no patterns or trends in any other laboratory parameters in any treatment group.

B.2.10.7.2.1 EDELWEISS 6 | Serum E2 levels

Median E2 levels were comparable across treatment groups at baseline. In the linzagolix groups, there was a trend towards a decrease in E2 levels from baseline up to month 12, with median E2 levels of 39.50–58.10 pg/mL in the linzagolix 75 mg group and 28.05–35.30 pg/mL in the linzagolix 200 mg plus ABT group.

In the placebo/linzagolix groups, an increase in E2 levels was observed from baseline to month 6, followed by a decrease after the first administration of linzagolix and stabilisation until the end of treatment period at month 12. In the placebo/linzagolix 75 mg group, median E2 levels were 56.20–98.10 pg/mL from day 1 to month 6 and 38.90–80.90 pg/mL from month 6 to month 12. In the placebo/linzagolix 200 mg plus ABT group, median E2 levels were 63.40–105.00 pg/mL from day 1 to month 6 and 29.90–80.70 pg/mL from month 6 to month 12.

Most patients in the linzagolix groups had an E2 level <60 pg/mL throughout the treatment period, with a higher percentage of patients in the linzagolix 200 mg plus ABT group. In the linzagolix 200 mg plus ABT group, approximately 17%–28% of patients maintained an E2 level <20 pg/mL, while approximately 56%–64% maintained E2 ≥20 and <60 pg/mL throughout the treatment period. In the linzagolix 75 mg group, E2 levels were suppressed to <20 pg/mL in approximately 15%–27% of patients, while approximately 30%–43% maintained E2 ≥20 and <60 pg/mL throughout the 12-month treatment period. Similar trends were observed for the placebo/linzagolix groups from month 6 to month 12.

Rapid reversibility of E2 suppression was observed after the end of treatment with linzagolix. In the post-treatment extension follow-up (ExFU) period, median E2 levels were 96.00–113.00 pg/mL in the placebo/linzagolix 75 mg group, 44.70–84.00 pg/mL in the placebo/linzagolix 200 mg plus ABT group, 93.85–98.90 pg/mL in the linzagolix 75 mg group and 58.35–62.30 pg/mL in the linzagolix 200 mg plus ABT

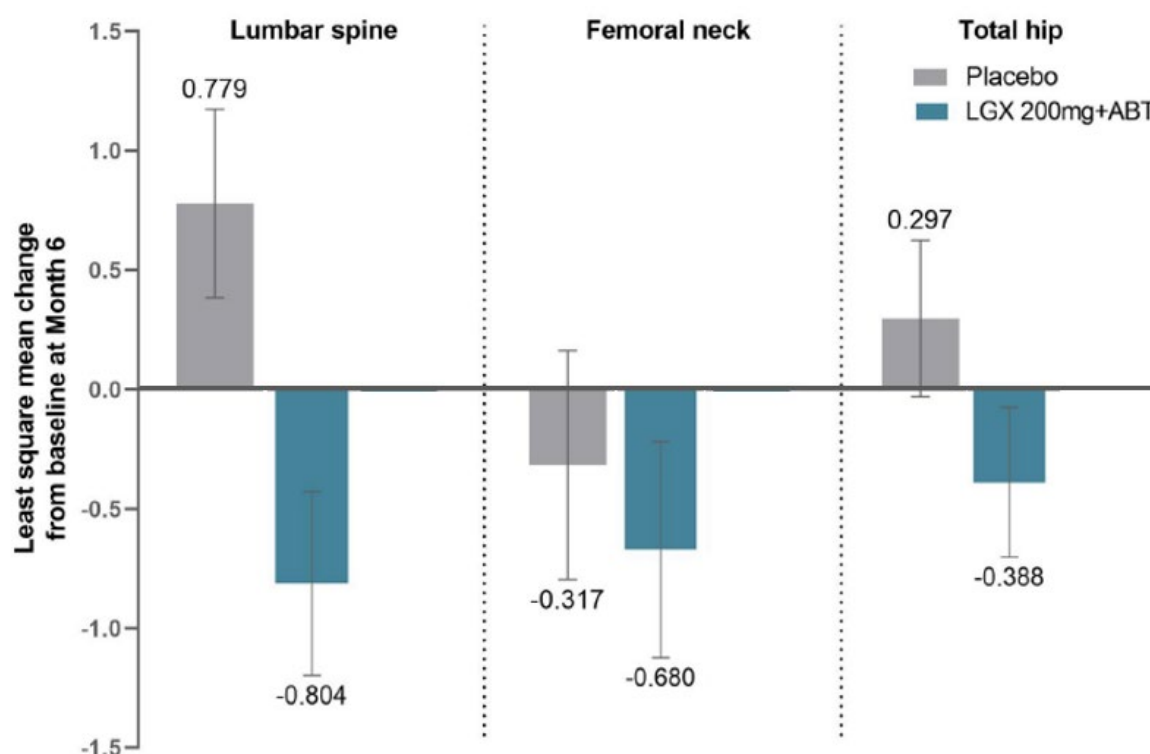
group. Most patients in the linzagolix 75 mg group had E2 levels ≥ 60 pg/mL at months 1 and 3 ExFU. In the linzagolix 200 mg plus ABT group, 49.0% of patients had E2 levels ≥ 60 pg/mL at month 1 ExFU, which increased to 52.8% at month 3 ExFU. Similar trends were observed for the placebo/linzagolix groups at the ExFU period.

B.2.10.8 EDELWEISS 3 and EDELWEISS 6 | Bone mineral density

BMD was largely unaffected by linzagolix treatment at month 6 (EDELWEISS 3) and month 12 (EDELWEISS 6).^{58,59,61} Some BMD increases were noted at 6 months after end of treatment (EDELWEISS 6 Month 6 ExFU), indicating partial recovery.

The least squares mean percentage change from baseline to month 6 in EDELWEISS 3 was $<1\%$ in all three groups at the lumbar spine, femoral neck and total hip (Figure 14).

Figure 14: EDELWEISS 3 | Percentage changes in bone mineral density from baseline at month 6 (SAF)



Error bars represent 95% confidence intervals.

Abbreviations: ABT, add-back therapy; LGX, linzagolix; SAF, safety analysis set

Source: Donnez et al 2024⁵⁸

Most patients in the linzagolix groups had either an increase, no change or $\leq 3\%$ decrease in BMD at month 6 in the lumbar spine (84.5%), femoral neck (88.2%) and total hip (94.3%; Table 31).

Table 31: EDELWEISS 3 | Percentage change in BMD by category from baseline at month 6 (SAF)

BMD, g/cm ² , % change from baseline	EDELWEISS 3		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)
Lumbar spine			
n (missing)	123 (39)	132 (28)	132 (30)
No change, increase, or decrease $\leq 3\%$, n (%)	118 (95.9)	109 (82.6)	114 (86.4)
Decrease $>3\%$, n (%)	5 (4.1)	6 (4.5)	18 (13.6)
Decrease $>8\%$, n (%)	0	1 (0.8)	0
Femoral neck			
n (missing)	121 (41)	130 (30)	132 (30)
No change, increase, or decrease $\leq 3\%$, n (%)	109 (90.1)	117 (90.0)	114 (86.4)
Decrease $>3\%$, n (%)	12 (9.8)	13 (9.8)	18 (13.6)
Decrease $>8\%$, n (%)	1 (0.8)	0	3 (2.3)
Total hip			
n (missing)	121 (41)	130 (30)	132 (30)
No change, increase, or decrease $\leq 3\%$, n (%)	114 (94.2)	122 (93.8)	125 (94.7)
Decrease $>3\%$, n (%)	7 (5.8)	8 (6.2)	7 (5.3)
Decrease $>8\%$, n (%)	0	0	1 (0.8)

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; SAF, safety analysis set
Source: EDELWEISS 3 CSR (data on file)⁵⁹

Changes in Z-scores at month 6 were similar for all three groups at all measured bone sites, although subgroup analyses showed more bone loss in all sites in patients aged ≥ 35 years, those weighing <63 kg and those with a BMI <23 kg/m² (Section B.2.7).^{58,59}

Changes in BMD during EDELWEISS 6 were also minimal,⁶¹ with most patients having an increase, no change or $\leq 3\%$ decrease in BMD at each measured site from baseline to month 12 (Table 32).

Table 32: EDELWEISS 6 | Percentage change in BMD from baseline at month 12 (ESAF)

BMD, g/cm ² , percentage change from baseline	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)
Lumbar spine				
n (missing)	39 (19)	42 (15)	78 (41)	86 (36)
Mean (SD) [95% CI] change	-0.74 (2.93) [-1.69, 0.21]	-0.45 (3.26) [-1.47, 0.56]	-1.10 (2.52) [-1.67, -0.53]	-1.10 (3.22) [-1.79, -0.41]
No change, increase, or decrease $\leq 3\%$, n (%)	31 (79.5)	31 (73.8)	60 (76.9)	63 (73.3)
Decrease $>3\%$, n (%)	8 (20.5)	11 (26.2)	18 (23.1)	23 (26.7)
Decrease $>8\%$, n (%)	0	0	1 (1.3)	2 (2.3)
Femoral neck				
n (missing)	39 (19)	42 (15)	77 (42)	85 (37)
Mean (SD) [95% CI] change	-0.93 (2.78) [-1.83, -0.03]	-0.93 (2.75) [-1.79, -0.08]	-0.57 (3.42) [-1.35, 0.20]	-0.70 (3.00) [-1.35, -0.06]
No change, increase, or decrease $\leq 3\%$, n (%)	32 (82.1)	34 (81.0)	56 (72.7)	69 (81.2)
Decrease $>3\%$, n (%)	7 (17.9)	8 (19.0)	21 (27.3)	16 (18.8)
Decrease $>8\%$, n (%)	1 (2.6)	0	2 (2.6)	1 (1.2)
Total hip				
n (missing)	39 (19)	42 (15)	77 (42)	85 (37)
Mean (SD) [95% CI] change	-0.41 (2.16) [-1.11, 0.29]	0.58 (1.77) [0.03, 1.13]	-0.37 (2.51) [-0.94, 0.20]	-0.52 (2.13) [-0.98, -0.06]
No change, increase, or decrease $\leq 3\%$, n (%)	35 (89.7)	42 (100.0)	67 (87.0)	76 (89.4)
Decrease $>3\%$, n (%)	4 (10.3)	0	10 (13.0)	9 (10.6)
Decrease $>8\%$, n (%)	0	0	0	1 (1.2)

Minimum month 12 Z-scores did not decrease below -2.0 at the lumbar spine, -1.4 at the femoral neck and -1.5 at the total hip. The minimum change from Baseline was relatively comparable across the linzagolix groups at all bone sites. Small fluctuations in the median Z-score values between baseline and month 12 were observed in all groups, with no defined pattern.

Some BMD increases were noted at 6 months after end of treatment (EDELWEISS 6 Month 6 ExFU), indicating partial recovery. Up to month 6 ExFU, most patients registered either no change or increase, or decrease $\leq 3\%$ in BMD at the lumbar spine (75.3%), femoral neck (78.0%) and total hip (90.2%). Decreases $> 8\%$ in BMD were observed at the femoral neck (4 patients in total) and at the total hip (1 patient in the linzagolix 75 mg group).⁶¹

B.2.10.9 EDELWEISS 3 and EDELWEISS 6 | Time to first post-treatment menses

Menses resumed within a median time of approximately 1 month after the end of treatment across groups in EDELWEISS 3 and EDELWEISS 6.

In EDELWEISS 3, menses resumed after cessation of therapy for all of the 51 patients (placebo n=15, linzagolix 75 mg n=15, linzagolix 200 mg plus ABT, n=21) who did not continue into the extension study. The estimated time to recovery of menses was 4–5 weeks due to rapid recovery of ovarian function (based on blood test results).⁵⁸ In the linzagolix 200 mg plus ABT group, post-treatment menses data were recorded for 19 patients (90.5%) and 2 patients (9.5%) were considered censored.⁵⁹ The median Kaplan–Meier (KM) estimate was 33.0 days (95% CI: 30.0–58.0 days). In the linzagolix 75 mg group, all 15 patients had events (menses). The median KM estimate was 24.0 days (95% CI: 4.0–26.0 days). The KM probability estimates were 0.929 (95% CI: 0.735–0.995) at 196 days for the linzagolix 200 mg plus ABT group and 0.933 (95% CI: 0.740–0.996) at 56 days for the linzagolix 75 mg group.⁵⁹

In EDELWEISS 6, post-treatment menses data were recorded as follows.⁶¹ For the placebo/linzagolix 75 mg group, data were available for 53 patients (98.1%) and one patient (1.9%) was considered censored; the median KM estimate was 24.0 days (95% CI: 21.0–26.0 days). In the placebo/linzagolix 200 mg plus ABT group, data were recorded for 49 patients (98.0%) and 1 patient (2.0%) was considered censored; the median KM estimate was 30.5 days (95% CI: 29.0–33.0 days). In the linzagolix 75 mg group, data were recorded for 108 patients (96.4%) and 4 patients (3.6%) were considered censored; the median KM estimate was 22.0 days (95% CI: 19.0–24.0 days). In the linzagolix 200 mg plus ABT group, data were recorded for 107 patients (94.7%) and 6 patients (5.3%) were considered censored; the median KM estimate was 32.0 days (95% CI: 31.0–33.0 days).

The KM probability estimates were 0.981 (95% CI: 0.912–0.998) at 140 days for placebo/linzagolix 75 mg, 0.960 (95% CI: 0.879–0.993) at 140 days for placebo/linzagolix 200 mg plus ABT, 0.967 (95% CI: 0.919–0.990) at 196 days for linzagolix 75 mg and 0.954 (95% CI: 0.902–0.983) at 168 days for linzagolix 200 mg plus ABT.⁶¹

B.2.10.10 EDELWEISS 3 and EDELWEISS 6 | Pathological changes in the endometrium

There were no clinically meaningful changes from baseline in gynaecological examinations or endometrial biopsies in any group during the EDELWEISS 3 or EDELWEISS 6 treatment periods.^{59,61}

Endometrial biopsies were performed on 99.4% of patients (n=481/162) at EDELWEISS 3 screening, most of whom (n=455/481) had assessable results. One patient (0.6%) in the placebo group had an abnormal finding of endometritis on the endometrial biopsy at screening, which was considered as not clinically significant. At month 6, endometrial biopsies were performed on 20.5% of patients (n=99/484). All 95 assessable endometrial biopsies were normal. All endometrial biopsies were classified as benign endometrium without hyperplasia or atypia at both screening and month 6 of the EDELWEISS 3 treatment period.

Endometrial biopsies were performed at month 6 and month 12 of EDELWEISS 6. At month 6, biopsies were performed on 22.8% of patients (n=81/356), most of whom (n=78/81) had assessable results; there were no abnormal findings. Biopsies were performed on 19.4% of patients (n=69/356) at month 12. All 63 assessable biopsies were normal. All endometrial biopsies were classified as benign endometrium without hyperplasia or atypia at both month 6 and month 12 of the EDELWEISS 6 treatment period.

During the EDELWEISS 6 ExFU period (after the end of treatment), endometrial biopsies were performed at ExFU months 1 (17.9% of patients [n=59/329], 54 assessable), 3 (20.1% of patients [n=66/329], 60 assessable) and 6 (12.5% patients [n=41/329], 35 assessable). All endometrial biopsies were classified as being benign endometrium without hyperplasia or atypia. At month 6 ExFU, one patient in the placebo/linzagolix 200 mg plus ABT group had an abnormal finding of benign (weakly) proliferative endometrium with breakdown change, which was considered as not clinically significant, and one patient in the linzagolix 200 mg plus ABT group had an abnormal finding (unspecified), which was considered to be clinically significant. However the biopsy for the patient with 'abnormal finding (unspecified)' had been assessed in a local laboratory, and additional information was not available. As this patient had an endometrial biopsy at Month 1 ExFU, which had been classified as being benign endometrium without hyperplasia or atypia, the unknown abnormality at Month 6 ExFU was not followed up further.

B.2.10.11 Safety conclusions

Linzagolix showed good overall tolerability in the EDELWEISS 3, EDELWEISS 2, and EDELWEISS 6 trials, with TEAEs similar to placebo. The incidence of severe TEAEs was low and comparable between groups, and no fatal or suicide-related TEAEs were reported. The safety profile for linzagolix for women with EAP was consistent with that observed previously for women with uterine fibroids.

The most common TEAEs with linzagolix 200 mg plus ABT were headaches (10.5% at month 6 in EDELWEISS 3), hot flushes (6.8%) and fatigue (6.8%).

In patients receiving linzagolix, serum E2 levels were maintained within a therapeutic range (20–60 pg/mL)⁷⁷ throughout the treatment period.

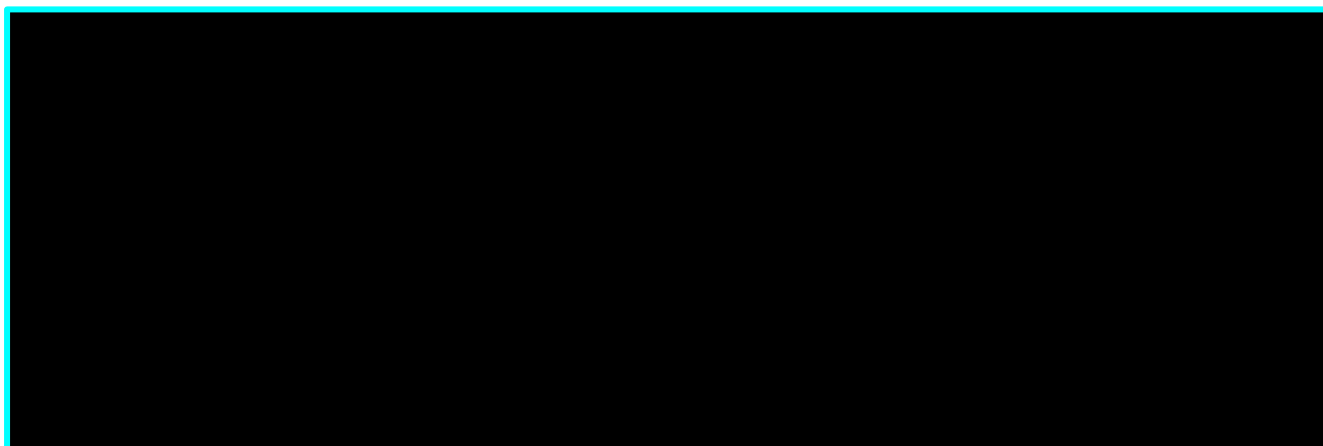
BMD was largely unaffected by linzagolix treatment at month 6 (EDELWEISS 3) and month 12 (EDELWEISS 6), with most patients having either an increase, no change or $\leq 3\%$ decrease in BMD at months 6 and 12 in the lumbar spine, femoral neck and total hip; some BMD increases were noted at 6 months after the end of treatment (EDELWEISS 6 month 6 extension follow-up), indicating partial recovery. Menses also resumed within a median time of approximately 1 month after the end of treatment in EDELWEISS 3 and EDELWEISS 6.

B.2.11 Ongoing trials

A multicentre, randomised, double-blind phase 3 study (BG2109-AB-301; NCT05894135) is currently evaluating the efficacy and safety of linzagolix (100 mg alone or 200 mg plus ABT) versus placebo in Chinese women with moderate to severe EAP. The trial design is summarised in Figure 15.

Please note that Theramex is not performing this study; Theramex has no jurisdiction over the design or conduct of the study; Kissei (partner company) has provided the following confidential details from the study owner (Bio Genuine (Shanghai) Biotech Co., Ltd). It is unlikely that results will be shared publicly before June 2025 but are provided for completeness.

Figure 15: NCT08594135 | study design



Abbreviations: ABT, add-back therapy; FU, follow-up; R, randomised
Source: Personal communication, Kissei

Other endpoints include dysmenorrhoea and NMPP response rate at week 12 and week 24, change of the interference of pain with ability to perform daily activities from baseline to week 24 using the EHP-30, change in OPP at week 24, dyspareunia, BMD and safety.⁷⁸

The trial is expected to recruit a total of 540 patients (n=180 per group). The primary completion date is June 2024 and the final study completion date is March 2025.⁷⁸

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence base

B.2.12.1.1 Comparative efficacy and safety of linzagolix versus placebo in the EDELWEISS 3 and EDELWEISS 6 studies

The efficacy and safety of up to 12 months of treatment with linzagolix 200 mg plus ABT for moderate-to-severe EAP in women of reproductive age were confirmed in the phase 3 EDELWEISS 3 study^{58,59} and its extension study EDELWEISS 6.⁶¹

The daily dose of linzagolix 200 mg plus ABT met the primary endpoint of EDELWEISS 3, demonstrating clinically meaningful and statistically significant reductions in dysmenorrhoea and NMPP at month 3 versus placebo, with stable or reduced use of analgesics. At month 3, the estimated percentage of responders for dysmenorrhoea was 72.9% (95% CI: 65.3–79.4) in the linzagolix 200 mg plus ABT group versus 23.5% (95% CI: 17.5–30.7) in the placebo group (OR 8.80 [97.5% CI: 4.86–15.91]; $p < 0.001$). Respective proportions for NMPP were 47.3% (95% CI: 39.5–55.3) with linzagolix 200 mg plus ABT versus 30.9% (95% CI: 24.1–38.6) with placebo (OR 2.01 [97.5% CI: 1.18–3.42]; $p = 0.007$).

Significant reductions versus placebo were also observed at month 6. This was accompanied by statistically significant improvements in the ranked secondary

endpoints of dyschezia, overall pelvic pain and ability to participate in daily activities (based on pain dimensions listed in the EHP-30).

The clinically meaningful improvements observed at month 6 (end of EDELWEISS 3 treatment period) generally increased at month 12 in the EDELWEISS 6 extension study. Reductions in EAP resulted in a reduced intention for surgery after 6 months in EDELWEISS 3 based on both the PSIQ and SSIQ in patients who received linzagolix versus placebo; least squares mean (LSM) differences for linzagolix 200 mg plus ABT versus placebo were -0.7 (97.5% CI: $-1.3, -0.1$; $p=0.017$) for the PSIQ and -0.9 (97.5% CI: $-1.6, -0.2$; $p=0.005$) for the SSIQ. The reduction in the PSIQ from baseline to month 6 in EDELWEISS 3 (LSM change -1.5 [97.5% CI: $-1.9, -1.2$]) became more pronounced at month 12 in EDELWEISS 6 (mean [SD] change from baseline -2.7 [2.8]).

Reductions in EAP were also accompanied by improved HRQoL as shown by improved scores for the EHP-30 and EQ-5D-5L Index and VAS.

The safety profile for linzagolix in women with EAP was consistent with that observed previously for women with uterine fibroids.^{10,76} Linzagolix showed good overall tolerability in the EDELWEISS 3,^{58,59} EDELWEISS 2⁶³ and EDELWEISS 6⁶¹ trials, with TEAEs being similar to placebo. The incidence of severe TEAEs was low and comparable between groups, and no fatal or suicide-related TEAEs were reported. The most common TEAEs with linzagolix 200 mg plus ABT in women with EAP were headaches (10.5% at month 6 in EDELWEISS 3), hot flushes (6.8%) and fatigue (6.8%). Serum E2 levels were maintained within a therapeutic range (20–60 pg/mL) throughout the treatment period in patients receiving linzagolix.

BMD was largely unaffected by linzagolix treatment at month 6 (EDELWEISS 3) and month 12 (EDELWEISS 6), with most patients having either an increase, no change or $\leq 3\%$ decrease in BMD at Months 6 and 12 in the lumbar spine, femoral neck and total hip; some BMD increases were noted at 6 months after end of treatment (EDELWEISS 6 month 6 extension follow-up), indicating partial recovery. Menses also resumed within a median time of approximately 1 month after end of treatment in EDELWEISS 3 and EDELWEISS 6.

B.2.12.1.2 Comparative efficacy of linzagolix versus other treatments based on an ITC

ITC data indicate that the efficacy and safety of linzagolix 200 mg plus ABT are comparable to leuprorelin.

Linzagolix was associated with a statistically significantly lower incidence of hot flashes versus leuprorelin.

B.2.12.2 Strengths and limitations of the clinical evidence base for linzagolix in the treatment of EAP

B.2.12.2.1 Strengths of the evidence base

Data from the Phase 3 EDELWEISS 3^{58,59} and EDELWEISS 6^{61,62} trials demonstrated the efficacy and safety of linzagolix 200 mg plus ABT versus placebo for women with EAP. The linzagolix 200 mg plus ABT dose met the primary endpoint of EDELWEISS 3, demonstrating clinically meaningful and statistically significant reductions in dysmenorrhoea and NMPP at month 3 versus placebo, with stable or reduced use of analgesics. Efficacy was observed across all pre-specified subgroups in EDELWEISS 3 and improved at month 12 in the EDELWEISS 6 extension study.

In addition to the compelling results from EDELWEISS 3 and EDELWEISS 6, the mechanism of action of linzagolix and other GnRH antagonists in endometriosis is well understood and documented (i.e. reducing the release of LH and FSH, leading to decreased serum concentrations of oestradiol, depriving the endometriosis lesion of its major growth stimulant).⁷⁹ For linzagolix, this mechanism of action is fully supported by previously assessed data in the pathophysiologically-related condition of uterine fibroids.^{12,13}

The approvals of other GnRH antagonists (relugolix and elagolix) in the EU and US, and recently in the UK for relugolix, for the treatment of symptoms of endometriosis provides strong and consistent evidence for the effectiveness of the GnRH antagonist class in the treatment of EAP and the need for alternative medicines for the management of endometriosis symptoms.^{50,80–83}.

B.2.12.2.2 Potential limitations of the evidence base

The EDELWEISS 3 and EDELWEISS 6 trials showed clear evidence for the efficacy and safety of linzagolix 200 mg plus ABT for women with EAP,^{58,59,61,62} compared with placebo, but do not provide a head-to-head comparison between linzagolix plus ABT and other potential active treatments. Therefore, an ITC was performed and indicated that the efficacy and safety of linzagolix are comparable to leuprorelin.

The EDELWEISS 3 and EDELWEISS 6 trials comprised mostly white women (98.6% in both studies).^{59,61} Patients from other ethnic groups were therefore not well represented in these trials.

B.3 Cost effectiveness

SUMMARY

- An SLR was undertaken to identify previous cost-effectiveness evidence relevant to the decision problem, with a total of 16 records identified, including seven full articles and nine conference abstracts. The evidence identified was used to inform the model structure and some of the inputs used in the analysis
- A *de novo* economic model was developed to assess the cost-effectiveness of linzagolix 200mg plus ABT versus GnRH agonists and conservative surgery, as a treatment for patients with moderate to severe EAP, and a history of previous medical or surgical treatment for their endometriosis
- The economic model simulates the complex treatment pathway for women with endometriosis at the point of treatment initiation with a GnRH analogue, including initial response to treatment and subsequent treatment with other medical therapies and/or surgical interventions. The model structure was aligned to established treatment guidelines and validated by clinical expert opinion^{10, 19, 35, 104}
- Model development was also informed by the NICE draft guidance issued for the ongoing relugolix CT STA, with steps taken to address key feedback provided by NICE and the evidence assessment group (EAG)
- The main comparator in the model is GnRH agonists (represented by leuprorelin), as linzagolix is most likely to be prescribed in situations where GnRH agonists are currently prescribed. It was assumed that GnRH agonists would be used in combination with ABT from the start of therapy for a duration of 1.5 years, based on expert clinical opinion.^{10, 104} Laparoscopic surgery was also included as an additional comparator in the model
- Response data based on the co-primary endpoints (clinically meaningful reduction from baseline in dysmenorrhea and NMPP, with no increase in use of analgesics) in EDELWEISS 3 and EDELWEISS 6 were used to determine efficacy of initial medical treatment in the model. Based on the results of an ITC, it was assumed that response rates for the GnRH agonists are equal to those for linzagolix
- It was deemed unfeasible to do an ITC comparing linzagolix to surgery (see Appendix M), therefore, response rates for laparoscopic surgery and pain recurrence following surgery were established with studies identified in the SLR
- Utility values for model health states were calculated from EQ-5D data collected within EDELWEISS 3 (health states related to treatment response and pain levels) and from relevant literature (disutilities for AEs and surgical complications). Alternative utility values based on different regression models and literature were tested in scenario analyses
- Costs were sourced from UK national resources in line with an NHS perspective and the literature. In the absence of published healthcare resource use (HRU) data specific to the target population, expert opinion informed HRU frequencies for disease management and regular monitoring
- In the base case analysis, linzagolix compared with leuprorelin was associated with incremental costs of £2,252 and incremental QALYs of 0.41, resulting in an incremental cost-effectiveness ratio (ICER) of £5,554 per QALY; below the UK cost-effectiveness threshold of £20,000-£30,000
- Linzagolix was also cost-effective versus surgery, with an incremental cost of £421 and an incremental QALY of 0.61, resulting in an ICER of £693
- Linzagolix remained cost-effective across sensitivity analyses performed, including deterministic, probabilistic and scenario analyses

B.3.1 Published cost-effectiveness studies

B.3.1.1 Summary of characteristics and results of the included cost-effectiveness evidence

Systematic database searches for this review were conducted on 11 July, 2024. Details are presented in Appendix G.

The cost-effectiveness review identified 3,583 records, of which 16 were included in the systematic review. Nine studies were conference abstracts, and the remaining seven full articles were accessed. However, two studies were irrelevant to the technology evaluation, and only five were discussed in detail. Table 33 presents a summary and outcomes of the seven full-text studies; noting that the first five studies were most relevant. The last two studies – Wu et.al (2018⁸⁴) and Sanghera et.al (2016⁸⁵) were of secondary interest as they focused on time to recurrence after treatment. Table 34 includes nine conference abstracts, where analyses of surgical treatment were of use due to the model construction (health states, transitions, health effects).

Among the 16 identified studies, there were two cost-utility studies, four cost-minimisation studies and ten cost-effectiveness studies. They analysed various treatment options for endometriosis such as: dienogest, (combined) oral contraceptives, goserelin, elagolix, leuprolide acetate, NSAIDs, short-acting reversible contraception (SARC) or long-acting reversible contraception (LARC).

Seven studies employed a simple Markov model; in four studies a decision tree was developed. In five studies, no specific model employed was clearly stated. Time horizons varied between 1 year in one of the basic scenarios in Wang et al. (2019⁸⁶), Marmarali et al. (2012⁸⁷), Ferracini et al. (2013⁸⁸) and Choi et al. (2011⁸⁹) and 18 years in cases of Wu et al. (2017⁸⁴) and Grand et al. (2019). Cycle lengths were of 1 month in Wu et al. (2017⁸⁴), Grand et al. (2019⁹⁰) and Sanghera et al. (2016⁸⁵) and of 3 months in Wang et al. (2019⁸⁶). Inputs were based on sources such as published literature, key opinion leader elicitations, and author's assumptions. Because of limited data availability and lack of evidence in several areas, authors broadly discussed uncertainties surrounding the results provided by their analyses.

Studies were conducted in different countries including the UK, US, China, Colombia, Argentina, Brazil, Turkey and Russia.

Table 33: Summary list of full text, published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Grand et al.⁹⁰	2019	State transition (Markov) with health states defined by pain levels, of cycle length of 1 month, and 18 years horizon.	Studies enrolling any number of females affected by endometriosis.	<i>No hormonal treatment</i>: 9.88 - OCs: 10.31	UK (£) <i>No hormonal treatment</i>: £1,707 - OCs: £1,113	<i>No hormonal treatment</i> dominated by OCs
Wang et al.⁸⁶	2019	State transition (Markov) with many states defined by symptoms and surgery/ post-surgery states, with 3 months cycle length and 1- and 2-years' time horizons.	Premenopausal women between the ages of 18 and 49 years who had received a surgical diagnosis of endometriosis in the previous 10 years and who had moderate or severe endometriosis-associated pain.	For 1-year time horizon: - Elagolix (150 mg QD): 0.741 - Leuprolide acetate: 0.730 For 2-years' time horizon: - Elagolix (150 mg QD): 1.500 - Leuprolide acetate: 1.483	US (\$) For 1-year time horizon: - Elagolix (150 mg QD): \$12,202 - Leuprolide acetate: \$16,683 For 2-years' time horizon: - Elagolix (150 mg QD): \$21,017 - Leuprolide acetate: \$21,607	Elagolix was dominant vs leuprolide acetate for both time horizons. Elagolix was cost-effective versus leuprolide acetate over a time horizon of 1 to 2 years.

Zhang et al.⁹¹	2024	A decision tree model, where recurrence is a presence of a cyst meeting certain criteria and horizon of 2 years after surgery.	Chinese population, individuals undergoing laparoscopic surgery for endometriosis.	- DNG: 0.749 - COCs: 0.735	US (\$) - DNG: \$1,625 - COCs: \$343	DNG vs COC: \$87,679/QALY This is 3 times China's per capita GDP and thus is not a cost-effective treatment strategy compared to COC therapy.
Dai et al.⁹²	2021	A decision tree model of 2 years horizon.	Participants were 18 years of age to before menopause (median age - 34.5 years).	- DNG 1.48 - Goserelin: 1.46	Yen (¥) - DNG: ¥22,809 - GnRH-a Goserelin: ¥30,164	No numerical ICER reported. DNG is more effective and cost- saving compared with a GnRH-agonist - goserelin in China.
Bohn et al.⁹³	2021	NR	Women, aged 18-45 in the US with endometriosis-related dysmenorrhoea.	QALY - Strategy 1: NSAIDs followed by surgery: 10.7 million - Strategy 2: NSAIDs, then SARC or LARC followed by surgery: 11.2 million - Strategy 3: NSAIDs, then a SARC or LARC, then a GnRH modulator followed by	US (\$) - Strategy 1: NSAIDs followed by surgery: 22.6 billion - Strategy 2: NSAIDs, then SARC or LARC followed by surgery: 12.9 billion - Strategy 3: NSAIDs, then a SARC or LARC, then a GnRH modulator	Strategy 1 vs strategy 2: -\$20,204/QALY Strategy 2 vs strategy 3: \$1,352/QALY Strategy 3 vs strategy 4: -\$17,269/QALY Strategy 4 had the highest cost with the lowest QALYs. This indicates that surgery, without a trial of any medications first, is inferior to the other three strategies as a standard, first-line approach.

				surgery: 11.4 million Strategy 4: Proceeding directly to surgery: 9.7 million	followed by surgery: 13.2 billion Strategy 4: Proceeding directly to surgery: 42.1 billion	
Wu et al.⁸⁴	2017	A Markov model with cycle length of one month, and 18 years horizon.	Patients who underwent conservative laparoscopic or laparotomic surgery for endometriosis, four endometriosis groups identified: ovarian, peritoneal, deep and other. Deep described in details.	Deep endometriosis: <i>No medical therapy</i>: 7.69 - OC strategy: 7.10 - GnRH-3 strategy: 7.39 - GnRH-6 strategy: 7.68 The results for other groups of endometriosis types differs, but conclusions are similar.	Euro (€) <i>No medical therapy</i>: €3,161 - OC strategy: €8,015 - GnRH-3 strategy: €8,817 - GnRH-6 strategy: €9,614 The results for other groups of endometriosis types differs, but conclusions are similar.	- OC vs <i>No medical therapy</i> 10,589/QALY - GnRH-3 vs <i>No medical therapy</i> 7,523/QALY - GnRH-6 vs <i>No medical therapy</i>: 6,185/QALY The GnRH-6 strategy was shown to be a dominant strategy, and the OC and GnRH-3 strategies were extended dominated (i.e., lower costs and higher ICERs) by the GnRH-6 strategy.

Sanghera et al.⁸⁵	2016	A state transition (Markov) model with a 36-month follow-up and a monthly time cycle.	Women with moderate to severe endometriosis pain	• <i>No treatment</i> : 2.27 • DMPA: 1.92 • COC: 1.92 • LNG-IUS: 1.88	• LNG-IUS: £651 • DMPA: £623 • COC: £600 • <i>No treatment</i>: £371	No numerical ICER reported. CEAC was calculated to show probabilities of each treatment being more cost-effective than the other. The results show that <i>No treatment</i> dominates all other treatments. When the strategies are compared with <i>No treatment</i>, <i>No treatment</i> has a greater probability of being cost-effective at least 80% for all threshold WTP.

Abbreviations: CEAC, cost-effectiveness acceptability curve; COC, combined oral contraceptive; DNG, dienogest; DMPA, depot-medroxyprogesterone acetate; GDP, gross domestic product; GnRH, gonadotropin releasing hormone; ICER, incremental cost-effectiveness ratio; LARC, long-acting reversible contraception LNG-IUS, levonorgestrel-releasing intrauterine system; NSAID, nonsteroidal anti-inflammatory drug; NR, not reported; OC, oral contraceptive; QALYs, quality-adjusted life years; QD, once daily; SARC, short-acting reversible contraception; WTP, willingness to pay

Table 34: Summary list of published economic conference abstracts

Study	Year	Type of economic evaluation and model	Patient population (average age in years)	Type of health benefit	Costs (currency) (intervention, comparator)	Study results
Bohn et al. ⁹⁴	2020	A cost-effectiveness analysis.	Women, aged 18-45 in the US with endometriosis-related dysmenorrhoea.	QALY No numerical values reported. Treatment strategies included 1) NSAIDs followed by surgery 2) NSAIDs, then SARCs or LARCs followed by surgery 3) NSAIDs, then a SARC or LARC, then a GnRH modulator followed by surgery 4) proceeding directly to surgery	US (\$) NR	Numerical ICER reported only for Strategy 2 All four treatment strategies were cost-effective at a standard willingness-to-pay threshold of \$100,000 per QALY gained; Strategy 2 was associated with the lowest cost per QALY gained (\$1,155).
Marmarali et al. ⁸⁷	2012	A cost-effectiveness analysis, a 2-year and 1-year Markov models.	Women age 18 to 49 eligible for GnRH analogue treatment.	No numerical values reported. Three health outcomes: treatment response, unresponsiveness and death; Clinical endpoints were QALY and respondent years gained. A 2-year model included supporting treatment and 1-year model not.	No numerical values reported. Dienogest had lower health care costs.	No numerical ICER reported. Dienogest was a more cost-effective treatment option than both GnRH analogue agents (leuprolide acetate and goserelin acetate implant).

				Treatment strategies included: 1) Dienogest 2) GnRH-a (leuprolide and goserelin acetate implant) Dienogest had the same efficiency as comparators for both the 1 (no supportive therapy) and 2-year models (with supporting treatment).		
Lukac et al. ⁹⁵	2011	A cost-utility Markov model with time horizon set at 2 years.	NR	Response rates and QALY. No numerical values reported.	Drug costs: - GnRH-agonist (leuprolide): €1,248 - Dienogest: €969 Laparoscopy costs: - GnRH-agonist: €274 - Dienogest: €103	Dienogest showed that it was cost-effective compared to a GnRH-agonist, with an overall cost reduction of €506 and a QALY gain of 0.002 per patient.
Martin et al. ⁹⁶	2012	A cost minimisation model with a time horizon set at 1 year.	Women with endometriosis diagnosis.	NR	Treatment 1: Colombia: Total treatment cost: - Dienogest: US\$986 - GnRH-a: US\$2.856 Argentina:	Treatment cost as study result. The use of Dienogest minimises the total cost in Colombia and Argentina from any perspective.

					Social work perspective: • Dienogest: US\$535 • GnRH-agonist: US\$881 Prepaid medical services perspective • Dienogest: \$491 • GnRH-agonist: \$812 Treatment 2 Social work perspective: • Dienogest: US\$535 • GnRH-agonist: US\$1,488 Prepaid medical services perspective: • Dienogest: \$491 • GnRH-agonist: US\$1,386	
Avxentyeva et al. ⁹⁷	2013	A cost-minimisation analysis for a period of 6 months.	NR	No numerical values reported. Effectiveness measured as reduction of pain associated with endometriosis.	• Triptorelin: €1,102 • Leuprorelin: €1,118 • Buserelin: €340 • Dydrogesterone: €369 • Dienogest: €295	Treatment cost as study result. Dienogest is the most efficient option leading to savings from 74€ to 823€ per patient in 6 months.

				GnRH analogues (including triptorelin, leuprorelin, buserelin plus ABT) are of the same efficacy as dienogest, while dydrogesterone is less effective and there was no significant difference vs. placebo.		
Choi et al. ⁸⁹	2011	A cost-effectiveness analysis, the decision tree model with one year horizon.	Patients requiring additional treatment because of pain after laparoscopy.	NR Treatment strategies included: 1) Dienogest 2) Leuprolide acetate	NR	At the base case analysis, dienogest was dominant vs GnRH-agonist leuprolide acetate.
Ferracini et al. ⁸⁸	2013	A cost-minimisation analysis, decision tree model.	NR	50% improvement in pelvic pain as a definition of a treatment response. Efficacies: 2 treatment sequence: 91.58% 3 treatment sequence: 97.87%	Private payer perspective 2TS: - Dienogest: BRL 1,020 - GnRH agonist: BRL 2,329 3TS: - Dienogest: BRL 1,461 - GnRH agonist: BRL 2,378 Public payer perspective: 2TS: - Dienogest: BRL 883 - GnRH agonist: BRL 768 3TS: - Dienogest: BRL 942	Treatment cost as study result Dienogest is a cost-saving alternative for the treatment of endometriosis-associated pelvic pain compared to leuprorelin acetate.

					GnRH agonist: BRL 858	
Tuletova et al. ⁹⁸	2014	A cost-minimisation analysis	180 female patients with endometriosis aged 19-35 years old were included into the study.	No definition of efficacy stated. Efficacy index: - Endo-surgery: 66.7% - Hormonal therapy: 70.0% - Combined methods: 91.7%	- Endo-surgery: 143.298 KT - Hormonal therapy: 92,428 KT - Combined methods: 115.718 KT; (1\$= 182KT)	Treatment cost as study result. Hormonal therapy was recognised as the cost-saving alternative vs. endo-surgery and combined methods.
Movilla et al. ⁹⁹	2019	A cost-effectiveness analysis, Markov model from time of patient presentation with moderate to severe pain, until time of patient death.	NR	QALY No numerical values reported. Treatment strategies presented below: 1) Elagolix 2) Laparoscopic conservative surgery	NR	Laparoscopic conservative surgery is strongly dominant and more cost-effective than elagolix.

Abbreviations: ABT, add-back therapy; EAPP, endometriosis-associated pelvic pain; GnRH, gonadotropin releasing hormone; ICER, incremental cost effectiveness ratio; LARC, long-acting reversible contraceptive; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; QALY, quality-adjusted life year; SARC, short-acting reversible contraceptive; KT, Kazakhstani Tenge; TS, treatment sequence(s)

B.3.2 Economic analysis

B.3.2.1 Patient population

The patient population considered in the analysis is adult pre-menopausal women, with moderate to severe EAP and a history of previous medical or surgical treatment for their endometriosis.

The patient population demographics applied in the base-case settings of the model are summarised in Table 35.

Table 35: Patient population demographics

Baseline characteristics	Value (mean)	Source
Age, years	34.9	EDELWEISS 3 (Table 8)
BMI, kg/m ²	24.27	
Time since seeking medical diagnosis/treatment, years	5.20	
Overall pelvic pain, VRS	1.90	
Non-menstrual pelvic pain, VRS	1.77	
Dysmenorrhoea, VRS	2.28	

Abbreviations: BMI, body-mass index; VRS, verbal rating scale

B.3.2.2 Model structure

The model simulates a cohort of premenopausal women diagnosed with symptomatic endometriosis who are eligible for treatment with linzagolix 200 plus ABT, over time. It encompasses 17* distinct health states that reflect the varied responses to both medical therapies and surgical interventions. This framework enables a comparative analysis of linzagolix 200 mg plus ABT against alternative treatment options currently available in the NHS, evaluated from a healthcare perspective over a 16-year time horizon extending until the average age of menopause, established at 50 years in the UK. The cost-effectiveness analysis utilises a semi-Markov cohort model, particularly suited for capturing the complexities of endometriosis management (see section B.1.3.3). This structure aligns with the clinical pathways experienced by patients, enhancing its

* Including one tunnel state with three sub-states.

applicability and relevance in real-world contexts. Markov chain models (MCMs) are effective for health conditions characterised by ongoing risks and recurrent health events, such as endometriosis. In this model, patients transition between defined states, each associated with specific health utilities and costs. This approach is appropriate for endometriosis due to the extended time horizon required to assess treatment impacts on outcomes and costs, as well as the complexity of interrelated health states that must be represented to accurately reflect the management of symptomatic endometriosis.

To capture clinically and economically significant aspects of managing symptomatic endometriosis, the model is divided into two main components. The first component employs a decision tree, wherein health states are determined by treatment response, defined as a meaningful reduction in pain levels. This segment consists of two, three-month cycles, culminating in a six-month period during which the decision to continue treatment is made. The three-month cycle aligns with the EDELWEISS 3 primary endpoints, which include a clinically meaningful reduction of dysmenorrhoea and NMPP to the last 28 days of randomised treatment up to month 3. The six-month period is consistent with clinical practice, where specialist consultations for treatment continuation typically occur biannually and allowed flexibility to build the tunnel-state pregnancy. Additionally, the Markov transitions during initial treatment at month 6 were based on EDELWEISS 6 data. Due to the relatively long cycle length, a half-cycle correction has been applied.

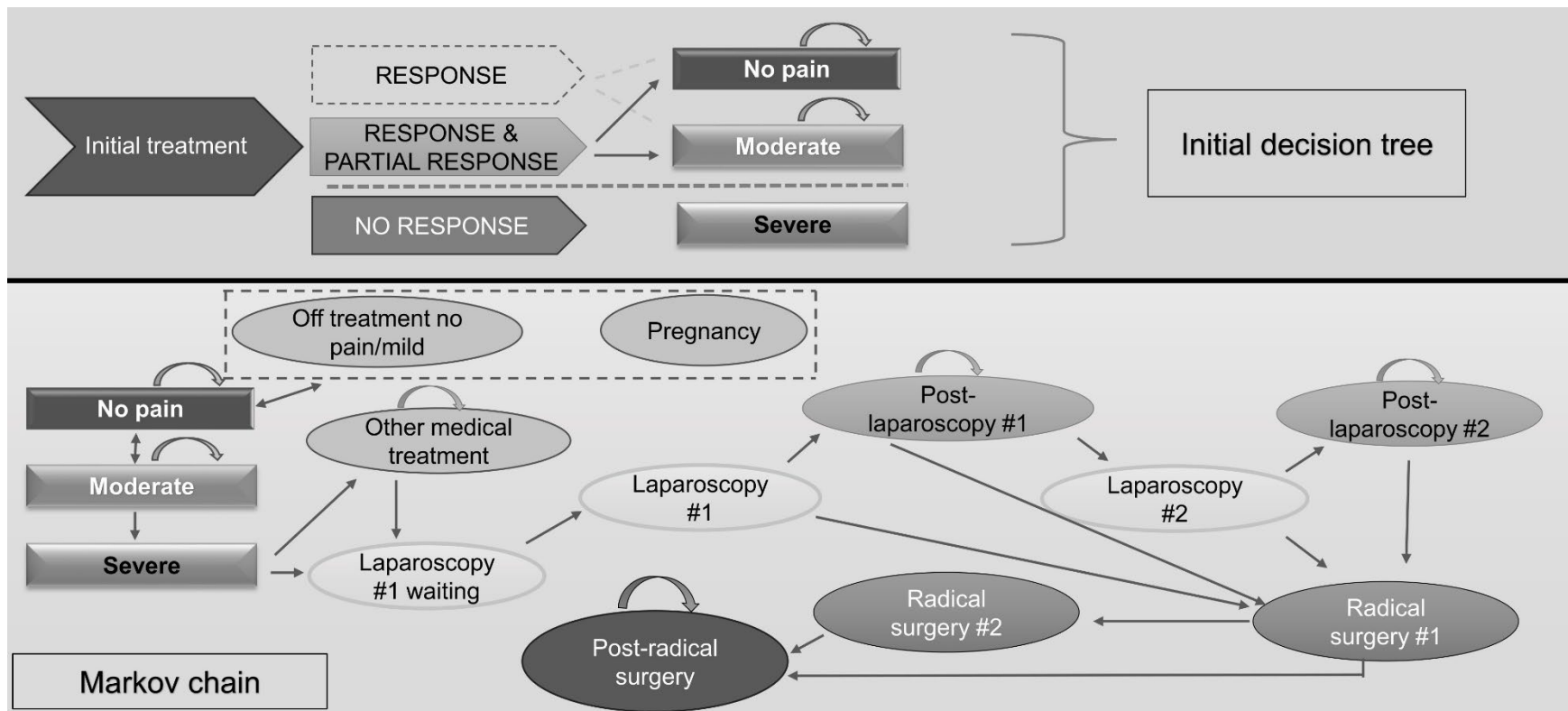
The second component focuses on health states contingent upon the level of pain experienced by the patient. The model structure is based on reviews of the study designs for EDELWEISS 3, as well as prior economic models for the treatment of symptomatic endometriosis identified through a targeted literature review [section B.3.1 and Appendix G] and established clinical practice guidelines.^{19,36} Additionally, the model structure and patient pathway have undergone validation by clinical experts.^{9,100} The various conditions or stages through which the model can transition over time are presented in Table 36.

Table 36: Health-states in the cost-effectiveness model

Health-state	Characteristic
Decision tree	
No response	Response status
Partial response	
Complete response	
Markov (state-transition) model	
No pain/mild	Pain level
Moderate	
Severe	
Off-treatment, no pain/mild	Treatment break
Pregnancy (tunnel health-state consisting of three model cycles)	Treatment break utilised to address patient's pregnancy
Other medical treatment	Subsequent medical therapy
Laparoscopy #1 waiting	Type of surgery
Laparoscopy #1	Type of surgery
Post-laparoscopy #1	Post-operative treatment aimed at sustaining surgical outcomes
Laparoscopy #2	Type of surgery
Post-laparoscopy #2	Post-operative treatment aimed at sustaining surgical outcomes
Radical surgery #1	Type of surgery
Radical surgery #2	Type of surgery
Post-radical surgery	Post-operative treatment aimed at sustaining surgical outcomes

The structure of the model corresponding to the table above is illustrated in Figure 16.

Figure 16: Model structure



The initial two cycles of the model last three months each. During this time, patients are categorised into one of three health-states based on their treatment responses (treatment response definitions are described in section B.3.3):

- **No response:** in this state, patients show no improvement, with pain levels remaining unchanged from the baseline
- **Partial response:** in this state, patients experience a reduction in pain, particularly in NMPP or dysmenorrhoea, indicating a partial therapeutic effect
- **Complete response:** in this state, patients exhibit a dual response, with significant reductions in both NMPP and dysmenorrhoea, reflecting an optimal treatment outcome

Following the two initial cycles, a new phase in the model starts (Markov model), where treatment cycles extend to six months. Patients responding to the treatment (Complete Response and Partial Response) are categorised into three pain-related health states based on OPP: **No pain/mild**, **Moderate**, or **Severe**[†]. Patients can transition between pain states until they transition into the Severe state (dependent on treatment waning assumption applied), until the maximal duration of therapy is reached (in the case of GnRH agonists) or until moving to the **Pregnancy** tunnel state.

- Patients entering the Severe pain state are transitioned to **Other Medical Treatment or Laparoscopy #1 Waiting**.
- When the maximum therapy time is reached, patients remaining in No pain/mild are transitioned to **Off-treatment no pain/mild**, and those remaining in the Moderate pain state transition to Other Medical Treatment or Laparoscopy #1 Waiting.
- Patients can enter the Pregnancy state from No pain/mild pain state (fixed probability per model cycle).

[†] No patient responding to the treatment according to the EDELWEISS 3 study criteria qualified to Severe state. However to remain the completeness of the model and remain its flexibility this state was included in the model structure.

After each of the two three-month cycles of initial treatment, patients who do not respond to treatment (No Response) are transitioned to subsequent treatment options, which may include the Other Medical Treatment health state or the Laparoscopy #1 Waiting health state. Patients remain in the Laparoscopy #1 Waiting state for one cycle of the model (six months[‡]) before progressing to the **Laparoscopy #1** state.

If symptoms recur whilst in the Other Medical Treatment state, patients transition to the Laparoscopy #1 Waiting state and subsequently to the Laparoscopy #1 state.

Laparoscopy #1 is a temporary state, and patients remain in it for one cycle of the model. This pathway assumes timely surgical intervention for patients experiencing symptom resurgence.

After conservative surgery is performed in Laparoscopy #1, patients enter a postoperative care phase in the **Post-Laparoscopy #1** state, aimed at maintaining the benefits of the surgical procedure. From this state, they may proceed to another surgical intervention, either conservative surgery **Laparoscopy #2** or a radical procedure - **Radical surgery #1**. Notably, patients who experience a recurrence of symptoms within three months of their initial surgery bypass the Post-Laparoscopy #1 state and move directly to the second surgical procedure. Following Laparoscopy #2, patients may enter the **Post-Laparoscopy #2** state, analogous to the Post-Laparoscopy #1 state, or proceed to a radical surgical intervention, specifically Radical surgery #1. After this intervention, patients transition to the **Post-Radical surgery** state. Alternatively, if they still have disease symptoms, they undergo a second radical surgery, **Radical surgery #2**. Post Radical surgery #2 they will also transition to the Post-Radical surgery state (for a description of the treatment applied in this health-state see section B.3.5.7).

Similar to Laparoscopy #1, the states Laparoscopy #2, Radical surgery #1, and Radical surgery #2 are temporary. Patients remain in these states for one model cycle, subsequently transitioning either to the next surgical intervention state or post-surgical intervention state.

[‡] Based on EMRS 2024 the average waiting time is around 18 months, however it was conservatively assumed this period would last only 6 months, which is equal to one model cycle in order to simplify already complex model.

Patients can only enter the Pregnancy state from the No pain/mild pain state (fixed probability per model cycle). Pregnancy is a tunnel state with three sub-states, each with one cycle duration. It was assumed that 18 months would be the minimum time for conception, pregnancy and breastfeeding. After three cycles (18 months) spent in this health state, patients move back to the No pain/mild pain state (with active initial treatment) or to the Off-treatment, no pain/mild state if the maximal therapy time of the initial treatment has been reached.

It is important to note that patients may transition to the "Dead" state from any health state within the model and the same mortality rate is applied across all states.

The analysis was performed from an NHS perspective, adhering to the existing NICE guidelines. Consequently, the base-case analysis considers all expenses associated with the healthcare sector. Both costs and outcomes are discounted at an annual rate of 3.5%, consistent with the NICE reference case.

B.3.2.3 Features of the economic analysis

Features of the economic analysis are presented in Table 37.

Table 37. Features of the economic analysis

	Previous evaluations	Current evaluation	
Factor	NICE relugolix CT STA ⁵¹	Chosen values	Justification
Time horizon	16 years	15.1 years	The average age in the EDELWEISS 3 study is 34.9 years. Therefore, the time horizon is set to 15.1 years which accounts for the starting age of 34.9 until 50 years old, the average age for a woman to reach menopause in the UK.
Treatment waning effect?	No	Considered in scenario analysis	NICE/EAG critique related to the absence of consideration for the treatment waning effect in relugolix CT submission ⁵¹
Source of utilities	EQ-5D-5L questionnaire from SPIRIT trials was first mapped to 3L using the NICE DSU age-sex-based	EQ-5D-5L questionnaire from EDELWEISS 3 was first mapped to 3L using the NICE	In line with the NICE reference case.

	mapping. Utilities were then derived using the UK value set published by Dolan for EQ-5D-3L.	DSU age-sex based mapping. Utilities were then derived using UK value set published by Dolan for EQ-5D-3L.	
Source of costs	BNF, NHS England national tariff 2022/23, relevant literature, and clinical expert opinion.	BNF, NHS England national tariff 2023/24, relevant literature, and clinical expert opinion.	Cost inputs were obtained from the BNF, NHS England national tariff 2023/24, and relevant literature. Where feasible, costs were sourced from UK national resources with an NHS perspective. In the absence of published HRU data, HRU frequencies for disease management and monitoring were informed by expert opinion.
Cycle length	3 months	First two cycles: 3 months	For the detailed justification see section B.3.2.2
		Next cycles: 6 months	
Discount rates	3.5 %	3.5%	In line with the NICE reference case
Efficacy of pharmacological treatments	Response at three and six months	Response at three and six months	According to expert opinion, the benefits of treatment are assessed after three to four months and then after every three to six months. ¹⁰⁰

Abbreviations: BNF, British National Formulary; EAG, external assessment group; EQ5D-3L, EuroQoL 5-Dimension 3-Level; EQ5D-5L, EuroQoL 5-Dimension 5-Level; HRU, healthcare resource use, relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate); STA, single technology appraisal

B.3.2.3.1 Modified surgery model – differences vs base model for medical therapies

Laparoscopic surgery is an additional comparator included in the analysis, at the request of NICE and the EAG, expressed during the decision problem meeting for linzagolix.

Compared with medical therapy, there are differences in the expected course of disease after surgery is performed. Surgery is a one-time event, after which a patient can either be a responder or a non-responder. Patients who respond remain in such a state until the recurrence of symptoms. This is a major difference compared to medical therapy, where a patient's level of response can be maintained or change over time as they receive ongoing treatment. To reflect these differences some changes were incorporated into the model structure for this comparator.

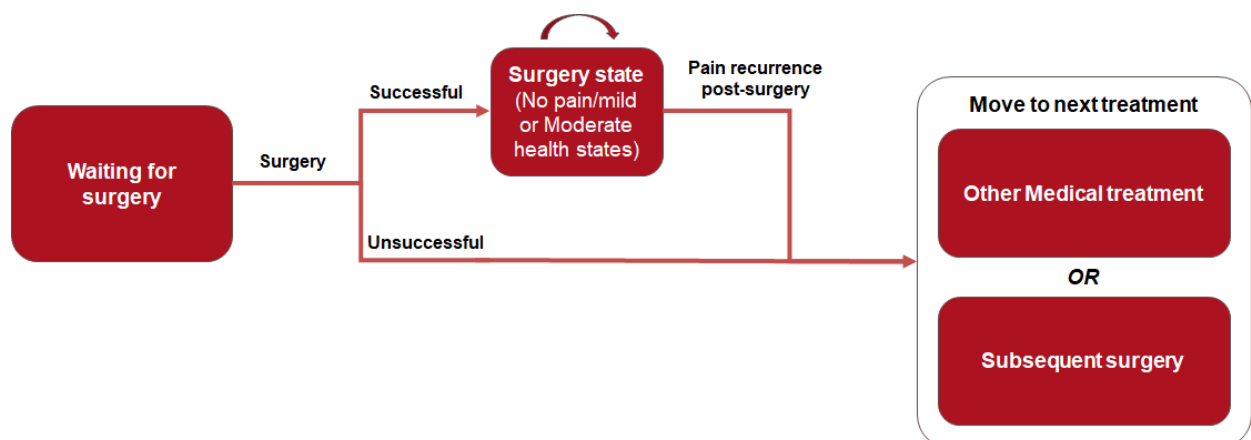
Based on UK clinical expert opinion, it is assumed that a patient waits an average of 18 months for surgical treatment on the NHS.^{19,100} This is reflected in the model where patients spend four cycles (two 3-month-cycles and two 6-month-cycles) in the Laparoscopy #1 waiting state before surgery is performed. Once surgery is performed, the patient is categorised as a responder (successful surgery) or a non-responder (unsuccessful surgery).

Patients responding to the treatment are subsequently categorised into three pain-related health states as in the base model (i.e., model for medical therapies), however the patient cannot transition between the three pain cycles (i.e., transitions based on data for medical therapies where patients can get better or worse). In the surgery model, the transition to a subsequent treatment is due to symptom recurrence (based on the literature), whereas for medical therapies, it is based on treatment discontinuation or waning assumptions.

In the surgery model, a non-responder or patient with symptom recurrence transitions to the next treatment, following the same subsequent model structure as a patient on medical therapy who experiences severe symptoms.

The part of the surgery model that is different to the base model is visualised in Figure 17. This replaces the initial decision tree part of the model that is used for medical therapies.

Figure 17: Initial model structure for laparoscopic surgery as comparator.



B.3.2.4 Intervention and comparators

The intervention evaluated in the model is linzagolix 200 mg plus ABT, administered orally once daily. Linzagolix 200 mg is designed to address endometriosis symptoms, through the reduction of EAP, while the addition of ABT preserves BMD. As a result, this regimen can be used continuously without a predefined treatment duration, except for cessation at the onset of menopause.

The comparators in the model are:

1. GnRH agonists; with the licensed agents in the UK of leuporelin acetate, goserelin, and triptorelin. All are administered via intramuscular or subcutaneous injection, available in both monthly and three-monthly formulations. All GnRH agonists were assumed to have equal efficacy and safety [see section B.2.9.7]
2. Laparoscopic surgery (see the description at the end of this section for more details)

To inform the model assumptions, the Endometriosis Market Research Survey (2024) and Expert Elicitation Reports (August and October 2024) were conducted among UK-based healthcare professionals to gather input on the use of GnRH agonists for managing endometriosis symptoms.^{9,19,100}

The Expert Elicitation Reports (2024) indicated considerable variability in prescribing practices, with no clear consensus on the most frequently used agent. Intranasal GnRH agonists (nafarelin and buserelin) were rarely prescribed, with all surveyed clinical experts reporting a preference for intramuscular or subcutaneous formulations.^{9,100} Consequently, only leuporelin acetate, goserelin, and triptorelin were considered comparators in the model, while intranasal formulations were excluded due to their limited clinical use.

In the base case analysis, leuprorelin acetate was selected as the GnRH agonist due to the assumption that all GnRH agonists have equivalent efficacy in this population. This approach is aligned to the submission for relugolix CT in this indication.⁵¹ The GnRH agonists have the same mechanism of action, specifically aimed at downregulating pituitary GnRH receptors. Evidence indicates that all GnRH agonists effectively inhibit endometriosis through this shared mechanism.¹⁰¹ In ESHRE recommendations, GnRH agonists are listed among the recommended hormonal treatments to reduce EAP pain, with no preference for specific agonists.³⁶ Furthermore, a Cochrane systematic review collectively reported for the entire group of GnRH agonists, and conclusions were derived without differentiating between specific pharmacological agents.¹⁰² Leuprorelin acetate was chosen as the base case comparator due to having the largest UK market share, according to clinical experts.¹⁰⁰ Goserelin and triptorelin, also commonly used in clinical practice, were evaluated in scenario analyses.

Based on input from UK gynaecologists, the model assumes that all patients treated with GnRH agonists receive ABT, initiated upon starting treatment.^{19,100} No differences are noted between the efficacy of GnRH agonists with or without ABT. A meta-analysis evaluating pain outcomes, including relief of dysmenorrhoea, dyspareunia and NMPP, indicated that results were comparable across both treatment groups, irrespective of the ABT use.¹⁰² Furthermore, no statistically significant differences were observed in most safety outcomes, except side effects of prolonged hypoestrogenism, such as climacteric symptoms (hot flashes, sweating, and vaginal dryness) and bone loss. Side effects of prolonged hypoestrogenism are expected for GnRH agonist treatment without ABT.¹⁰²

ESHRE treatment guidelines recommend limiting the use of GnRH agonists to 12 months when combined with ABT, emphasising the limited evidence for extended use, particularly in adolescents where there are concerns about long-term consequences.³⁶ To align with clinical expert opinion, the treatment duration of leuprorelin acetate in the model was extended to 18 months.¹⁹ NICE and EAG feedback during the relugolix CT single technology appraisal also indicated that the treatment duration with GnRH agonists should align with clinical practice and extend beyond one year.¹⁰³ Clinical experts also highlighted that problems with adherence to long-term treatment with GnRH

agonists are related to the inconvenient route of administration for patients and can lead to discontinuation. Overall, they concluded that it was very unlikely that treatment would be continued for more than 24–36 months. In scenario analyses, a six-month treatment duration with leuporelin acetate in line with the standard clinical indication, was also evaluated.

The treatment duration for linzagolix is consistent with the model used for the relugolix CT STA, where it is assumed that GnRH antagonists can be administered continuously until menopause, reflecting their long-term use in managing endometriosis symptoms.⁵¹

Laparoscopic surgery was included as an additional comparator only, as it is more likely to be used as a complementary treatment to pharmacotherapy.⁹ According to clinical experts, whether or not surgery could be considered a direct comparator to medical therapies is dependent on the type of endometriosis. As GnRH agonists are already available and widely used in patients with endometriosis, it is assumed that the decision to prescribe linzagolix 200 mg plus ABT would primarily be in situations where gynaecologists are currently prescribing GnRH agonists. Due to the wide variety of surgery types, laparoscopic excision and ablation were chosen to be the most representative surgeries as they are used most frequently in the relevant treatment setting.^{19,36}

B.3.3 Clinical parameters and variables

The principal source of data used to inform the effectiveness of linzagolix 200 mg plus ABT is EDELWEISS 3, a randomised, double-blind, placebo-controlled, multicentre phase 3 study conducted in women of reproductive age with moderate to severe EAP (B.2.6).

Clinical input encompasses the entire treatment pathway within the model, including key parameters such as treatment efficacy, probabilities of various events occurring, and decisions related to disease management. This includes patient withdrawal from treatment, selection of surgical interventions, instances of repeat surgeries and the scheduling of treatment regimens, all of which are essential for accurately simulating clinical outcomes.

B.3.3.1 Treatment response

Two sets of health states are used in the model to address patient response to treatment. The first set, applied during the initial decision tree, includes three possible response states: no response, partial response and complete response. The second set, based on EAP levels, is used after the first six months of treatment and consists of three OPP states (no pain/mild, moderate, and severe). Both sets are derived from patient responses to treatment and individual patient-level data from EDELWEISS 3.

B.3.3.2 Treatment response in the initial decision tree

The definition of treatment response in the model is fixed and based on the co-primary endpoints from EDELWEISS 3. This includes a clinically meaningful reduction in dysmenorrhoea and NMPP, from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP.

The model allows for the selection of three different definitions of partial response:

1. **Dysmenorrhoea-based definition:** A clinically meaningful reduction in dysmenorrhoea (i.e., a reduction of ≥ 1.10 points on the VRS) from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP.
2. **NMPP-based definition:** A clinically meaningful reduction in NMPP (i.e., a reduction of ≥ 0.8 points on the VRS) from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP.
3. **Dysmenorrhoea- or NMPP-based definition:** A clinically meaningful reduction in either dysmenorrhoea (as above) or NMPP (as above) from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP.

Patients with no response at the month 3 switch to a different treatment, while those with partial response may either lose their response, maintain a partial response or achieve a complete response (by month 6). A decision to continue treatment is made after the

month 6. In the base case analysis, treatment is continued for patients with a complete response or partial response, defined as by dysmenorrhoea or NMPP response criteria outlined above. Based on the results of the ITC (Section B.2.9) it was assumed that response rates for GnRH agonists are equal to those derived for linzagolix plus ABT. The probabilities of response used in the model are presented in Table 38.

Table 38: Probabilities of response after three and six months

Response type	Linzagolix 200 mg plus ABT	GnRH agonist	Source
Complete response all patients after three months	38.27%	38.27%	EDELWEISS 3, individual patient- level data
Partial response all patients after three months	39.51 %	39.51 %	
Complete response from partial response after six months	34.38%	34.38%	
Partial response from partial response after six months	50.00%	50.00%	

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

B.3.3.3 Treatment response based on EAP pain levels (Markov model)

After the sixth month of treatment, patients continuing therapy are assigned to health states based on their level of OPP, defined as follows:

1. No pain/mild: OPP, VRS scale < 1
2. Moderate: $1 \leq \text{OPP}$, VRS scale ≤ 2
3. Severe: OPP, VRS scale > 2

The probability of patients being in a specific pain state after six months (Table 39) were estimated based on the OPP levels of patients who demonstrated at least a partial response to treatment (see section B.3.3.2). These probabilities were calculated from individual patient-level data for EDELWEISS 6 (for detailed description of study see Section B.2). Based on the results of the ITC (see section B.2.9) it was assumed that probabilities for GnRH agonists would be equal to those derived for linzagolix plus ABT.

Table 39: Probabilities of transition to a specific pain state after 6 months

Transition	Linzagolix 200 mg plus ABT	GnRH agonist	Source
Complete response to no pain/mild	87.88%	87.88%	EDELWEISS 6, individual patient-level data
Complete response to moderate	12.12%	12.12%	
Complete response to severe	0.00%	0.00%	
Partial response to no pain/mild	41.67%	41.67%	
Partial response to moderate	58.33%	58.33%	
Partial response to severe	0.00%	0.00%	

Abbreviations: GnRH, gonadotropin-releasing hormone

In subsequent cycles of the model, the severity of pain experienced by patients may fluctuate, facilitating transitions between various pain-related health states. In instances where pain escalates to severe (OPP >2 in VRS scale) the treatment is changed. Table 40 presents the probabilities of transitioning among pain-related health states. These probabilities were derived from individual patient-level data obtained from EDELWEISS 6, specifically focusing on patients assessed after six months of treatment. The analysis was restricted to those patients who demonstrated at least a partial response to treatment during this timeframe. This approach is congruent with the model design, which stipulates that only patients exhibiting a partial or complete response continue their treatment following the initial decision tree phase.

Table 40: Probabilities of transitions between pain-related health states

Transition	Linzagolix 200 mg plus ABT	GnRH agonist	Source
No pain/mild to no pain/mild	94.52%	94.52%	EDELWEISS 6, individual patient-level data
No pain/mild to moderate	5.48%	5.48%	
No pain/mild to severe	0.00%	0.00%	
Moderate to no pain/mild	31.03%	31.03%	
Moderate to moderate	65.52%	65.52%	
Moderate to severe	3.45%	3.45%	

Abbreviations: GnRH, gonadotropin-releasing hormone

B.3.3.4 Treatment distributions

Pain management strategies, particularly the use of analgesics, are integral to the treatment of endometriosis as they address the primary symptom experienced by patients. Consequently, the model incorporates analgesics as part of the treatment regimen alongside linzagolix 200 mg plus ABT, GnRH agonists, and surgery.

Furthermore, analgesic use is included in all health states (as part of a medical therapies basket), encompassing subsequent strategies to manage EAP following the discontinuation of intervention or comparator treatments.

The proportion of patients using analgesics for the intervention/comparator treatment in is based on the NICE STA submission for relugolix CT and can be found in Table 41.⁵¹

Table 41: Proportion of patients using analgesics during the treatment of linzagolix 200 mg plus ABT and comparators

Treatment	Before response	After response	Source
Linzagolix 200 mg plus ABT	90.00%	28.90%	NICE STA Relugolix ⁵¹
GnRH agonist	90.00%	28.90%	
Surgery	90.00%	28.90%	

Abbreviations: ABT, add-back therapy; GnRH, gonadotropin-releasing hormone; STA, single technology appraisal

The first subsequent treatment following the failure of the intervention or comparator therapy is either conservative surgery (32% of patients) or other medical treatment (67%), which constitutes a weighted basket of potential therapeutic options, as illustrated in Table 42.¹⁹

Table 42: Other medical treatment weighted basket

Therapy	Basket therapy split*	Source
LNG-IUS	13%	Endometriosis Market Research Survey 2024 ¹⁹
NSAIDs/Pain killers	3%	
Common oral contraceptives	4%	
Oral progestogen	5%	
Synthetic steroids	4%	
Aromatase inhibitors	4%	
GnRH agonists	25%	
GnRH antagonists	8%	

Abbreviations: GnRH, Gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; NSAID, non-steroidal anti-inflammatory drug

*Does not sum to 100% because only medical treatments are shown (i.e., laparoscopic surgery not included). In the model this was recalculated to 100%.

The distribution of NSAIDs/painkillers in the weighted medical therapies basket (Table 43) is based on literature representative of the UK population and excludes other medications or drugs that may be used concurrently for different health issues.⁶

Table 43: NSAIDs/painkillers split in the medical therapies weighted basket

Analgesics group	Weight (%)
NSAIDS	63
Opioids	30
Paracetamol	7

Abbreviations: NSAID, non-steroidal anti-inflammatory drug

In the case of symptom recurrence following the first conservative surgery (Laparoscopy #1 health-state) or failure of subsequent medical therapy (Other medical treatment health-state), patients in the model are directed towards the next therapeutic options in accordance with clinical practice (see section B.1.3.3) and the treatment pathway illustrated in Figure 16 (see section B.3.2.2.).¹⁹ The probabilities of patients transitioning to various therapeutic options in the base case analysis are presented in Table 44, with different probabilities tested in the scenario analysis (see section B.3.11.).

Table 44: Probabilities of patients transitioning to health-states in the model

Therapy	Probability	Rationale
Other treatment to Laparoscopy #1 waiting	32.00%	Surgery as a second line treatment after recurrence of symptoms. ¹⁹
Laparoscopy #1 to Radical surgery #1	2.04%	Patients with laparoscopy as a first surgical procedure type and radical surgery as a second surgical procedure type: time before recurrence after unsuccessful surgical intervention 0–3 months. ¹⁹
Laparoscopy #1 to Laparoscopy #2	2.93%	Patients with conservative surgery as a first and second surgical procedure type: time before recurrence after unsuccessful surgical intervention of 0-3 months. ¹⁹
Post-laparoscopy #1 to Laparoscopy #2	8.10%	Patients with conservative surgery as a first and second surgical procedure type: treatment decision following the recurrence after surgery (repeat surgery). ¹⁹
Post-laparoscopy #1 to Radical surgery #1	5.63%	Patients with laparoscopy as a first surgical procedure type and radical surgery as a second surgical procedure type: treatment decision following the recurrence after surgery (repeat surgery). ¹⁹
Laparoscopy #2 to Radical surgery #1	0.48%	Patients with at least three endometriosis-related surgical procedures over lifetime, and second surgical procedure type is radical surgery: time before recurrence after unsuccessful surgical intervention of 0-3 months. ¹⁹
Radical surgery #1 to Radical surgery #2	2.79%	Annual recurrence rate following radical surgeries recalculated for 6 months. ¹⁹
Post-laparoscopy #2 to Radical surgery #1	5.63%	Patients with laparoscopy as a first surgical procedure type and radical surgery as a second surgical procedure type: treatment decision following recurrence after surgery (repeat surgery). ¹⁹

In the health-states Laparoscopy #1 waiting, Post-Laparoscopy #1, and Post-Laparoscopy #2: a proportion of patients receives pharmacological treatment: 50% for the Laparoscopy #1 waiting state; 57% for the Post-Laparoscopy #1 state; and 100% for the Post-Laparoscopy #2 state.^{19,100} The distribution of specific medical procedures for patients having laparoscopic or radical surgery is based on the literature and detailed in Table 45.⁶

Table 45: Medical procedures corresponding to respective health states

Parameter	Health state	Percentage
Percentage of women with laparoscopic excision (weight for laparoscopy cost)	Laparoscopy #1 and Laparoscopy #2	33%
Percentage of women with laparoscopic ablation (weight for laparoscopy cost)		50%
Percentage of women with hysterectomy	Radical surgery #1 and Radical surgery #2	21%
Percentage of women with oophorectomy		17%

B.3.3.5 Treatment discontinuation

During each model cycle in which patients receive either the intervention or the comparator, there is a probability that they will discontinue treatment. In the model, treatment discontinuation is interpreted as a loss of efficacy (i.e., patients shifting into the severe health-state, OPP >2.0 on the VRS), intolerability to treatment, a break in the state of no pain/mild symptoms, or due to pregnancy and breastfeeding. The discontinuation rates for linzagolix 200 mg plus ABT were derived from different sources, depending on the cause and timing of discontinuation. The rate of patients who discontinue due to loss of efficacy was estimated based on EDELWEISS 3 and 6. The percentage of women discontinuing treatment due to pregnancy was estimated from the live birth rate in the UK.¹⁰⁴

In the EDELWEISS 3 and 6 studies, discontinuation was primarily attributed to factors such as COVID-19, political reasons, or the withdrawal of patient consent from the study. Such instances of discontinuation, which were clearly unrelated to the medical intervention, were excluded from the analysis. Following the exclusion of these cases, discontinuation rates were assessed at three and six months of treatment using individual patient-level data, and the resulting discontinuation coefficients were determined and are presented in Table 46.

Table 46: Discontinuation rates used in the model

Discontinuation	Probability	Source
From Partial response health-state after three months	0.62%	EDELWEISS 3 (patient level data)
From Complete response health-state after three months	1.23%	EDELWEISS 3 (patient level data)
From no Pain/mild and moderate health-states	3.03%	EDELWEISS 6 (patient level data)
From no pain/mild health-state due to the pregnancy	5.8%	Office for National Statistics 104

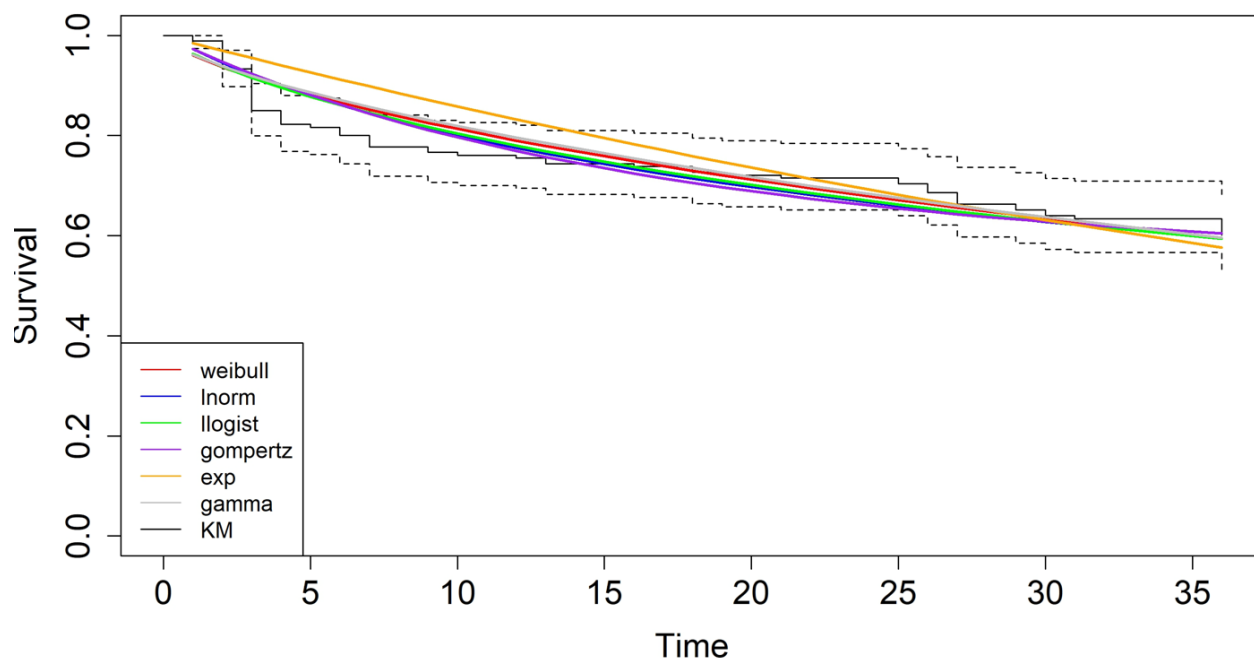
B.3.3.6 Clinical parameters for additional comparator: laparoscopic surgery

Response rate for laparoscopic surgery and pain recurrence following surgery were established with studies found in the SLR described in Appendix M.

Response rate for laparoscopic surgery was set to 50% based on Johnson et al. 2004.⁷⁰ The response definition provided in this study (at least 50% reduction of pain on the VAS) was considered most consistent with the response definition applied for the pharmacological treatments. As different definitions of pain response and timepoints were available in this study, conservatively (in favour of surgery vs linzagolix), the highest response rate was selected. The response rate for surgical treatment was validated with clinical expert opinion.^{19,100} The split between complete and partial responders was assumed similar to the one adopted for pharmacological treatments.

Pain recurrence following surgery was established based on the KM curve for the recurrence of moderate to severe pain based on the Vercellini et al. 2003 (Figure 18).¹⁰⁵

Figure 18: Fitted parametric survival curves for recurrence of moderate to severe pain following laparoscopic surgery – observed period



Recurrence rates that could be extracted based on this study are similar to clinical expert opinion.^{19,100} Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to assess goodness of fit and a log normal curve was used in the model (Table 47).

Table 47: Parametric survival curves for recurrence of moderate to severe pain following laparoscopic surgery

Model	AICs	BICs
Exponential	706.269	709.462
Gamma	699.624	706.010
Gompertz	696.046	702.432
llogist	696.071	702.457
lnorm	690.035	696.421
Weibull	698.384	704.770

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion

Parameters and their values used in the model for laparoscopic surgery as a comparator are summarised in Table 48. Other parameters were in line with the base model for pharmacological treatments.

Table 48: Clinical parameters adopted for laparoscopic surgery (additional comparator)

Parameter	Value	Source
Response to surgical treatment	50%	Johnson et al. (2004) ⁷⁰
Pain recurrence following surgery	Probabilities calculated based on KM curve	Vercellini et al. (2003) ⁴¹

Abbreviations: KM: Kaplan–Meier

The full list of studies with their characteristics, that were considered for populating the response rate for laparoscopic surgery are presented in Table 49.

Table 49: Clinical studies presenting response rates of laparoscopic surgery (additional comparator)

Study	Population	Intervention	Response definition	Time of response evaluation	Responders	N	Response rate
Abbot 2004, UK ⁶⁹	Thirty-nine women with histologically proven endometriosis; with all stages of endometriosis; UK - The James Cook University Hospital in Middlesbrough.	Excision of endometriosis by laparoscopy.	Any improvement in pain (assumed as result of VAS).	6 months	16	20	80%
Lalchandani 2005, Germany ¹⁰⁶	Women with minimal to moderate endometriosis.	Women in the surgical arm had either ablation or excision of all endometriotic lesions with helium thermal coagulator therapy.	Symptom-free	At the end of 12 months	9	17	53%
Sutton 1994, UK ⁷¹	Women seen in the gynaecological outpatient clinic with pain suggestive of endometriosis and had not received any treatment (medical or surgical) for endometriosis in the previous 6 months; minimal, mild, and moderate endometriosis (AFS stages I to III).	Laser ablation of endometriotic deposits and laparoscopic uterine nerve ablation.	Any improvement on VAS (0-10)	6 months	20	32	63%
			Any improvement on VAS (0-10)	6 months	14	19	74%
			Any improvement on VAS (0-10)	3 months	18	32	56%
Johnson 2004, New Zealand ⁷⁰	Women with endometriosis, a history of chronic pelvic pain (either dysmenorrhoea, NMPP, defecatory pain or deep	Surgery with and without laparoscopic	Pelvic pain VAS (0-10 scale) completely or partially resolved.	24 hours post-operative	29	67	43%

Study	Population	Intervention	Response definition	Time of response evaluation	Responders	N	Response rate
	dyspareunia for more than six months).	uterine nerve ablation.	VAS $\geq$ 50% reduction NMPP	3 months post-operative	27	62	43.5%
			VAS $\geq$ 50% reduction NMPP	12 months post-operative	26	52	50.0%
			VAS $\geq$ 50% reduction in dysmenorrhoea	3 months post-operative	17	54	31.5%
			VAS $\geq$ 50% reduction in dysmenorrhoea	12 months post-operative	18	45	40.0%

Abbreviations: AFS American Fertility Society; NMPP, non-menstrual pelvic pain; VAS, visual analogue scale

B.3.3.7 Adverse events and surgical complications

Adverse events (AEs) were incorporated into the cost-effectiveness model within the scenario analysis, based on the absence of significant (grade 3 or 4) adverse events, such as depression, headache, hot flushes or increased blood pressure in the EDELWEISS 3 study. These events, along with surgical complications and their influence on HRQoL, are detailed in Section B.3.4; data informing their impact on HRQoL and their frequency were sourced from the literature.

B.3.4 Measurement and valuation of health effects

Health effects in the cost-effectiveness model were based on evidence collected in a clinical trial and systematically sourced from the literature (see Appendix H), in line with the NICE hierarchy of preferred HRQoL evidence.¹⁰⁷ The methods for measurement and valuation of health effects are described in the following subsections, outlining how HRQoL data were collected, processed and incorporated into the model. These subsections provide a detailed overview of both trial-based and literature-sourced data integration.

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

In EDELWEISS 3 and 6, two instruments were used to collect HRQoL data: the disease-specific EHP-30 and the EQ-5D-5L questionnaire.^{58,62} However, only EQ-5D data were utilised in the model due to their consistency with the NICE reference case and suitability for cost-effectiveness analysis.

The EQ-5D is a self-administered, generic utility instrument developed by the EuroQoL Group in 1990. The EQ-5D consists of 2 parts: a descriptive system of 5 dimensions and a 20-cm vertical VAS with endpoints 0 and 100. It was collected by the subjects in the EDELWEISS 3 study at day 1, month 1, month 3 and month 6. The descriptive system includes five single-item dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Subjects choose between five levels of difficulty (from 1 to 5) in accomplishing tasks in each dimension. The health states were described in as five-digit numbers based on the answers to each of the five questions. The states were then

converted into a single index score using the Time Trade-Off method. An index score based on the individual dimensions was calculated using a scoring algorithm and the US Index from Crosswalk value set downloaded from the EuroQoL website.¹⁰⁸

Baseline mean EQ-5D-5L index resulting from EDELWEISS 3 was similar across treatment groups (Section B.2.6.2.4). During treatment, substantial improvements in the EQ-5D-5L index value versus placebo were observed at month 6 in the linzagolix 200 mg plus ABT group, as indicated by 95% CIs in Table 17.

Since the cost-effectiveness model utilised HRQoL from EDELWEISS 3 rather than EDELWEISS 6 (due to the possible attrition bias), the values obtained from the latter study have not been detailed in this description.

B.3.4.1.1 Clinical trial based HRQoL regression models

The EQ-5D-5L five-digit health states were sourced from individual patient data from EDELWEISS 3 and mapped using the NICE DSU mapping function according to the algorithm presented in Hernández-Alava and Pudney et al. (2017).¹⁰⁹ The mapping algorithm facilitates the conversion of EQ-5D-5L health states into EQ-5D-3L utility scores through a joint statistical model that employs a multi-equation ordinal regression framework. This approach utilises EQ-5D-5L dimension data alongside demographic factors such as age and gender. Utilities were then derived using the UK value set.

For the base analysis, the mapped values were used to develop two separate regression models: response model and pain model aimed to estimate the HRQoL for patients with endometriosis in different pain-related health states as specified in the cost-effectiveness model (No response, Partial response, Complete response—defined by dysmenorrhea and NMPP reduction and No pain/mild, Moderate, Severe – based on overall pelvic pain measured on the VRS scale as described in section B.3.2).

Additionally, to enhance the accuracy of the regression model, a comprehensive grey literature search was conducted alongside references identified in a SLR. This approach aimed to identify quality of life predictors relevant to the patient population to build the adjusted regression model. The predictors identified through this search, which matched

available patient characteristics reported in EDELWEISS 3, were subsequently tested using univariate analysis (Table 50). For this purpose, multiple binary variables were created with groups defined by the median value. Variables found to be statistically significant ($p\text{-value} \leq 0.05$), were then incorporated into the linear mixed-effects regression model. Linear mixed-effects regression models were utilised if more than one measurement was available (baseline, month 3, month 6). As outlined in Table 50, the following variables were considered: baseline pain, BMI, baseline EQ-5D-3L, opiate use, dyspareunia, dyschezia, pain level and response status.

Table 50: Univariate analysis results

Variable	Estimate	P-value
Age	<0.005	0.988
Age*	<0.005	0.812
Base pain*	0.0970	<0.005
BMI*	-0.0464	<0.005
Base EQ-5D-3L*	0.476	<0.005
Pregnancy history*	-0.030	0.698
Opiate use*	-0.108	<0.005
Months to diagnosis*	0.0183	0.286
Dyspareunia*	0.129	<0.005
Dyschezia*	0.143	<0.005
Treatment arm 2 (linzagolix 75 mg)	0.0206	0.237
Treatment arm 3 (linzagolix 200 mg plus ABT)	0.0358	0.0386
No/mild pain	0.320	<0.005
Moderate pain	0.185	<0.005
Endometriosis diagnosis <2 years	<0.005	0.930
Endometriosis diagnosis ≥ 2 and <5 years	-0.0521	<0.005
Partial response	0.123	<0.005
Complete response	0.234	<0.005

*Variables introduced as binary ones with groups defined by median; in bold if statistically significant at the level of 0.05

Abbreviations: ABT, add-back therapy; BMI, body mass index; EQ-5D-3L, EuroQoL 5-Dimension 3-Level

B.3.4.1.2 Response-based regression model for utility values

In the regression model developed to assess the HRQoL of patients in EDELWEISS 3, the same response criteria used for the co-primary endpoints of EDELWEISS 3 and EDELWEISS 6 were applied (see section B.2.6).

- Complete response was defined as a patient meeting the response criteria for both dysmenorrhoea and NMPP endpoints, indicating a comprehensive improvement in pain management and overall well-being
- Partial response was characterised by a patient achieving a response in either dysmenorrhoea or NMPP but not both, potentially reflecting a more limited benefit from the treatment
- Non-responders were those who did not meet the criteria for any of the endpoints, indicating a lack of therapeutic effect.

Table 51 summarises EQ-5D-3L data from all the treatment arms in the EDELWEISS 3 study in the context of the patient's response.

Baseline observations were excluded from the response regression model. However, baseline utility values were incorporated into the cost-effectiveness model, assigned to patients at the model's initial stage (1st model cycle). The regression model predicting health states related to treatment response utilised data from the 3- and 6-month assessments of EDELWEISS 3. This is because patients in the no-response health state showed higher utility values at the 3-month mark compared with baseline (Table 51), suggesting some improvement in overall health and a reduction in EAP despite the lack of a response. Since utility values in the cost-effectiveness model apply to health states after the first three-month treatment cycle, it was important to account for this observed improvement and exclude baseline data from the regression model. This approach ensured that the model accurately reflects patient-reported outcomes while appropriately utilising baseline utility values at the initial stage of the analysis.

Table 51: EQ-5D-3L data for all treatment arms in the EDELWEISS 3 study in the context of patient's response

Response type/ no response*	Month 3 (n)	Month 6 (n)
Baseline: 0.631 (484)		
Dysmenorrhoea responders	0.825 (220)	0.856 (219)
NMPP responders	0.858 (185)	0.867 (226)
Dysmenorrhoea only responders	0.745 (91)	0.751 (64)
NMPP only responders	0.805 (56)	0.809 (71)
Non responders	0.704 (195)	0.708 (181)
Partial responder	0.768 (147)	0.783 (135)
Complete responders	0.881 (129)	0.892 (155)

Abbreviations: EQ-5D-3L, EuroQoL 5-Dimension 3-Level; NMPP, non-menstrual pelvic pain

* The threshold for response in this clinical trial was defined for months 3 and 6, therefore the table includes EQ-5D-3L values for baseline as well as these months

Multiple models were tested for best fit to the data, with the selection based on AIC and BIC criteria. The models used for the final structure were built on the full dataset of patients that could be categorised to any of the response groups. Table 52 presents the five best-performing models that were fitted in the regression analysis.

Table 52: Five best-performing response-based models that were tested during the regression analysis

Model	AIC	BIC
Base pain level*, dyschezia*, partial response status, complete response status, no response status	-691.189	-654.865
Base pain level*, opiate use*, dyschezia*, partial response status, complete response status, no response status	-688.806	-647.292
BMI*, base pain level*, dyschezia*, partial response status, complete response status, no response status	-688.192	-646.697
BMI*, base pain level*, opiate use*, dyschezia*, partial response status, complete response status, no response status	-685.047	-638.365
Base pain*, partial response status, complete response status, no response status	-678.720	-647.585

Abbreviations: BMI, body mass index; AIC, Akaike Information Criterion; BIC, Bayesian information criterion

* Variables introduced as binary ones with groups defined by median

After evaluating multiple regression models, the first model was selected due to its superior performance, as indicated by AIC and BIC. In the context of the response-based model, the most significant predictors identified were baseline pain level and dyschezia. All variables demonstrated statistical significance (p-value ≤ 0.05).

Specifically, baseline OPP and dyschezia were associated with increases in EQ-5D-3L scores of 0.0801 and 0.0644, respectively. Additionally, partial and complete responses were linked to increases in HRQoL of 0.0577 and 0.148, respectively, compared to no response. For the final prediction, the percentages of observations corresponding to each combination within each response category were calculated and used as weights to derive the final utility values for health states. The utility values derived from the response model for the health states of no response, partial response, and complete response are presented in Table 53.

Table 53: Utility values derived from response-based model for health-states: no response, partial response and complete response

Health state	Utility value
Complete response	0.876
Partial response	0.775
No response	0.713

B.3.4.1.3 Pain-based regression model for utility values

The levels of pain associated with dysmenorrhoea and NMPP significantly impact the quality of life of patients suffering from endometriosis. To capture both types of pain, a single outcome of OPP was employed in the second HRQoL analysis.^{9,100} In EDELWEISS 3, pain was measured on VRS (dysmenorrhoea and NMPP) and NRS (OPP) scales using an electronic diary (eDiary). Given the profound influence of pain on quality of life, the decision was made to develop a regression model that incorporates pain severity in dysmenorrhoea and NMPP combined into OPP as key predictors of HRQoL. By linking pain to HRQoL metrics the model aims to elucidate the relationship between pain experiences and overall patient outcomes.

The regression model for health states defined by pain intensity represented as a single OPP value in the VRS scale was constructed similarly to the regression model based on response categories. Pain intensity was categorised into three distinct levels based on OPP: no pain/mild, moderate pain and severe pain (see section B.3.3.3 for criteria definitions). Table 54 summarises EQ-5D-3L data from all treatment arms in EDELWEISS 3 study in the context of the patient's pain level.

Table 54: EQ-5D-3L values reported for all treatment arms in the EDELWEISS 3 study

Pain level	Baseline (n)	Month 1 (n)	Month 3 (n)	Month 6 (n)
No pain/mild	0.798 (13)	0.860 (86)	0.872 (194)	0.878 (217)

Moderate	0.695 (247)	0.725 (293)	0.735 (220)	0.747 (173)
Severe	0.547 (216)	0.577 (81)	0.543 (43)	0.489 (33)

Abbreviations: EQ-5D-3L, EuroQoL 5-Dimension 3-Level

The same auxiliary predictors evaluated in the response-based model were utilised to construct the regression model focused on pain intensity. This methodology ensured analytical consistency and provided a comprehensive understanding of the factors influencing both pain intensity and overall QoL. Subsequently, a series of multiple models were tested to determine the most appropriate fit for the data, with the selection process guided by statistical criteria, specifically the AIC and BIC.

Table 55 presents the five best-performing models tested during the regression analysis, detailing their respective performances and the predictors included in each model.

Table 55: Five best-performing pain-base models that were tested during the regression analysis

Model	AIC	BIC
OPP no pain/mild, OPP moderate, OPP severe	-795.510	-770.404
Dyschezia*, OPP no pain/mild, OPP moderate, OPP severe	-794.182	-764.055
BMI*, OPP no pain/mild, OPP moderate, OPP severe	-791.179	-761.074
BMI*, dyschezia*, OPP no pain/mild, OPP moderate, OPP severe	-789.521	-754.399
Base pain*, OPP no pain/mild, OPP moderate, OPP severe	-786.905	-756.779

*Variables introduced as binary ones with groups defined by median

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian information criterion; BMI, body mass index; OPP, overall pelvic pain

Initially, two models were developed based on different patient populations. The first model was constructed exclusively from the dataset comprising only partial and complete responders at the six-month follow-up. The justification for this was that only patients demonstrating partial or complete response continue treatment within the cost-effectiveness framework. As a result, these patients were categorised according to health states associated with pain, to which utilities derived from this model were assigned. However, the decision to consider only month six observations of responders (either partially or completely) was ultimately reconsidered, because only one patient was available for the severe pain state, rendering the estimate highly unreliable. Consequently, the second model was developed using the 6-month observations of all patients and employed in the base analysis.

All variables in the base case model are statistically significant (p-value ≤ 0.05). Specifically, Moderate and No/mild pain states are associated with an average increase in HRQoL of 0.264 and 0.399, respectively, when compared to the severe pain state. Since the optimal pain model included only pain levels, there was no necessity to adjust the results for other predictors. The utility values derived from the pain-based model for the health states of No pain/mild, Moderate, and Severe are presented in Table 56.

Table 56: Utility values derived from pain model for health-states: no pain/mild, moderate and severe

Health state	Utility value
No pain/mild	0.876
Moderate	0.741
Severe	0.477

B.3.4.1.4 Scenario analysis regression models for utility values

An alternative response-based model was developed, incorporating observations from month 3 and 6, and baseline data. The objective of this approach was to assess how the exclusion of baseline patients affected the expected HRQoL. The model structure mirrored that of the base case response model but was constructed using a larger

number of observations. Additionally, the predictions were weighted according to the percentage representation of each profile within the health states. The most notable differences were observed among non-responders. In this alternative model, the utility values for the non-response state were primarily derived from baseline observations (patients who had not yet begun treatment), resulting in a significantly lower utility value compared to the base case model (0.661 vs 0.713), in which non-responders benefited from treatment (Table 57).

Table 57: Utility values derived from scenario analysis response model for health-states: no response, partial response and complete response

Health state	Utility value
Complete response	0.888
Partial response	0.779
No response	0.661

The alternative pain-based model was employed, featuring all available observations (baseline, 3- and 6-months) for partial and complete responders to test how it would influence the results. The difference between scenario and base case pain models is observable, especially for the severe health state (0.554 vs 0.477; Table 58).

Table 58: Utility values derived from scenario analysis pain model for health-states: no pain/mild, moderate and severe

Health state	Utility value
No pain/mild	0.874
Moderate	0.739
Severe	0.554

B.3.4.2 Mapping

B.3.4.3 Health-related quality-of-life studies

Utility data were obtained from published studies identified through an SLR conducted in July 2024 (see Section B.2.1) and EDELWEISS 3. For the base case scenario, utility values were primarily derived from EDELWEISS 3, except for disutility values associated with infertility and surgical complications, which were sourced from the existing literature. Detailed methodologies and an overview of the studies and results are provided in Section B.2.1 and Appendix H.

B.3.4.3.1 Health states utility values from the literature

The SLR identified 11 studies potentially relevant to the decision problem. Upon further evaluation, two studies were of special interest based on the model population and structure (they included health states with similar definitions to the model).

Aubry et al., 2017 reported EQ-5D scores for a cohort of patients experiencing symptoms not captured by the clinical trial data, specifically focusing on infertility.¹¹⁰ The utility values derived from this study informed the disutility associated with the post-hysterectomy/bilateral oophorectomy health state within the model. A discrepancy was noticed regarding the utility decrement reported for patients with infertility in this study, and the authors were contacted to clarify. However, no response was received by the date of submission. The utility value reported for patients with infertility was higher than the utility value reported for patients without infertility – these numbers were swapped for the analysis. Due to this uncertainty, results from this study were included in scenario analysis only.

Kent et al., 2016¹¹¹ provided utility values for patients with severe endometriosis undergoing various treatments, including GnRH agonists, laparoscopy, and conservative surgery/pelvic clearance. Data extracted from this study were employed in the scenario analysis to inform utility values for the following health states: laparoscopy (#1 and #2), post-laparoscopy (#1 and #2), hysterectomy/bilateral oophorectomy (#1 and #2), and post-hysterectomy/bilateral oophorectomy.

The summary of health-state utility values sourced from literature is presented in Table 59.

Table 59: Summary of health-state values from the literature

Author, year (country)	Study population	Cohort size (no of responders)	Intervention	HRQoL instrument	HRQoL values used in the model	Health-state in model
Aubry et al., 2017 (France) ¹¹⁰	Patients over 18 years old with proven endometriosis, consulting and treated for painful symptoms of at least 3 months' duration or for infertility.	216 (133)	Medical hormone as the first-line treatment, surgery indicated in case of medical treatment failure or in women refusing hormonal therapy, in case of diagnosis uncertainty, or in case of infertility without assisted reproductive technology indications.	French version of EQ-5D questionnaire.	Infertility-related disutility derived from HRQoL before treatment of infertile (0.56) and fertile (0.66) patients ($p=0.011$). <i>[values swapped – assumed typo in the study]</i>	Disutility added to post-radical surgery health-state in model.
Kent et al., 2016 (UK) ¹¹¹	Patients who required surgery for severe endometriosis (stage IV) with bowel involvement.	137 (100)	Laparoscopy as a first surgery, extinction of any residual endometriosis: pelvic clearance and conservative surgery as a second surgery, GnRH analogues. given for	EQ-5D (values in Kent et al. 2015 were presented on a scale up to 100 (e.g. 60 for All patients pre-operative). Results were divided by 100 to obtain numerical	All patients preoperative: patients in severe state before the extinction of rectovaginal endometriosis: 0.60 ($p<0.01$).	Scenario analysis: Laparoscopy #1 waiting.
					Mean of All patients preoperative:	Scenario analysis:

Author, year (country)	Study population	Cohort size (no of responders)	Intervention	HRQoL instrument	HRQoL values used in the model	Health-state in model
			approximately 3-6 months before the first surgery.	values of maximum 1.)	patients in severe state before the extinction of rectovaginal endometriosis: 0.60 ($p<0.01$) • All patients 2 months post-operative: patients initially in severe state, 2 months after the extinction of rectovaginal endometriosis: 0.75 ($p<0.01$) • All patients 6 months post-operative: patients initially in severe state, 6 months after the extinction of rectovaginal endometriosis: 0.713 ($p<0.01$)	Laparoscopy #1 and #2
					All patients 12 months post-operative: patients	Scenario analysis:

Author, year (country)	Study population	Cohort size (no of responders)	Intervention	HRQoL instrument	HRQoL values used in the model	Health-state in model
					initially in severe state, 12 months after the extinction of rectovaginal endometriosis: 0.80 ($p < 0.01$)	Post- laparoscopy #1 and #2.
					Pelvic clearance pre- operative: patients after laparoscopic extinction of rectovaginal endometriosis, before pelvic clearance: 0.58 ($p < 0.01$).	Scenario analysis: Radical surgery #1 and #2.
					All patients 12 months post-operative: patients initially in severe state, 12 months after the extinction of rectovaginal endometriosis: 0.80 ($p < 0.01$) minus one-time HRQoL loss calculated from all health-states above.	Scenario analysis: Post-radical surgery.

Abbreviations: EQ-5D, EuroQol-5-Dimension; HRQoL, health-related quality of life

While the SLR did not yield results specifically focused on HRQoL associated with AEs, studies included in B.2 did report on the occurrence and frequency of such events (severe AEs were considered only).^{58,112} Consequently, utility data pertaining to AEs and surgical complications were obtained through references derived from economic evaluations discussed in B.3.1, and supported by expert opinion.^{9,100} It is important to highlight that the regression model utilised in this analysis was developed using individual patient data from EDELWEISS 3, and therefore, inherently incorporates the AEs experienced by patients during the trial. However, it should be noted that surgical complications were not reported in EDELWEISS 3 due to the specific nature of the intervention. As a result, their impact on QoL relied exclusively on data sourced from the literature.

B.3.4.3.2 Health states utility values from Reulgolix STA

The disutility value for patients with infertility was assumed to be similar to the relugolix CT model at the level of 0.18.^{51,113}

B.3.4.4 Adverse reactions

B.3.4.4.1 Adverse reactions from literature

The impact of grade 3-4 AEs has been incorporated into the model scenario analysis. To account for these events, references were verified from studies in the SLR of cost-effectiveness studies (see Appendix G) and the NICE STA for relugolix.⁵¹

Table 60 presents disutility data related to AEs, sourced from the literature, that have been incorporated into the model scenario analysis.

Table 60: Adverse event disutility values from the literature

Disutility	Value	Reference
Depression	-0.12	Wang et al, 2019 ⁸⁶
Headache	-0.027	Wang et al, 2019
Hot flushes	-0.011	Wang et al, 2019

Disutility	Value	Reference
Increased blood pressure	-0.011	Wang et al, 2019

The frequency of AEs used in the scenario analysis were sourced from EDELWEISS 3 (for the intervention) and literature (for comparators), and are presented in Table 61.

Table 61: Frequency of adverse reactions sourced from the literature

AE	Linzagolix 200 mg plus ABT	Source	Relugolix CT	Source	GnRH agonist	Source
Depression	0.00%	EDELWEISS 3; month 6	0.24%	NICE STA Relugolix ⁵¹	0.47%	NICE STA Relugolix ⁵¹
Headache	0.00%		1.67%		1.71%	
Hot flushes	0.00%		0.00%		0.40%	
Increased blood pressure	0.00%		0.00%		0.24%	

Abbreviations: ABT, add-back therapy; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate); STA, single technology appraisal

B.3.4.4.2 Surgery complications based on the literature

Data on surgical complications were not available in EDELWEISS 3 and 6. As a result, the disutility and frequency of these events were sourced from the literature for both the base case and scenario analyses: references from the studies found in the SLR of cost-effectiveness studies were analysed (see Appendix G). This search aimed to identify and include data on surgery complications not fully captured in the clinical trial setting but relevant to real-world outcomes in the subsequent lines of treatment in the model.

The disutility associated with surgical complications and the frequency of specific complications are presented in Table 62 and Table 63.

Table 62: Surgical complications disutility values from the literature

Disutility	Value	Incorporated in	Reference
Radical surgery complications	-0.07	Base case analysis	Roberts et al, (2011) ¹¹⁴
	-0.05	Scenario analysis	Sculpher et al, (2004); ¹¹⁵ Geale et al, (2017) ¹¹⁶
laparoscopy complications	-0.07	Base case analysis	Roberts et al, (2011) ¹¹⁴
	-0.04	Scenario analysis	Sculpher et al, (2004); ¹¹⁵ Geale et al, (2017) ¹¹⁶

Table 63: Surgical complications frequency sourced from literature

Type of complication	Probability of complication – Base case analysis based on NICE STA Relugolix ⁵¹	Probability of complication – Scenario analysis based on literature and expert clinical opinion ^{100,117}
Laparoscopy complications (Laparoscopy #1 and Laparoscopy #2 health-states)		
Febrile event	0.00%	7.50%
Wound infection	0.00%	0.00%
Urinary tract infection	0.00%	5.00%
Impact on other organs	0.00%	0.00%
Fistula	0.00%	0.00%
Hysterectomy and oophorectomy complications (Radical surgery #1 and Radical surgery #2 health-states)		
Febrile event	0.00%	1.32%
Wound infection	0.00%	0.66%
Bleeding or hematoma	0.00%	0.66%
Ileus	0.00%	0.66%
Urinary retention	1.42%	0.66%
Urinary tract infection	1.42%	0.00%
Fistula	0.04%	0.00%
Impact on other organs	3.00%	0.00%
Anastomotic leakage	0.00%	10.00%

Abbreviations: STA, single technology appraisal

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

HRQoL data have been systematically categorised into two primary groups corresponding to distinct health states within the model. The first group is related to the initial decision tree and includes the initial patient response to treatment and subsequent intensity of NMPP and dysmenorrhea (collectively defined as OPP).

The second group includes health states related to various interventions, such as other medical treatment, waiting for laparoscopic surgery, the surgical procedures themselves (Laparoscopy #1 and #2), post-laparoscopic care (Post-laparoscopy #1 and #2), Radical surgery (#1 and #2), and subsequent post-surgical treatment. Additionally, this group incorporates the off-treatment state, which reflects the quality of life experienced by patients following the cessation of treatment.

B.3.4.5.1 Pain-related health-states utility values

The utility values assigned to pain-related health states (no response, partial response, complete response, no pain/mild, moderate-, and severe- pain) were derived from the proportion of patients occupying each health state during each cycle of the model. These utility values were informed by a regression model developed from individual patient-level data collected in EDELWEISS 3 (see section B.3.4). In the model base case, no disutilities (infertility, AEs) were applied to these health states, as it was assumed that they were already captured within EDELWEISS 3 EQ-5D data measurements. Additionally, no infertility disutilities were assumed during linzagolix treatment (and conservatively, any other medical therapy) as the half-life of linzagolix is approximately 15 hours and ovarian activity may recover within days of treatment cessation.⁴⁶ As indicated by clinical expert opinion, patients wanting to conceive can stop medical therapy at any time, therefore no infertility disutility would apply whilst on therapy.⁹

The regression model's foundation on individual patient data collected directly from the clinical trial and its subsequent mapping to the EQ-5D-3L instrument lend credibility to the derived utility values. Consequently, these values accurately represent the real-world quality of life experienced by patients undergoing treatment for EAP.

B.3.4.5.2 Other health-states utility values

The HRQoL for additional health states within the model was developed by leveraging the utility values associated with pain-related states, utilising the regression model from EDELWEISS 3 data. To effectively capture quality-of-life implications for patients undergoing specific medical interventions, the following algorithm was employed:

1. Health states to which patients transition from the No pain/mild health state (including off-treatment, no pain/mild, off-treatment during the washing period, and the initial stages of conception) were assigned the HRQoL values corresponding to the No pain/mild state as it is assumed that they experience the same level of pain. The assumption regarding the maintenance of treatment effects is derived from EDELWEISS 6.
2. For health states associated with other medical treatments, including patients categorised as No response, No pain/mild, Moderate, and Severe: the mean HRQoL value of these states was assigned in line with the algorithm presented in Wang et al., 2019.⁸⁶ The HRQoL for the waiting period for laparoscopy was calculated similarly, excluding the No pain/mild state from the average, as patients with No/mild pain typically do not require surgical intervention. As these patients were already heavily pretreated (with surgery and a multitude of pharmacological therapies, including GnRH analogues), the approach was deemed to be conservative. Most patients are assumed to continue sub-optimal therapy whilst waiting for the next surgical treatment.
3. For Laparoscopy #1 and #2, weighted averages were computed, incorporating the utility loss associated with undergoing surgery (177 days) and a designated period (3 days) during which utility was set to zero, due to the invasive nature of surgery. A similar methodology was applied to the radical surgery (#1 and #2) states, with an extension to the 'zero' period (7 days). Number of days with zero utility was based on assumptions in Wang et al. 2019.⁸⁶ Disutilities for complications were applied only to the proportion of patients experiencing respective complications
4. Utilities for post-laparoscopy health states (#1 and #2) were derived from the HRQoL values assigned to other medical treatments and the off-treatment state.

This allocation was proportionately based on the transitions of patients from these states to the post-laparoscopy state (see section B.3.3.4).

5. The HRQoL for post-radical surgery was assumed to align with the No pain/mild health state, with an additional infertility-related disutility applied only to the proportion of patients who wish to preserve fertility.^{19,100} The value estimated for this health-state is higher than Post-laparoscopy #1 and #2, which is in line with the literature.¹¹¹ This could be because most patients are assumed to be cured from endometriosis symptoms after radical surgery (especially after bilateral oophorectomy), whereas some patients would still experience EAP after laparoscopic surgery.

This comprehensive approach to defining HRQoL across various health states reflects the complexities of patient experiences and outcomes associated with endometriosis treatment. The summary of utility values for the cost-effectiveness analysis can be found in Table 64.

A conservative approach was taken for some of the utility assumptions related to surgical procedures. It was assumed that the HRQoL of patients during and after successive conservative surgeries remained the same (Laparoscopy #1 HRQoL is equal to Laparoscopy #2 HRQoL; Post-laparoscopy #1 HRQoL is equal to Post-laparoscopy #2 HRQoL). According to clinical experts, subsequent surgical procedures tend to be more invasive, leading to more complications.¹⁰⁰ Additionally, patients waiting for surgery were associated with a higher HRQoL than those entering the model. It was assumed that some patients receive pharmacological treatment to manage symptoms during this period.

Table 64: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	Reference in submission (section and page number)	Justification
No response	0.713	B.3.4.1.2, Table	The regression model is based on individual patient-level data.

State	Utility value: mean	Reference in submission (section and page number)	Justification
Partial response	0.775	B.3.4.1.2, Table 53	The regression model is based on individual patient-level data.
Complete response	0.876	B.3.4.1.2, Table 53	The regression model is based on individual patient-level data.
No pain/mild	0.876	B.3.4.1.3, Table 56	The regression model is based on individual patient-level data.
Moderate	0.741	B.3.4.1.3, Table 56	The regression model is based on individual patient-level data.
Severe	0.477	B.3.4.1.3, Table 56	The regression model is based on individual patient-level data.
Off-treatment, no pain/mild	0.876	B.3.4.1.3, Table 56	<i>As no pain/mild*</i>
Off treatment - washing period and conceive (pregnancy 1st step)	0.876	B.3.4.1.3, Table 56	<i>As no pain/mild*</i>
Pregnancy and breastfeeding (2 nd and 3 rd step)	0.876	B.3.4.1.3, Table 56	<i>As no pain/mild*</i>
Other medical treatment	0.702	Calculation	Mean of ^{**} : <i>no response; no pain/mild; moderate; severe</i>
Laparoscopy #1 waiting	0.644	Calculation	Mean of ^{**} : <i>no response; moderate; severe</i>
Laparoscopy #1	0.688	Calculation	Mean of ^{***} : <i>no response; no pain/mild; moderate; severe</i> and disutilities related to laparoscopic SCs
Laparoscopy #2	0.688	Calculation	Mean of ^{***} : <i>no response; no pain/mild; moderate; severe</i> and

State	Utility value: mean	Reference in submission (section and page number)	Justification
			disutilities related to laparoscopic SCs
Post-laparoscopy #1	0.758	Calculation	Weighted value of health states: <i>other medical treatment</i> (patients with symptoms or requiring medical treatment after laparoscopic surgery) and <i>off-treatment</i> (patients without symptoms after laparoscopic surgery)
Post-laparoscopy #2	0.758	Calculation	Weighted value of health states: <i>other medical treatment</i> (pts with symptoms or requiring medical treatment after laparoscopic surgery) and <i>off-treatment</i> (patients without symptoms after laparoscopic surgery)
Radical surgery #1	0.615	Calculation	Mean of**: <i>no response</i> ; <i>moderate</i> ; <i>severe</i> and disutilities related to laparoscopic SCs
Radical surgery #2	0.615	Calculation	Mean of**: <i>no response</i> ; <i>moderate</i> ; <i>severe</i> and disutilities related to laparoscopic SCs
Post-radical surgery	0.763	Calculation	As <i>no pain/mild</i> and disutilities related to infertility (applied only to the proportion of patients who wish to preserve fertility)
Death	0	Not available	Assumption

Abbreviations: EQ-5D; EuroQol-5-Dimension; SCs, surgical complications

*based on EDELWEISS 6 follow-up data: within six months of linzagolix withdrawal, patients did not transition from their current pain state to the *severe* pain state, nor was there is a significant decrease in EQ-5D utilities.

**based on the health states to which a patient can move whilst in a particular health state.

***based on the health states to which a patient can move whilst in a particular health state; plus no pain/mild assuming a proportion of patients can respond within the model cycle.

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

A cost and resources SLR was conducted to identify any relevant cost or healthcare resource use data relevant to the model. Full details of the SLR and results are presented in Appendix I.

The model includes several cost categories to reflect the key cost components related to drug therapies, surgical procedures, disease management, the natural course of pregnancy, and management of fertility issues in patients with endometriosis.

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.2 Drug acquisition costs

The costs of medical therapy (linzagolix 200 mg plus ABT and GnRH agonists) were applied in model cycles relating to patients on treatment i.e., within a decision tree in the initial response states and whilst in No pain/mild or Moderate pain states thereafter. The duration of therapy for the intervention and comparator was assumed to be fixed (1.5 years for GnRH agonists) or without restriction (linzagolix). Drug acquisition costs were not applied for treatment breaks (in the Off-treatment, No pain/mild and Pregnancy health-states).

A 50:50 split was assumed between patients treated with the short- (1-month) and long- (3-month) acting GnRH agonists - leuprorelin acetate, goserelin and triptorelin. This assumption was based on the equivalent parameter in the NICE STA for relugolix and indicated by expert opinion.^{51,100}

No wastage or compliance was considered in the base case analysis. However, compliance for linzagolix and ABT was used in the scenario analysis, based on data from the EDELWEISS 6 study and relugolix CT long-term study.^{61,118}

The calculation of drug costs is shown in Table 65.

Table 65: Drug costs and dosing

Drug therapy	Cost per pack	Doses per package	Administrations		Cost per cycles	
			1&2	3+	1&2	3+
Linzagolix 200 mg	£80.00	28	91	183	£260.00	£522.86
Leuprorelin acetate, 1-month	£75.24	1	3	6	£225.72	£451.44
Leuprorelin acetate, 3-month	£225.72	1	1	2		
Other GnRH						
Goserelin, 1-month	£70.00	1	3	6	£222.50	£445.00
Goserelin, 3-month	£235.00	1	1	2		
Triptorelin, 1-month	£81.69	1	3	6	£226.04	£452.07
Triptorelin, 3-month	£207.00	1	1	2		

Abbreviations: GnRH, gonadotropin-releasing hormone; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)

B.3.5.3 Add-back therapy

Market research and expert opinion indicate that the majority of patients treated with GnRH agonists use ABT, which is prescribed upon initiating treatment with the GnRH agonist.^{19,100} Therefore, ABT was included for all patients on GnRH agonists and linzagolix 200 mg for the entire treatment duration. Additionally, according to the NICE STA for relugolix, ABT is also used in patients after oophorectomy, therefore it was incorporated for all patients within the Post-radical surgery health-state.⁵¹ The costs of ABT are presented in Table 66.

Table 66: Add-back therapy costs and dosing

ABT	Cost per pack	Doses per package	Administrations		Cost per cycles	
			1&2	3+	1&2	3+
Klivance tablets	£13.20	84	91	183	£14.30	£28.76

B.3.5.4 Administration costs

Forms of treatment administration for the intervention, comparator and subsequent therapies include oral administration, intramuscular or subcutaneous injection, or IUD implantation. For tablets (linzagolix 200 mg, relugolix CT and ABT), no administration cost was included as they are administered orally. For GnRH agonists, it was assumed

that the injections or implants would be administered by a nurse in the GP's office during a 30-minute visit. The assumption regarding the timing of administration for GnRH agonists was based on the NICE STA for relugolix and expert opinion.^{51,100} The additional cost of an outpatient visit to a gynaecologist for IUD implementation was also included in the model. The unit costs of treatment administration are gathered in Table 67.

Table 67: Administration costs

Route of administration	Administration method	Unit cost	Source
Oral	Self-administration	£0.00	Assumed no cost for self-administration
Intramuscular or subcutaneous injection	Administered by healthcare professionals	£26.50	Costs and unit estimations for a GP practice nurse (band 5) per 30 minutes; ¹¹⁹ Consultation time based on NICE STA Relugolix ⁵¹
Implantation of intrauterine device	Outpatient, gynaecology	£257.98	Implantation of intrauterine device: Outpatient. Gynaecology code MA35Z ¹²⁰

Abbreviations: GP, general practitioner; STA, single technology appraisal

B.3.5.5 Concomitant medications

Concomitant medications including analgesics for pain management were included for patients on initial therapy (linzagolix 200 mg plus ABT and GnRH agonists plus ABT) based on response status (see section B.3.3). In addition, analgesics were included as part of the basket of therapies for Other medical treatment, and for patients in surgical health and post-surgical health-states.

The distribution of NSAIDs/painkillers was based on literature representative of the UK population, as described previously (see section B.3.3). Average unit costs of analgesics and cost of concomitant medications are presented in Table 68 and Table 69. All included formulations of concomitant medications are listed in the Appendix K.

Table 68: Analgesics cost and dosing

Analgesics	Dose (mg)	Cost per dose administration	Administrations		Cost per cycles	
			1&2	3+	1&2	3+
Ibuprofen	200	£0.01	318.5	641	£3.96	£7.96

Tramadol	50	£0.01	91	183	£1.30	£2.61
Codeine	30	£0.02	227.5	458	£5.14	£10.34
Hydrocodone	30	£0.05	182	366	£9.47	£19.04
Paracetamol	500	£0.01	227.5	458	£3.08	£6.19

Table 69: Concomitant medications

Analgesics group	Weights distribution ⁶	Cost per analgesics per cycle	
		1&2	3+
NSAIDs	63%	£3.96	£7.96
Opioids [^]	30%	£5.30	£10.66
Paracetamol	7%	£3.08	£6.19
Weighted average cost		£4.29	£8.63

Abbreviations: NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; [^]Cost for opioids are estimated as average cost of Tramadol, Codeine and Hydrocodone

B.3.5.6 Medical procedures

The cost of different surgical procedures and health-states were derived from data available from the NHS¹²⁰ and some additional parameters based on the NICE STA for relugolix.⁵¹ The cost of laparoscopic surgery, ablation and hysterectomy were based on the weighted average of procedure currency codes presented in Table 70. The cost calculated for hysterectomy is in line with the NICE STA for relugolix, using the weighted costs of procedures representing the different routes of hysterectomy (abdominal / vaginal and laparoscopic route weighted with percentages of patients - 67%, 30% and 3% respectively).⁵¹ As there was no cost for oophorectomy or bilateral oophorectomy, the cost of these procedures was estimated using the same method as in the NICE STA of relugolix; calculated as 61% of the cost of hysterectomy using cost proportions according to the UK Collaborative Trial of Ovarian Cancer Screening.¹²¹

The total costs of medical procedures are presented in Table 70.

Table 70: Medical procedures unit costs

Surgical procedure	Unit cost	Source
Laparoscopic surgery	£3,495.94	Intermediate, Laparoscopic or Endoscopic, Upper Genital Tract Procedures, with CC Score 0-1 (MA09B) and with 2+ (MA09A) ¹²⁰
Ablation	£1,261.25	Resection or Ablation Procedures for Intrauterine Lesions (MA12Z) ¹²⁰
Hysterectomy	£5,937.28	Weighted cost of abdominal hysterectomy (weighted average of codes MA07G, MA07F, MA07E) and laparoscopic/vaginal hysterectomy (weighted average of codes MA07G, MA09A, MA09B). ¹²⁰ Weights for type of hysterectomy were based on NICE STA Relugolix ⁵¹
Oophorectomy / bilateral oophorectomy	£3,647.67	Based on NICE STA Relugolix, proportion 61% of hysterectomy ⁵¹

Abbreviations: STA, single technology appraisal; CC, complications and comorbidities

Additional parameters for calculating costs associated with different health states (e.g., treatment and surgery distributions [Table 71]) were based on literature and expert clinical opinion as described previously (see section B.3.3).^{6,100}

Table 71: Additional parameters for medical procedures

Parameter	Percentage	Source
Percentage of patients with laparoscopy excision (weight for laparoscopy cost)	33%	NCEPOD 2024 ⁶
Percentage of patients with laparoscopy ablation (weight for laparoscopy cost)	50%	NCEPOD 2024 ⁶
Percentage of patients with hysterectomy	21%	NCEPOD 2024 ⁶
Percentage of patients with oophorectomy	17%	NCEPOD 2024 ⁶

Abbreviations: NCEPOD, National Confidential Enquiry into Patient Outcome and Death

Parameters and unit costs enabled the calculation of a cost per health-state, as presented in Table 72.

Table 72: Medical procedures costs per health-state

Health-state	One-off costs
Laparoscopy #1	£2,149.74

Laparoscopy #2	£3,495.94
Radical surgery #1	£4,902.50

B.3.5.7 Health-state unit costs and resource use

Ongoing management and resource use (e.g., visits to healthcare professionals or performance of certain tests) are required to monitor patients undergoing medical therapy, follow up patients during treatment breaks, and undergo medical procedures.

At therapy initiation and evaluation of response, it was assumed that patients would need one visit to the gynaecologist per event. Patients continuing initial therapy after response assessment were subject to regular monitoring by a nurse at a frequency of 4 visits per year. Long-term management of therapy was based on the NICE STA for relugolix.⁵¹

Additionally, it was assumed that patients on a treatment break with No/mild pain would still require monitoring by a nurse. However, the frequency was reduced to one visit per year. It was assumed that patients on an Off-treatment break in the first pregnancy state (Pregnancy #1) would require a visit to the gynaecologist or fertility specialist; 0.67 gynaecologist visits and 0.33 fertility specialist visits per year, were included respectively based on clinical expert opinion.¹⁰⁰

All patients switching to another therapy (i.e., entering the next line of treatment) required one consultation, which was included as the cost of a gynaecologist visit.¹⁰⁰

For the Other medical treatment health-state, monitoring by a nurse was applied at the same frequency as initial therapy (i.e., four visits per year). Additionally, it was assumed that the proportion of patients who would be treated pharmacologically whilst waiting for (50%), during (57%) and after (100%) laparoscopic surgery, would require the same monitoring frequency, i.e. 1.99, 2.28 and four visits per year for the respective health-states.^{19,100}

It was assumed that ultrasound and MRI would be performed before surgery (conservative or radical) and ultrasound would be performed once per year after

surgery. The type of exams and their frequencies were based on the relugolix STA.⁵¹ The additional cost of a gynaecologist follow-up visit was included.

Unit costs for the included resources are summarised in Table 73.

Table 73: Resource use costs

Resource use	Unit cost	Source
Gynaecologist, visit	£181.26	Consultant led. Gynaecology (502). WF01A. Non-admitted face-to-face attendance, follow-up ¹²⁰
Gynaecologist, telephone contact	£135.61	Consultant led. Gynaecology (502). WF01A. Non-admitted non face-to-face attendance, follow-up ¹²⁰
General practitioner, visit	£49.00	Per surgery consultation lasting 10 minutes (including direct care staff costs; with qualification costs) ¹¹⁹
General practitioner, telephone contact	£20.27	Costs and unit estimations for a telephone triage; GP-led ¹¹⁹
Nurse or midwife, visit	£53.00	Costs and unit estimations for a GP practice nurse (band 5);per hour ¹¹⁹
Nurse or midwife, telephone contact	£9.04	Costs and unit estimations for a telephone triage; Nurse-led ¹¹⁹
Fertility specialist, visit	£64.00	Annual and unit costs for qualified nurses; band 6 (Nurse specialist/team leader); per hour ¹¹⁹
Ultrasound scans	£235.60	Outpatient. Gynaecology (502). MA36Z. Transvaginal Ultrasound ¹²⁰
MRI Scan	£208.17	National schedule of NHS costs 2021/22 (MRI weighted average; RD01A, RD02A, RD03Z, RD04Z, RD05z, RD06Z, RD07Z; Total HRGs) ¹²⁰

Abbreviations: GP, general practitioner; MRI, magnetic resonance imaging

The resources and unit costs detailed above were used to calculate the cost applied to the health-states included as one-off costs or per model cycle. All costs are presented in Table 74 and Table 75.

Table 74: Health-state one-off costs

Health-state	Resource use costs - one-off
No response / response evaluation	£181.26
Entering next line	£181.26
Pregnancy (tunnel health-state, first cycle)	£142.56
Pregnancy (tunnel health-state, second cycle)	£0.00
Pregnancy (tunnel health-state, third cycle)	£0.00
Laparoscopy #1	£625.04
Laparoscopy #2	£625.04
Radical surgery #1	£625.04
Radical surgery #2	£625.04

Table 75: Health-state costs per model cycle

Health-state	Resource use costs – per model cycle	
	1&2	3+
Initial treatment	£53.00	£106.00
Off treatment - no pain/mild	£13.25	£26.50
Other medical treatment	£53.00	£106.00
Laparoscopy #1 waiting	£26.39	£52.79
Post-laparoscopy #1	£134.37	£268.75
Post-Laparoscopy #2	£111.90	£223.80
Post-radical surgery	£104.22	£208.43

B.3.5.8 Adverse reaction unit costs and resource use

The cost of AEs was included only in the scenario analysis and applied as an acute event in the first cycle for all patients starting therapy. AE probabilities were based on EDELWEISS 3 and the NICE STA for relugolix (see section B.3.4.4) and presented in Table 76.

Table 76: Adverse events probabilities

Adverse event	Probabilities				
	Linzagolix 200 mg	Relugolix CT	Leuprorelin acetate	Goserelin	Triptorelin
Headache	0.0%	0.2%	0.5%	0.5%	0.5%

Hot flush	0.0%	1.7%	1.7%	1.7%	1.7%
Depression	0.0%	0.0%	0.4%	0.4%	0.4%
Increased blood pressure	0.0%	0.0%	0.2%	0.2%	0.2%

Abbreviations: relugolix CT, relugolix combined therapy (relugolix-oestradiol-norethisterone acetate)

The cost for AEs was assumed to be the same as the cost of a GP consultation and is presented in Table 77.

Table 77: Adverse events costs

Adverse event	Unit cost per event	Source
Headache	£49.00	Per surgery consultation lasting 10 minutes (including direct care staff costs; with qualification costs) ¹¹⁹
Hot flush		
Depression		
Increased blood pressure		

In the base case analysis, surgery complication probabilities were based on the NICE STA for relugolix. Values from the literature and expert clinical opinion were used in the scenario analysis (presented in Table 78).

Table 78: Complication probabilities

Type of complication	Probability of complication – base-case analysis based on NICE STA Relugolix ⁵¹	Probability of complication – scenario analysis based on literature and expert clinical opinion ^{100,117}
Laparoscopy and ablation complications (Laparoscopy #1 and Laparoscopy #2 health-states)		
Febrile event	0.00%	7.50%
Wound infection	0.00%	0.00%
Urinary tract infection	0.00%	5.00%
Impact on other organs	0.00%	0.00%
Fistula	0.00%	0.00%
Hysterectomy and oophorectomy complications (Radical surgery #1 and Radical surgery #2 health-states)		
Febrile event	0.00%	1.32%
Wound infection	0.00%	0.66%

Bleeding or haematoma	0.00%	0.66%
Ileus	0.00%	0.66%
Urinary retention	1.42%	0.66%
Urinary tract infection	1.42%	0.00%
Fistula	0.04%	0.00%
Impact on other organs	3.00%	0.00%
Anastomotic leakage	0.00%	10.00%

Abbreviations: STA, single technology appraisal

Surgery complication costs were sourced from price lists available from the NHS, including weighted averages of relevant codes, which are detailed in Table 79.¹²⁰

Table 79: Complication costs

Type of complication	Unit cost per complication	Source
Laparoscopy and ablation complications (Laparoscopy #1 and Laparoscopy #2 health-states)		
Febrile event	£850.09	Code LA04S
Wound infection	£2,209.49	Weighted average of codes: WH07A, WH07B, WH07C, WH07D, WH07E, WH07F, WH07G [
Urinary tract infection	£2,219.67	Weighted average of codes: LA04H, LA04J, LA04K, LA04L, LA04M, LA04N, LA04P, LA04Q, LA04R, LA04S
Impact on other organs	£1,159.31	Code: FE32Z, Non-Elective Inpatient - Long Stay
Fisula	£3,294.49	Code: YQ42Z
Hysterectomy and oophorectomy complications (Radical surgery #1 and Radical surgery #2 health-states)		
Febrile event	£850.09	Code: LA04S
Wound infection	£1,118.39	Weighted average of codes: WH07C, WH07D
Bleeding or hematoma	£1,768.59	Weighted average of codes: WH07C, WH07D [
Ileus	£7,842.15	Weighted average of codes: FF33A, FF33B, FF34A, FF34B, FF34C
Urinary retention	£2,036.71	Code LA04Q

Urinary tract infection	£2,219.67	Weighted average of codes: LA04H, LA04J, LA04K, LA04L, LA04M, LA04N, LA04P, LA04Q, LA04R, LA04S
Fisula	£3,294.49	Code YQ42Z
Impact on other organs	£1,159.31	Code FE32Z, Non-Elective Inpatient - Long Stay
Anastomic leakage	£4,973.78	Weighted average of codes: WH07C, WH07D, WH07E, WH07F, WH07G

Source: National schedule of NHS costs 2021/22¹²⁰

B.3.5.9 Miscellaneous unit costs and resource use

B.3.5.10 Subsequent therapies

Medical therapy costs were applied to patients in subsequent lines of treatment, i.e. treated in the Other medical treatment health-state, whilst waiting for laparoscopy, and in Post-surgical states. Average costs applied to different medical therapies are presented in Table 80. All included formulations are listed in Appendix K.

Table 80: Cost of medical therapies utilised in different health-states

Therapy	Drug acquisition costs – per model cycle		Administration cost – per model cycle	
	1&2	3+	1&2	3+
LNG-IUS	£1.94	£3.87	£17.20	£34.40
NSAIDs/painkillers	£4.29	£8.63	£0.00	£0.00
Common oral Contraceptives	£0.16	£0.00	£0.00	£0.00
Oral progestogen	£0.80	£0.00	£0.00	£0.00
Synthetic steroids	£283.24	£569.59	£0.00	£0.00
Aromatase inhibitors	£5.72	£11.50	£0.00	£0.00
GnRH agonists	£224.75	£449.50	£53.00	£106.00
GnRH antagonists	£234.00	£470.57	£0.00	£0.00

Abbreviations: GnRH, Gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; NSAID, non-steroidal anti-inflammatory drug

It was assumed that in the Other medical treatment health-state, all patients would be treated, and an average cost of a therapy basket was applied. The same cost was applied to 50% of patients waiting for Laparoscopy #1 (Laparoscopy #1 waiting health-state) and 57% patients after first laparoscopy state based on the Endometriosis Market

Research Survey 2024.¹⁹ According to expert clinical opinion, drug therapy intensifies after further surgeries. Therefore, for patients in the Post-laparoscopy #2 health-state it was assumed that all patients would be on medical therapy.¹⁰⁰ The distribution of therapies in the respective health-states was based on the Endometriosis Market Research Survey 2024, as described in section B.3.3.¹⁹

The distributions of medical therapy based on current health state and previous treatment, are summarised in Table 81, and average costs per cycle in Table 82.

Table 81: Distribution of medical therapies utilised in different health-states

Therapy	Other medical treatment		Laparoscopy #1 waiting		Post-laparoscopy #1 and Post-laparoscopy #2	
	Previous treatment		Previous treatment		Previous treatment	
	GnRH antagonist	GnRH agonist	GnRH antagonist	GnRH agonist	GnRH antagonist	GnRH agonist
LNG-IUS	22%	32%	0%	0%	0%	0%
NSAIDs/Painkillers	5%	7%	26%	33%	13%	20%
Common oral Contraceptives	7%	10%	20%	26%	21%	32%
Oral progestogen	9%	12%	20%	26%	18%	27%
Synthetic steroids	7%	10%	3%	4%	3%	5%
Aromatase inhibitors	7%	10%	2%	3%	3%	5%
GnRH agonists	43%	0%	28%	0%	33%	0%
GnRH antagonists	0%	20%	0%	7%	7%	11%

Abbreviations: GnRH, Gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; NSAID, non-steroidal anti-inflammatory drug

Table 82: Pharmacological cost per health-states after initial medical treatment

Medical therapies in respective health states	Drug acquisition costs - per model cycle		Administration cost – per model cycle	
	1&2	3+	1&2	3+
Other medical treatment – previous treatment with GnRH antagonist	£117.54	£235.14	£26.70	£53.40
Other medical treatment – previous treatment with GnRH agonist	£74.89	£150.37	£5.45	£10.91

Laparoscopy #1 waiting - previous treatment with GnRH antagonist	£36.55	£72.97	£7.38	£14.76
Laparoscopy #1 waiting - previous treatment with GnRH agonist	£14.60	£29.12	£0.00	£0.00
Post-laparoscopy #1 - previous treatment with GnRH antagonist	£58.59	£117.15	£10.10	£20.19
Post-laparoscopy #1 - previous treatment with GnRH agonist	£23.71	£47.38	£0.00	£0.00
Post-Laparoscopy #2 - previous treatment with GnRH antagonist	£102.97	£205.89	£17.75	£35.49
Post-Laparoscopy #2 - previous treatment with GnRH agonist	£41.67	£83.26	£0.00	£0.00

Abbreviations: GnRH, Gonadotropin-releasing hormone

B.3.6 Severity

In assessing the proportional and absolute QALY shortfall, it is not anticipated that the treatment of linzagolix 200mg plus ABT for endometriosis will be applicable for any form of severity weighting.

B.3.7 Uncertainty

The EDELWEISS studies provide robust clinical evidence for the benefit of linzagolix 200mg plus ABT in the treatment of symptomatic endometriosis. However, due to the range of surgical interventions, evolving surgical techniques, difficulty assessing surgery via an RCT, and inconsistency of outcomes assessed for surgery (see Appendix M), there is a lack of high-quality evidence for surgical interventions and consequently, it is challenging to compare medical therapy (i.e., linzagolix plus ABT) to surgery.

B.3.8 Managed access proposal

Not applicable.

B.3.9 Summary of base-case analysis inputs

Due to the complexity of base-case analysis inputs, this summary is provided in Appendix N.

B.3.9.1 Assumptions

The summary of assumptions applied in the economic model is presented in Table 83.

Table 83: The summary of assumptions applied in the economic model

Variable	Assumption	Rationale
Time horizon	The time horizon in the base case is 15.1 years.	The average age in the EDELWEISS 3 study is 34.9 years. Therefore, the time horizon is set to 15.1 years which accounts for the starting age of 34.9 until 50 years old, the average age for a woman to reach menopause in the UK.
Treatment continuation	After six months, the decision to continue treatment is made for patients who have either responded or partially responded (with partial response understood as a response in dysmenorrhoea or NMPP).	According to the opinion of clinical experts, a significant reduction in pain associated with NMPP or dysmenorrhoea is considered sufficient to improve the overall well-being of patients with moderate to severe endometriosis. ^{9,100} This improvement is regarded as a reliable indicator of treatment efficacy, and, therefore, provides a strong rationale for continuing therapy.
Infertility disutility	Infertility disutility in the model is applied only to the Post-radical surgery health state, to the proportion of patients who wish to preserve fertility.	The proportion of patients affected by infertility disutility in the model is assumed to be equivalent to the percentage of patients with endometriosis who wish to preserve their fertility. Consequently, only those patients who lose their fertility due to radical surgery experience this disutility. Additionally, the model considers that patients in the No pain/mild health-state may become pregnant, resulting in a temporary interruption of their treatment; thus, it is assumed that patients on treatment do not experience infertility disutility during this period.
Discontinuation	The same discontinuation rate is assumed for all medical therapies except GnRH agonists; which are assumed to be terminated after 1.5 years. Data on discontinuation were derived from EDELWEISS 3 and 6 studies (discontinuation due to intolerability to the treatment, or break in the state of no pain or mild symptoms) and from the Office of National Statistics (discontinuation due to pregnancy). ¹⁰⁴	Data on discontinuation from the EDELWEISS 3 and 6 trials is assumed to be most relevant for the cost-effectiveness analysis of linzagolix 200 mg plus ABT for the treatment of endometriosis symptoms. An indirect treatment comparison showed no statistically significant difference in terms of treatment discontinuation due to adverse events between linzagolix 200 mg plus ABT and comparators.

Treatment duration	Patients on GnRH antagonists continue treatment if they respond, or until menopause (with a probability of treatment discontinuation). Patients in health-states: Other medical treatment, Post-laparoscopy #1, and Post-laparoscopy #2 continue treatment until recurrence of symptoms. Patients treated with a GnRH agonist will discontinue treatment after 1.5 year,	The growth of endometriotic tissue is driven by oestrogen, making endometriosis primarily a pre-menopausal condition. It is assumed that once a significant pain reduction (the defined treatment response) is achieved, patients can remain on therapy until discontinuation for other reasons. For GnRH agonists, however, a maximum treatment duration of 1.5 years is assumed based on the opinion of clinical experts. ¹⁹
Adverse events	Adverse events were not considered in the base analysis.	In the EDELWEISS 3 trial, which is considered most relevant for the comparative safety profile of linzagolix 200 mg plus ABT, no significant (grade 3 or 4) adverse events, such as depression, headache, hot flushes, or increased blood pressure, were observed. These adverse events, for which incidence rates are available in comparator studies, did not occur in the EDELWEISS trials.
First conservative surgery waiting time	The waiting time for the first conservative surgery is set for six months (one model cycle). During that time, 50% of patients are assumed to receive medical treatment (the same weighted basket as in Other medical treatment health-state).	It is assumed that patients wait six months before undergoing the first conservative surgery (Laparoscopy #1). Based on the opinion of clinical experts ¹⁹ , the average waiting time is around 18 months, however, a simplifying and conservative assumption that this period would last only 6 months was used (equal to one model cycle).
Post-operative treatment aimed at sustaining surgical outcomes	During the post-operative treatment after conservative surgeries (Post-laparoscopy #1 and Post-laparoscopy #2 health-states), patients are assumed to receive medical treatment aimed at sustaining surgical outcomes. 57% of patients are medically treated after the first conservative surgery and 100% after the second.	Based opinion of clinical experts, the majority of patients receive medical treatment following surgery, which plays a critical role in maintaining pain relief achieved through the surgical procedure. ^{9,100} Moreover, the need for postoperative treatment becomes increasingly important as patients undergo multiple surgeries, as each additional procedure may heighten the risk of pain recurrence and other complications.

Use of analgesics	The model incorporates the use of analgesics as part of the treatment regimen alongside linzagolix 200 mg plus ABT, GnRH agonists, and surgery (as a separate comparator). Analgesic use is also included in all subsequent health states (by being a part of medical therapies basket). The proportion of patients using analgesics during the intervention/ comparator treatment in the model is based on NICE STA Relugolix submission⁵¹	Pain management strategies, particularly the use of analgesics, are integral to the treatment of endometriosis, as they address the primary symptom experienced by patients. An indirect treatment comparison revealed no statistically significant differences in the treatment effects between linzagolix 200 mg plus ABT and the comparators. As a result, it is assumed that the use of analgesics will be similar across all treatments
Pregnancy health-state	The model incorporates a treatment break to account for patients' pregnancies, applied to a fixed percentage of those in a No pain/mild pain state. No pregnancy costs and health benefits have been included in the model, as these are assumed to be similar between the intervention and the comparators.	The population in the model consists of pre-menopausal women, for whom successful treatment of endometriosis may improve fertility and increase the likelihood of pregnancy. It is assumed that the pregnancy rate for patients in the No pain/mild pain state will be the same as that of the general population of women of similar age in the UK.¹⁰⁴
Diagnosis tests	No diagnosis test and associated costs have been included in the model.	The patient population considered in the analysis is adult pre-menopausal women, aged 18 to 49 years (average age of 34.6 years), with surgically and, if available, histologically confirmed pelvic endometriosis and with moderate to severe EAP. It is, therefore, assumed that all patients are diagnosed.
Mortality rate	No increased mortality linked to endometriosis or endometriosis-related surgeries is applied.	Endometriosis is not assumed to have an impact on mortality.

Abbreviations: ABT, add-back therapy; EAP, Endometriosis-associated pain; GnRH, Gonadotropin-releasing hormone; NMPP, non-menstrual pelvic pain; STA, single technology appraisal

B.3.10 Base-case results

B.3.10.1 Base-case incremental cost-effectiveness analysis results

The base-case cost-effectiveness model results are presented in Table 84 and Table 85. Compared with leuprorelin, linzagolix 200 mg plus ABT is associated with incremental costs of £2,252 and incremental QALYs of 0.41, resulting in an ICER of £5,554 per QALY, which is below UK cost-effectiveness threshold of £20,000 to £30,000 per QALY. Linzagolix 200 mg plus ABT is also cost-effective versus surgery, with an

incremental cost of £421 and an incremental QALY of 0.61, resulting in an ICER of £693.

Table 84: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Linzagolix 200 mg plus ABT	14,897	11.76	9.33	-	-	-	-
Leuprorelin	12,646	11.76	8.93	2,252	0.00	0.41	5,554
Surgery	14,476	11.76	8.73	421	0.00	0.61	£693

Abbreviations: ABT, add-back therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 85: Net marginal benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
Linzagolix 200 mg plus ABT	14,897	9.33	-	-	-	-
Leuprorelin	12,646	8.92	2,252	0.41	5,856	9,910
Surgery	14,476	8.73	421	0.61	11,732	17,809

Abbreviations: ABT, add-back therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net marginal benefit; QALYs, quality-adjusted life years

B.3.11 Exploring uncertainty

A range of sensitivity analyses were conducted to explore the underlying uncertainty in the base-case cost-effectiveness results. These include deterministic sensitivity analyses, probabilistic sensitivity analyses, and scenario analyses. The results for net marginal benefit are presented only for the base-case scenario, but are available within the cost-effectiveness model. For comparison with laparoscopic surgery, no probabilistic or deterministic cost effectiveness analyses were conducted as this is additional comparator only, however, two alternative scenarios on surgery efficacy were performed.

B.3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to explore the uncertainty around key model parameters. PSA was conducted by varying these parameters using their upper and lower bound values based on an assigned distribution. 1,000 simulations were run for the PSA, by which time the ICERs had converged to a stable mean, represented by the probabilistic ICERs. The probabilistic ICER vs leuprorelin (£5,810) lies closely to the base-case ICER (£5,554) indicating that the cost-effectiveness results are robust (See Table 85 and Table 86).

Output from the PSA iterations is presented as scatter points on the cost-effectiveness plane in Figure 19 for linzagolix vs. leuprorelin. All scatter points, which represent the simulated incremental costs and QALYs, are in the northeast quadrant for linzagolix vs. leuprorelin. This indicates that linzagolix plus ABT is associated with both higher costs and QALYs compared to leuprorelin, that is, linzagolix plus ABT is both more effective and more costly.

The PSA results were also plotted in the form of a cost-effectiveness acceptability curve (CEAC), as shown in Figure 20 for linzagolix vs. leuprorelin. The CEAC shows the probability of cost effectiveness for linzagolix vs. leuprorelin given varying willingness to pay thresholds for a QALY. According to the CEAC, the probability of linzagolix vs. leuprorelin being cost-effective is 63% at a willingness to pay of £5,000/QALY. The probability is close to 100% at £10,000/QALY.

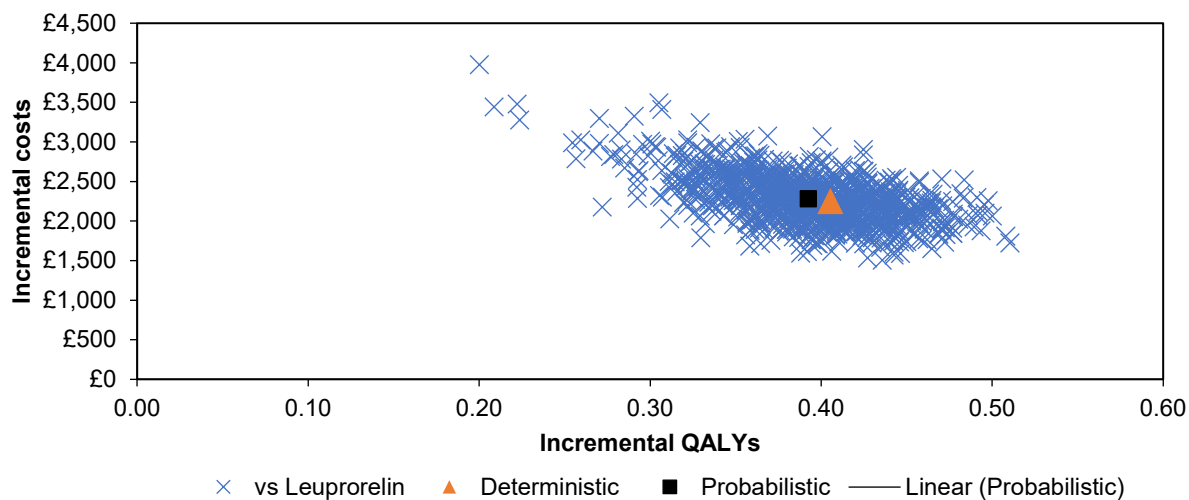
Figure 20 for linzagolix vs. leuprorelin. The CEAC shows the probability of cost effectiveness for linzagolix vs. leuprorelin given varying willingness to pay thresholds for a QALY. According to the CEAC, the probability of linzagolix vs. leuprorelin being cost-effective is 63% at a willingness to pay of £5,000/QALY. The probability is close to 100% at £10,000/QALY.

Table 86: Probabilistic cost-effectiveness results – linzagolix 200 mg plus ABT vs. leuprorelin

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Linzagolix 200 mg plus ABT	14,901	11.76	9.32	-	-	-	-
Leuprorelin	12,621	11.76	8.92	2,280	0.00	0.39	5,810

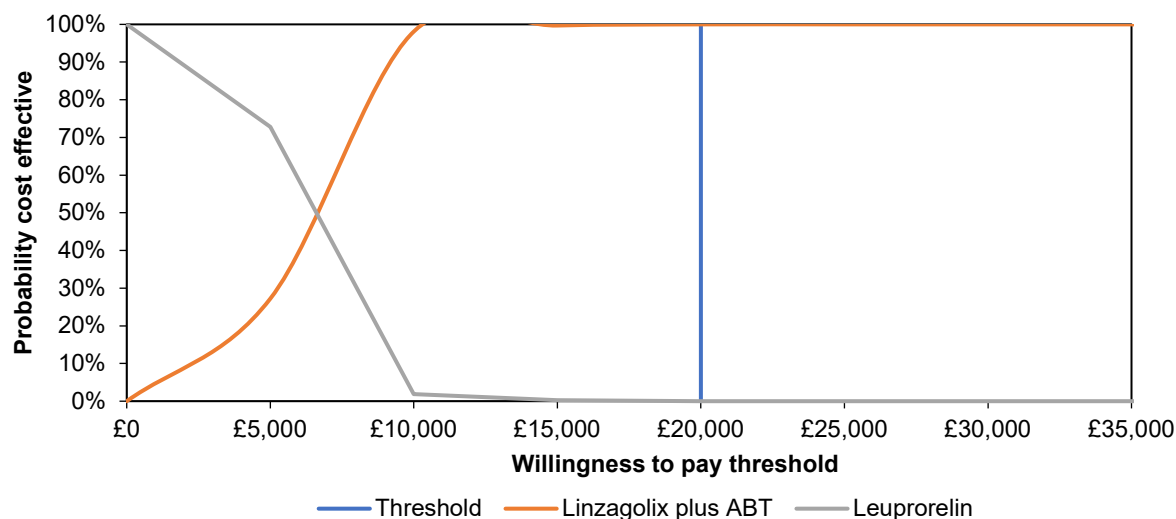
Abbreviations: ABT, add-back therapy; LYG, life years gained; QALYs, quality-adjusted life years

Figure 19: PSA output on the cost-effectiveness plane, linzagolix 200 mg plus ABT vs. leuprorelin



Abbreviations: ABT, add-back therapy; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 20: Cost-effectiveness plane – linzagolix 200 mg plus ABT vs. leuprorelin



Abbreviations: ABT, add-back therapy

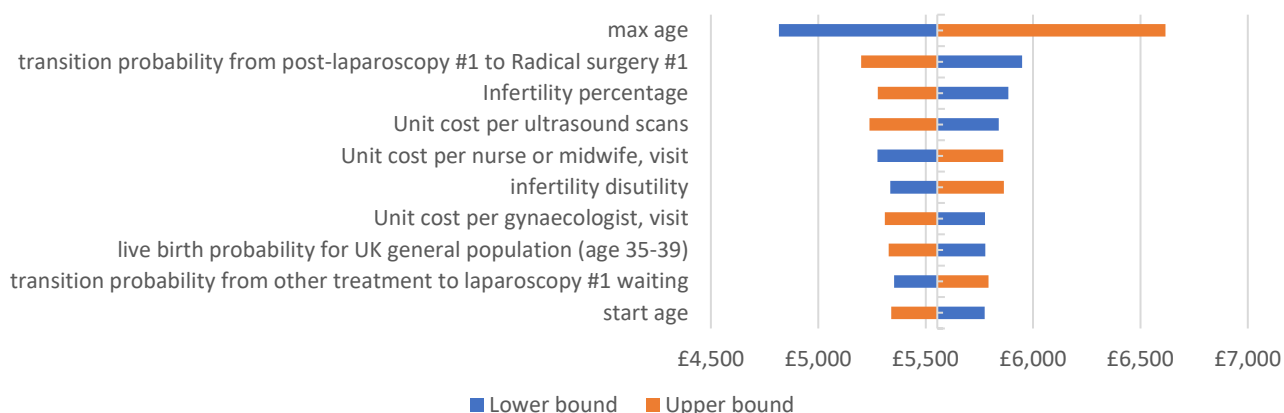
B.3.11.2 Deterministic sensitivity analysis

One-way deterministic sensitivity analyses (OWSA) were conducted to examine the sensitivity of the model result to lower and upper estimates of parameter values.

The results from the OWSA are presented in the form of a tornado diagram where the ten parameters with the largest influence on the ICER are presented in Figure 21 for linzagolix vs. leuprorelin.

The tornado diagram below shows that the maximum age of patients with endometriosis has the largest impact on the ICER. Overall, the results appear robust and none of the parameters have a considerable impact upon the ICER, as it does not exceed £7,000 per QALY in any of the OWSAs.

Figure 21: Tornado diagram – linzagolix 200 mg plus ABT vs. leuprorelin



Abbreviations: ABT, add-back therapy

B.3.11.3 Scenario analysis

The sensitivity of the model results to changes in key assumptions or parameters was explored through several scenario analyses. The scenario analyses results are presented below, with pairwise ICERs presented (Table 87). The most impactful scenarios are related to the time horizon parameters: different time horizons, or alternative starting or maximum age of patients with the disease. Other significant scenarios included an alternative probability algorithm for health state transitions, alternative rules for continuing initial treatment (i.e., minimum health benefit required to continue therapy), assumptions applied to the Pregnancy health-state, and infertility disutility and utility values utilised in surgery-related health-states (e.g. Laparoscopy #1, Post-laparoscopy #1, Radical surgery #2 etc.).

The overall conclusion differed from the base case in only one scenario: setting the time horizon to 1.5 years resulted in linzagolix generating equal QALYs compared to leuprorelin and reduced treatment costs.

Table 88 describes alternative approaches to obtaining health states transitions in the model. All probabilities were calculated using the Endometriosis Market Research Survey.¹⁹

Table 87: Results of scenario analyses – linzagolix 200 mg plus ABT vs. leuprorelin

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Base-case			£2,252	0.00	0.41	£5,554
Time horizon	15.1 years	1.5 year	£-20	0.00	0.00	Less costly, equal effective
Time horizon	15.1 years	5 years	£1,011	0.00	0.11	£9,573
Start age	34.9	18	£4,253	0.00	0.52	£8,158
Alternative transitions between health states post initial treatment (scenario 2)	Base case probabilities of patients transitioning to health-states in the model (see section B.3.3)	Alternative probabilities of patients transitioning to health-states in the model (see Table 88)	£3,120	0.00	0.40	£7,811
Response criteria for continuing treatment after 6 months	Dysmenorrhoea or NMPP responders	Only complete responders and NMPP responders	£2,023	0.00	0.26	£7,758
Infertility disutility applied to states with medical therapies after initial treatment	No	Yes applied to health states: Other medical treatment, Post-laparoscopy #1 and Post-laparoscopy #2)	£2,252	0.00	0.64	£3,505
Infertility and pregnancy assumptions	Base case assumption applied in the model (see section B.3.9)	Soliman et al. 2017 ¹²²	£2,267	0.00	0.30	£7,526

Alternative transitions between health states post initial treatment (scenario 1)	Base case assumption applied in the model (see Section B.3.9)	Alternative probabilities of patients transitioning to health-states in the model (see Table 88)	£2,900	0.00	0.40	£7,251
Pregnancy state included/excluded	Included	Excluded from the model	£2,804	0.00	0.40	£6,984
Discount rate for health effects	Discount rate for health effects: 3.5%	Discount rate for health effects: 0%	£2,252	0.00	0.53	£4,283
Utility values for the CE model health-states based on regression model 1 and literature	Utility values for all health-states based on the regression model only	Utility values for health-states related to surgical procedures based on the literature (see Table 59: Summary of health-state values from literature)	£2,252	0.00	0.34	£6,561

Abbreviations: ABT, add-back therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMPP, non-menstrual pelvic pain; QALYs, quality-adjusted life years

Table 88: Alternative between states transition probabilities

Transition	Base case	Scenario analysis 1	Scenario analysis 2
Other treatment to Laparoscopy #1 waiting	Next line after recurrence of symptoms.	Next line after recurrence of symptoms.	Next line after recurrence of symptoms.
Laparoscopy #1 to Radical surgery #1	(First surgical procedure type) x (second surgical procedure type - radical) x (time before recurrence after unsuccessful surgical intervention 0-3 months).	(Annual recurrence rate on laparoscopic surgery) x (% of immediate recurrence: 0-3 months) x (% of repeat surgery) x (adjusted % of radical surgery).	(Annual recurrence rate on laparoscopic surgery) x (% of immediate recurrence: 0-3 months) x (% of repeat surgery) x (unadjusted % of radical surgery).
Laparoscopy #1 to Laparoscopy #2	(First surgical procedure type) x (second surgical procedure type - conservative) x (time before recurrence after unsuccessful surgical intervention 0-3 months).	(Annual recurrence rate on laparoscopic surgery) x (% of immediate recurrence: 0-3 months) x (% of repeat surgery) x (adjusted % of conservative surgery).	(Annual recurrence rate on laparoscopic surgery) x (% of immediate recurrence: 0-3 months) x (% of repeat surgery) x (unadjusted % of conservative surgery).
Post-laparoscopy #1 to Laparoscopy #2	(First surgical procedure type) x (second surgical procedure type) x (treatment decision following the recurrence after surgery: repeat surgery).	(Annual recurrence rate on laparoscopic surgery) x (% of late recurrence: 4-12 months) x (% of repeat surgery) x (adjusted % of radical surgery).	(Annual recurrence rate on laparoscopic surgery) x (% of late recurrence: 4-12 months) x (% of repeat surgery) x (unadjusted % of radical surgery).
Post-laparoscopy #1 to Radical surgery #1	(First surgical procedure type) x (second surgical procedure type) x (treatment decision following the recurrence after surgery: repeat surgery).	(Annual recurrence rate on laparoscopic surgery) x (% of late recurrence: 4-12 months) x (% of repeat surgery) x (adjusted % of conservative surgery).	(Annual recurrence rate on laparoscopic surgery) x (% of late recurrence: 4-12 months) x (% of repeat surgery) x (unadjusted % of conservative surgery).

Laparoscopy #2 to Radical surgery #1	(How many surgeries over lifetime: 3) x (second surgical procedure type) x (time before recurrence after unsuccessful surgical intervention 0-3 months).	Same as: Laparoscopy #1 to Radical surgery #1	Same as: Laparoscopy #1 to Radical surgery #1
Radical surgery #1 to Radical surgery #2	Annual recurrence rate following surgical procedures: hysterectomy plus oophorectomy.	Same as: Laparoscopy #1 to Laparoscopy #2	Same as: Laparoscopy #1 to Laparoscopy #2
Post-laparoscopy #2 to Radical surgery #1	As Post-laparoscopy #1 to Radical surgery #1	Same as: Post-laparoscopy #1 to Radical surgery #1	Same as: Post-laparoscopy #1 to Radical surgery #1

Two alternative scenarios were tested in the comparison of linzagolix 200 mg plus ABT with laparoscopic surgery. These scenarios used alternative values for the response rate to surgical treatment and the recurrence rate following successful surgery. These values were explored in the scenario analyses because they were both sourced from the literature in the base case analysis, whereas values informing the efficacy of GnRH analogues were sourced from the EDELWEISS trials and the ITC.

To assess the robustness of this assumption, more conservative values (i.e., less favourable for linzagolix plus ABT vs surgery) were tested in the scenario analysis. The response rate presented in Sutton et al. 1994⁷¹ was used because the definition of response was less strict (any pain improvement on VAS scale, 0-10) compared to the response rate for pharmacological therapies (see section B.3.3.2). Similarly, the recurrence rates based on Shakiba et al. 2008 were used because the definition was less strict (reoperation free survival) in this study compared to Vercellini et al. 2003¹⁰⁵ (recurrence of moderate or severe DYS). According to the Shakiba et al. 2008¹²³ definition of recurrence, patients could use pharmacological treatment if pain recurred, and they would not be qualified as a recurrent patient.

The overall conclusions did not change in either of the scenarios tested. When the response rate based on Sutton et al. 1994⁷¹ was applied, treatment with linzagolix plus ABT was more expensive (£771) and generated an additional 0.55 QALYs compared to laparoscopic surgery, resulting in an ICER of £1,394 per QALY. Similarly, when the recurrence rate was based on Shakiba et al. 2008, linzagolix 200 mg plus ABT was more expensive (£244) and generated an additional 0.62 QALYs compared with laparoscopic surgery, resulting in an ICER of £392 per QALY. The results of the scenario analysis confirmed the robustness of the base case analysis.

Table 89: Results of scenario analyses – linzagolix 200 mg plus ABT vs. laparoscopic surgery

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs (£)	Incremental QALYs	Incremental LYGs	ICER (£/QALY)
Base-case			£421	0.61	0.00	£693 / QALY
Surgery response rate	50% (Johnson et al. 2004 ⁷⁰)	63% (Sutton et al. 1994 ⁷¹)	£771	0.55	0.00	£1,394 / QALY
Recurrent rate after laparoscopic surgery	KM curve based on Vercellini et al. 2003 ¹⁰⁵ (log-normal fit)	KM curve based on Shakiba et al. 2008 (exponential fit)	£244	0.62	0.00	£392 / QALY

Abbreviations: ABT, add-back therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; KM, Kaplan–Meier; QALYs, quality-adjusted life years

B.3.12 Subgroup analysis

No subgroups were analysed in the economic analysis.

B.3.13 Benefits not captured in the QALY calculation

Prescribing linzagolix 200 mg plus ABT for the treatment of endometriosis offers non-quantifiable savings that could have a significant benefit to public payers. Effective symptom management can lead to increased productivity and reduced absenteeism from work. Whilst not directly measurable in healthcare costs or captured in the cost-effectiveness model, this can have a substantial positive impact on the economy and society.

Further benefits of linzagolix plus ABT vs GnRH agonists not captured in the model include: oral administration at home, removing the need to arrange and attend monthly/3-monthly appointments in primary care for a GnRH agonist depot injection; rapid return of periods/fertility after stopping treatment; and the ability to discontinue treatment immediately in the event of intolerable adverse events (as opposed to depot GnRH injections).

B.3.14 Validation

B.3.14.1 Validation of cost-effectiveness analysis

The model has undergone thorough internal validation to reveal possible errors and incorrect operation of individual model modules. The Drummond and Jefferson checklist was used in the validation process. Internal validation included testing the values of key parameters entered into the model. This included checking that zero or extreme values had the expected impact on model results. For instance, setting drug acquisition costs for linzagolix to zero only affects cost reduction in the linzagolix arm; setting utility value in the *no response on initial treatment* state to 0 (1) decreases (increases) the number of QALYs; using a shorter time horizon decreases the number of QALYs and reduces total costs, etc. In each cycle, the sum of

proportions across health states, including cumulative mortality, is equal to 100% in each modelled arm.

As part of the convergence validation, the model was compared with other models for the same health problem, identified based on the literature search conducted by two independent reviewers (section B.3.1). The individual cost-effectiveness studies were shown to validate the model design, the defined health states, and the choice of cost categories. Nevertheless, most of the compared studies were performed over a much shorter time horizon than included in this economic analysis, which affects the results obtained.

As a part of external validation, the clinical experts verified the most impactful assumptions used in the model, and its structure^{9,100}. In particular, clinical experts validated model health-states, assumptions regarding initial and long-term treatment continuation (pain endpoints used in clinical trials utilised in the model), resource use, comparators, and the treatment pathway.

B.3.15 Interpretation and conclusions of economic evidence

Compared with the current standard second-line medical treatment (GnRH agonists), linzagolix 200 mg plus ABT is highly cost-effective when assessed against the NICE cost-effectiveness threshold of £20,000 to £30,000 per QALY. Linzagolix 200 mg plus ABT is associated with increased QALYs and an acceptable increase in costs.

The tangible benefits of linzagolix 200 mg plus ABT include the potential for it to be prescribed for a longer duration than GnRH agonists, ease of administration, rapid onset of therapeutic effect, and quick reversibility of its effects. Additionally, it is expected that using linzagolix 200 mg plus ABT will help avoid more radical laparoscopic and abdominal surgeries, which could impair patient HRQoL, particularly in patients requiring multiple surgeries due to early onset of the disease and/or symptom recurrence over time.

The cost-effectiveness analysis has some limitations. The treatment pathway is individualised with a variety of possible treatment options. Therefore, an economic model cannot fully capture the complexities of endometriosis management. To address uncertainties, a broad range of scenario analyses was performed to confirm the robustness of the results. Another limitation relates to the health utility inputs; for

some health states, utilities were derived directly from the EDELWEISS 3 study (for initial pharmacological treatment). However, for health states related to surgical procedures, some assumptions were necessary, and a conservative approach was applied to avoid overestimating the treatment benefit of linzagolix 200 mg plus ABT. Furthermore, the long-term maintenance of the linzagolix 200 mg plus ABT treatment effect was based on only a six-month period from the EDELWEISS 3 study. This assumption was validated by clinical experts, who do not expect any treatment-waning effect for GnRH antagonist therapy. The treatment waning effect was also tested in scenario analyses.

The economic analysis supports the expectation that linzagolix 200 mg plus ABT provides a cost-effective treatment option in NHS England practice for patients with symptoms of endometriosis.

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B.5 Appendices

The following appendices are provided as separate documents:

Appendix C: Summary of product characteristics (SmPC)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality of life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Systematic literature review and feasibility assessment of an indirect treatment comparison with surgery

Appendix N: Parameters used in the cost-effectiveness model

**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Single technology appraisal
Linzagolix for treating symptoms of
endometriosis
[ID6357]

Summary of Information for Patients (SIP)

October 2024

File name	Version	Contains confidential information	Date
ID6357 Linzagolix Endometriosis SIP [noCON] 30Oct2024	1.0	No	30 Oct 2024

Summary of Information for Patients (SIP)

What is the SIP?

The SIP is written by the company seeking approval from NICE for their treatment to be sold to the National Health Service (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 **Summary of Information for Patients** 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):

Generic name: Linzagolix

Brand name: Yseltly®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Adult women requiring symptomatic treatment of endometriosis, who are of reproductive age and have a history of previous medical or surgical treatment for their endometriosis.

In this indication, linzagolix should be taken in combination with hormonal add-back therapy, and therefore is not suitable for women who are not able to, or prefer not to, take hormone-based therapies.

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.

Marketing authorisation in the UK for the indication of symptomatic treatment of endometriosis is pending. Details of the marketing authorisation status are provided in the company submission, Section B1.2.

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:

Theramex has no existing collaborations with endometriosis patient groups.

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.

Endometriosis is a condition where cells similar to the ones in the lining of the womb (uterus) are found elsewhere in the body. These cells react to the menstrual cycle each month and also bleed. However, there is no way for this blood to leave the body. This can cause inflammation, pain and the formation of scar tissue.¹

Some patients with endometriosis may have no or mild symptoms, whilst at the other end of the spectrum, symptoms can be severe and debilitating. Symptoms vary for each individual depending on where their endometriosis is, with severe, chronic pelvic pain being the most common symptom. Women with endometriosis may experience fatigue, depression, an inability to conceive, problems in working and social life, and relationship or sexual issues. There is no definitive cure for endometriosis, and it can severely impact quality of life and wellbeing.¹

Endometriosis is a condition which usually affects those assigned female at birth between puberty and menopause. Globally, endometriosis is estimated to affect approximately 10% of women of reproductive age, however a study based on data from a UK population estimated a lower prevalence of 2% in women of reproductive age.^{1,2}

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?

The process of getting a diagnosis can take some time because the symptoms are often similar to other conditions. The only definitive way to diagnose endometriosis is laparoscopy, an operation in which a camera (a laparoscope) is inserted into the pelvis via a small cut near the navel. The surgeon uses the camera to see the pelvic organs and look for any signs of endometriosis.^{3,4}

In the UK, patients with endometriosis wait, on average, 9 years for a diagnosis, which is a significant issue as it can lead to prolonged suffering, ill health and risks to fertility.⁵

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.

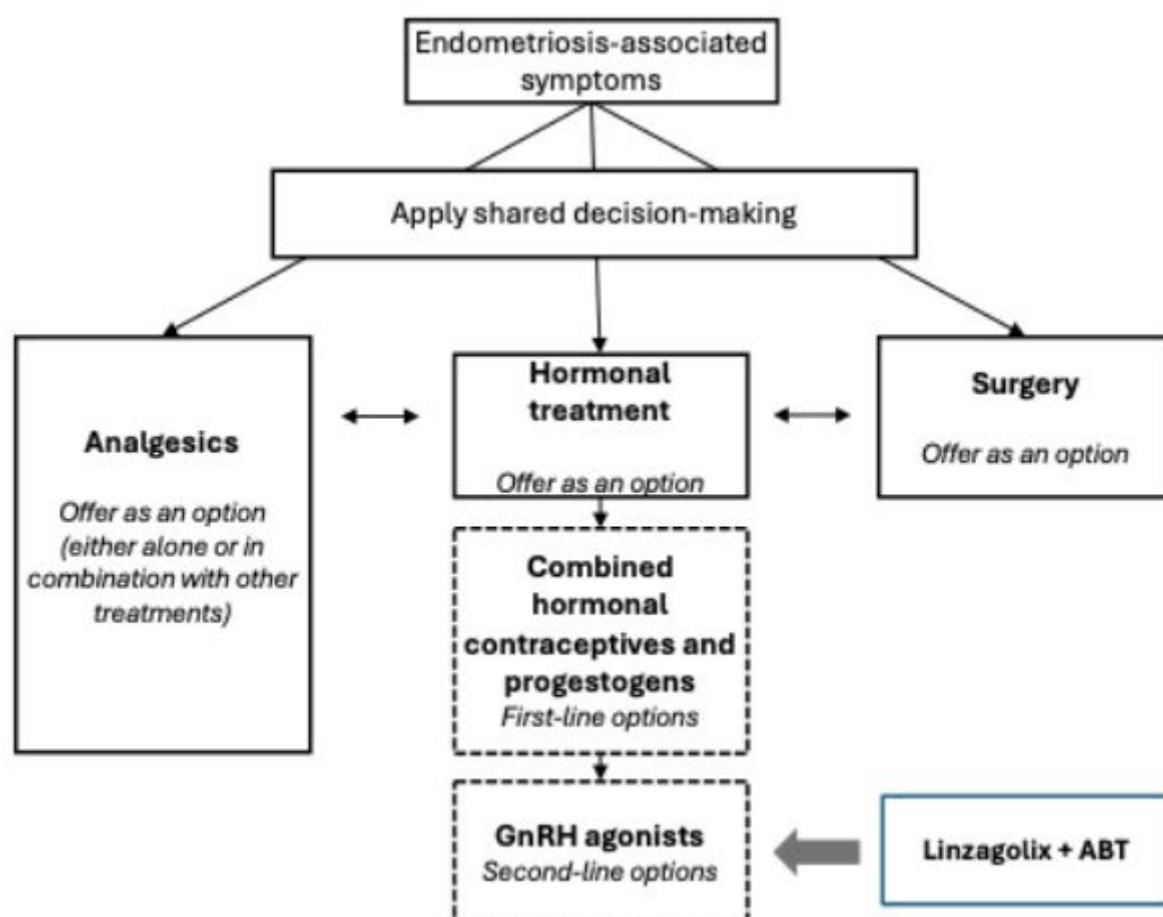
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There is no cure for endometriosis and current treatment options aim to manage the symptoms of endometriosis. Treatment options are diverse and consist of analgesic therapies, hormonal therapies, surgery, or a combination of these.⁴ The type of treatment a patient receives for endometriosis depends on the individual case, needs and priorities and should be decided in partnership with a healthcare professional; age, severity of symptoms and family planning are key considerations.¹

Hormonal contraceptives, including the combined pill, the progestogen-only pill and long-acting reversible contraception, are generally the first kind of hormone treatment tried.⁴ Another type of hormonal treatment, gonadotropin-releasing hormone (GnRH) agonists, are reserved as second-line hormonal treatment. To minimise or prevent some of the side effects of GnRH agonists, these are often prescribed in combination with hormone-based therapy, known as add-back therapy (ABT; oestrogen or progestin or a combination of both).⁶

If approved for use in the UK, it is anticipated that linzagolix plus ABT will be used as a second-line hormonal treatment option, as an alternative to GnRH agonists, after surgery, hormonal treatments, and analgesics (painkillers) have been considered and have failed to adequately control symptoms (Figure 1).

Figure 1: Proposed place of linzagolix plus ABT in the current treatment pathway



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

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.

All-party parliamentary group report on the burden of endometriosis (2020):⁷

- A survey of 10,000 people living in the UK who were diagnosed with endometriosis
- In the survey, 95% and 81% of respondents said that endometriosis had had a negative, or very negative, impact on their wellbeing and mental health, respectively, and 89% felt isolated due to their condition
- The following symptoms had a negative or very negative impact: pelvic pain (95%); fatigue (93%); heavy menstrual bleeding (86%); painful bowel movements (84%); pain during or after sex (83%); urinary symptoms (60%); difficulty getting pregnant (for those for whom this was relevant) (83%)
- In respect of treatment options, the prominent concerns were around pain and a lack of pain management support, lack of information, access to, and availability of treatments, and concern around treatment effectiveness

Endometriosis UK, “Dismissed, ignored and belittled” The long road to endometriosis diagnosis in the UK Diagnosis (2024)⁵

- An online survey to determine the average length of time to secure a diagnosis of endometriosis, which included 4,371 UK participants diagnosed with endometriosis
- Revealed a lengthy route to diagnosis; diagnosis times in the UK increased to an average of 8 years and 10 months in 2023, up from 8 years in 2020

UK National Confidential Enquiry into Patient Outcome and Death survey (2024):⁸

- A study on the pathway and quality of care in endometriosis, part of which was an online survey on the views of 941 patients
- The study highlighted deficiencies in pathways of care, holistic and medical management, and follow-up of patients with endometriosis
- 43% of respondents experienced no improvement with medication. Despite this, most (82%) had no further investigation by their GP.

World Endometriosis Research Foundation EndoCost study:⁹

- A cross-sectional questionnaire-based survey among 931 women with endometriosis treated in 12 tertiary care centres in 10 countries
- In this survey, 56% reported problems with pain/discomfort, 29% reported problems with usual activities, 29% reported being unable to work due to endometriosis, and 16% of women reported (some or major) problems with mobility. In addition, 36% of women reported problems with anxiety/depression.

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.

Linzagolix blocks the action of a hormone, GnRH, that helps to regulate the release of female sex hormones oestradiol and progesterone. These hormones trigger women's periods (menstruation). When blocked, the levels of the hormones oestrogen and progesterone circulating in the body are reduced.¹⁰ By decreasing their levels, linzagolix stops or reduces menstrual bleeding and decreases pain and pelvic discomfort and other symptoms associated with endometriosis.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- 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 (3g) focus on data that relate to the combination, rather than the individual treatments.

Linzagolix, for the treatment of symptomatic endometriosis, is taken once daily together with ABT. The ABT is important as it helps to reduce side effects including the risk and extent of bone mineral density loss.¹⁰

Linzagolix is therefore not suitable for women who are not able to, or prefer not to, take hormone-based therapies, including those wishing to conceive.

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?

The recommended dose for the treatment of symptoms of endometriosis is 200 mg once daily (single tablet) with concomitant ABT.¹⁰

There is no fixed treatment duration. Treatment continuation depends on the risk of bone mineral density loss. Bone mineral density is determined by a scan after the first 12 months of treatment to see if treatment can continue. If treatment is continued beyond one year, bone mineral density should be checked at regular intervals.¹⁰

Both linzagolix and the ABT are orally administered and do not require administration by a healthcare professional, unlike, for example, the injectable forms of GnRH agonists.

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 and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Completed main clinical trials (Phase 3)

The efficacy (how well a treatment works) and safety of linzagolix with or without ABT were evaluated in a phase 3 clinical trial (EDELWEISS 3) over 6 months. This was immediately followed by its extension study (EDELWEISS 6) for a further 6 months.^{11–14} Although the EDELWEISS 3 and EDELWEISS 6 trials evaluated two doses of linzagolix (linzagolix 200 mg plus ABT and linzagolix 75 mg alone) versus placebo, the linzagolix 200 mg plus ABT dose met the co-primary efficacy endpoints (i.e. achieved the main assessment criteria as explained below) and is the dose for symptomatic treatment of endometriosis stated in the Summary of Product Characteristics. This submission, therefore, focuses on the evidence for linzagolix 200 mg plus ABT in women with endometriosis-associated pain (EAP) requiring symptomatic treatment.

EDELWEISS 3

EDELWEISS 3 (NCT03992846) was a phase 3 placebo-controlled trial that assessed the efficacy and safety of linzagolix (linzagolix 200 mg plus ABT and linzagolix 75 mg alone) in women of reproductive age with moderate to severe EAP. The trial was classed as ‘double-blind’, meaning that neither the doctors nor the patients knew who was taking linzagolix or placebo. A double-blind approach is often used in clinical trials so that knowledge of which treatment (or placebo) is being received doesn’t affect (bias) the drug assessment.

Patients were randomised (split randomly) into three groups. One group of patients were given placebo (a substance with no medicinal activity that is given in an identical way to the medicine under investigation), one group was given linzagolix alone at a dose of 75 mg; the third group was given linzagolix at a dose of 200 mg along with ABT (linzagolix 200 mg plus ABT).

The co-primary (main) endpoint (assessment) of the EDELWEISS 3 trial was how good linzagolix was at reducing dysmenorrhoea (period pain) and non-menstrual pelvic pain (NMPP; pain experienced in between periods) along with stable or decreased use of analgesics (painkillers) after 3 months of treatment. The study also looked at the effect of linzagolix on dysmenorrhoea, NMPP, dyschezia (difficulty emptying the bowel), overall pelvic pain (OPP), interference of pain with the ability to perform daily activities (based on the Endometriosis Health Profile-30 [EHP-30] questionnaire), and dyspareunia (painful sexual intercourse), and no analgesic / no opiate (a type of strong painkiller) use for EAP during the preceding 4-week period at month 6.

To enter the study, patients had to be women of reproductive age with surgically confirmed pelvic endometriosis in the past 10 years. Prior to screening, patients had to exhibit moderate-to-severe EAP, based on dysmenorrhoea and NMPP over the previous month. Full inclusion and exclusion criteria are published.¹¹

EDELWEISS 6

Patients who completed the 6-month treatment period in the EDELWEISS 3 study were invited to enter the EDELWEISS 6 extension study (NCT04335591), which aimed to assess the maintenance of efficacy of linzagolix with or without ABT for up to an additional 6 months (up to 12 months of treatment in total) in women who had already completed 6 months of linzagolix treatment in EDELWEISS 3.

In EDELWEISS 6, patients who received placebo in EDELWEISS 3 were randomised 1:1 to linzagolix 75 mg or linzagolix 200 mg plus ABT. Patients who received active treatment (linzagolix 75 mg or linzagolix 200 mg plus ABT) in EDELWEISS 3 continued the same treatment.

3e) Efficacy

Efficacy is the measure of 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.

As outlined in Section 3d, the efficacy of linzagolix plus ABT was evaluated in the EDELWEISS 3 trial over 6 months, followed by its extension study EDELWEISS 6 for a further 6 months.^{11–14}

Endometriosis-associated pain

Linzagolix 200 mg plus ABT met (achieved) the co-primary endpoint of the EDELWEISS 3 study, demonstrating clinically meaningful and statistically significant reductions in dysmenorrhoea and NMPP (reductions of ≥ 1.10 and ≥ 0.8 points on the verbal rating scale for dysmenorrhoea and NMPP, respectively) from baseline to the last 28 days of randomised treatment up to month 3, with stable or reduced use of analgesics. At month 3, the estimated percentage of responders (people with reduced pain and stable or reduced use of analgesics [painkillers]) for dysmenorrhoea was 72.9% in the linzagolix 200 mg plus ABT group versus 23.5% in the placebo group. Respective proportions for NMPP were 47.3% with linzagolix 200 mg plus ABT versus 30.9% with placebo.

Further improvements were observed at month 12 in EDELWEISS 6 in the linzagolix 200 mg plus ABT group. At month 12, the estimated percentage of responders in the linzagolix 200 mg plus ABT group was 91.0% for dysmenorrhoea and 67.6% for NMPP.

In EDELWEISS 3, statistically significant and clinically meaningful improvements from baseline to month 6 with linzagolix 200 mg plus ABT versus placebo were also observed at month 6 for dysmenorrhoea, NMPP, dyschezia, OPP and ability to participate in daily activities. Steady improvements in these measures were observed throughout the treatment period in EDELWEISS 6.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a 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.

Along with the observed reductions in EAP and the ability to perform daily activities based on EHP-30 pain scores with linzagolix 200 mg plus ABT versus placebo in EDELWEISS 3, there were improvements in broader health-related quality of life aspects.¹³ The EHP-30 dimensions of

‘control and powerlessness’, ‘emotional wellbeing’, ‘social support’ and ‘self-image’ also showed statistically significant improvements (score reductions) from baseline to month 6 in the linzagolix 200 mg plus ABT group versus placebo, although improvement in the ‘modular sexual relationship’ dimension was not statistically significant versus placebo. The improvement (increase) in EuroQoL 5-Dimension 5-Level (EQ-5D-5L) scores from baseline to month 6 was also significantly greater with linzagolix 200 mg plus ABT versus placebo.

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 in relation to 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.

The safety profile for linzagolix in women with EAP in EDELWEISS 3 and EDELWEISS 6 was consistent with that observed previously for women with uterine fibroids.^{15,16} Linzagolix showed good overall tolerability, with side effects similar to placebo.^{11,13,14} Most side effects (approximately 99% overall) were mild or moderate in intensity. The incidence of severe side effects was low and comparable between groups, and no fatal or suicide-related side effects were reported. The proportion of patients who discontinued treatment in EDELWEISS 3 due to side effects in the linzagolix 200 mg plus ABT group (3.1%) was similar to that for the placebo group (2.5%), although the rate was slightly higher for the linzagolix 75 mg group (5.6%).

The most common side effects (regardless of whether or not they were related to the treatment) were headaches, which were reported for similar proportions of patients in each group (EDELWEISS 3: 10.5% of patients in the linzagolix 200 mg plus ABT group, 8.1% in the linzagolix 75 mg group, 8.0% in the placebo group). Hot flushes were more common in the linzagolix groups (6.8% in the linzagolix 200 mg plus ABT group, 7.5% in the linzagolix 75 mg group) than the placebo group (2.5%) in EDELWEISS 3.

Headaches (linzagolix 200 mg plus ABT: 6.2%, linzagolix 75 mg: 7.5%, placebo, 3.7%) and hot flushes (linzagolix 200 mg plus ABT: 6.8%, linzagolix 75 mg: 7.5%, placebo, 2.5%) were also the most common side effects considered to be related to linzagolix treatment in EDELWEISS 3.

Bone mineral density was largely unaffected by linzagolix treatment at month 6 (EDELWEISS 3) and month 12 (EDELWEISS 6).^{11,13,14} Some bone mineral density increases were noted at 6 months after the end of treatment (EDELWEISS 6 follow-up), indicating partial recovery. The average (least squares mean) percentage change from baseline to month 6 in EDELWEISS 3 was <1% in all three treatment groups at the lumbar spine, femoral neck and total hip.

Periods resumed within a median time of approximately 1 month after the end of treatment across groups in EDELWEISS 3 and EDELWEISS 6.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration.

Key benefits for patients being treated with linzagolix include:

- Oral administration at home, removing the need to arrange and attend monthly/3-monthly appointments in primary care for a GnRH agonist depot injection
- Choice of hormonal ABT, which can be tailored to patient preferences or modified if needed to improve tolerability (as opposed to a combination tablet)
- Rapid return of periods after stopping treatment
- Ability to discontinue treatment immediately in the event of intolerable adverse events (as opposed to depot GnRH injections)

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 when 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 mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

A potential disadvantage for patients treated with linzagolix is the need for separate hormonal ABT (as opposed to a combination tablet).

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).¹⁷ This looks at the cost-effectiveness of the product in question – in this case, linzagolix plus ABT – 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.

How the economic assessment of linzagolix was conducted

The cost-effectiveness analysis took into account the various treatments available on the NHS for treating the symptoms of endometriosis. This included other medicines and different types of surgery.

A new model was created to show how a patient with a confirmed diagnosis of endometriosis and previous medical or surgical treatment would be treated in the NHS, and estimate both the benefits (in terms of QALYs) and costs of different treatment options. The relative effectiveness of the different treatments, in terms of treating pain, and their impact on the quality of life of patients was informed by clinical studies, and an indirect treatment comparison. Literature and expert opinion were also used to provide data unavailable from the EDELWEISS 3 and 6 clinical studies, including data needed to compare linzagolix versus surgery. The costs captured within the analysis include drug, administration, healthcare resource use, surgery, and adverse event-related costs.

The model structure captures both the initial response to treatment and patient health status over a period of time extending until menopause. The model includes health states that reflect the varied responses to medical therapies, pain symptoms and surgical interventions that can be experienced by this population. The model includes a scenario comparing linzagolix against laparoscopic surgery. This required a modified initial structure of the model, to account for surgery as a 'one-time' event with potential disease recurrence, versus ongoing treatment with medical therapy that is assumed for the base model.

The value proposition for linzagolix 200 mg plus ABT

Based on the modelling approach summarised above linzagolix 200mg plus ABT shows the following:

- Linzagolix 200mg plus ABT is cost-effective versus leuprorelin plus ABT: linzagolix is associated with higher costs and higher QALYs, resulting in an ICER below the UK threshold of £20,000 per QALY (the threshold below which NICE generally consider a treatment to be cost-effective)
- Linzagolix is also cost-effective versus laparoscopic surgery as patients initially treated with linzagolix are associated with higher QALYs, and only slightly higher costs

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)

There is a significant unmet need in patients with endometriosis who do not have adequate pain relief despite use of conventional hormonal therapies or surgical treatment. Use of GnRH agonists is often limited due to undesirable side effects.⁶ In addition, administration of injectable GnRH

agonists can be uncomfortable, may result in injection site reactions and need to be given under the supervision of a healthcare professional, increasing the burden on healthcare systems and placing a time burden on patients.¹⁸

GnRH antagonists, including linzagolix, with ABT, are an effective and innovative new treatment option for symptoms of endometriosis that may be administered orally at home without physician supervision.¹⁹

Due to its mechanism of action, linzagolix has a rapid onset of therapeutic effects, as well as rapid recovery of hormone secretion, meaning periods return quickly after stopping treatment.²⁰ In addition, as opposed to depot GnRH injections, treatment can be discontinued immediately if needed, e.g. due to intolerable adverse events.

3I) 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

Although linzagolix 200 mg plus ABT is expected to be indicated for the symptomatic treatment of endometriosis in adult women of reproductive age with a history of previous medical or surgical treatment for their endometriosis, this should not prevent the use of linzagolix by people with endometriosis who do not identify as a woman.

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.

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: [Guidance for 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: [European Observatory on Health Systems and Policies - Policy Brief](#)

Further information on endometriosis

Endometriosis UK: <https://www.endometriosis-uk.org/> Further information on linzagolix:

- EDELWEISS 3 publication: Donnez J, et al. Linzagolix therapy versus a placebo in patients with endometriosis-associated pain: a prospective, randomized, double-blind, Phase 3 study (EDELWEISS 3). Hum Reprod. 2024 Jun 3;39(6):1208–21. <https://pubmed.ncbi.nlm.nih.gov/38648863/>
- EDELWEISS 6 conference abstract: Dolmans M, et al. Long term efficacy of Linzagolix in women with endometriosis-associated pain. Presented at ESHRE 2024; 2024. Available from: <https://www.eshre.eu/ESHRE2024/Programme/ESHRE-2024-Searchable-scientific-programme#/cmcore/abstractdetails/config/ams2024normal/03633e97ca0a86313b84475172b04b20c32f1056bba08f3e341729d201fbb5db>

4b) Glossary of terms

Hormonal add-back therapy (ABT): an hormonal treatment (oestrogen or progestin or a combination of both) given alongside linzagolix 200 mg and some other gonadotropin-releasing hormone (GnRH) analogue treatments to prevent the loss of bone mineral density without affecting the efficacy of the GnRH analogue treatment.⁶

Adverse event: an unintended medical event that occurs while you are taking a medicine, although it may not necessarily be caused by that medicine.

Analgesics: painkillers.

Baseline: the start of a clinical trial. Trials often assess changes from baseline to a certain timepoint, e.g. 3 months, to assess the effect of taking a drug for 3 months.

Bone mineral density: a measure of how dense bones are; bones that are less dense may be weaker and more prone to fractures in the future.

Double-blind: a design often used in clinical trials meaning that neither the doctors nor the patients knew which treatment group (e.g. a particular drug or placebo) a patient was assigned to. A double-blind approach is used so that knowledge of which treatment (or placebo) is being received doesn't affect (bias) the drug assessment.

Dyschezia: difficulty emptying the bowel.

Dysmenorrhoea: period pain.

Dyspareunia: painful sexual intercourse.

Efficacy: how well a treatment works (this term is usually used when reporting clinical trial data).

Endometriosis Health Profile-30 (EHP-30): a patient-reported outcome (PRO) questionnaire that asks patients about the effects of endometriosis on various aspects of their quality of life.

EuroQoL 5-Dimension 5-Level (EQ-5D-5L): a patient-reported outcome (PRO) questionnaire that asks patients about their health-related quality of life or 'health state'.²¹ It is used in patients with many different health conditions, so it is often termed a 'generic PRO'.

Femoral neck: part of the hip.

Gonadotropin-releasing hormone (GnRH) analogue: a drug that targets gonadotropin-releasing hormone (GnRH) receptors to reduce the amount of oestrogen produced. There are two types of GnRH analogues, GnRH agonists and GnRH antagonists (such as linzagolix), that work in slightly different ways to reduce oestrogen levels.²²

ICER: incremental cost-effectiveness ratio. A measure of the cost-effectiveness of a medicine against other treatments currently used to treat the condition. In the UK, NICE generally consider an ICER below the threshold of £20,000 per QALY to be cost-effective, although this can vary for some conditions.

Indirect treatment comparison: A statistical approach used to compare two different treatments in cases where those treatments have not been directly compared in the same study (e.g. a clinical trial).

Laparoscopic surgery: a type of keyhole surgical procedure that can be used for people with endometriosis, where small cuts are used to perform surgery inside the abdomen and pelvis.

Lumbar spine: lower backbone.

Marketing authorisation: approval from a regulatory body to market a medicine in a specified country (e.g. Great Britain, United Kingdom) or region (e.g. European Union).

NCT number: the number assigned to a clinical trial when registered on <https://clinicaltrials.gov>, a database that lists clinical trials and provides details of their status (e.g. 'recruiting', 'completed'), methods and results.

Non-menstrual pelvic pain (NMPP): pain experienced in between periods.

Opiate: a type of strong painkiller.

Patient reported outcomes (PROs): information regarding health conditions and their effects on quality of life that are reported directly by patients (often using a questionnaire) without any interpretation from doctors.

Placebo: a 'dummy drug' given to patients in the control group of a clinical trial. A placebo is designed to look the same as the drug being investigated so that people do not know if they received the actual drug or the placebo. A placebo is given to compare the effects of receiving the drug being investigated versus no drug (over and above any 'placebo effect').

Phase 3 trial: a late-stage clinical trial that usually involves large numbers of patients and is often used as the primary source of data for applications for marketing authorisation of a drug.

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 (split randomly) to a group in the trial (e.g. the group being given the medicine, or the group being given a placebo).

Responder: the term ‘responder’ was used in the EDELWEISS 3 and EDELWEISS 6 trials to refer to people with reduced pain (dysmenorrhoea and NMPP) and stable or reduced use of analgesics (painkillers).

Second-line: the second treatment used for a particular disease/condition.

Single technology appraisal (STA): technology appraisal guidance from NICE covering a single drug or treatment for a single indication (e.g. a particular disease or a specified group of people with a particular disease).

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. Endometriosis UK. Understanding endometriosis [Internet]. 2024 [cited 2024 Sep 18]. Available from: <https://www.endometriosis-uk.org/sites/default/files/2024-09/Understanding%20endometriosis%20FINAL.pdf>
2. Cea Soriano L, López-García E, Schulze-Rath R, García Rodríguez LA. Incidence, treatment and recurrence of endometriosis in a UK-based population analysis using data from The Health Improvement Network and the Hospital Episode Statistics database. *Eur J Contracept Reprod Health Care*. 2017 Oct;22(5):334–43.
3. Endometriosis UK. Getting diagnosed [Internet]. 2024 [cited 2024 Sep 18]. Available from: <https://www.endometriosis-uk.org/getting-diagnosed-0>
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6. European Society of Human Reproduction and Embryology. ESHRE Guideline Endometriosis [Internet]. 2022. Available from: <https://www.eshre.eu/Guideline/Endometriosis>
7. All Party Parliamentary Group on Endometriosis. Endometriosis in the UK: time for change, APPG on Endometriosis Inquiry Report. 2020.
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11. Donnez J, Becker C, Taylor H, Carmona Herrera F, Donnez O, Horne A, et al. Linzagolix therapy versus a placebo in patients with endometriosis-associated pain: a prospective, randomized, double-blind, Phase 3 study (EDELWEISS 3). *Hum Reprod*. 2024 Jun 3;39(6):1208–21.
12. Dolmans MM et al. Long term efficacy of Linzagolix in women with endometriosis-associated pain [Internet]. Presented at ESHRE 2024; 2024. Available from: <https://www.eshre.eu/ESHRE2024/Programme/ESHRE-2024-Searchable-scientific-programme#/cmcore/abstractdetails/config/ams2024normal/03633e97ca0a86313b84475172b04b20c32f1056bba08f3e341729d201fbb5db>
13. EDELWEISS 3 CSR (data on file).
14. EDELWEISS 6 CSR (data on file).
15. Donnez J, Taylor HS, Stewart EA, Bradley L, Marsh E, Archer D, et al. Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. *Lancet*. 2022 Sep 17;400(10356):896–907.
16. NICE final draft guidance: Linzagolix for treating moderate to severe symptoms of uterine fibroids [Internet]. Available from: <https://www.nice.org.uk/guidance/gid-ta11131/documents/674>
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Linzagolix Endometriosis ID6357

Clarification questions

03 December 2024

File name	Version	Contains confidential information	Date
[ID6357] Linzagolix Endometriosis – Company Response to Request for clarification 03Dec2024 [noCON]	1.0	No (redacted)	03 December 2024

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Section A: Clarification on effectiveness data

Literature searches

A 1. Priority question. Clinical effectiveness searches (Appendix D). The EAG thanks the Company for providing individual strategies for each database replacing the earlier reporting of all three resources via a single table, and for confirming that no subject headings were used apart from in the Pubmed search for linzagolix and endometriosis where the “all fields” search option was selected. Looking at the revised strategies the EAG has the remaining questions:

- a) The 2023 Pubmed comparator search appears to be missing line #10. Please confirm if this is a reporting error and provide a corrected search strategy.**
- b) Whilst CDSR was mentioned in section D2.2.1 (Appendix D) the EAG noted that line #35 of the comparators search appeared to remove all Cochrane records except for those in CENTRAL. Please confirm if CDSR was searched for either clinical effectiveness searches.**
- c) Please confirm that other than reference checking, no grey literature searching was undertaken to inform the clinical effectiveness section. If further searches were undertaken, please provide full details, including resource name, host, date searched, and date span and hits retrieved.**
- d) Please provide the date span for the Embase search (i.e. 1974- Current or 1980-Current, etc.).**
- e) The original submission reported that searches for the intervention were completed on 2nd September 2024 (all databases); searches for comparators were carried out on 3rd September 2024 (Cochrane Library, Embase) and 10th September 2024 (MEDLINE). The revised strategies reported 3.9.24 for all searches, please confirm which is correct.**

Response A1a

We confirm that this is a reporting error and provide the correct search strategy below.

Search	Actions	Details	Query
#34	...	>	Search: #30 AND #31 Filters: from 2023/12/22 - 2024/9/2 Sort by: Most Recent
#33	...	>	Search: #30 AND #31 Filters: from 2023/12/22 - 2024/9/10 Sort by: Most Recent
#32	...	>	Search: #30 AND #31 Sort by: Most Recent
#31	...	>	Search: (random[Title/Abstract] OR randomised[Title/Abstract] OR randomized[Title/Abstract] OR randomly[Title/Abstract] OR randomisation[Title/Abstract] OR randomization[Title/Abstract] OR RCT[Title/Abstract] OR blind[Title/Abstract] OR blinded[Title/Abstract] OR blinding[Title/Abstract] OR mask[Title/Abstract] OR masked[Title/Abstract] OR masking[Title/Abstract]) Sort by: Most Recent
#30	...	>	Search: #1 AND #29 Sort by: Most Recent
#29	...	>	Search: #2 OR #12 OR #28 Sort by: Most Recent
#28	...	>	Search: #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 Sort by: Most Recent
#27	...	>	Search: (histrelin[Title/Abstract] OR histerelin[Title/Abstract] OR "orf 17070"[Title/Abstract] OR orf17070[Title/Abstract] OR "rl 0903"[Title/Abstract] OR rl0903[Title/Abstract] OR "rwj 17070"[Title/Abstract] OR rwj17070[Title/Abstract] OR "spd 424"[Title/Abstract] OR spd424[Title/Abstract] OR supprelin[Title/Abstract] OR vantas[Title/Abstract] OR "vp 002"[Title/Abstract] OR vp002[Title/Abstract] OR "IBHPE-LHRH"[Title/Abstract]) Sort by: Most Recent
#26	...	>	Search: ("zoptarelin doxorubicin"[Title/Abstract] OR "aezs 108"[Title/Abstract] OR aezs108[Title/Abstract] OR "an 152"[Title/Abstract] OR "an-152"[Title/Abstract] OR an152[Title/Abstract] OR "d 81858"[Title/Abstract] OR d81858[Title/Abstract] OR "zen 008"[Title/Abstract] OR zen008[Title/Abstract]) Sort by: Most Recent
#25	...	>	Search: (triptorelin[Title/Abstract] OR arvekap[Title/Abstract] OR "ay 25650"[Title/Abstract] OR ay25650[Title/Abstract] OR "bim 21003"[Title/Abstract] OR bim21003[Title/Abstract] OR "bn 52014"[Title/Abstract] OR bn52014[Title/Abstract] OR "cl 118532"[Title/Abstract] OR cl118532[Title/Abstract] OR "d trp 6 lhrh"[Title/Abstract] OR "debio 8200"[Title/Abstract] OR "debio 8206"[Title/Abstract] OR debio8200[Title/Abstract] OR debio8206[Title/Abstract] OR decapeptyl[Title/Abstract] OR detryptorelin[Title/Abstract] OR diphereline[Title/Abstract] OR fertipeptil[Title/Abstract] OR gonapeptyl[Title/Abstract] OR "isr 048"[Title/Abstract] OR "isr 48"[Title/Abstract] OR isr048[Title/Abstract] OR isr48[Title/Abstract] OR "ly 01007"[Title/Abstract] OR ly01007[Title/Abstract] OR microreltin[Title/Abstract] OR moapar[Title/Abstract] OR "neo decapeptyl"[Title/Abstract] OR ovugel[Title/Abstract] OR pamorelin[Title/Abstract] OR salvacyl[Title/Abstract] OR spherotide[Title/Abstract] OR trelstar[Title/Abstract] OR triptodur[Title/Abstract] OR triptofem[Title/Abstract] OR triptorelin[Title/Abstract] OR triptoreline[Title/Abstract] OR tryptorelin[Title/Abstract] OR "wy 42422"[Title/Abstract] OR "wy 42462"[Title/Abstract] OR wy42422[Title/Abstract] OR wy42462[Title/Abstract]) Sort by: Most Recent
#24	...	>	Search: (peforelin[Title/Abstract] OR mapreltin[Title/Abstract]) Sort by: Most Recent
#23	...	>	Search: ovurelin[Title/Abstract] Sort by: Most Recent

#22	...	 >	Search: ("onvitrelin ucalontide"[Title/Abstract] OR "ep 100"[Title/Abstract] OR ep100[Title/Abstract]) Sort by: Most Recent
#21	...	 >	Search: (nafarelin[Title/Abstract] OR "rs 94991"[Title/Abstract] OR rs94991[Title/Abstract] OR synarel[Title/Abstract] OR synarela[Title/Abstract]) Sort by: Most Recent
#20	...	 >	Search: (lutrelin[Title/Abstract] OR "wy 40972"[Title/Abstract] OR "wy40972"[Title/Abstract] OR "wy 40,972"[Title/Abstract] OR "wyeth 40972"[Title/Abstract] OR "wy-40,972F"[Title/Abstract]) Sort by: Most Recent
#19	...	 >	Search: (leuprorelin[Title/Abstract] OR "a 43818"[Title/Abstract] OR a43818[Title/Abstract] OR "abbott 43818"[Title/Abstract] OR "cam 2032"[Title/Abstract] OR cam2032[Title/Abstract] OR camcevi[Title/Abstract] OR carcinil[Title/Abstract] OR "ckd 841"[Title/Abstract] OR ckd841[Title/Abstract] OR daronda[Title/Abstract] OR "depo lupron"[Title/Abstract] OR "depo-eligard"[Title/Abstract] OR eligard[Title/Abstract] OR eliprogel[Title/Abstract] OR elityran[Title/Abstract] OR enanton[Title/Abstract] OR enantone[Title/Abstract] OR fensolvi[Title/Abstract] OR "fp 001"[Title/Abstract] OR fp001[Title/Abstract] OR ginecrin[Title/Abstract] OR klebrocid[Title/Abstract] OR "la 2575"[Title/Abstract] OR la2575[Title/Abstract] OR leptoprol[Title/Abstract] OR lerin[Title/Abstract] OR leuplin[Title/Abstract] OR "leupro-sandoz"[Title/Abstract] OR leuprogel[Title/Abstract] OR leuprol[Title/Abstract] OR leuprolid[Title/Abstract] OR leuprolide[Title/Abstract] OR leupron[Title/Abstract] OR leuprone[Title/Abstract] OR leuporelina[Title/Abstract] OR leuprostin[Title/Abstract] OR "lorelin depot"[Title/Abstract] OR lucrin[Title/Abstract] OR lupride[Title/Abstract] OR luproxel[Title/Abstract] OR lupron[Title/Abstract] OR lutrate[Title/Abstract] OR "nh 901"[Title/Abstract] OR nh901[Title/Abstract] OR "ovarest"[Title/Abstract] OR poltrate[Title/Abstract] OR "procren depot"[Title/Abstract] OR procrin[Title/Abstract] OR prostap[Title/Abstract] OR prostapant[Title/Abstract] OR reliser[Title/Abstract] OR sixantone[Title/Abstract] OR "sot 375"[Title/Abstract] OR sot375[Title/Abstract] OR staladex[Title/Abstract] OR "tap 144"[Title/Abstract] OR tap144[Title/Abstract] OR tapros[Title/Abstract] OR "tol 2506"[Title/Abstract] OR tol2506[Title/Abstract] OR trenantone[Title/Abstract] OR viadur[Title/Abstract] OR "vp 4896"[Title/Abstract] OR vp4896[Title/Abstract] OR zeulide[Title/Abstract] OR zeulidedepot[Title/Abstract]) Sort by: Most Recent
#18	...	 >	Search: (goserelin[Title/Abstract] OR "buserelin carbamazide"[Title/Abstract] OR "ici 118 630"[Title/Abstract] OR "ici 118630"[Title/Abstract] OR ici118630[Title/Abstract] OR "ly 01005"[Title/Abstract] OR ly01005[Title/Abstract] OR novimp[Title/Abstract] OR prozoladex[Title/Abstract] OR reseligo[Title/Abstract] OR "zd 9393"[Title/Abstract] OR zd9393[Title/Abstract] OR zoladex[Title/Abstract] OR zoreline[Title/Abstract] OR xanderla[Title/Abstract]) Sort by: Most Recent

#17	...	>	Search: folligen[Title/Abstract] Sort by: Most Recent
#16	...	>	Search: (deslorelin[Title/Abstract] OR "lhrh t"[Title/Abstract] OR somagard[Title/Abstract] OR suprelorin[Title/Abstract] OR ovuplant[Title/Abstract]) Sort by: Most Recent
#15	...	 >	Search: (dalarelin[Title/Abstract] OR surfagon[Title/Abstract] OR "wy 18481"[Title/Abstract] OR wy18481[Title/Abstract]) Sort by: Most Recent
#14	...	 >	Search: (buserelin[Title/Abstract] OR bigonist[Title/Abstract] OR busereline[Title/Abstract] OR etilamide[Title/Abstract] OR receptal[Title/Abstract] OR superfact[Title/Abstract] OR suprefact[Title/Abstract] OR profact[Title/Abstract] OR tiloryth[Title/Abstract] OR suprecur[Title/Abstract] OR "HOE 766"[Title/Abstract] OR HOE766[Title/Abstract]) Sort by: Most Recent
#13	...	 >	Search: (avorelin[Title/Abstract] OR meterelin[Title/Abstract] OR "ep 23904"[Title/Abstract] OR ep23904[Title/Abstract] OR "mf 6001"[Title/Abstract] OR mf6001[Title/Abstract]) Sort by: Most Recent
#12	...	 >	Search: #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 Sort by: Most Recent
#11	...	>	Search: (sufugolix[Title/Abstract] OR tak013[Title/Abstract] OR "tak 013"[Title/Abstract]) Sort by: Most Recent
#10	...	>	Search: merigolix[Title/Abstract] - Schema: all Sort by: Most Recent
#9	...	 >	Search: (abarelix[Title/Abstract] OR plenaxis[Title/Abstract] OR ppi149[Title/Abstract] OR "ppi 149"[Title/Abstract] OR r3827[Title/Abstract] OR "r 3827"[Title/Abstract]) Sort by: Most Recent
#8	...	 >	Search: (ganirelix[Title/Abstract] OR orgalutran[Title/Abstract] OR orgalutron[Title/Abstract] OR antagon[Title/Abstract] OR ganirest[Title/Abstract] OR org37462[Title/Abstract] OR "org 37462"[Title/Abstract] OR rs26306[Title/Abstract] OR "rs 26306"[Title/Abstract]) Sort by: Most Recent
#7	...	 >	Search: (degarelix[Title/Abstract] OR firmagon[Title/Abstract] OR gonax[Title/Abstract] OR asp3550[Title/Abstract] OR "asp 3550"[Title/Abstract] OR fe200486[Title/Abstract] OR "fe 200486"[Title/Abstract] OR uglypeptide1[Title/Abstract]) Sort by: Most Recent
#6	...	 >	Search: (cetrorelix[Title/Abstract] OR ovurelix[Title/Abstract] OR cetrotide[Title/Abstract] OR dicetrorelix[Title/Abstract] OR aezs102[Title/Abstract] OR "aezs 102"[Title/Abstract] OR ns75a[Title/Abstract] OR "ns 75a"[Title/Abstract] OR ns75a[Title/Abstract] OR "ns 75a"[Title/Abstract] OR sb75[Title/Abstract] OR "sb75"[Title/Abstract] OR d20453[Title/Abstract] OR "d 20453"[Title/Abstract] OR d20761[Title/Abstract] OR "d 20761"[Title/Abstract] OR d20762[Title/Abstract] OR "d 20762"[Title/Abstract]) Sort by: Most Recent

#5	...	 >	Search: (opigolix[Title/Abstract] OR asp1707[Title/Abstract] OR "asp 1707"[Title/Abstract]) Sort by: Most Recent
#4	...	>	Search: (elagolix[Title/Abstract] OR orilissa[Title/Abstract] OR abt620[Title/Abstract] OR "abt 620"[Title/Abstract] OR nbi56418[Title/Abstract] OR "nbi 56418"[Title/Abstract] OR oriahnn[Title/Abstract]) Sort by: Most Recent
#3	...	 >	Search: (relugolix[Title/Abstract] OR relumine[Title/Abstract] OR orgovyx[Title/Abstract] OR mvt601[Title/Abstract] OR "mvt 601"[Title/Abstract] OR rvt601[Title/Abstract] OR "rvt 601"[Title/Abstract] OR t1331285[Title/Abstract] OR "t 1331285"[Title/Abstract] OR tak385[Title/Abstract] OR "tak 385"[Title/Abstract] OR myfembree[Title/Abstract] OR ryeqo[Title/Abstract]) Sort by: Most Recent
#2	...	 >	Search: (GnRH[Title/Abstract] OR " Gn RH"[Title/Abstract] OR "gonadotropin-releasing"[Title/Abstract] OR "gonadotrophin-releasing"[Title/Abstract] OR gonadorelin[Title/Abstract] OR gonadoliberin[Title/Abstract] OR antigonadorelin[Title/Abstract] OR "gnrh antagonist"[Title/Abstract] OR "lh rh antagonist"[Title/Abstract] OR "LHRH antagonist"[Title/Abstract] OR "lhrh a""[Title/Abstract] OR "lrf antagonist"[Title/Abstract] OR lhrf[Title/Abstract] OR lrh[Title/Abstract] OR luliberin[Title/Abstract] OR "lh releasing"[Title/Abstract] OR "luteinising hormone releas""[Title/Abstract] OR "luteinizing hormone releas""[Title/Abstract] OR "LHFSH releasing"[Title/Abstract] OR "LH FSH releasing"[Title/Abstract] OR "releasing hormone, LHFSH"[Title/Abstract] OR LHRH[Title/Abstract] OR "LH RH"[Title/Abstract] OR LHFSHRH[Title/Abstract] OR LFRH[Title/Abstract] OR "FSH releasing"[Title/Abstract] OR factrel[Title/Abstract] OR fertagyl[Title/Abstract] OR fertiral[Title/Abstract] OR cystorelin[Title/Abstract] OR kryptocur[Title/Abstract] OR cryptocur[Title/Abstract] OR dirigestran[Title/Abstract] OR ay24031[Title/Abstract] OR "ay 24031"[Title/Abstract] OR "ay24, 031"[Title/Abstract] OR "ay 24, 031"[Title/Abstract] OR hoe471[Title/Abstract] OR "hoe 471"[Title/Abstract] OR "hoechst 471"[Title/Abstract] OR ici88262[Title/Abstract] OR "ici 88262"[Title/Abstract] OR luforan[Title/Abstract] OR luliberine[Title/Abstract] OR lutal[Title/Abstract] OR lutamin[Title/Abstract] OR pulstim[Title/Abstract] OR relisorm[Title/Abstract] OR dirigestran[Title/Abstract] OR "gnrh serono"[Title/Abstract]) Sort by: Most Recent
#1	...	>	Search: ("endometriosis"[Title/Abstract] OR endometri*[Title/Abstract] OR adenomyosis[Title/Abstract] OR "endometrial adenoma"[Title/Abstract]) Sort by: Most Recent

Response A1b

The Cochrane Database of Systematic Reviews was searched but the records were not screened due to the scope of the systematic literature review (SLR). According to the population, intervention, outcomes, and study design (PICOS) criteria, only randomised controlled trials were to be included.

Response A1c

The grey literature was not searched beyond the reference checking.

Response A1d

Embase database was used via the Elsevier® website. The date span for the database was 1974-Current.

Response A1e

We confirm that the correct search dates are as follows: searches for intervention were carried out on 2nd September 2024 (all databases); searches for comparators were carried out on 3rd September 2024 (Cochrane Library, Embase) and the 10th September 2024 (MEDLINE).

Questions regarding cost effectiveness searches (Appendix G):

- f) Please explain the rationale behind not including Emtree or MeSH subject headings in the search strategies and what impact this may have had on the recall of results.**
- g) Please provide the date span for the Embase search.**
- h) The Embase search strategy appears to contain non-Ovid syntax (for example, the use of hash tags in the line combination in line 4). Please provide the original search as run in the database.**

Response A1f

In the systematic literature review on cost-effectiveness, Medical Subject Heading (MeSH) terms in PubMed and Emtree terms in Ovid were not used. This approach was chosen to avoid potential limitations associated with controlled vocabulary indexing, for example, the variability in how scientific publications are indexed. The use of natural language keywords allowed a broader and more inclusive retrieval of studies by capturing variations in terminology used by authors, that may appear in titles or abstracts but are not reflected in MeSH or Emtree terms. While this method may reduce the precision of search results, as indexing terms can refine searches to highly relevant papers, it minimises the risk of omitting important articles that might otherwise be overlooked due to incomplete or inconsistent indexing. As a result of not using MeSH terms and Emtree terms, more results were obtained by the

systematic literature search, many of which proved to be irrelevant to the topic. However, this approach ensured that no significant evidence was missed, as the broader search captured all potentially relevant studies. According to NICE's manual: when identifying subject headings, variations in thesaurus and indexing terms for each database should be considered, for example MeSH (Medical Subject Headings) in MEDLINE and Emtree in Embase. Not all databases have indexing terms, and some contain records that have not yet been indexed. It was decided that a search strategy based on free-terms and synonyms would be sufficient to cover relevant publications.

Response A1g

The date span for the Embase database was 1974-Current.

Response A1h

The fourth line in the provided search strategy for the Embase database included syntax incompatible with Ovid. While the first three lines in the table accurately replicate the original searches, the fourth line is intended as a representation of what was done; however, no explicit query was used. In the table below, the third step is rewritten to a precise form, while the final query is unchanged from the first submission. The parts were joined manually to address the fact that Ovid does not provide a button, which directly enables the exclusion of the third row. Table 1 shows the direct representation of searches.

Table 1: Ovid (Embase) search 11 July 2024

No.	Search Term	Results
#1	("endometriosis" or "endometri*" or "adenomyosis" or "endometrial adenoma").ab,kw,ti.	171,029
#2	("economic model" or "cost effectiveness" or "cost-utility" or "economic evaluation" or "cost effectiveness analysis" or "Analysis, Cost-Effectiveness" or "Cost Effectiveness Analysis" or "Cost Effectiveness" or "Effectiveness, Cost" or "Cost Effectiveness Ratio" or "Cost Effectiveness Ratios" or "Effectiveness Ratio, Cost" or "Ratio, Cost Effectiveness" or	907,774

No.	Search Term	Results
	"cost minimization analysis" or "cost benefit analysis" or "Analysis, Cost-Benefit" or "Cost-Benefit Analyses" or "Cost Benefit Analysis" or "Analyses, Cost Benefit" or "Analysis, Cost Benefit" or "Cost Benefit Analyses" or "Cost Benefit" or "Cost and Benefit" or "Benefit and Cost" or "Benefits and Costs" or "Costs and Benefits" or "Cost-Benefit Data" or "Cost Benefit Data" or "Data, Cost-Benefit" or "Cost-Utility Analysis" or "Analysis, Cost-Utility" or "Cost-Utility Analyses" or "Cost Utility Analysis" or "Marginal Analysis" or "Analysis, Marginal" or "Marginal Analyses" or "Economic Evaluation" or "Economic Evaluations" or "Evaluation, Economic" or "cost-effectiveness" or "cost-utility" or "cost effectiveness" or "cost utility" or "cost minimization" or "cost minimisation or cea" or "cua" or "decision tree*" or ("cost" and ("effect*" or "utility*" or "benefit" or "conseq*" or "minimi*" or "qaly*" or "quality adjusted life year*" or "life year*")) or "icer" or "qaly" or "quality adjusted life year*" or (("simulat*" or "markov" or "discrete*") and "model*")).ab,ti.	
#3	(((review.pt. or "review literature as topic".af. or "state-of-the-art review".af. or "state of the art review".af. or "state-of-the-art reviews".af. or "reviews, state-of-the-art".af. or "review, state-of-the-art".af. or "state of the art reviews".af. or "literature review".ti.) not (meta-analysis.pt. or "meta-analysis as topic".af. or "meta analysis as topic".af. or "clinical trial overviews".af. or "clinical trial overview".af. or "overview, clinical trial".af. or "data pooling".af. or "data poolings".af. or "overviews, clinical trial".af. or "systematic review".ti. or "systematic literature review".ti. or "meta-analysis".ti,ab. or "meta analysis".ti,ab.)) or "case report*".ti,ab. or "case series".ti,ab. or (("animal".ab,ti. or "animal".af. or "animalia".af. or "metazoa".af.) not (("animal".ab,ti. or "animal".af. or "animalia".af. or "metazoa".af.) and ("human".ab,ti. or "man, modern".af. or "modern man".af. or "human".af. or "man, taxonomy".af. or "homo sapiens".af.))) or "letter".pt. or "editorial".pt.	10,525,620
#4	1 and 2	2,698
#5	((((("endometriosis" or "endometri*" or "adenomyosis" or "endometrial adenoma").ab,kw,ti.) and (("economic model" or "cost effectiveness" or "cost-utility" or "economic evaluation" or "Analysis, Cost-Effectiveness" or "Cost Effectiveness Analysis" or "Cost Effectiveness" or "Effectiveness,	2,243

No.	Search Term	Results
	Cost" or "Cost Effectiveness Ratio" or "Cost Effectiveness Ratios" or "Effectiveness Ratio, Cost" or "Ratio, Cost Effectiveness" or "cost minimization analysis" or "Analysis, Cost-Benefit" or "Cost-Benefit Analyses" or "Cost Benefit Analysis" or "Analyses, Cost Benefit" or "Analysis, Cost Benefit" or "Cost Benefit Analyses" or "Cost Benefit" or "Cost and Benefit" or "Benefit and Cost" or "Benefits and Costs" or "Costs and Benefits" or "Cost-Benefit Data" or "Cost Benefit Data" or "Data, Cost-Benefit" or "Cost-Utility Analysis" or "Analysis, Cost-Utility" or "Cost-Utility Analyses" or "Cost Utility Analysis" or "Marginal Analysis" or "Analysis, Marginal" or "Marginal Analyses" or "Economic Evaluation" or "Economic Evaluations" or "Evaluation, Economic" or "cost-effectiveness" or "cost-utility" or "cost effectiveness" or "cost utility" or "cost minimization" or "cost minimisation" or "cea" or "cua" or "decision tree*" or (("qaly" or "quality adjusted life years") and "cost") or ("cost" and ("effect*" or "utility*" or "benefit" or "conseq*" or "minimi*" or "qaly*" or "quality adjusted life year*" or "life year*")) or "icer" or "qaly" or "quality adjusted life year*" or (("simulat*" or "markov" or "discrete*") and "model*")).ab,ti.)) not (((("review".pt. or "review literature as topic".af. or "state-of-the-art review".af. or "state of the art review".af. or "state-of-the-art reviews".af. or "reviews, state-of-the-art".af. or "review, state-of-the-art".af. or "state of the art reviews".af. or "literature review".ti.) not ("meta-analysis".pt. or "meta-analysis as topic".af. or "meta analysis as topic".af. or "clinical trial overviews".af. or "clinical trial overview".af. or "overview, clinical trial".af. or "data pooling".af. or "data poolings".af. or "overviews, clinical trial".af. or "systematic review".ti. or "systematic literature review".ti. or "meta-analysis".ti,ab. or "meta analysis".ti,ab.)) or "case report*".ti,ab. or "case series".ti,ab. or ("animal".ab,ti. or "animal".af. or "animalia".af. or "metazoa".af. not ("animal".ab,ti. or "animal".af. or "animalia".af. or "metazoa".af. and "human".ab,ti. or "man, modern".af. or "modern man".af. or "human".af. or "man, taxonomy".af. or "homo sapiens".af.)) or "letter".pt. or "editorial".pt.))	

Questions regarding health-related quality of life (HRQoL) searches (Appendix H):

- i) Please explain the rationale behind not including Emtree or MeSH subject headings in the search strategies and what impact this may have had on the recall of results.**
- j) The Embase search strategy appears to contain non-Ovid syntax (for example, the use of hash tags in the line combination in line 4). Please provide the original search as run in the database.**
- k) The PRISMA search flow diagram (Appendix H, Figure 1.) mentions 10 records found through 'other sources', please provide further details, including full search strategies if appropriate.**

Response A1i

In the SLR on HRQoL in patients with endometriosis, MeSH terms in PubMed and Emtree terms in Ovid were not used. This approach was chosen to avoid potential limitations associated with controlled vocabulary indexing, for example, the variability in how scientific publications are indexed. The use of natural language keywords allowed a broader and more inclusive retrieval of studies by capturing variations in terminology used by authors, that may appear in titles or abstracts but are not reflected in MeSH or Emtree terms. While this method may reduce the precision of search results, as indexing terms can refine searches to highly relevant papers, it minimises the risk of omitting important articles that might otherwise be overlooked due to incomplete or inconsistent indexing. As a result of not using MeSH terms and Emtree terms, more results were obtained by the systematic literature search, many of which proved irrelevant to the topic. However, this approach ensured that no significant evidence was missed, as the broader search captured all potentially relevant studies. According to NICE's manual: when identifying subject headings, variations in thesaurus and indexing terms for each database should be considered, for example MeSH in MEDLINE and Emtree in Embase. Not all databases have indexing terms, and some contain records that have not yet been indexed. It was decided that a search strategy based on free-terms and synonyms would be sufficient to cover relevant publications.

Response A1j

The fourth line of the attached search strategy for the Embase database contains syntax inappropriate for Ovid. The first three lines in the table accurately reflect the original searches, whereas the fourth line serves as a shorthand representation. The fourth query was achieved by combining all three queries, as shown in Table 2.

Table 2: Embase® (via Ovid) search terms (10 July 2024)

S. No.	Search Term	No. of Hits
#1	endometriosis.ab,kw,ti. or endometri*.ab,kw,ti. or adenomyosis.ab,kw,ti. or endometrial adenoma.ab,kw,ti.	171 029
#2	'utility'.ab,kw,ti. or 'utilities'.ab,kw,ti. or 'disutility'.ab,kw,ti. or 'disutilities'.ab,kw,ti. or 'sf 36'.ab,kw,ti. or 'sf-36'.ab,kw,ti. or 'sf 6'.ab,kw,ti. or sf6.ab,kw,ti. or 'short form 6'.ab,kw,ti. or 'shortform 6'.ab,kw,ti. or 'sf six'.ab,kw,ti. or sfsix.ab,kw,ti. or 'shortform six'.ab,kw,ti. or 'short form six'.ab,kw,ti. or euroqol.ab,kw,ti. or 'euro qol'.ab,kw,ti. or 'euro-qol'.ab,kw,ti. or 'euroqol 5d'.ab,kw,ti. or 'euroqol-5d'.ab,kw,ti. or 'euroqol 5-d'.ab,kw,ti. or eq5d.ab,kw,ti. or 'eq 5d'.ab,kw,ti. or 'health utility index'.ab,kw,ti. or hui.ab,kw,ti. or hui2.ab,kw,ti. or 'hui-2'.ab,kw,ti. or hui3.ab,kw,ti. or 'hui-3'.ab,kw,ti. or 'standard gamble'.ab,kw,ti. or 'time trade off'.ab,kw,ti. or 'time tradeoff'.ab,kw,ti. or timetradeoff.ab,kw,ti. or tto.ab,kw,ti. or 'patient preference'.ab,kw,ti. or 'european quality of life 5 dimensions'.ab,kw,ti. or '5d'.ab,kw,ti. or '5 d'.ab,kw,ti. or '5-d'.ab,kw,ti. or '5 dimension'.ab,kw,ti. or '5-dimension'.ab,kw,ti. or 'five dimension'.ab,kw,ti. or 'five-dimension'.ab,kw,ti. or '5 dimensions'.ab,kw,ti. or '5-dimensions'.ab,kw,ti. or 'five dimensions'.ab,kw,ti. or 'five-dimensions'.ab,kw,ti. or '6d'.ab,kw,ti. or '6 d'.ab,kw,ti. or '6-d'.ab,kw,ti. or '6 dimension'.ab,kw,ti. or '6 dimensions'.ab,kw,ti. or '6-dimension'.ab,kw,ti. or '6-dimensions'.ab,kw,ti. or 'six dimension'.ab,kw,ti. or 'six dimensions'.ab,kw,ti. or 'six-dimension'.ab,kw,ti. or 'six-dimensions'.ab,kw,ti. or '36d'.ab,kw,ti. or '36 d'.ab,kw,ti. or '36-d'.ab,kw,ti. or '36 dimension'.ab,kw,ti. or '36 dimensions'.ab,kw,ti. or '36-dimensions'.ab,kw,ti. or 'thirty-six dimension'.ab,kw,ti. or 'thirty-six dimensions'.ab,kw,ti. or wellbeing.ab,kw,ti. or 'well being'.ab,kw,ti. or 'well-being'.ab,kw,ti. or 'QWB'.ab,kw,ti. or '15 d'.ab,kw,ti. or 15d.ab,kw,ti. or '15-d'.ab,kw,ti. or '15 dimension'.ab,kw,ti. or '15 dimensions'.ab,kw,ti. or 'fifteen dimension'.ab,kw,ti. or 'fifteen dimensions'.ab,kw,ti. or 'multi-attribute'.ab,kw,ti. or 'multi-attributes'.ab,kw,ti. or 'multiattribute'.ab,kw,ti. or 'multiattributes'.ab,kw,ti. or 'multi attribute'.ab,kw,ti. or 'multi attributes'.ab,kw,ti. or 'ENDOCARE'.ab,kw,ti. or 'EHP-30'.ab,kw,ti. or 'EHP'.ab,kw,ti. or 'aqol2'.ab,kw,ti.	715 112

S. No.	Search Term	No. of Hits
#3	((review.pt. or "review literature as topic".af. or "state-of-the-art review".af. or "state of the art review".af. or "state-of-the-art reviews".af. or "reviews, state-of-the-art".af. or "review, state-of-the-art".af. or "state of the art reviews".af. or "literature review".ti.) not (meta-analysis.pt. or "meta-analysis as topic".af. or "meta analysis as topic".af. or "clinical trial overviews".af. or "clinical trial overview".af. or "overview, clinical trial".af. or "data pooling".af. or "data poolings".af. or "overviews, clinical trial".af. or "systematic review".ti. or "systematic literature review".ti. or "meta-analysis".ti,ab. or "meta analysis".ti,ab.)) or "case report".ti,ab. or "case series".ti,ab. or (("animal".ab,ti. or "animal".af. or "animalia".af. or "metazoa".af.) not (("animal".ab,ti. or "animal".af. or "animalia".af. or "metazoa".af.) and ("human".ab,ti. or "man, modern".af. or "modern man".af. or "human".af. or "man, taxonomy".af. or "homo sapiens".af.))) or "letter".pt. or "editorial".pt.	10 525 620
#4	((endometriosis or endometri* or adenomyosis or endometrial adenoma) and ('utility' or 'utilities' or 'disutility' or 'disutilities' or 'sf 36' or 'sf-36' or 'sf 6' or 'sf6' or 'short form 6' or 'shortform 6' or 'sf six' or 'sfsix' or 'shortform six' or 'short form six' or 'euroqol' or 'euro qol' or 'euro-qol' or 'euroqol 5d' or 'euroqol-5d' or 'euroqol 5-d' or 'eq5d' or 'eq 5d' or 'health utility index' or 'hui' or 'hui2' or 'hui-2' or 'hui3' or 'hui-3' or 'standard gamble' or 'time trade off' or 'time tradeoff' or 'timetradeoff' or 'tto' or 'patient preference' or 'european quality of life 5 dimensions' or '5d' or '5 d' or '5-d' or '5 dimension' or '5-dimension' or 'five dimension' or 'five-dimension' or '5 dimensions' or '5-dimensions' or 'five dimensions' or 'five-dimensions' or '6d' or '6 d' or '6-d' or '6 dimension' or '6 dimensions' or '6-dimension' or '6-dimensions' or 'six dimension' or 'six dimensions' or 'six-dimension' or 'six-dimensions' or '36d' or '36 d' or '36-d' or '36 dimension' or '36 dimensions' or '36-dimensions' or 'thirty-six dimension' or 'thirty-six dimensions' or 'wellbeing' or 'well being' or 'well-being' or 'QWB' or '15 d' or '15d' or '15-d' or '15 dimension' or '15 dimensions' or 'fifteen dimension' or 'fifteen dimensions' or 'multi-attribute' or 'multi-attributes' or 'multiattribute' or 'multiattributes' or 'multi attribute' or 'multi attributes' or 'ENDOCARE' or 'EHP-30' or 'EHP' or 'aqol2')).ab,kw,ti. not (((review.pt. or "review literature as topic".af. or "state-of-the-art review".af. or "state of the art review".af. or "state-of-the-art reviews".af. or "reviews, state-of-the-art".af. or "review, state-of-the-art".af. or "state of the art reviews".af. or "literature review".ti.) not (meta-analysis.pt. or "meta-analysis as topic".af. or "meta analysis as topic".af. or "clinical trial overviews".af. or "clinical trial overview".af. or "overview, clinical trial".af. or "data pooling".af. or "data poolings".af. or "overviews, clinical trial".af. or "systematic review".ti. or "systematic literature review".ti. or "meta-analysis".ti,ab. or "meta analysis".ti,ab.)) or "case report".ti,ab. or "case series".ti,ab. or (("animal".ab,ti. or "animal".af. or "animalia".af. or "metazoa".af.) not (("animal".ab,ti. or "animal".af. or "animalia".af. or "metazoa".af.) and ("human".ab,ti. or "man, modern".af. or "modern man".af. or "human".af. or "man, taxonomy".af. or "homo sapiens".af.))) or "letter".pt. or "editorial".pt.)	2 979

Response A1k

To ensure comprehensive identification of relevant studies, references cited in all retrieved review articles were systematically screened. This process involved an examination of the bibliographies of these articles to identify any additional studies that might meet the inclusion criteria but were not captured through the primary database searches. As a result of this screening, 10 additional studies were identified. However, upon further evaluation on abstract level, none of these studies were suitable for the full text verification. Therefore, in accordance with the criteria outlined in Appendix H of the company submission (CS), these studies were not included in further analysis.

Questions regarding cost and healthcare resource identification searches (Appendix I):

- l) The Ovid search (September 2024) reports a single search strategy for both MEDLINE and Embase searches. Please confirm if this is a simultaneous search of both resources using a single strategy or a single search of the Embase database conducted on the understanding that it now contains all records from MEDLINE.**
- m) The Ovid search strategy appears to contain non-Ovid syntax (for example, the use of hash tags in the line combination in line 4). Please provide the original search as run in the database.**
- n) Please explain the rationale behind not including Emtree or MeSH subject headings in the Ovid search and what impact this may have had on the recall of results.**

Response A1l

The Ovid® search strategy was run simultaneously for both databases.

Response A1m

The fourth line in the provided search strategy for the Embase database included syntax that is incompatible with Ovid. While the first three lines in the table

accurately replicate the original searches, the fourth line is intended as a representation of what was done, however not an explicit query used. In Table 3 below the third step is rewritten to a precise form, while the final query is unchanged from the first submission. The parts were joined manually to address the fact that Ovid does not provide a button, which directly enables the exclusion of third row. Table 3 shows the direct representation of searches.

Table 3: Embase & Ovid MEDLINE(R) (via Ovid) search terms (06.09.2024)

S. No.	Search Term	No. of Hits
#1	(endometriosis or endometri* or Adenomyosis or endometrial adenoma).ab,kw,ti.	270 208
#2	("health care costs" or "hospital costs" or "health care utilization" or "resource allocation" or (healthcare adj1 cost*) or (unit adj1 cost*) or (resource* adj2 allocat*) or (healthcare adj1 (utilisation or utilization)) or ("health care" adj1 (utilisation or utilization)) or (resource adj1 (utilisation or utilization or use*)) or (cost* adj3 (treat* or therap*)) or ((total or direct or indirect or medical or drug or administration or laborat* or diagnos* or productivity or illness or disease) adj2 (cost or costs)) or "hospitalization costs" or "costs and cost analysis" or "direct service costs" or "health expenditures" or "capital expenditures" or "economics, medical" or "economics, hospital" or "budgets").ab,kw,ti.	514 049
#3	((review.pt. or "review literature as topic".af. or "state-of-the-art review".af. or "state of the art review".af. or "state-of-the-art reviews".af. or "reviews, state-of-the-art".af. or "review, state-of-the-art".af. or "state of the art reviews".af. or "literature review".ti.) not (meta-analysis.pt. or "meta-analysis as topic".af. or "meta analysis as topic".af. or "clinical trial overviews".af. or "clinical trial overview".af. or "overview, clinical trial".af. or "data pooling".af. or "data poolings".af. or "overviews, clinical trial".af. or "systematic review".ti. or "systematic literature review".ti. or "meta-analysis".ti,ab. or "meta analysis".ti,ab.)) or "case report".ti,ab. or "case series".ti,ab. or (("animal".ab,ti. or "animal".af. or "animalia".af. or "metazoa".af.) not (("animal".ab,ti. or "animal".af. or "animalia".af. or "metazoa".af.) and ("human".ab,ti. or "man, modern".af. or "modern man".af. or "human".af. or "man, taxonomy".af. or "homo sapiens".af.))) or "letter".pt. or "editorial".pt	15 077 608

#4	1 and 2	1 777
#5	((((endometriosis or endometri* or Adenomyosis or endometrial adenoma) and ("health care costs" or "hospital costs" or "health care utilization" or "resource allocation" or (healthcare adj1 cost*) or (unit adj1 cost*) or (resource* adj2 allocat*) or (healthcare adj1 (utilisation or utilization)) or ("health care" adj1 (utilisation or utilization)) or (resource adj1 (utilisation or utilization or use*)) or (cost* adj3 (treat* or therap*)) or ((total or direct or indirect or medical or drug or administration or laborat* or diagnos* or productivity or illness or disease) adj2 (cost or costs)) or "hospitalization costs" or "costs and cost analysis" or "direct service costs" or "health expenditures" or "capital expenditures" or "economics, medical" or "economics, hospital" or "budgets")) not (((endometriosis or endometri* or Adenomyosis or endometrial adenoma) and ("health care costs" or "hospital costs" or "cost of illness" or "health care utilization" or "resource allocation" or (healthcare adj1 cost*) or (unit adj1 cost*) or (resource* adj2 allocat*) or (healthcare adj1 (utilisation or utilization)) or ("health care" adj1 (utilisation or utilization)) or (resource adj1 (utilisation or utilization or use*)) or (cost* adj3 (treat* or therap*)) or ((total or direct or indirect or medical or drug or administration or laborat* or diagnos* or productivity or illness) adj2 (cost or costs)) or "hospitalization costs" or (burden adj2 (disease* or illness)) or "costs and cost analysis" or "direct service costs" or "health expenditures" or "capital expenditures" or "value of life" or "economics, medical" or "economics, hospital" or "budgets" or fee or fees or (value adj2 money) or (cost adj2 illness*) or (adverse* adj2 management*)) not (((review or "review literature as topic" or "state-of-the-art review" or "state of the art review" or "state-of-the-art reviews" or "reviews, state-of-the-art" or "review, state-of-the-art" or "state of the art reviews" or "literature review") not (meta-analysis or "meta-analysis as topic" or "meta analysis as topic" or "clinical trial overviews" or "clinical trial overview" or "overview, clinical trial" or "data pooling" or "data poolings" or "overviews, clinical trial" or "systematic review" or "systematic literature review" or "meta-analysis" or "meta analysis")) or "case report*" or "case series" or (("animal" or "animal" or "animalia" or "metazoa") not (("animal" or "animal" or "animalia" or "metazoa") and ("human" or "man, modern" or "modern man" or "human" or "man, taxonomy" or "homo sapiens")))) or "letter" or "editorial")))).af.	965
#6	remove duplicates from #5	849
#7	6 and 2013:2024.(sa_year)	431

Response A1n

In the SLR on cost and healthcare resource searches, MeSH terms in PubMed were not used, as only the Ovid database was interrogated. Emtree terms in Ovid were not used to avoid potential limitations associated with controlled vocabulary indexing, for example, the variability in how scientific publications are indexed. The use of natural language keywords allowed a broader and more inclusive retrieval of studies by capturing variations in terminology used by authors, that may appear in titles or abstracts but are not reflected in Emtree terms. While this method may reduce the precision of search results, as indexing terms can refine searches to highly relevant papers, it minimises the risk of omitting important articles that might otherwise be overlooked due to incomplete or inconsistent indexing. As a result of not using Emtree terms, more results were obtained by the systematic literature search, many of which proved to be irrelevant to the topic. However, this approach ensured no significant evidence was missed, as the broader search captured all potentially relevant studies. According to NICE's manual: when identifying subject headings, variations in thesaurus and indexing terms for each database should be considered, for example MeSH in MEDLINE and Emtree in Embase. Not all databases have indexing terms, and some contain records that have not yet been indexed. It was decided that a search strategy based on free-terms and synonyms would be sufficient to cover relevant publications.

Question regarding feasibility assessment – indirect treatment comparison (Appendix M)

- o) The Ovid search (August 2024) reports a single search strategy for both MEDLINE and Embase searches. Please confirm if this is a simultaneous search of both resources using a single strategy or a single search of the Embase database conducted on the understanding that it now contains all records from MEDLINE.**

Response A1o

The Ovid® search strategy was run simultaneously for both databases and the search strategy implemented both Emtree and MeSH subject headings.

Decision problem

A 2. Priority question. Surgery is included as a comparator in the Decision Problem and the cost-effectiveness analysis. However, it is not included in the clinical effectiveness evidence. The only other comparator is leuprorelin.

- a) Please provide adequate justification for the comparators that have been included.**
- b) Please include clinical and cost-effectiveness evidence for a comparison with all comparators that are might be used in clinical practice in the NHS regardless of market share.**

Response A2a

Linzagolix is anticipated to be indicated for [REDACTED]

[REDACTED] Based on clinical expert opinion in the UK, and in line with European clinical guidelines, gonadotropin-releasing hormone (GnRH) antagonists (including linzagolix) will be used as second-line hormonal treatment options, as an alternative to GnRH agonists (see Figure 5 in Company Submission Document B, Section B1.3.5.2). The comparators included in the submission are based on those treatments used at the same point of the treatment pathway.

As such the following treatments are not considered to be comparators:

- Analgesics, which are recommended for the initial management of endometriosis-associated pain (EAP), and may be used alone or in combination with other treatments.
- Neuromodulators, which are reserved for patients with exceptionally difficult-to-manage pain secondary to endometriosis, and are prescribed after referral to a specialist pain service rather than as part of routine supportive care.

Clinical experts advised that it is unusual for patients to require neuromodulators, with <5% of patients prescribed such treatments.²

- Combined hormonal contraception, oral progestogens and intrauterine devices which are used as first-line hormonal therapies.

GnRH agonists are reserved as second-line hormonal treatment, and are therefore considered to be appropriate comparators. The following GnRH agonists are indicated for the treatment of endometriosis: goserelin (depot injection), leuprorelin (depot injection), nafarelin (nasal spray), buserelin (nasal spray), and triptorelin (depot injection). Intranasal GnRH agonists (nafarelin and buserelin) are rarely prescribed, with all surveyed clinical experts reporting a preference for intramuscular or subcutaneous formulations, therefore only leuprorelin acetate, goserelin, and triptorelin were considered comparators in the model.^{2,3} Leuprorelin, as a representative of all GnRH agonists, is included in the base case (see response to question A5 for further discussion).

While surgery is an important part of the treatment pathway for women with endometriosis, the clinical decision to perform surgery is based on individual circumstances independent of the choice to prescribe a GnRH analogue. Women who wish to conceive immediately would be prioritised for surgical treatment, while those not currently planning a family may try hormonal therapies to manage their symptoms before considering surgery.² Surgery is not considered to be a direct comparator to linzagolix because:

- 1) Linzagolix would be used in situations where GnRH agonists are currently prescribed, and where medical therapy is preferred over surgical intervention.
- 2) Treatment decisions are guided by the need to balance treatment priorities regarding fertility and pain management. Women who do not wish to take hormonal therapy due to priorities regarding fertility would not be suitable for linzagolix treatment and would be prioritised for surgical treatment.
- 3) Clinical experts suggest that when included in the overall pathway, GnRH analogues impact when and how surgery might be used. GnRH analogues may be used as a complementary treatment to reduce the risk of symptom recurrence post-surgery or to provide symptom relief whilst women are waiting for surgery, and in this case, do not directly replace surgical treatment.

The feasibility of an indirect treatment comparison (ITC) versus surgery was explored; however, there are considerable methodological challenges in comparing medical therapy with surgery due to differences in study objectives, study design and endpoints. Adding complexity, a range of different surgical interventions may be used to treat endometriosis. As described in the CS (Document B section B2.9, page 72 and Appendix M) an indirect treatment comparison with surgical treatments was not feasible. Therefore, outcomes following surgical treatment (laparoscopy) were modelled using data identified in the published literature and validated with clinical experts, as described in the Company Submission (section B3.3.6).

Relugolix combination therapy (relugolix-oestradiol-norethisterone acetate, relugolix-CT) has not yet been received positive guidance by NICE for use in England and Wales and therefore was not included as a comparator in the original submission, however at NICE's request we are now able to provide comparative data, **see addendum to clarification response – comparison with relugolix.**

Response A2b

As described in the response to A2a, it is not appropriate to include analgesics and first-line hormonal therapies as comparators. These would be used before linzagolix

in clinical practice, whilst neuromodulators are used in special circumstances in a small minority of patients. The submission, therefore focussed on the main treatment expected to be replaced by linzagolix, i.e., GnRH agonists. While surgery was also not considered to be a direct comparator to linzagolix for the reasons described above, the company has undertaken a thorough review of the available evidence. Limitations in the data available for surgical treatments precluded an ITC, however results from published studies were used to inform the economic analysis, as described in the CS Document B Section B3.3.6.

Whilst relugolix is not yet “approved” by NICE, an indirect treatment comparison comparing linzagolix with relugolix has been provided, with results incorporated into the economic analysis (**see addendum to clarification response – comparison with relugolix**).

A 3. Priority question. The Decision Problem population is described as requiring a: “...history of previous medical or surgical treatment for their endometriosis” (Table 1).

- a) Please provide details of the precise nature of these medical and surgical treatments.**
- b) Please indicate if there is a different treatment history for those patients where the comparator is leuprorelin as opposed to those where the comparator is surgery or for any of the other comparators (see question A4).**
- c) If there are systematic differences in treatment history (see question b) the please confirm that these differences would imply different subgroups.**

Response A3a

Table 1 of the CS Document A refers to the intended indication specified in the summary of product characteristics (SmPC). The SmPC (section 5.1) also states "The majority of the study population of EDELWEISS 3 reported having undergone previous surgeries/procedures for endometriosis treatment before inclusion into the

EDELWEISS studies. Previous medical treatments consisted of analgesics for pelvic pain, including opioids. The most frequently reported other pharmacotherapies for endometriosis treatment included dienogest, hormonal oral contraceptives and GnRH agonists."

Most patients (93.8%) in the EDELWEISS 3 safety analysis set (SAF) had undergone prior surgeries or procedures to treat endometriosis. The most commonly performed procedures involved laparoscopies.

Prior medications were taken by 69.6% of patients in the EDELWEISS 3 SAF; the use of prior medications was similar across treatment groups (66.3% to 73.5%). The most commonly used (by $\geq 5\%$ of the SAF) prior medications were in the following Anatomical Therapeutic Chemical (ATC) classes: genito-urinary system and sex hormones (43.8%), musculoskeletal system (38.2%), nervous system (10.5%), alimentary tract and metabolism (8.9%), antineoplastic and immunomodulating agents (8.3%), and systemic hormonal preparations excluding sex hormones and insulins (7.0%). The most commonly used (i.e., at least 2% of the SAF) prior medications were: ibuprofen (33.1%), dienogest (25.8%), dienogest/ethinyloestradiol (10.3%), levothyroxine sodium (5.2%), goserelin (4.1%), paracetamol (3.7%), drotaverine hydrochloride (2.3%) and diclofenac (2.1%).

The treatments received prior to linzagolix in EDELWEISS 3 are reflective of the treatments that would be received in UK clinical practice before treating with linzagolix (as outlined in Response 2a and according to clinical expert opinion and NICE/ESHRE guidelines).

Response A3b

As described in the response to Question A2a, clinical expert opinion in the UK suggests that linzagolix would be used as a second-line hormonal treatment option, most likely as an alternative to GnRH agonists, which is in line with European clinical guidelines. The comparators included in the submission are based on those treatments used at the same point of the treatment pathway.

For patients treated with leuprorelin, other GnRH agonists or conservative surgery at this point in the treatment pathway, a similar mix of previous treatments to linzagolix would be expected. The choice of treatment (medical therapy or surgery) is largely driven by patient circumstances relating to pregnancy and family planning, therefore many women receive medical therapies before surgery. Clinical expert opinion indicated that while waiting for surgery, patients may receive combined oral contraceptives, progestogens and non-steroidal anti-inflammatory drugs (NSAIDs), which is in line with medications that would be tried prior to GnRH agonists, as well as those expected to be used prior to linzagolix (and as reflected in EDELWEISS 3). Most women diagnosed with endometriosis will undergo multiple surgical procedures. Therefore women receiving surgery at this point in the treatment pathway may have undergone previous surgery; this is in line with the EDELWEISS 3 study population, and the population expected to be treated with linzagolix and GnRH agonists in UK clinical practice.

Response A3c

No systematic differences in treatment history across comparators are expected for the population considered within the decision problem.

A 4. Priority question. The intervention includes add-back therapy (ABT), but its precise nature does not seem to have been presented in the description of the intervention or the EDELWEISS 3 trial and only one treatment is listed in the cost-effectiveness section i.e. Kliovance, which is a combination of estradiol hemihydrate and norethisterone acetate.

- a) Please provide a full definition of add-back therapy (ABT).**
- b) If there is more than one treatment or treatment combination, then please provide a full list of all treatments or treatment combinations that would be used in clinical practice in the NHS.**

Response A4a

For EDELWEISS 3, ABT comprised oestradiol (E2) 1 mg/norethisterone acetate 0.5 mg. This is stated in the footnote of the CS, Document A Figure 3 (Document B

Figure 6). Table 1 of Document A (Table 2 of Document B) states 'oestradiol/norethisterone' for ABT.

In clinical practice, a range of different type of ABT may be used (see Response A4b).

Response A4b

In practice, the prescription of linzagolix offers clinicians and patients the choice of accompanying ABT. Some options are combined formulations (see Table 4 below) although oestrogen and progesterone can also be prescribed separately – for which there are many potential combinations. For combination and individual products, we have provided a range of annual costs. We anticipate clinicians will prescribe ABT according to local preferences for hormone replacement therapies, and the preference of the patient.

Table 4: ABT treatments and treatment combinations in the UK

Name/Brand	Type	Active ingredients	Unit size	Dosing	Units per year	Price per unit	Price per year
COMBINED OESTROGEN PROGESTERONE							
Kliovance tablets / Novo Nordisk Ltd	Oral	Estradiol 1mg, Norithesterone 500ug	84 tablets	1 per day	4.35	£13.20	£57.36
Elleste Duet Conti tablets / Exeltis UK Ltd	Oral	Estradiol 2mg, Norithesterone 1mg	84 tablets	1 per day	4.35	£17.02	£73.96
Kliefem tablets / Novo Nordisk Ltd	Oral	Estradiol 2mg, Norithesterone 1mg	84 tablets	1 per day	4.35	£17.02	£73.96
Exeltis UK Ltd	Oral	Estradiol 1mg, Norithesterone 1mg	36 tablets	1 per day	4.35		
Novo Nordisk Ltd	Oral	Estradiol 1mg, Norithesterone 1mg	36 tablets	1 per day	4.35		
ReSource Medical UK Ltd	Oral	Estradiol 2mg, Norithesterone 1mg	36 tablets	1 per day	4.35		
Exeltis UK Ltd	Oral	Estradiol 2mg, Norithesterone 1mg	36 tablets	1 per day	4.35		
Novo Nordisk Ltd	Oral	Estradiol 2mg, Norithesterone 1mg	30 tablets	1 per day	4.35		

Name/Brand	Type	Active ingredients	Unit size	Dosing	Units per year	Price per unit	Price per year
Novo Nordisk Ltd	Oral	Estradiol 4mg, Norithesterone 1mg	30 tablets	1 per day	4.35		
Elleste Duet 1mg tablets / Exeltis UK Ltd	Oral	Unstated	84 tablets	1 per day	4.35	£9.20	£39.98
Elleste Duet 2mg tablets / Exeltis UK Ltd	Oral	Unstated	84 tablets	1 per day	4.35	£9.20	£39.98
Novofem tablets / Novo Nordisk Ltd	Oral	Unstated	84 tablets	1 per day	4.35	£11.43	£49.67
Trisequens tablets / Novo Nordisk Ltd	Oral	Unstated	84 tablets	1 per day	4.35	£11.10	£48.23
Evorel Conti patches / Theramex HQ UK Ltd	Transdermal patch	Estradiol 50ug per 24 hour, Norithesterone 170ug per 24 hour	8 patches	2 per week	13.00	£14.56	£189.28
Evorel Conti patches / Theramex HQ UK Ltd	Transdermal patch	Estradiol 50ug per 24 hour, Norithesterone 170ug per 24 hour	24 patches	2 per week	4.33	£43.68	£189.28
Evorel Conti patches / Theramex HQ UK Ltd	Transdermal patch	Estradiol 50ug per 24 hour, Norithesterone 170ug per 24 hour	4 patches	2 per week	26.00		
Evorel Sequi patches / Theramex HQ UK Ltd	Transdermal patch	Unstated	8 patches	2 per week	13.00	£14.56	£189.28
OESTROGEN							
Elleste Solo 1mg tablets / Exeltis UK Ltd	Oral	Estradiol 1mg	84 tablets	1 per day	4.35	£5.06	£21.99
Estradiol 1mg tablets / Abbott Healthcare Products Ltd	Oral	Estradiol 1mg	42 tablets	1 per day			
Estradiol 1mg tablets / Exeltis UK Ltd	Oral	Estradiol 1mg	48 tablets	1 per day			
Estradiol 1mg tablets / Novo Nodisk Ltd	Oral	Estradiol 1mg	18 tablets	1 per day			
Estradiol Valerate 1mg tablets / Bayer Plc	Oral	Estradiol valerate 1mg	6 tablets	1 per day			
Estradiol Valerate 1mg tablets / Viatrix UK Healthcare Ltd	Oral	Estradiol valerate 1mg	11 tablets	1 per day			

Name/Brand	Type	Active ingredients	Unit size	Dosing	Units per year	Price per unit	Price per year
Progynova 1mg tablets / Bayer Plc	Oral	Estradiol valerate 1mg	84 tablets	1 per day	4.35	£7.30	£31.72
Zumenon 1mg tablets / Viatris UK Healthcare Ltd	Oral	Estradiol 1mg	84 tablets	1 per day	4.35	£6.89	£29.94
Elleste Solo 2mg tablets / Exeltis UK Ltd	Oral	Estradiol 2mg	84 tablets	1 per day	4.35	£5.06	£21.99
Estradiol 2mg tablets / Exeltis UK Ltd	Oral	Estradiol 2mg	48 tablets	1 per day			
Estradiol 2mg tablets / Novo Nodisk Ltd	Oral	Estradiol 2mg	36 tablets	1 per day			
Estradiol 2mg tablets / ReSource Medical UK Ltd	Oral	Estradiol 2mg	48 tablets	1 per day			
Estradiol Valerate 2mg tablets / Imported (Germany)	Oral	Estradiol valerate 2mg	11 tablets	1 per day			
Estradiol Valerate 2mg tablets / Orion Pharma (UK) Ltd	Oral	Estradiol valerate 2mg	70 tablets	1 per day			
Estradiol Valerate 2mg tablets / Viatris UK Healthcare Ltd	Oral	Estradiol valerate 2mg	11 tablets	1 per day			
Progynova 2mg tablets / Bayer Plc	Oral	Estradiol valerate 2mg	84 tablets	1 per day	4.35	£7.30	£31.72
Zumenon 2mg tablets / Viatris UK Healthcare Ltd	Oral	Estradiol 2mg	84 tablets	1 per day	4.35	£6.89	£29.94
Estradiol Valerate 3mg tablets / Bayer Plc	Oral	Estradiol valerate 3mg	6 tablets	1 per day			
Estradiol 4mg tablets / Novo Nodisk Ltd	Oral	Estradiol 4mg	36 tablets	1 per day			
Estradiol 10ug pessaries / A A H Pharmaceuticals Ltd	Pessary	Estradiol 10ug	24 pessaries	1 per day for 2 weeks, then 2 per week	4.75	£19.80	£94.05
Estradiol 10ug pessaries / Accord-UK Ltd	Pessary	Estradiol 10ug	24 pessaries	1 per day for 2 weeks, then 2 per week	4.75	£8.70	£41.33
Estradiol 10ug pessaries / Advanz Pharma	Pessary	Estradiol 10ug	24 pessaries	1 per day for 2 weeks, then 2 per week	4.75	£15.00	£71.25

Name/Brand	Type	Active ingredients	Unit size	Dosing	Units per year	Price per unit	Price per year
Estradiol 10ug pessaries / Alliance Healthcare Ltd	Pessary	Estradiol 10ug	24 pessaries	1 per day for 2 weeks, then 2 per week	4.75	£10.75	£51.06
Estradiol 10ug pessaries / Medihealth (Northern) Ltd	Pessary	Estradiol 10ug	24 pessaries	1 per day for 2 weeks, then 2 per week	4.75	£8.70	£41.33
Estradiol 10ug pessaries / Sun Pharma UK Ltd	Pessary	Estradiol 10ug	24 pessaries	1 per day for 2 weeks, then 2 per week	4.75	£8.70	£41.33
Vagifem 10ug vaginal tablets / Novo Nordisk Ltd	Pessary	Estradiol 10ug	24 pessaries	1 per day for 2 weeks, then 2 per week	4.75	£16.72	£79.42
Vagirux 10ug vaginal tablets / Gedeon Richter (UK) Ltd	Pessary	Estradiol 10ug	24 pessaries	1 per day for 2 weeks, then 2 per week	4.75	£11.34	£53.87
Estring 7.5mg/24 hours vaginal delivery system / Pfizer Ltd	Vaginal delivery system	Estradiol (as Estradiol hemihydrate) 7.5ug per 24 hour	1 device	1 per 90 days	4.06	£31.42	£127.43
Sandrena 500ug gel sachets / Orion Pharma (UK) Ltd	Transdermal gel	Estradiol (as Estradiol hemihydrate) 500ug	28 sachets	1 per day	13.04	£5.08	£66.22
Sandrena 1mg gel sachets / Orion Pharma (UK) Ltd	Transdermal gel	Estradiol (as Estradiol hemihydrate) 1mg	28 sachets	1 per day	13.04	£5.85	£76.26
Oestrogel Pump-Pack 0.06% gel / Besins Healthcare (UK) Ltd	Transdermal gel	Estradiol 600ug per 1 gram	80 grams	1 per day		£9.15	
Estraderm MX 25 patches / Norgine Pharmaceutical Ltd	Transdermal patch	Estradiol 25ug per 24 hour	8 patches	2 per week	13.00	£5.50	£71.50
Estradot 25ug/24hours patches / Sandoz Ltd	Transdermal patch	Estradiol 25ug per 24 hour	8 patches	2 per week	13.00	£7.38	£95.94
Evorel 25 patches / Theramex HQ UK Ltd	Transdermal patch	Estradiol 25ug per 24 hour	8 patches	2 per week	13.00	£4.35	£56.55
Estradot 37.5ug/24hours	Transdermal patch	Estradiol 37.5ug per 24 hour	8 patches	2 per week	13.00	£7.39	£96.07

Name/Brand	Type	Active ingredients	Unit size	Dosing	Units per year	Price per unit	Price per year
patches / Sandoz Ltd							
Estraderm MX 50 patches / Norgine Pharmaceutical Ltd	Transdermal patch	Estradiol 50ug per 24 hour	8 patches	2 per week	13.00	£5.51	£71.63
Estradot 50ug/24hours patches / Sandoz Ltd	Transdermal patch	Estradiol 50ug per 24 hour	8 patches	2 per week	13.00	£7.41	£96.33
Evorel 50 patches / Theramex HQ UK Ltd	Transdermal patch	Estradiol 50ug per 24 hour	8 patches	2 per week	13.00	£4.35	£56.55
FemSeven 50 patches / Theramex HQ UK Ltd	Transdermal patch	Estradiol 50ug per 24 hour	4 patches	1 per week	13.00	£6.04	£78.52
Progynova TS 50ug/24hours transdermal patches / Bayer PLC	Transdermal patch	Estradiol 50ug per 24 hour	12 patches	1 per week	4.33	£18.90	£81.90
Estraderm MX 75 patches / Norgine Pharmaceuticals Ltd	Transdermal patch	Estradiol 75ug per 24 hour	8 patches	2 per week	13.00	£6.42	£83.46
Estradot 75ug/24hours patches / Sandoz Ltd	Transdermal patch	Estradiol 75ug per 24 hour	8 patches	2 per week	13.00	£8.62	£112.06
Evorel 75 patches / Theramex HQ UK Ltd	Transdermal patch	Estradiol 75ug per 24 hour	8 patches	2 per week	13.00	£4.35	£56.55
FemSeven 75 patches / Theramex HQ UK Ltd	Transdermal patch	Estradiol 75ug per 24 hour	4 patches	1 per week	13.00	£6.98	£90.74
Estraderm MX 100 patches / Norgine Pharmaceuticals Ltd	Transdermal patch	Estradiol 100ug per 24 hour	8 patches	2 per week	13.00	£6.66	£86.58
Estradot 100ug/24hours patches / Sandoz Ltd	Transdermal patch	Estradiol 100ug per 24 hour	8 patches	2 per week	13.00	£8.95	£116.35
Evorel 100 patches / Theramex HQ UK Ltd	Transdermal patch	Estradiol 100ug per 24 hour	8 patches	2 per week	13.00	£4.35	£56.55
FemSeven 100 patches / Theramex HQ UK Ltd	Transdermal patch	Estradiol 100ug per 24 hour	4 patches	1 per week	13.00	£7.28	£94.64
Progynova TS 100ug/24hours transdermal	Transdermal patch	Estradiol 100ug per 24 hour	12 patches	1 per week	4.33	£20.70	£89.70

Name/Brand	Type	Active ingredients	Unit size	Dosing	Units per year	Price per unit	Price per year
patches / Bayer PLC							
PROGESTERONE							
Gepretix 100mg capsules / Exeltis UK Ltd	Oral	Progesterone 100mg	30 capsules	24 capsules per 28 day cycle	10.43	£4.62	£48.18
Progesterone micronised 100mg capsule / A A H Pharmaceuticals Ltd	Oral	Progesterone 100mg	30 capsules	24 capsules per 28 day cycle	10.43	£10.02	£104.49
Progesterone micronised 100mg capsule / Accord-UK Ltd	Oral	Progesterone 100mg	30 capsules	24 capsules per 28 day cycle	10.43	£5.99	£62.47
Progesterone micronised 100mg capsule / Alliance Healthcare (Distribution) Ltd	Oral	Progesterone 100mg	30 capsules	24 capsules per 28 day cycle	10.43	£6.60	£68.83
Progesterone micronised 100mg capsule / Besins Healthcare (UK) Ltd	Oral	Progesterone 100mg	30 capsules	24 capsules per 28 day cycle	10.43	£6.60	£68.83
Progesterone micronised 100mg capsule / Zentiva Pharma UK Ltd	Oral	Progesterone 100mg	30 capsules	24 capsules per 28 day cycle	10.43	£6.27	£65.39
Utrogestan 100mg capsules / Besins Healthcare (UK) Ltd	Oral	Progesterone 100mg	30 capsules	24 capsules per 28 day cycle	10.43	£6.60	£68.83
Cyclogest 200mg pessaries / L.D. Collins & Co. Ltd	Pessary	Progesterone 200mg	15 pessaries	~1 unit per month	12	£8.95	£107.40
Cyclogest 400mg pessaries / L.D. Collins & Co. Ltd	Pessary	Progesterone 400mg	15 pessaries	~1 unit per month	12	£12.96	£155.52

Abbreviations: ABT, add-back therapy

Source: British National Formulary; price listed if available

A 5. Priority question. The DP (see Table 1, CS) states that leuprorelin was chosen specifically as a representative of all GnRH agonists. However, the company seems to believe that other GnRH agonists are used in clinical practice, as shown by them being included in the costing (see Table 65, CS). Table 65 also refers to short- (1-month) and long- (3- month) acting

GnRH agonists, but no such distinction was made in the indirect treatment comparison (ITC).

- a) Please provide justification for the use of leuprorelin specifically as a representative of all GnRH agonists.**
- a) Why was another GnRH agonist approved by NICE for this indication (e.g. goserelin, triptorelin or histrelin) not selected?**
- b) Why was no distinction made between short- and long-acting forms of leuprorelin in the ITC?**
- c) Please include all GnHR that might be used in clinical practice, differentiating between short- and long- acting forms of leuprorelin as required, as comparators in both analysis of clinical effectiveness and cost effectiveness.**

Response A5a

As noted in the response to question A2a, only leuprorelin acetate, goserelin and triptorelin were considered comparators in the model.

Only one study investigating a GnRH agonist for the treatment of EAP was identified that could be used in an ITC with the EDELWEISS 3 study. This was a placebo-controlled randomised controlled trial (RCT) and its long-term extension study that investigated the efficacy and safety of leuporelin and relugolix for the treatment of EAP, reported by Osuga et al (Osuga et al 2021a/2021b^{4,5}). As outlined in Company Submission Appendix D (Section D3.2.1), this study included outcome data that could be compared with the results of the co-primary endpoints of EDELWEISS 3 in a Bucher analysis.

In the base case analysis, leuprorelin acetate was used as the representative GnRH agonist based on the assumption that all GnRH agonists have equivalent efficacy in this population. As noted in the CS (Document B, page 126), this approach was deemed appropriate since all GnRH agonists effectively inhibit endometriosis through a shared mechanism of action, and is aligned to the submission for relugolix

CT in this indication, as well as NICE and ESHRE guidelines which do not distinguish between the different agonists.^{6–8} As also noted in the CS, leuprorelin acetate is the GnRH agonist most commonly used for the treatment of endometriosis in the UK.³

Response A5b

None of the GnRH agonists are specifically “approved” by NICE for the treatment of endometriosis: there are no technology appraisals available in this indication, and the recently updated NICE endometriosis guidelines do not recommend specific GnRH agonists for use in the treatment of endometriosis.⁹ In addition, it should be noted that histrelin is not indicated for the treatment of symptoms of endometriosis and is no longer available in the UK.¹⁰

As described in A5a, no studies investigating goserelin and triptorelin for the treatment of EAP were identified that could be included in an indirect comparison with linzagolix. Goserelin and triptorelin were evaluated in scenario analyses of the cost-effectiveness analysis.

Response A5c

To clarify, the formulation of GnRH agonists is not specifically ‘short’ or ‘long’ acting; this notation applies to the length of coverage of the depot injection. Clinicians and patients can choose the one-month depot or three-month depot and expect no difference in clinical efficacy or safety of the active drug. This is why there is no distinction made between the two formulations in the ITC.

In practice, prescribing clinicians advised that a one-month depot is most often prescribed at treatment initiation.³ This allows for a review within four weeks to determine if there has been a clinical effect and/or if any adverse events have been reported. A three-month depot may be chosen for convenience when a patient is keen to continue treatment. However, this would not change any outcomes for the patient versus the administration of three one-month depot injections as an alternative.³ In some centres, patients remain on a one-month depot, given every

four weeks until treatment cessation; in others, patients are offered the opportunity to switch to the three-month depot.

The search strategy was broad, and no distinction was made between “short- and long-acting” forms of leuporelin. The approach identified all evidence available, regardless of the form of leuporelin. While reviewing the evidence, the criteria were established to include studies on both forms of leuporelin. Only one trial was found in the process (Osuga et al 2021a/2021b^{4,5}), in which patients received leuporelin once a month.

Response A5d

The following GnRH agonists are indicated for the treatment of endometriosis in the UK: goserelin (depot injection), leuporelin (depot injection), nafarelin (nasal spray), buserelin (nasal spray), and triptorelin (depot injection). In clinical practice in the UK, however, none of the prescribers consulted during expert elicitation reported prescribing nasal formulations. With reference to A5c (above) and the Budget Impact Analysis, Section 4.2 Table 2, in clinical practice, both one-month and three-month depot formulations of leuporelin, goserelin and triptorelin are prescribed in the UK. The budget impact analysis assumes a 50:50 split between these two formulations based on the NICE single technology appraisal (STA) for relugolix and expert opinion.³

A 6. Priority question. The Decision Problem includes a broad set of comparators representing established clinical management without linzagolix. However, the company’s SLR appears to limit the scope of comparators in several areas. Please provide a detailed justification when comparators deviate from the NICE scope e.g. are listed in the NICE scope but were not used in the company submission and provide clarification on the following points:

- a) The scope includes a variety of hormone-based treatments, such as combined hormonal contraception and oral progestogens, as potential comparators. Please clarify why these additional hormonal treatments were not included in the GnRH analogue SLR.**

- b) The scope specifies surgical comparators as “excision/ablation with or without hysterectomy.” Please explain the rationale for limiting surgical comparators in the surgical SLR to minimally invasive procedures only, excluding hysterectomy.**
- c) The scope lists analgesics, NSAIDs, and neuromodulators as part of established clinical management without linzagolix. Please clarify why these treatments were not included as comparators in the SLRs.**

Response A6a

As described in response to question A2a, combined hormonal contraception and oral progestogens are used as first line hormonal therapies in UK practice and were therefore not considered to be comparators in the submission.

Response A6b

In the NICE endometriosis guideline (published in 2017 and updated in 2024⁹) the suggested surgical approaches involve laparoscopic excision or ablation plus adhesiolysis and laparoscopic ovarian cystectomy, depending on the location of the lesions. Hysterectomy is advised only if other surgical options have been offered, failed or are inappropriate, and research with clinical experts indicated that hysterectomy tends to be a last resort rather than considered early in the treatment pathway.² Additionally, hysterectomy is indicated if treatment-resistant adenomyosis or heavy menstrual bleeding is present. Linzagolix is a treatment indicated for the treatment of adult women of reproductive age - in this population it might be a priority to maintain fertility. When performing a hysterectomy the fertility is not maintained. Therefore, it was decided not to include it in the feasibility analysis.

Response A6c

Analgesics and NSAIDs are routinely prescribed as first-line therapies in endometriosis (often before a formal diagnosis has been made). Expert elicitation revealed an expectation that once GnRH agonists (or antagonists) are introduced, there is a clinical expectation that the need for such treatments should reduce or cease.² Neuromodulators are reserved for patients with exceptionally difficult-to-

manage pain secondary to endometriosis. Prescription would be started after referral to a specialist pain service rather than as part of routine supportive care. As such, the proportion of patients prescribed neuromodulators is limited and not part of routine practice.

A 7. Priority question. The NICE technical team notes that relugolix CT has not been included as a potential comparator in the company's submission. The company states "relugolix CT has not yet been approved by NICE." However the NICE scope references this treatment as a potential comparator if recommended by NICE. Please either provide more context to this rationale for exclusion given that relugolix CT and linzagolix are likely to be used in the same populations, and that relugolix, if recommended, would likely be the most appropriate comparator, or please provide an updated analysis including relugolix CT as a comparator.

See **Addendum to clarification response – comparison with relugolix and the updated economic model.**

Systematic review

A 8. Please describe the process used for data extraction and risk of bias assessment of the included studies (for intervention and comparator data).

Data extraction was performed by one reviewer and quality-checked by the other reviewer. The extraction was performed in tables. Additionally, if available in the identified publications, graphs were provided. Data from graphs was not extracted if specific values were not provided, due to the possibility of introducing bias to the analysis .

The process of risk of bias assessment is described in Appendix D (Section D.3.7). The methodological quality of each trial was assessed independently by two reviewers using the Cochrane Collaboration's revised risk-of-bias tool for randomised trials (RoB 2). Disagreements were resolved by consensus. The risk of bias was defined as low for all the trials included in the Bucher analysis. This demonstrates the high quality of the studies. The specific results of the risk of bias analysis were provided in Table 31.

A 9. Please provide risk of bias assessment of EDELWEISS 6 and EDELWEISS 2 using appropriate tools.

The risk of bias assessment was performed using the Cochrane Risk of Bias Tool (RoB 2).

Table 5: Risk of bias assessment - EDELWEISS 6 and EDELWEISS 2

Nr	Signalling questions	EDELWEISS 6	EDELWEISS 2
1.1	Was the allocation sequence random?	Yes	Yes
1.2	Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	Yes
1.3	Did baseline differences between intervention groups suggest a problem with the randomisation process?	No	No
Risk-of-bias judgement		Low risk	Low risk
2.1	Were participants aware of their assigned intervention during the trial?	No	No
2.2	Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No	No
2.3	If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Not applicable	Not applicable
2.4	If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Not applicable	Not applicable
2.5	If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Not applicable	Not applicable
2.6	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes
2.7	If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Not applicable	Not applicable
Risk-of-bias judgement		Low risk	Low risk
3.1	Were data for this outcome available for all, or nearly all, participants randomized?	Yes	No*
3.2	<i>If N/PN/NI to 3.1 Is there evidence that the result was not biased by missing outcome data?</i>	Not applicable	Not applicable
3.3	<i>If N/PN to 3.2 Could missingness in the outcome depend on its true value?</i>	Not applicable	Not applicable
3.4	<i>If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?</i>	Not applicable	Not applicable

Nr	Signalling questions	EDELWEISS 6	EDELWEISS 2
Risk-of-bias judgement		Low risk	Some concerns
4.1	Was the method of measuring the outcome inappropriate?	No	No
4.2	Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No
4.3	If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No	No
4.4	If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable	Not applicable
4.5	If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable	Not applicable
Risk-of-bias judgement		Low risk	Low risk
5.1	Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes	Not applicable
5.2	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No	Not applicable
5.3	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No	Not applicable
Risk-of-bias judgement		Low risk	Some concerns
Overall risk-of-bias judgement		Low risk	Some concerns

***Early study termination due to COVID-19**

Low risk of bias: The study is judged to be at low risk of bias for all domains for this result.

Some concerns: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.

High risk of bias: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

A 10. Appendix D Table 1 and Table 2 indicates that only studies published in English language were included in the SLR. Please explain the impact of exclusion of studies published in non-English languages on the estimates in the submission.

In the SLR performed for the intervention and comparators (GnRH antagonists), no abstract or full text was excluded solely because of language restrictions. For each

abstract or full text, other reasons for exclusion of each of the abstracts were identified (i.e., non-eligible study design, intervention, comparator or population). Therefore, we conclude that allowing for the inclusion of the studies published in non-English languages would not affect the estimates in the submission.

Clinical effectiveness evidence

A 11. Priority question. Please provide a full list of all types of ABT with number of patients taking each in EDELWEISS 3.

For EDELWEISS 3, ABT comprised oestradiol (E2) 1 mg/norethisterone acetate 0.5 mg. This is stated in the footnote of Document A Figure 3 (Document B Figure 6). ABT was administered to all patients taking linzagolix 200 mg (n=162) and was not administered to the placebo (n=162) or linzagolix 75 mg (n=160) groups.

Indirect treatment comparison (ITC)

A 12. Priority question. Only one treatment, leuprorelin, is included as comparator in the ITC, and with no distinction between short- and long-acting forms. Please provide a network analysis (NMA) of linzagolix versus all comparators (see questions A2 and A5).

When search strategies were developed, no distinction was made to specify “long- or short-acting” forms of leuprorelin. All trials, regardless of the acting form, were included. The treatment was administered once a month in the trial on leuprorelin included in the ITC.

A 13. Priority question. Several studies (e.g. D’Hooghe 2019, Harada 2021 and Bergqvist 2000) seem to have been excluded from the ITC because there was no placebo arm. However, a NMA could have been conducted that enabled the inclusion of such studies if there had been another (active treatment) common comparator between any comparator in the scope and any of the treatments in such an excluded study. Some studies also seem to have been excluded because of problems with data presentation i.e. as a graph or missing standard deviation/standard error.

- a) Please assess the feasibility of an NMA that includes all comparators (see questions A2 and A5) and that does not limit to only placebo as common comparator.**
- b) Please provide full justifications/reasons for excluding relevant identified studies from the NMA.**
- c) Please consider the incorporation of data from graphs and the imputation of standard errors in any ITC or NMA.**

Response A13a

Based on the clinical SLR performed (including studies limited to placebo as a common comparator) and analysing other published SLRs (Veth et al., 2023¹¹), we discovered significant variability in the studies reporting the efficacy and safety of different interventions. The heterogeneity is not limited to differing inclusion and exclusion criteria but extends to variability in the reported endpoints and scales used to measure the outcomes. Furthermore, many studies are outdated, methodology and population descriptions are not provided in certain instances and are unclear when reported, with some results only presented graphically (with no numerical values provided) and/or without variability measures (like standard deviation) – see Responses A13b and A13c.

Based on the results of the SLRs, we concluded that it is appropriate to compare linzagolix with other GnRH agonists based on the simple pairwise indirect comparison, provided that it was possible to evaluate and minimise the risk of bias.

In the base case analysis, we provided a pairwise comparison based on the two studies (EDELWEISS 3 and Osuga 2021a/b). While we consider it the most credible approach, it requires numerous assumptions and has limitations, even with just two trials included. Introducing any additional studies would result in further limitations, making conclusions more difficult to interpret and results more prone to bias.

We believe that including studies comparing GnRH agonists versus other medical technologies into the ITC and building more complex networks might bring additional uncertainties (i.e., risk of bias, difficult or impossible to measure) and certainly would

not address remaining uncertainties (after conducting the pairwise comparison) regarding effectiveness of linzagolix vs GnRH agonists.

Finally, as we were only able to link linzagolix with leuprorelin (EDELWEISS 3 and Osuga studies), it can be assumed that including trials comparing GnRH agonists vs active treatments would not offer any benefits to the ITC. To address this, studies comparing different GnRH agonists with placebo, and studies linking different GnRH agonists vs other GnRH agonists, directly or indirectly, are required. We have only one GnRH agonist which we can compare with linzagolix via placebo.

Building an NMA would not be credible in this therapeutic area for the reasons already mentioned above.

Response A13b

The list of excluded studies, along with the reasons for exclusion, was provided in Appendix D (section D.3.1.2.).

Response A13c

As agreed with NICE during the clarification meeting (21.11.2024), a response to this question will be provided as a supplement by 10th December 2024.

Adverse events

A 14. Priority question. The EDELWEISS 2 trial was terminated early and, therefore, lacks efficacy data, providing only limited safety information. Please elaborate on the rationale for including EDELWEISS 2 safety data within this submission, despite the absence of efficacy results.

Adverse event data from EDELWEISS 2 were presented in the submission as they are included in the SmPC. This is stated in Section B.2.2. of the submission dossier.

A 15. Priority question. Given that EDELWEISS 2 was conducted in the US and Canada, where patient demographics, healthcare practices, and systems differ from those in the UK, please provide further justification for the inclusion of EDELWEISS 2 data in this submission, given the potential

differences in patient profiles and healthcare environments between the US/Canada and the UK.

Adverse event data from EDELWEISS 2 were presented in the submission as they are included in the SmPC; efficacy data were unavailable from EDELWEISS 2 as stated in Section B.2.2. of the submission dossier. As the EDELWEISS 2 data are for adverse events only, they are unlikely to be affected by healthcare practices/systems, and we have no reason to believe that adverse event profiles for patients in the US and Canada would be clinically different to those for patients in the UK. Most adverse event data in the submission are from the larger EDELWEISS 3 population (from Europe and the US).

A 16. Priority question. The EDELWEISS 2 AE data are referenced in the clinical effectiveness section but is not included in the cost-effectiveness analysis. Please explain the reason for this discrepancy.

The EDELWEISS 2 trial was terminated early and provided only limited safety information. The EDELWEISS 3 trial was preferred as a completed study, for comparison with comparator studies concerning time for reporting safety outcomes.

Section B: Clarification on cost-effectiveness data

Literature review

B 1. The appendices present the results of systematic literature reviews on cost-effectiveness studies (appendix G) and resource use related to endometriosis (appendix I). It is unclear which specific data on resource use and costs were considered across all these studies in the literature. Please clarify whether any of these studies could have been used to inform certain parts of the economic analysis, particularly regarding healthcare use for disease management and monitoring/follow-up of women with endometriosis, which estimates now entirely relied on expert opinion (as mentioned in Table 37 of the CS).

The resource use related to endometriosis was utilised based on the NICE Relugolix CT STA, which provided a comprehensive and reliable source of information for the

modelled patient population. In developing the economic model, priority was given to ensuring that the costs and resource use data allowed for a robust comparison of linzagolix 200 mg plus ABT with all comparators, including future potential comparator relugolix CT. Furthermore, efforts were made to use reliable and complete data sources, where available, for the UK population. Consequently, if credible data on costs and resource use were available in the NICE relugolix CT STA, they were prioritised over other sources.

Table 37 of the CS contains an error: the frequencies for disease management and monitoring were mostly informed by the NICE Relugolix CT STA. Any data gaps were addressed using expert opinion (due to the lack of literature data for UK population addressing those gaps). The corrected Table 37 can be found below (Table 6; **bold text** indicates data that has been changed).

Table 6: Features of the economic analysis (corrected CS Table 37)

	Previous evaluations	Current evaluation	
Factor	NICE relugolix CT STA	Chosen values	Justification
Time horizon	16 years	15.1 years	The average age in the EDELWEISS 3 study is 34.9 years. Therefore, the time horizon is set to 15.1 years which accounts for the starting age of 34.9 until 50 years old, the average age for a woman to reach menopause in the UK.
Treatment waning effect?	No	Considered in scenario analysis	NICE/EAG critique related to the absence of consideration for the treatment waning effect in relugolix CT submission ⁸
Source of utilities	EQ-5D-5L questionnaire from SPIRIT trials was first mapped to 3L using the NICE DSU age-sex-based mapping. Utilities were then derived using the UK value set published by Dolan for EQ-5D-3L.	EQ-5D-5L questionnaire from EDELWEISS 3 was first mapped to 3L using the NICE DSU age-sex based mapping. Utilities were then derived	In line with the NICE reference case.

	Previous evaluations	Current evaluation	
Factor	NICE relugolix CT STA	Chosen values	Justification
		UK value set published by Dolan for EQ-5D-3L.	
Source of costs	BNF, NHS England national tariff 2022/23, relevant literature, and clinical expert opinion.	BNF, NHS England national tariff 2023/24, relevant literature, and clinical expert opinion.	Cost inputs were obtained from the BNF, NHS England national tariff 2023/24, and relevant literature. Where feasible, costs were sourced from UK national resources with an NHS perspective. HRU frequencies for disease management and monitoring were informed by NICE STA Relugolix and expert opinion.
Cycle length	3 months	First two cycles: 3 months	For the detailed justification see section B.3.2.2
		Next cycles: 6 months	
Discount rates	3.5 %	3.5%	In line with the NICE reference case
Efficacy of pharmacological treatments	Response at three and six months	Response at three and six months	According to expert opinion, the benefits of treatment are assessed after three to four months and then after every three to six months. ³

Abbreviations: BNF, British National Formulary; CS, company submission; EAG, external assessment group; EQ-5D-3L, EuroQoL 5-Dimension 3-Level; EQ-5D-5L, EuroQoL 5-Dimension 5-Level; HRU, healthcare resource use; NHS, National Health Service; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate); STA, single technology appraisal

Population

B 2. Priority question:

- a) Please clarify whether the population demographics in the economic model (i.e., the EDELWEISS 3 trial population) can be generalised to the patient population in England and Wales, given that the trial did not include any patients from the UK.

- b) Also, the decision problem described “Adults with symptoms of endometriosis” while in Table 1 of the CS it is stated that the population considered are “women with a history of previous medical or surgical treatment for their endometriosis”. Please resolve that discrepancy.**
- c) Please explain the difference in the population as defined by the NICE scope and the population considered by the company.**
- d) Please clarify what exactly the “previous history” can entail. Please explain if that means that linzagolix can only be administered as 2nd or 3rd line of treatment.**

Response B2a

The EDELWEISS 3 trial population is considered to be generalisable to the patient population in England and Wales. Patients in EDELWEISS 3 were enrolled across Europe (65 centres in Austria, Bulgaria, Czech Republic, France, Hungary, Poland, Romania, Spain and Ukraine) and the US (26 centres). We have no reason to believe that there would be clinically relevant differences between overall patient populations in Europe, the US and UK, but acknowledge in Section B.2.12.2.2 that the patient population in EDELWEISS 3 was mostly white, so patients from other ethnic groups were not well represented. The mean age of patients in EDELWEISS 3 was 35 years, which is similar to the mean age of women in the UK with endometriosis.¹²

Response B2b

The wording on the population in the decision problem Table 1 “Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis” was added to reflect the wording of the expected indication for linzagolix in the UK and the position of linzagolix in the treatment pathway.

Response B2c

The only difference is that, according to the expected indication, linzagolix would not be used as a 1st line therapy in adults with symptoms of endometriosis, and would only be indicated when other treatments (either medical, surgical or both) have been tried. This positioning aligns with expert clinical opinion and the patient population in clinical studies of linzagolix (see response to B2d), and is identical to the relugolix indication in endometriosis.^{2,13}

Response B2d

It is correct that linzagolix is intended for 2nd or later-line therapy after conventional hormone therapy (see response to question A3a). As stated in section 5.1 of the SmPC, "The majority of the study population of EDELWEISS 3 reported having undergone previous surgeries/procedures for endometriosis treatment before inclusion into the EDELWEISS studies. Previous medical treatments consisted of analgesics for pelvic pain, including opioids. The most frequently reported other pharmacotherapies for endometriosis treatment included dienogest, hormonal oral contraceptives and GnRH agonists."

Model Structure

B 3. Priority question: Regarding Figure 1 that presents the model structure:

- a) Please confirm if patients can stay on linzagolix treatment for as long they remain in the no pain or moderate pain health states.**
- b) Please define explicitly the conditions in the model under which patients can continue receiving linzagolix treatment.**

Response B3a

In the initial decision tree, patients continue linzagolix treatment if they achieve either a full or partial response to therapy, defined by improvements in dysmenorrhoea or non-menstrual pelvic pain (NMPP) symptoms as specified in the EDELWEISS 3 study. After completing the six-month decision tree (comprising two, three-month

cycles), patients transition into pain-related health states. Patients can remain on linzagolix treatment while in the no pain/mild pain or moderate pain health states, as these conditions meet the criteria for continued therapy (specified in Response B3b). In the no pain/mild pain health-state, pain severity is reported as <1 on the verbal rating scale (VRS), while in the moderate pain health-state, pain does not exceed two on the VRS. However, it is important to note that there is a probability of discontinuation from these health states for reasons other than pain severity. This probability, set at 3.03%, represents the six-month discontinuation rate after the initial six months of treatment as determined in the EDELWEISS 6 study. The reasons for discontinuation comprised adverse events and the request of patients to discontinue treatment. Patients in the no pain/mild health-state can also transition to the pregnancy state and thus discontinue treatment with linzagolix.

Response B3b

In the model, patients continue linzagolix treatment under specific conditions tied to their response and pain states. During the initial six-month decision tree phase, comprising two three-month cycles, patients remain on treatment if they demonstrate a full or partial response. These responses are defined based on improvements in dysmenorrhoea or NMPP pain levels, as specified in the EDELWEISS 3 study. After the initial decision tree, patients can stay on linzagolix while in the no pain/mild pain or moderate pain health states. The no pain/mild pain health state corresponds to a pain level of <1 on the VRS, whereas the moderate pain health state is defined by a pain level of 2 or less on the VRS. The assumption is in line with clinical expert opinion presented in the expert elicitation reports (2024^{2,3}), stating that patients will continue therapy as long as pain symptoms are managed.

B 4. Priority question: On page 121 of the CS, it is mentioned that “patients who experience a recurrence of symptoms within three months of their initial surgery bypass the Post-Laparoscopy #1 state and move directly to the second surgical procedure.” Please explain how this input is informed in the model. Please clarify if that implies that the 6-month cycle-length may also be too long for the economic model. Please explain why a 3-

**month cycle was not considered for the total structure of the model
instead of switching from 3- to 6-months in different parts of the model.**

The assumption that patients experiencing a recurrence of symptoms within three months of their initial surgery bypass the Post-laparoscopy #1 state and move directly to the second surgical procedure is informed by expert opinion, which indicates that a subset of patients (16.28%) may still experience symptoms directly after unsuccessful surgical intervention within this timeframe.¹⁴ Therefore, it is less relevant to focus on three or six months recurrence and more appropriate to consider a lack of response (i.e. captured as a proportion of patients with recurrence at three months assumed to be non-responders). In such cases, it is assumed that patients are referred for a subsequent surgical procedure (e.g., a second laparoscopy or radical surgery) as soon as possible, taking into account waiting time. It was also assumed that a six-month cycle length would adequately capture the waiting time for subsequent laparoscopic surgery (in line with [Response B8](#)). This reflects clinical practice (in line with the opinion of clinical experts, who indicated that some patients do not respond to laparoscopic surgical treatment, which is separate from the initial response and annual recurrence³). This does not imply that the six-month cycle length is too long for the economic model.

The three-month cycle is used selectively in the model during the initial decision tree to align with the EDELWEISS 3 co-primary endpoints, which evaluate the significant reduction in dysmenorrhoea and NMPP up to month 3. Conversely, the six-month cycle length corresponds to standard clinical practice, where treatment reviews or continuation typically occur biannually. This longer cycle length also provides flexibility to incorporate tunnel states (like pregnancy health-state) without a need to implement too many sub-states and further increase model complexity. Markov transitions at every six months are informed by the EDELWEISS 6 data, reporting results of six months of treatment, ensuring alignment of probabilities with the time of reported clinical evidence. It is worth noting that a half-cycle correction has been applied to address potential biases introduced by the longer model cycle. The combination of three- and six-month cycles reflects the need to capture both short-term clinical outcomes and long-term treatment pathways while maintaining consistency with real-world practices and the requirements of economic modelling.

This hybrid approach balances accuracy and practicality in representing treatment pathways and patient outcomes.

B 5. Priority question: On page 116 of the CS, it is mentioned that a 16-year time horizon is used to extend “until the average age of menopause, established at 50 years in the UK.”

- a) Please provide the source used to inform the average age of menopause in the UK.**
- b) Please justify why the current time horizon used by the company in the base-case analysis (i.e., 15.1-year time horizon) is not a lifetime time horizon.**
- c) In section B.1.3.1.1 it is mentioned that a small proportion of women (~2–5%) experience post-menopausal endometriosis. Please discuss if these women should be considered in the analysis by extending the time horizon of the model. Please explain the potential impact of linzagolix on these women.**
- d) Please adjust the model to allow for a lifetime time horizon or, if the company declines this request, please discuss the expected impact on the cost-effectiveness results of using a lifetime time horizon.**

Response B5a

The source for the average age of menopause in the UK is the National Health Service website: <https://www.nhs.uk/conditions/menopause/>

Response B5b

The development of endometriotic tissue depends on oestrogen levels and is linked to the period between menarche and menopause. Consequently, the initial submission set the time horizon at 15.1 years, representing the difference between the expected age at initiation of linzagolix treatment and the age at which patients typically reach menopause in the UK. This duration was sufficient to capture all significant differences in costs and outcomes between the compared technologies.

Response B5c

It was estimated that with a very small proportion of women who experience post-menopausal endometriosis and a high discount rate after 15 years, the impact of extending the time horizon would be marginal and not affect the overall conclusions.

Response B5d

As indicated in B.5.c the expected impact on the cost-effectiveness results using a lifetime time horizon should be marginal. Most patients would complete linzagolix treatment at menopause (incurring no further costs) and, on average, experience higher utility values over the longer term compared to the comparator arm (due to fewer surgical interventions with long-term complications).

B 6. Priority question: Patients in the model are assumed to enter the pregnancy health state from the 'No pain/mild pain' health state using a fixed probability per model cycle. Please provide evidence supporting this assumption. Furthermore, please justify why patients following surgeries such as post-laparoscopic patients (with no or moderate pain due to endometriosis) are not allowed to enter the pregnancy health state. If transitions from more health states to the pregnancy health state are allowed within the economic model, please update Figure 16 with arrows indicating all possible transitions.

The assumption that patients in the model transition to the pregnancy health-state from the no pain/mild state with a fixed probability (estimated from the live birth rate in the UK) per cycle is based on population norms. It assumes that women with endometriosis have similar desires and probability of pursuing pregnancy as the general UK population, as there is no evidence to suggest otherwise. This approach ensures that the model reflects real-world reproductive intentions without introducing unnecessary bias.

The inclusion of a pregnancy health state was motivated by NICE's feedback on the Relugolix STA, which questioned the handling of infertility-related disutility. This state was introduced to capture future reproductive aspirations of women undergoing GnRH analogue therapy and to ensure that infertility disutility was not inappropriately

applied to this group. Hormonal treatment is intended for women who wish to preserve their fertility for the future (according to NICE guidelines and expert clinical opinion^{2,9}) and do not wish to conceive immediately. Women can stop treatment at any time if they wish to conceive. Therefore, pregnancy was not intended to be the central element of the cost-effectiveness model, as this would require further detailed modelling beyond the scope of this submission. The aim was to demonstrate that for women treated with GnRH analogues, it is possible to temporarily withdraw therapy and conceive. The model and health-states concentrate on pain symptoms and related utility values, in line with primary endpoints of the EDELWEISS clinical trials.

The decision to exclude the transition to the pregnancy state from other health-states (e.g., the post-laparoscopy health-state) was primarily made to maintain model simplicity. A scenario analysis has been provided to assess the impact of the pregnancy health state on the base case results, which excludes this health state from the model (Table 7). It is important to note that, as with initial treatment, no infertility disutility is applied to other health states in the model except those representing radical surgical interventions where infertility would be permanent.

Table 7: Scenario analysis – impact of the pregnancy health state

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Linzagolix 200 mg plus ABT	15,725	11.76	9.29	-	-	-	-
Leuprorelin	12,921	11.76	8.89	2,804	0.00	0.40	6,984
Surgery	14,476	11.76	8.73	1,128	0.00	0.52	2,175
Relugolix CT	14,820	11.76	9.29	905	0.00	0.00	N/A

B 7. Priority question: The model assumes that patients once pregnant spend 3 cycles (in total 18 months) in the pregnancy health state and then move back to the no pain/mild pain state (with active initial treatment or to the Off treatment). Please provide evidence supporting this assumption.

The assumption of three cycles (in total 18 months) in the pregnancy health state was made to align with the six-month cycle length and the tunnel state structure of the model. This duration was chosen as the optimal balance: two cycles (12 months) would be too short to account for conception, pregnancy, and breastfeeding, while more cycles would further complicate the already very complex cost-effectiveness model. Eighteen months effectively captures the necessary timeline while keeping the model focused on its primary objectives.

B 8. Priority question: The model assumes a waiting time of 18-months for surgeries within NHS when comparing linzagolix with laparoscopic surgery. However, for the comparison of linzagolix with the other medical treatments the waiting time for laparoscopy #1 is only 6 months.

- a) Please comment on the validity of this assumption. What is the justification for this difference?**
- b) Please run a scenario analysis in which the waiting time for laparoscopy is also 6 months in the comparison of linzagolix with laparoscopic surgery.**

According to the Endometriosis Market Research Survey the average surgery wait time in the UK is estimated to be 18.8 months. It is correct that the model assumed a waiting time of 18 months for surgeries when comparing linzagolix with laparoscopic surgeries but only six months for laparoscopic surgeries performed in subsequent treatment lines. This approach was taken to maintain model simplicity and not introduce additional tunnel states within the cost-effectiveness model. As the health-state utility value of Laparoscopy #1 waiting is lower compared with Post-laparoscopy #1 (0.644 vs 0.758) the analysis is conservative with respect to the impact on the incremental cost-effectiveness ratio (ICER). The six month waiting

time is not in line with UK clinical practice, and structural changes to the model would be required to enable an 18-month waiting time (which would not be feasible within the required timeframe for the responses to the clarification questions). Therefore we do not feel it is appropriate to run the additional scenario analysis.

B 9. Priority question: On page 123 of the CS, it is mentioned that “surgery is a one-time event, after which a patient can either be a responder or a non-responder.” Nonetheless, later on it is mentioned that “the split between complete and partial responders was assumed similar to the one adopted for pharmacological treatments” when referring to the response inputs for laparoscopic surgery (on page 135 of the CS). Please clarify the contradictory statements. Please also discuss the impact of splitting the response status to complete and partial for laparoscopic surgery. Please run a scenario analysis which only considers responders and non-responders for laparoscopic surgery.

The argumentation cited from page 123 was introduced to highlight that the results of surgery are immediate or almost immediate, and it is not expected that patients will further improve after three or six months. In contrast, this is possible with pharmacological therapy. The focus here was not on being precise about the further split into complete or partial response in the cost-effectiveness model. In Table 8, a scenario where all responders to surgery are assumed to be complete responders, instead of being split between partial and complete responders is presented.

Table 8: Scenario analysis – complete or no response following surgery

Results	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Base case results							
Linzagolix	14,897	11.76	9.33	-	-	-	-
Laparoscopic surgery	14,476	11.76	8.73	421	0.00	0.61	693
Scenario analysis with all responders on laparoscopic surgery as assumed to be complete responders							
Linzagolix	14,897	11.76	9.33	-	-	-	-
Laparoscopic surgery	14,432	11.7633	8.80	465	0.00	0.53	881

Abbreviations: LYG, life years gained; QALY, quality-adjusted life year

B 10. Priority question: In section B.3.11 of the CS, it is mentioned that a range of sensitivity analyses were conducted to explore the underlying uncertainty in the base-case cost-effectiveness results. However, regarding the comparison with laparoscopic surgery, no probabilistic or deterministic sensitivity analyses were conducted “as this is additional comparator only”. For the comparison with laparoscopic surgery, only two alternative scenarios on surgery efficacy were performed. Please provide sensitivity analyses for the comparison with surgery (similar to those for the comparison with the other comparator (leuprorelin)) or provide a solid argument for not performing these sensitivity analyses.

The results of sensitivity analyses were provided below.

Probabilistic sensitivity analysis

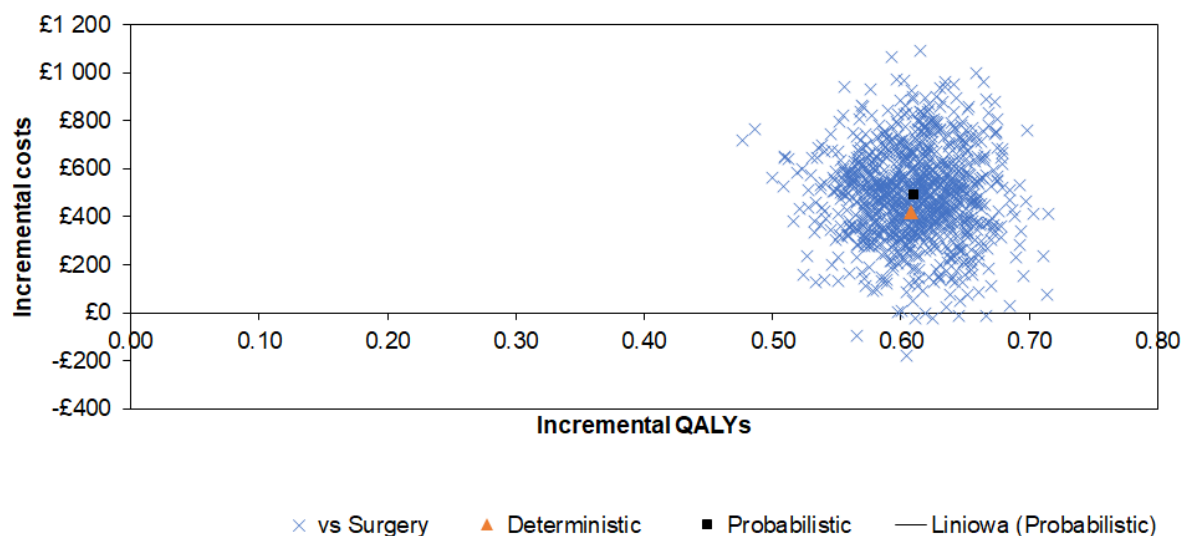
A probabilistic sensitivity analysis (PSA) was conducted to explore the uncertainty around key model parameters. PSA was performed by varying these parameters using their upper and lower bound values based on an assigned distribution. 1,000 simulations were run for the PSA, by which time the ICERs had converged to a stable mean, represented by the probabilistic ICERs. The probabilistic ICER vs laparoscopic surgery (£804) lies closely to the base-case ICER (£693) indicating that the cost-effectiveness results are robust (Table 9). According to the cost-effectiveness acceptability curve (CEAC), the probability of linzagolix versus laparoscopic surgery being cost-effective is already 100% at a willingness to pay of £2,000/quality-adjusted life year (QALY; Figure 2).

Table 9. Probabilistic cost-effectiveness results – linzagolix 200 mg plus ABT versus laparoscopic surgery

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Linzagolix 200 mg + ABT	14 902	11.76	9.32	491	0.00	0.61	804
Laparoscopic surgery	14 411	11.76	8.71				

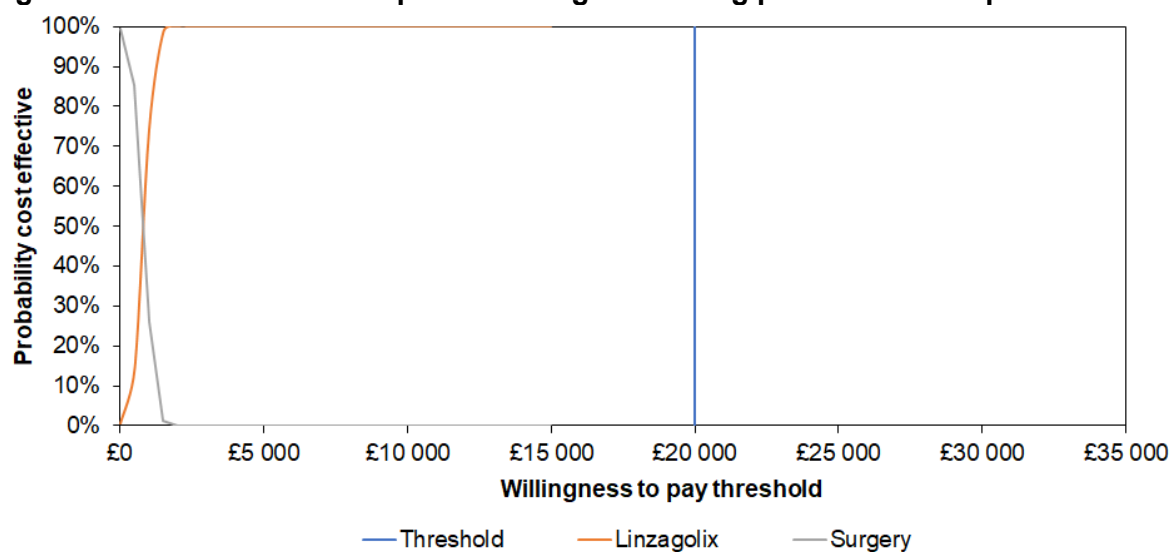
Abbreviations: ABT, add-back therapy; LYG, life years gained; QALY, quality-adjusted life year

Figure 1. PSA output on the cost-effectiveness plane, linzagolix 200 mg plus ABT vs. laparoscopic surgery



Abbreviations: ABT, add-back therapy; PSA, probabilistic sensitivity analysis

Figure 2. Cost -effectiveness plane – linzagolix 200 mg plus ABT vs. leuporelin



Abbreviations: ABT, add-back therapy

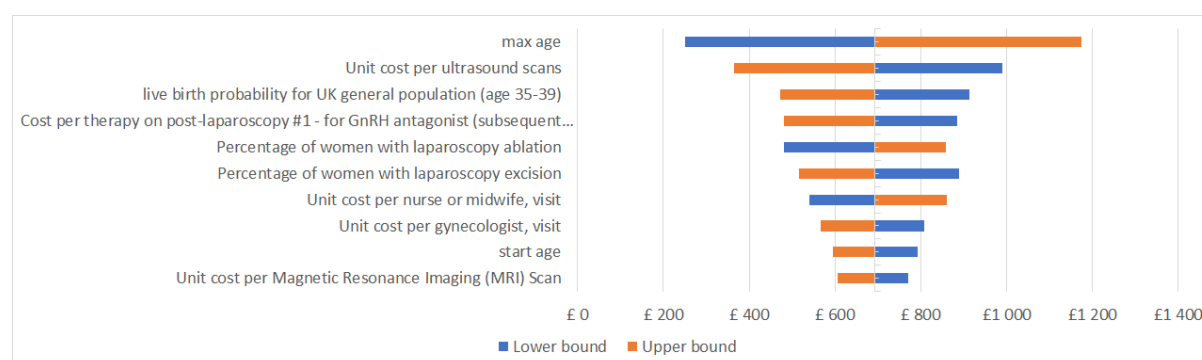
Deterministic sensitivity analysis

One-way deterministic sensitivity analyses (OWSAs) were conducted to examine the sensitivity of the model result to lower and upper estimates of parameter values.

The results from the OWSA are presented in the form of a tornado diagram where the ten parameters with the largest influence on the ICER are presented in Figure 3.

The tornado diagram below shows that the maximum age of patients with endometriosis (age until patients on average experience symptoms of endometriosis) has the largest impact on the ICER. Overall, the results appear robust and none of the parameters have a considerable impact upon the ICER, as it does not exceed £1,200 per QALY in any of the OWSAs.

Figure 3. Tornado diagram – linzagolix 200 mg plus ABT vs. laparoscopic surgery



Abbreviations: ABT, add-back therapy

Scenario analysis

Table 10. Results of scenario analyses – linzagolix 200 mg plus ABT vs. laparoscopic surgery

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Base-case			£421	0.00	0.61	£693
Time horizon: 1.5 year	15.1 years	1.5 years	£1 424	0.00	0.15	£9 608
Pregnancy excluded from the model	Pregnancy health-state included in the model	Pregnancy health-state excluded from the model	£1 128	0.00	0.52	£2 175
Start age: 18	34.9	18	£1 454	0.00	0.73	£1 996
Basket split for post-laparoscopy health-state	Based on EMRS 2024 ¹⁴	Based on Soliman 2017 ¹⁵	£1 051	0.00	0.61	£1 730
Time horizon: 5 years	15.1 years	5 years	£7	0.00	0.37	£19

Percentage of women treated during waiting for surgery	49.8% based on EMRS 2024 ¹⁴	100% (assumption)	£25	0.00	0.61	£41
Time horizon: 10 years	15.1 years	10 year	£110	0.00	0.51	£216
Alternative transitions between health states post initial treatment (scenario 2)	Base case probabilities of patients transitioning to health-states in the model (see section B.3.3 of CS)	Alternative probabilities of patients transitioning to health-states in the model (see Table 88 of CS)	£674	0.00	0.60	£1 116
Ablation/laparoscopy weights	50.3%/33.2 % based on NCEPOD 2024 ¹²	50%/50% (assumption)	£173	0.00	0.61	£284
Patients continuing treatment after 6 months	Partial (DYS or NMPP) and complete responders	only complete responders and NMPP responders	£335	0.00	0.31	£1 075

Abbreviations: ABT, add-back therapy; CS, company submission; DYS, dysmenorrhoea; LYG, life years gained; NCEPOD, National Confidential Enquiry into Patient Outcome and Death; NMPP, non-menstrual pelvic pain; QALY, quality-adjusted life year; EMRS – Endometriosis Market Research Survey

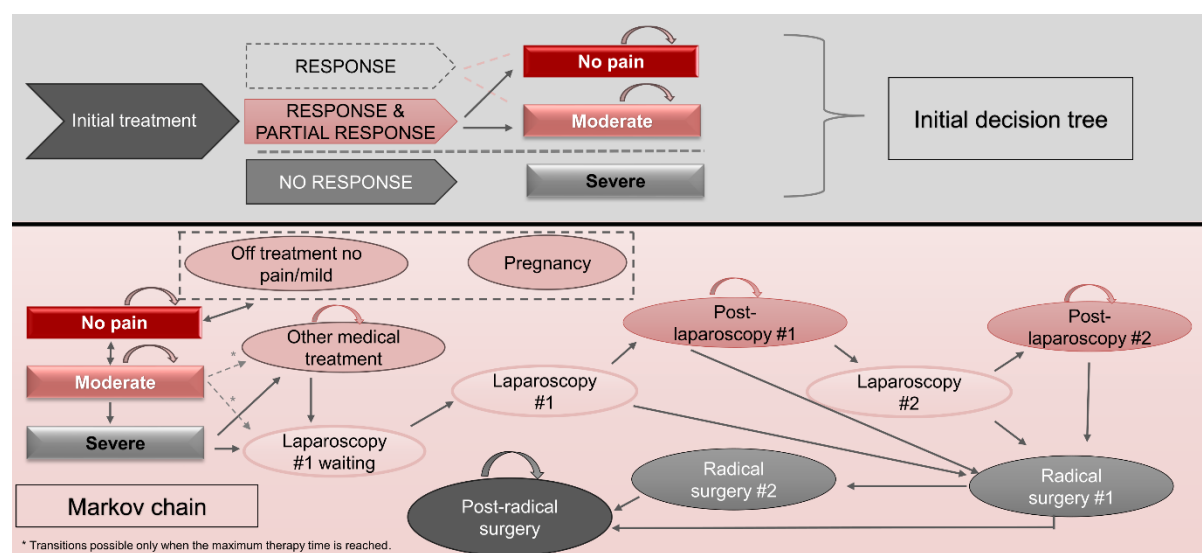
B 11. On page 120 of the CS, it is mentioned that “when the maximum therapy time is reached, patients remaining in No pain/mild are transitioned to Off-treatment no pain/mild, and those remaining in the Moderate pain state transition to Other Medical Treatment or Laparoscopy #1 Waiting”. Please confirm if this sentence only refers to GnRH agonists treatments. Please explain why then there is no arrow in Figure 16 to describe the transition of patients from “moderate pain” to “other medical treatment”? If needed please provide an update of Figure 16, in which arrows will describe all potential transitions.

The sentence on page 120 of the CS, stating that “when the maximum therapy time is reached, patients remaining in No pain/mild are transitioned to Off-treatment no pain/mild, and those remaining in the Moderate pain state transition to Other Medical Treatment or Laparoscopy #1 Waiting,” does indeed apply to GnRH agonist

treatments. This transition mechanism is applicable to both the intervention and comparators in the model. However, this specific transition does not occur for linzagolix because the treatment duration for linzagolix equals the model's time horizon.

The figure has been updated to address the absence of an arrow in Figure 16 depicting the transition of patients from the "Moderate pain" state to Other Medical Treatment or Laparoscopy #1 Waiting health-states. Additional (dashed) arrows have been included to represent those transitions accurately, and the revised version of Figure 16 is provided below (Figure 4).

Figure 4: Model structure (revised CS Figure 16)



Abbreviations: CS, company submission

B 12. Please describe the types of surgeries that are considered in the radical surgery health state(s).

Two types of surgeries are considered: partial/total hysterectomy and oophorectomy. This is in line with the UK clinical practice.¹⁴

B 13. Patients in the model are assumed to remain in the waiting for laparoscopy health state for one cycle of six months before progressing to laparoscopy. Please explain if this assumption aligns with clinical practice in the UK.

In line with the clinical practice in the UK patients wait on average 18.8 months for surgical procedure.¹⁴ The waiting for laparoscopy health state one cycle of six months was implemented to maintain model simplicity and not introduce additional tunnel states within the CE model. As the health-state utility value of Laparoscopy #1 waiting is lower compared with Post-laparoscopy #1 (0.644 vs 0.758) the solution is conservative regarding impact on the ICER (as patients in comparator arms are assumed to progress quicker to laparoscopy health-states).

Comparator

B 14. Priority question: According to the NICE scope, the relevant comparators should include ‘surgery such as excision/ablation with or without hysterectomy’. In the CE analysis, the company includes laparoscopic surgery as an additional comparator to GnRH agonists.

- a) Please explain what the alternative surgery options for the population of interest are.**
- b) Please justify why radical surgeries such as hysterectomy or oophorectomy are not relevant comparators.**
- c) Please explain if subgroup analysis would be relevant for patients requiring radical surgeries such as hysterectomy or oophorectomy versus linzagolix.**

Response B14a

The patient population considered in the analysis comprises adult pre-menopausal women with moderate to severe endometriosis-associated pain and a history of previous medical or surgical treatment for their endometriosis. It was assumed that for this population, the alternative surgical options to linzagolix are limited to conservative procedures. GnRH antagonists are a treatment of choice for patients wishing to preserve fertility, as radical surgeries such as hysterectomy or oophorectomy do not align with this goal. This is especially true once patients still have alternative treatments to use.

Response B14b

In clinical practice, radical surgeries are typically reserved for heavily pretreated patients with recurrent disease, where both pharmacological treatments and conservative surgeries have proven ineffective. Furthermore, patients who are offered radical surgeries in the earlier stage of their treatment pathway are generally not candidates for pharmacological therapy (unlike patients who want to preserve their fertility for the future). Radical surgeries, unlike pharmacological options, close the path to pregnancy for those patients.

We understand that radical surgery is used in the management of endometriosis, but not at the time a patient would initiate treatment with GnRH analogues, where there is an aim to preserve fertility for the future.

Response B14c

Subgroup analysis comparing patients requiring radical surgeries, such as hysterectomy or oophorectomy, with patients eligible for linzagolix treatment would not be relevant for several reasons based on clinical practice and patients' characteristics.

Radical surgeries are typically considered for patients who have exhausted all other treatment options, including pharmacological therapies and conservative surgeries, and for whom these approaches have proven ineffective or sub-optimal. This subgroup represents a clinical population distinct from patients earlier in their treatment pathway, where linzagolix may be considered a treatment option. For patients who are offered radical surgeries in the early stages of their treatment pathway, pharmacological treatment is usually considered as less, or not, effective. Radical surgeries are definitive procedures that preclude the possibility of future pregnancy, whereas linzagolix offers an approach that aligns with the goal of fertility preservation.

As a result, the treatment goals and clinical outcomes of radical surgeries and linzagolix treatment are fundamentally different and not directly comparable.

B 15. Priority question: Page 127 of the CS mentions that “according to clinical experts, whether or not surgery could be considered a direct comparator to medical therapies is dependent on the type of endometriosis.” Please clarify for which types of endometriosis surgery can be seen as a direct comparator, and provide a subgroup analysis if there are indeed certain patients (depending on the type of endometriosis) for whom surgery is either a comparator or not.

According to expert clinical opinion,² surgery might be considered a direct comparator to pharmacological treatments, depending on the type of endometriosis, clinical management, and patient-specific characteristics and/or preferences. However, clinical experts lacked consensus regarding the types of endometrioses for which surgery could be considered a direct comparator.

Concerning deep endometriosis, the complexity and high risk of complications were an indication to prioritise pharmacological therapies for some respondents. For others, surgical intervention might be prioritised to remove/shrink big deposits, i.e., treating clinicians reported different experiences and recommendations for clinical management. Patients also have different priorities and characteristics that may favour either pharmacological or surgical intervention. In summary, the definition of specific subgroups for which surgery could be seen as a direct comparator to pharmacological therapies (and specifically linzagolix 200mg +ABT) is not possible.

B 16. Priority question: On page 125 of the CS, it is stated that “only leuprorelin acetate, goserelin, and triptorelin were considered comparators in the model, while intranasal formulations were excluded due to their limited clinical use”. Of the subcutaneous GnRH agonists, only leuprorelin is included in the ITC presented in section B.2.9 of the CS. Please clarify why the other treatment options were not part of the ITC.

Intranasal formulations were excluded based on the key opinion leader's feedback provided in The Expert Elicitation Reports (2024). Such formulations are not used in UK clinical practice and are not appropriate for the analysis. In line with the response provided to questions A12 and A13, it was possible to perform an ITC vs leuprorelin

only. This should not be perceived as a limitation in line with the response to question A5.

Clinical effectiveness parameters

B 17. Priority question: On page 127, the company reports that “the principal source of data used to inform the effectiveness of linzagolix 200 mg plus ABT is EDELWEISS 3”. Also, section B.3.3.1 mentions that “both sets are derived from patient responses to treatment and individual patient-level data from EDELWEISS 3.” However, on page 117 of the CS, it is reported that the “markov transitions during initial treatment at month 6 were based on EDELWEISS 6 data”. Please explain why these transitions were only informed from EDELWEISS 6 data and not EDELWEISS 3 or both. Please also explain why the transitions to the health states contingent upon the level of pain experienced by the patient are only informed from EDELWEISS 3 trial data and not EDELWEISS 6 data. On the other hand, Table 40 of the CS also presents the probabilities of transitioning among pain-related health states, and these were informed from EDELWEISS 6. Please describe in detail the inputs that are informed from EDELWEISS 3 and the inputs that are informed from EDELWEISS 6 trial data. Please also explain in short, the rationale behind using a certain trial population for each of the (set) of inputs.

In the CS document, section B.3.3.1 contains an error and should be written as follows:

Two sets of health states are used in the model to address patient response to treatment. The first set, applied during the initial decision tree, includes three possible response states: no response, partial response and complete response. The second set, based on EAP levels, is used after the first six months of treatment and consists of three overall pelvic pain states (no pain/mild, moderate, and severe). **Both sets are derived from patient responses to treatment and individual patient-level data. Response-based health-states and transitions are informed by the EDELWEISS 3 study, while pain-based health-states and transitions are informed by the EDELWEISS 6 study.**

The selection of data from EDELWEISS 3 and its extension, EDELWEISS 6, in the economic model was guided by the specific context of each transition and the relevance of the trial populations. Transitions in the initial decision tree were based on EDELWEISS 3, as its co-primary endpoint at three months provided the foundation for response-based health-states. Moreover, the EDELWEISS 3 population closely mirrors the modelled cohort at this stage—patients initiating GnRH antagonist therapy after a diagnosis of endometriosis and with a history of prior treatment. Transitions between response-related health states and pain-related health states at the sixth month, as well as subsequent transitions between pain-related states in the Markov chain beyond the sixth month, were informed by EDELWEISS 6 data, as the EDELWEISS 6 population more accurately represents patients who have already undergone six months of linzagolix treatment. The use of EDELWEISS 6 data enabled the representation of transitions between pain-related health states during ongoing GnRH antagonist therapy.

B 18. Priority question: Table 42 of the CS presents the basket of potential medical treatments for subsequent therapies following the failure of the intervention or comparator therapies.

- a) Please explain if this distribution of treatments of subsequent medical treatments applies to all treatment arms considered in the economic model (linzagolix, surgery, GnRH agonists). Would for example 25% of patients on subsequent medical treatments receive GnRH agonists, following a failure with an initial GnRH agonist treatment?**
- b) For the distribution of the different treatments, there is a reference to source 19 (Theramex. Data on File: Endometriosis Market Research Survey for Yselty® (Linzagolix)). However, this source is missing from the reference pack. Please add this source to the reference pack.**

Response B18a

Table 42 of the CS does not present the distribution of therapies for subsequent medical treatments across all treatment arms. Instead, it reflects the percentage share of medical therapies in the second-line treatment for recurrent endometriosis

symptoms, as informed by expert opinion.¹⁴ In the model, these percentages represent the proportion of therapies within the weighted basket. However, the “distribution” of therapies patients receive in the model during the subsequent medical treatment is a weighted distribution based on the data from Table 42 of the CS. It is dependent on the treatment previously received by the patient, and the health-state they are currently in, as presented in Table 81 of the CS. It was assumed that patients with the previous GnRH agonist treatment would not be prescribed this treatment again (in line with clinical expert opinion).² The same assumption was applied to treatment with GnRH antagonists.

Table 11: “Distribution” of medical therapies utilised in different health-states

Therapy	Other medical treatment		Laparoscopy #1 waiting		Post-laparoscopy #1 and Post-laparoscopy #2	
	Previous treatment		Previous treatment		Previous treatment	
	GnRH antagonists	GnRH agonists	GnRH antagonists	GnRH agonists	GnRH antagonists	GnRH agonists
LNG-IUS	22%	32%	0%	0%	0%	0%
NSAIDs/Painkillers	5%	7%	26%	33%	13%	20%
Common oral Contraceptives	7%	10%	20%	26%	21%	32%
Oral progestogen	9%	12%	20%	26%	18%	27%
Synthetic steroids	7%	10%	3%	4%	3%	5%
Aromatase inhibitors	7%	10%	2%	3%	3%	5%
GnRH agonists	43%	0%	28%	0%	33%	0%
GnRH antagonists	0%	20%	0%	7%	7%	11%

Abbreviations: GnRH, Gonadotropin-releasing hormone; LNG-IUS, levonorgestrel-releasing intrauterine system; NSAID, non-steroidal anti-inflammatory drug

Response B18b

The source is provided in the reference pack.

B 19. Priority question: On page 134 it is noted that the percentage of women discontinuing treatment due to pregnancy was estimated from the live birth rate in the UK. Please comment on the validity of this assumption. In your response, please explain why the birth rate of the general population would be applicable to a population with endometriosis.

The assumption to estimate the percentage of women discontinuing treatment due to pregnancy based on the live birth rate in the general UK population was made due to the absence of data on pregnancy rates for women with symptomatic endometriosis undergoing GnRH antagonist therapy. While the live birth rate in the general population may not fully reflect the population with symptomatic endometriosis, it serves as a proxy to address this parameter conservatively (the pregnancy rate is expected to be lower as compared with the percentage of women trying to get pregnant).

B 20. It is noted that some clinical parameters such as the response rate for laparoscopic surgery (informed from Johnson et al. 2004), the pain recurrence following surgery (informed from Vercellini et al. 2003), and disutility value for patients with infertility (informed from Relugolix NICE committee papers with the original source published in the 1990) are based on some relatively old studies. Please explain if there is a reason these studies were considered more appropriate over more recent ones.

Based on the SLR described in the Appendix M of the CS we have identified four studies that could potentially be used to inform response rates for laparoscopic surgery: Johnson et al. 2004, Sutton et al. 1994, Lalchandani et al. 2005 and Abbot et al. 2004 (Table 12).^{16–19} All four studies were incorporated into the cost-effectiveness model of the CS. The SLR did not identify more recent studies.

Johnson et al. 2004 were selected as the patient population, and the definition of response was most in line with the population and response rate considered for GnRH analogues. Based on Johnson et al. 2004 we utilised values for visual analogue scale (VAS) $\geq 50\%$ reduction in NMPP, as it was the highest value from all response endpoints reported in this study (which varied between 31.5–50%),

reflecting a conservative approach. In scenario analyses, we tested the response rate from Sutton et al. 1994, which was less preferred as the definition of response was based on any improvement on VAS (0–10), and the study population comprised women with pain *suggestive* of endometriosis. Lalchandani et al. 2005 was not selected as this study included women with minimal to moderate endometriosis and reported symptom-free outcomes. Abbot et al. 2004 was not selected as the response in this study was defined as any improvement in pain.

The response rates utilised in base case and scenario analysis also align with the expert's opinion.^{2,3}

Table 12: Studies including data on response rate with laparoscopic surgery

Study	Population	Intervention	Response definition	Time of response evaluation
Abbot 2004, UK ¹⁷	Thirty-nine women with histologically proven endometriosis; with all stages of endometriosis; UK - The James Cook University Hospital in Middlesbrough.	Excision of endometriosis by laparoscopy.	Any improvement in pain (assumed as result of VAS).	Not clear (assumed 6 months).
Lalchandani 2005, Germany ¹⁸	Women with minimal to moderate endometriosis.	Women in the surgical arm had either ablation or excision of all endometriotic lesions with HTC therapy.	Symptom-free	At the end of 12 months.
Sutton 1994, UK ¹⁹	Women seen in the gynaecological outpatient clinic with pain suggestive of endometriosis and had not received any treatment (medical or surgical) for endometriosis in the previous 6 months; minimal, mild, and moderate endometriosis. (AFS stages I to III)	Laser ablation of endometriotic deposits and laparoscopic uterine nerve ablation	Any improvement on VAS (0–10)	6 months
			Any improvement on VAS (0–10)	6 months
			Any improvement on VAS (0–10)	3 months
Johnson 2004, New Zealand ¹⁶	Endometriosis, a history of chronic pelvic pain (either	Surgery with and without LUNA.	Pelvic pain VAS (0–10 scale)	24 hours post-operative

Study	Population	Intervention	Response definition	Time of response evaluation
	dysmenorrhoea, NMPP, defecatory pain or deep dyspareunia for more than six months).		completely or partially resolved	
			VAS $\geq$ 50% reduction NMPP	3 months post-operative
			VAS $\geq$ 50% reduction NMPP	12 months post-operative
			VAS $\geq$ 50% reduction DYS	3 months post-operative
			VAS $\geq$ 50% reduction DYS	12 months post-operative

Abbreviations: AFS, American Fertility Society; DYS, dysmenorrhoea; LUNA, laparoscopic uterine nerve ablation; NMPP, non-menstrual pelvic pain; VAS, visual analogue scale, HTC - helium thermal coagulator;

Three studies were considered to inform pain recurrence following surgery: Vercellini et al. 2003, Shakiba et al. 2008 (found via SLR described in the Appendix M of the CS) and Soliman 2017 (found via SLR described in the Appendix G).^{15,20,21} Vercellini et al. was selected for a base case as the study population and reported outcomes were most comparable with the study population and outcomes applied for linzagolix. In addition, it was possible to digitise data from Kaplan–Meier curves presented in this study. Vercellini et al. reported a probability of recurrence of moderate to severe dysmenorrhea in patients who were undergoing first-line operative laparoscopy for symptomatic minimal to severe endometriosis and who reported pelvic pain of more than 6 months duration. The other studies reported reoperation free survival (Shakiba et al. 2008) or reoperation free survival or retreatment free survival (Soliman et al. 2017). We found these endpoints less accurate and incorporated data from Shakiba et al. 2008 for scenario analysis as it was possible to digitise it more accurately (in Soliman et al. 2017, curves are already smoothed, which makes it difficult to digitise and reconstruct properly).

We used the disutility value for patients with infertility based on the WHO report (2024²²) to maintain consistency with the relugolix STA. In the SLR described in Appendix H of the CS, we have found only one alternative source to inform this parameter, but due to a possible typographical error we have not used values presented in that source in the base case (Aubry et al. 2017²³). We tried to contact the authors for a second time but did not receive any response.

B 21. Section 3.4.4. focuses on the adverse events (AEs), also referred to as adverse reactions, associated with linzagolix and its comparator, which were included in the scenario analyses. As shown in Table 61, the incidence of these AEs (depression, headache, hot flushes, and increased blood pressure) was set to 0.0% for linzagolix, based on data from the EDELWEISS 3 trial. Please clarify the rationale for this assumption, as information in the clinical effectiveness section (Section B.2.10) suggests that these adverse reactions do indeed occur in patients treated with linzagolix. For that matter, while depression and increased blood pressure were among the adverse reactions included in the cost-effectiveness model, they appear not to be recorded as adverse reactions in the clinical effectiveness section of the CS (which does mention “mood swings”).

In accordance with the applied methodology (Section B.3.4.3 of CS), the cost-effectiveness model included only severe adverse events (grade 3 or higher). As mentioned in Section B.2.10.2 of the CS, most treatment-emergent adverse events (TEAEs) during the EDELWEISS 3 study were mild or moderate in intensity, and the incidence of severe TEAEs was low and comparable between groups (Placebo: 1 severe TEAE; linzagolix 200 mg plus ABT: 2 severe TEAE). For this reason, it was decided to use data on adverse events from the NICE STA for relugolix and include them in the model exclusively for scenario analysis, in which probabilities of such events for linzagolix were set to be 0. Due to generally low instances of severe AEs during endometriosis treatment with GnRH analogues, its inclusion has a very limited influence on the cost-effectiveness model results.

B 22. In the model, on sheet ‘efficacy’, cells D14 and E14 add to PR+CR=69.75%, and cells D15 and E15 to 46.29%, respectively. However, Figure 9 of the CS shows these results as 72.9% and 47.3% respectively. Please explain this discrepancy.

In the model, on sheet ‘efficacy’, cells D14 and E14, and D15 and E15 were informed by individual patient-level data, whereas Figure 9 of the CS represents the estimated proportions of responders according to logistic regression analyses (based on the overall baseline pain score). Therefore, such a slight discrepancy (~1% and ~3%, respectively) is possible. To ensure that this discrepancy is solely due to the

method of deriving the data, the exact numbers of responders for dysmenorrhoea and NMPP and the total number of patients evaluated for the endpoints were cross-checked with the EDELWEISS 3 clinical study report (CSR). The only identified difference was the inclusion of the number of missing patients (n=6, these were not excluded from the total evaluated patients number in the model / denominator) as part of the total dataset and no errors were identified.

Health-related quality of life

B 23. Priority question: It is stated that since HRQoL data were extracted from EDELWEISS 3 rather than EDELWEISS 6 (due to the possible attrition bias), and therefore the values obtained from EDELWEISS 6 were not described.

- a) Please provide a detailed explanation of the “possible attrition bias” argument.**
- b) Please provide a detailed description of the EDELWEISS 6 HRQoL data.**

Response B23a

Patients who completed the six-month treatment period in the EDELWEISS 3 study were invited to enter the EDELWEISS 6 extension study. The primary objective of EDELWEISS 6 was to assess the maintenance of efficacy of linzagolix for up to an additional six months (up to 12 months of treatment in total) in women who had already completed six months of linzagolix treatment at a dose of 75 mg alone or 200 mg plus ABT in EDELWEISS 3. As a result, the population of EDELWEISS 6 consisted of patients who had already experienced six months of treatment with linzagolix and chose to continue. Specifically, there is a potential risk, that patients who did not perceive therapeutic benefits or who experienced the AEs during the initial six months were less likely to enroll in the extension study. Consequently, EDELWEISS 6 might represent a population with more favourable responses to linzagolix, leading to an overestimation of its impact on health-related quality of life. Examining the HRQoL data from EDELWEISS 3 and EDELWEISS 6 underscores the potential impact of attrition bias in the extension study. The mean changes from

baseline to month 6 in the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) index scores reveal that patients in EDELWEISS 6 exhibited greater improvements compared with those in EDELWEISS 3 (Table 13).

Table 13: Change from baseline to month 6 in EQ-5D-5L index in EDELWEISS 6 and EDELWEISS 3 studies

	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
Baseline, mean (SD)	0.73 (0.16)	0.71 (0.18)	0.72 (0.17)	0.74 (0.15)
Change from baseline to month 6, mean (SD)	0.08 (0.19)	0.07 (0.19)	0.12 (0.18)	0.14 (0.18)
	EDELWEISS 3			
	Placebo (N=162)		Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)
Baseline, mean (SD)	0.72 (0.16)		0.74 (0.16)	0.74 (0.15)
Change from baseline to month 6, mean (95% CI)	0.08 (0.06; 0.10)		0.09 (0.07; 0.11)	0.11 (0.09; 0.13)

Abbreviations: ABT, add-back therapy; CI, confidence interval; EuroQoL 5-Dimension 5-Level; SD, standard deviation

To mitigate the influence of attrition bias on our CE model, we adopted a conservative approach by utilising HRQoL data from EDELWEISS 3. This study includes the broader initial patient population, encompassing both responders and non-responders to the treatment, thereby providing a more balanced and unbiased dataset. By using data from EDELWEISS 3, we aim to ensure that our regression model accurately reflects the real-world effectiveness of linzagolix without the skewing effects that could arise from the selective continuation of patients in EDELWEISS 6.

Response B23b

HRQoL data for EDELWEISS 3 and EDELWEISS 6 are presented in section B.2.6.2.4. of the submission dossier. The focus is on EDELWEISS 3 data (Table 17 of Document B) but we note that improvements continued during EDELWEISS 6. Data for EHP-30 pain dimension from EDELWEISS 6 are presented in Table 13 of Document B along with other pain and analgesia secondary endpoints. A table of further HRQoL data from EDELWEISS 6 is presented in Table 14.

Table 14: EDELWEISS 6 | Change from baseline in health-related quality of life (TEAS)

	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
EHP-30 Pain^a				
Baseline, mean (SD)	50.56 (15.40)	52.92 (13.45)	51.83 (14.30)	52.08 (15.00)
Change from baseline to month 12, mean (SD)	-29.68 (20.91)	-33.04 (21.69)	-31.65 (22.88)	-41.89 (20.21)
EHP-30 Control and powerlessness^a				
Baseline, mean (SD)	58.63 (19.60)	62.80 (16.05)	58.12 (19.76)	60.90 (19.24)
Change from baseline to month 12, mean (SD)	-33.01 (25.11)	-39.98 (23.39)	-34.98 (29.24)	-48.28 (22.86)
EHP-30 Emotional wellbeing^a				
Baseline, mean (SD)	45.18 (17.71)	50.74 (19.53)	48.61 (19.40)	46.39 (20.17)
Change from baseline to month 12, mean (SD)	-23.48 (21.58)	-21.88 (22.89)	-24.41 (27.24)	-27.24 (24.62)
EHP-30 Social support^a				
Baseline, mean (SD)	44.63 (25.12)	51.23 (24.61)	47.01 (24.81)	44.17 (24.42)
Change from baseline to month 12, mean (SD)	-20.79 (27.19)	-26.44 (29.31)	-23.64 (28.82)	-30.90 (25.27)
EHP-30 Self-image^a				

Baseline, mean (SD)	39.91 (25.58)	48.36 (26.66)	43.59 (23.14)	41.60 (25.22)
Change from baseline to month 12, mean (SD)	-16.03 (25.66)	-25.96 (28.71)	-19.65 (29.21)	-25.15 (28.66)
EHP-30 Modular sexual relationship^a				
Baseline, mean (SD)	54.94 (28.20)	57.34 (23.73)	53.98 (25.42)	58.72 (23.73)
Change from baseline to month 12, mean (SD)	-24.88 (28.06)	-33.54 (26.18)	-30.15 (29.06)	-36.90 (27.13)
EQ-5D-5L Index value^b				
Baseline, mean (SD)	0.73 (0.16)	0.71 (0.18)	0.72 (0.17)	0.74 (0.15)
Change from baseline to month 12, mean (SD)	0.14 (0.20)	0.14 (0.18)	0.14 (0.18)	0.17 (0.19)
EQ-5D-5L VAS score^c				
Baseline, mean (SD)	59.0 (20.6)	61.0 (21.4)	61.7 (20.1)	60.7 (19.6)
Change from baseline to month 12, mean (SD)	18.2 (22.6)	14.8 (21.7)	13.5 (25.5)	18.0 (30.0)

Abbreviations: ABT, add-back therapy; EHP-30, Endometriosis Health Profile-30; EQ-5D-5L: EuroQoL 5-Dimension 5-Level; SD, standard deviation; TEAS, Treatment Extension Analysis Set; VAS, visual analogue scale.

^aEHP-30 Scale Score was computed as the sum of each scale question score/(number of items*4)*100 and ranges from 0 (best possible health status) to 100 (worst possible health status).

^bThe index score ranges from -0.109 to 1. A higher Index value indicates a better quality of life.

^cThe VAS Score ranges from 0 to 100. A higher VAS score indicates a better quality of life.

Source: EDELWEISS 6 CSR (data on file)²⁴

B 24. Priority question: In the model, it is not feasible to switch to all the regression models for the estimation of quality of life utilities. Furthermore, a regression model that excludes any covariates except for the different health states have not been described in the CS and the model.

- a) Please also perform a regression analyses excluding any other covariates except the covariates for the health states and the report the AIC and the BIC for these models. Please also include that regression model in the electronic model.

- b) Please add the other regression models to the model, to enable the EAG to explore the impact of the other regression models

As agreed with NICE during the clarification meeting (21.11.2024), a response to this question will be supplemented by 10th December 2024.

B 25. Priority question: On page 143 of the CS, it is stated that the baseline observations were excluded from response regression models because patients in the no-response state showed higher utility values at the 3-month mark compared with baseline. At the other hand, it is shown in Table 50 of the CS that base EQ-5D-5L is associated with higher utility score.

- a) Please reflect on the validity of excluding base EQ-5D-3L although it is associated with a better HRQoL at later time points
- b) Please also include base EQ-5D-3L as covariate in the quality of life regression models and allow the use of these regression models in the estimation of health-related quality of life utilities.

As agreed with NICE during clarification meeting (21.11.2024), a response to this question will be supplemented by 10th December 2024.

B 26. Priority question: Section B.3.4.1.4 presents alternative response-based models used to health state utilities in the scenario analysis. The models incorporated observations from month 3 and 6, and baseline data.

- a) Please clarify which observations were included in the baseline data. On page 140 of the CS, it is stated that EQ-5D was collected at day 1, month 1, month 3 and month 6. Does the baseline data contain data from both day 1 and month 1?
- b) Table 57 shows that the alternative models produced a significantly lower utility value compared to the base case model (0.661 vs 0.713) for the non-response health state. This was due to the fact the non-response state values were primarily derived from baseline observations including patients who had not yet begun treatment. It

would be expected the change for the severe pain health state to go in the same direction. However, scenario analysis produced a higher utility value for the severe pain health state as compared to the base case model (0.554 vs 0.477). Please justify why the scenario analysis led to an increase in the utility of patients in the severe health state, while led to a decrease in the utility value for the non-response health state.

Response 26a

Baseline data contain data from day 1.

Response B26b

Scenarios were built based on methodological consistency. The base case scenario includes two regression models that do not include baseline observations, as they are irrelevant for treatment outcomes (patients at month 3 or 6 are assumed to be different vs patients at baseline). The second scenario includes two regression models which do include baseline observations as relevant for the analysis outcomes (only response status or severity is relevant). The difference can be explained with the following justification:

- In the response model in the base case we utilised 3 and 6 months data only, where the patients' response status was known. In scenario analysis, we additionally assumed that all patients at baseline were non-responders. It is possible that some of these patients had relatively high utility values at baseline and these patients also responded to treatment and subsequently transferred to response health (as baseline utility was found predictive of the future utility value under response).
- In the pain model in base case we utilised data set with sixmonths observations only. It is possible that only the most severe and resistant patients remained in this health-state after the treatment with linzagolix, as compared with the full data set utilised in the scenario analysis;

B 27. Priority question: On page 158 of the CS, it is noted that according to clinical expert opinion, patients wanting to conceive can stop medical

therapy at any time. For this reason, there was no disutility assumed due to infertility whilst on therapy.

a) Please comment if this approach may be neglecting the trade-off in quality of life that some patients may encounter when they must decide on the management of endometriosis symptoms as compared to their child wish, which is inhibited by the medical treatment.

b) Please add a scenario to the model that includes a disutility for infertility whilst on therapy.

Response B27a

The potential trade-off in quality of life for patients managing endometriosis symptoms while considering their fertility aspiration is an important consideration. However, in the case of medical therapy, which is often the therapy of choice, alternative options for patients who wish to conceive (i.e., laparoscopic surgery) are available and may mitigate this trade-off.

This trade-off in quality of life particularly affects patients with a long treatment history, for whom subsequent therapies may no longer represent a treatment of choice but rather the only remaining option. However, such patients are generally not treated with medical therapy but are instead referred for radical surgical interventions.

The model accounts for the disutilities experienced by patients most significantly affected by this trade-off. The first group, considered in the base case, comprising patients who have undergone radical surgeries, experiences a reduction in quality of life due to the inability to conceive following such procedures. The second group, consisting of patients in more pretreated health-states with limited remaining treatment options (post-laparoscopy states and other medical treatment) who must decide between managing endometriosis symptoms and preserving their fertility aspirations, was represented in one of the scenarios where infertility-related disutility was incorporated into the quality of life for patients undergoing medical therapies.

Response B27b

As utility values were calculated on the data set from the linzagolix study EDELWEISS 3, adding additional infertility disutilities to patients in health states where pharmacological treatment is used (especially while patients are on linzagolix therapy) does not feel justifiable.

We suggest another scenario be considered to address remaining uncertainties, where no infertility disutility is applied in any health-state. The results for such a scenario are presented in Table 15 and Table 16.

Table 15: Scenario results without application of infertility disutilities to any of health-states

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Linzagolix 200 mg plus ABT	14,897	11.76	9.52	-	-	-	-
Leuprorelin	12,646	11.76	9.22	2,252	0.00	0.29	7 722
Surgery	14,476	11.76	8.93	421	0.00	0.59	719
Relugolix	14,897	11.76	9.52	£835	0.00	0.00	Dominated

Abbreviations: ABT, add-back therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Table 16: Scenario results with the application of infertility disutilities to all health-states

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Linzagolix 200 mg plus ABT	14,897	11.76	8.27	-	-	-	-
Leuprorelin	12,646	11.76	8.05	2,252	0.00	0.22	10 175
Surgery	14,476	11.76	7.66	421	0.00	0.61	693
Relugolix	14,897	11.76	8.27	£835	0.00	0.00	Dominated

Abbreviations: ABT, add-back therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

B 28. Priority question: Please provide a scenario analysis in which the quality of life utilities were based upon the observed utility values of the EDELWEISS 3 trial.

Response B28

As agreed with NICE during the clarification meeting (21.11.2024), a response to this question will be supplemented by 10th December 2024.

B 29. Priority question: Please provide the input and source used to inform the proportion of patients who wish to preserve fertility.

This value was sourced from Theramex Data on File: Endometriosis Market Research Survey for Yselty®¹⁴ (factors determining initial treatment choice: Top 2: 'Wish for bearing child' - 63% of respondents ranked it in their top 2 factors).

B 30. On page 142 of the CS, it is stated that linear mixed-effects regression models were utilised if more than one measurement was available. This statement implies that linear mixed-effects models are not used in all circumstances.

- a) Please confirm that this statement relates to the univariate analyses for which the results are shown in Table 50 of the CS**
- b) Please indicate whether there were circumstances in which only one measurement was available and which analyses were performed in those circumstances.**

Response B30a

Yes, linear regression model applies to Table 50 of the CS (univariate analysis results) and the pain-based model in the base case scenario (regression model 1) as it was built with only month 6 observations (one observation per patient).

Response B30b

There were no such circumstances in which only one measurement was available.

B 31. Please provide a justification for the calculation of the utility scores for the other medical treatment and surgery treatment health states. How valid is the use the average utility scores of health states from which patients can transition to those states? Patients transition to another health state because the symptoms deteriorates or don't improve, wouldn't that mean that the quality of life utility also deteriorates?

The calculations of utility scores for other medical treatment and surgical treatment health states were designed to capture the quality of life implications for patients undergoing specific medical interventions while aligning well with data from the literature. The use of average utility scores of health-states from which patients transition to other medical treatment and surgery treatment states reflects the range of symptom severity and outcomes experienced by patients on subsequent therapy. Although transitions often occur due to symptom deterioration or lack of therapeutic effect, the methodology accounts for this by incorporating lower utility values from severe and no-response health states into the average. This approach aligns with established frameworks, such as the one described by Wang et al., 2019.²⁵ Applying this approach, patients who are more pretreated have lower quality of life as compared to patients responding to initial treatments.

Resource use and costs

B 32. Priority question: Table 45 describes the distribution of procedures for patients having laparoscopic or radical surgery. Please provide more details on the source used to inform these inputs. Please also explain why the % of laparoscopic excision and ablation as well as the % of hysterectomy and oophorectomy do not add to 100%. What are the remaining procedures that were not considered in this analysis?

The source for Table 45 was the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report Endometriosis: A Long and Painful Road – A review of the quality of care provided to adult patients diagnosed with endometriosis (2024)¹²

for the distribution of laparoscopic procedures, and Theramex Data on File: Endometriosis Market Research Survey for Yselt[®] (Linzagolix)¹⁴ for radical (hysterectomy and oophorectomy) surgeries. The percentages in this table represent the proportions of patients who underwent specific surgical procedures and are used as inputs in the model. The calculation formula for the costs of these surgeries is divided by the sum of the proportions, meaning that the proportions do not need to sum to 100%. No additional procedures for either conservative or radical surgeries were included in the analysis beyond those mentioned in Table 45 of CS.

B 33. For GnRH agonist treatments, the additional cost of an outpatient visit to a gynaecologist for IUD implementation is included in the model. Please explain if these additional costs apply to all patients on GnRH agonist treatment.

This cost is applied only to patients treated with levonorgestrel-releasing intrauterine system (LNG-IUS) in the 'Other medical treatment' health state. It is not applied to patients treated with GnRH agonists.

B 34. The costs of all adverse events included in the scenario analysis (i.e., headache, hot flushes, depression, and increased blood pressure) were set at £49.00, based on the assumption that these adverse events resulted in one 10-minute consultation with a healthcare professional (Table 77 of the CS). Please substantiate this assumption, as this seems quite a low estimate of the healthcare resource use resulting from (some of) these adverse events, and consider varying this in a sensitivity analysis. (Of note, the cost price of £49.00 was already varied in the one-way sensitivity analysis.)

Due to generally low instances of severe adverse events during endometriosis treatment with GnRH analogues, its inclusion has a very limited influence on the cost-effectiveness model results. For this reason, adverse events were included only in scenario analyses. As it does not significantly impact the results, changing the service (and costs) of adverse event management would not influence the results significantly.

Validation

B 35. On page 117 it is stated that “the model structure is based on reviews of the study designs for EDELWEISS 3, as well as prior economic models for the treatment of symptomatic endometriosis identified through a targeted literature review and established clinical practice guidelines”. Please specify which elements of the model structure were used from other cost-effectiveness studies, which elements were adjusted, and why.

The conceptual structure of the cost-effectiveness model for linzagolix was primarily based on two key sources: the NICE STA for Relugolix and the publication by Wang et al., 2019, identified during a systematic review of other economic evaluations. The comparison of the key model concepts between these two models and the cost-effectiveness model developed for linzagolix is presented in Table 17.

Table 17: Comparison of Linzagolix model with other cost-effectiveness studies

Model concept	NICE STA Relugolix	Wang et al., 2019	Linzagolix model
Framework	Semi-Markov cohort model simulating progression in women with endometriosis symptoms treated with Relugolix-CT and comparator (GnRH agonists).	Markov model with health-state transitions assessing cost-effectiveness of relugolix versus leuprolide acetate in moderate-to-severe endometriosis pain.	Semi-Markov cohort model with initial decision tree simulating progression in women with endometriosis symptoms treated with linzagolix and comparator (GnRH agonists and laparoscopic surgery).
Health-states	Twelve health states representing responses to either medical or surgical interventions.	Twelve health states, including three on-treatment (no/mild, moderate, severe symptoms), off-treatment,	Seventeen ¹ distinct health states that reflect the varied responses to both

¹ Including one tunnel state with three sub-states.

Model concept	NICE STA Relugolix	Wang et al., 2019	Linzagolix model
		surgical states, and mortality.	medical therapies and surgical interventions.
Time horizon	16 years, reflecting expected time until menopause in the UK.	1 or 2 years, reflecting the treatment duration and immediate impact of interventions.	15.1 years, reflecting expected time until menopause in the UK.
Cycle length	3 months	3 months	3 months for initial decision tree; 6 months in Markov chain
Patient population	Adult women with moderate to severe endometriosis-related pain, as represented in the SPIRIT trials.	Premenopausal women aged 18–49 years with moderate-to-severe endometriosis pain based on Elaris EM-I and EM-II trials.	Premenopausal women with a history of previous medical or surgical treatment for their endometriosis as represented in EDELWEISS 3/6 trials
Discontinuation rates	Uniform rates across treatments, except for GnRH agonists, capped at 1 year.	Treatment-specific premature discontinuation rates derived from Phase III trials; e.g., 11.3% for relugolix 150 mg and 12.3% for relugolix 200 mg.	Uniform rates across treatments, except for GnRH agonists, capped at 1.5 year.
Analgesic use	Assumed similar for all patients, whether on Relugolix-CT, GnRH agonists, or after surgery. Proportion of patients	Not explicitly modeled; assumed similar use across treatments.	Assumed similar for all patients, whether on linzagolix, GnRH agonists, or after surgery. Proportion of patients using

Model concept	NICE STA Relugolix	Wang et al., 2019	Linzagolix model
	using analgesics based on SPIRIT trials.		analgesics based on SPIRIT trials
Bone mineral density	Stable BMD across treatments, with add-back therapy mitigating BMD loss for Relugolix-CT and GnRH agonists.	BMD loss not explicitly modelled but assumed negligible fracture risk over 1–2 years; partial recovery observed post-treatment.	Stable BMD across treatments, with add-back therapy mitigating BMD loss for linzagolix and GnRH agonists.
Treatment duration	Relugolix-CT is assumed to continue until menopause or discontinuation, while GnRH agonists are limited to 12 months.	Elagolix: up to 24 months for 150 mg or 6 months for 200 mg; leuprolide acetate: 12 months with add-back therapy for the last 6 months.	Linzagolix is assumed to continue until menopause or discontinuation, while GnRH agonists are limited to 18 months.

Abbreviations: BMD, bone mineral density; GnRH, gonadotropin-releasing hormone; relugolix CT, Relugolix combination therapy (relugolix-oestradiol-norethisterone acetate); STA, single technology appraisal

Electronic model

B 36. On sheet ‘Controls’, rows 67, 68, 72 and 73, changing the user defined value has no impact on the results. What setting in the model needs to be changed in order to use the user defined values for the calculation of the results?

In the electronic model, user-defined values are entered in dedicated tabs, while the Controls tab only displays these values. Specifically:

- 1) Infertility disutility (Controls, row 67) is defined by entering a value in the Utility values tab (cell C29);
- 2). The percentage of patients affected by infertility disutility (Controls, row 68) is defined by entering a value in the Utility values tab (cell C32);

3). Laparoscopy complications disutility (Controls, row 72) is defined by entering a value in the Utility values tab (cell C39);

4) Hysterectomy/bilateral oophorectomy complications disutility is defined in the Utility values tab (cell C36).

We acknowledge that this setup may not feel entirely intuitive. However, it reflects the principle of keeping user-defined values related to utility in the Utility values tab, thereby maintaining the Controls tab in a more streamlined and readable format.

Section C: Textual clarification and additional points

C 1. Table 46 of the CS presents the discontinuation rates that were used in the electronic model for the alternative health states. The rate for the no Pain/mild and moderate health-states is set at 3.03%. However, on the “efficacy” sheet of the electronic model this value was set at 6.45% for in the leuprorelin, while the value of 3.03% is used for other GnRH agonists. Please comment if this an error in the electronic model or the CS document. Please correct the error if that pertains to the electronic model and provide updated results.

The values presented in Table 46 of the CS document are correct. However, a technical error was identified in the electronic model, specifically in the "efficacy" sheet, where the discontinuation rate for leuprorelin was erroneously displayed as 6.45%. Despite this, the correct value of 3.03% was applied in the calculations throughout the model. The error has been corrected, and the results were recalculated to confirm consistency. As expected, the corrected model produced identical results, and therefore no updates to the CS document were necessary. The revised model has been provided.

C 2. Table 63 of the CS defines the frequency of surgical complications. The impact on other organs for laparoscopic complications is set at 0% in Table 63, while the value is set at 3% in the electronic model. Please

explain which are correct, and if necessary, please provide a revised model and updated results

The value used in the electronic model (the frequency of the impact of laparoscopic surgery on other organ: 3%) is correct; however, corrections are required in Table 63 (Surgical complications frequency sourced from literature) and, consequently, in Table 78 (Complication probabilities) from the CS, where a similar error was identified. The corrected tables are provided below.

Table 18: Surgical complications frequency sourced from literature

Type of complication	Probability of complication – Base case analysis based on NICE STA Relugolix ⁸	Probability of complication – Scenario analysis based on literature and expert clinical opinion ^{3,26}
Laparoscopy complications (Laparoscopy #1 and Laparoscopy #2 health-states)		
Febrile event	0.00%	7.50%
Wound infection	0.00%	0.00%
Urinary tract infection	0.00%	5.00%
Impact on other organs	3.00%	0.00%
Fistula	0.00%	0.00%
Hysterectomy and oophorectomy complications (Radical surgery #1 and Radical surgery #2 health-states)		

Febrile event	0.00%	1.32%
Wound infection	0.00%	0.66%
Bleeding or hematoma	0.00%	0.66%
Ileus	0.00%	0.66%
Urinary retention	1.42%	0.66%
Urinary tract infection	1.42%	0.00%
Fistula	0.04%	0.00%
Impact on other organs	3.00%	0.00%
Anastomotic leakage	0.00%	10.00%

Abbreviations: STA, single technology appraisal

Table 19: Complication probabilities

Type of complication	Probability of complication – base-case analysis based on NICE STA Relugolix ⁸	Probability of complication – scenario analysis based on literature and expert clinical opinion ^{3,26}
Laparoscopy and ablation complications (Laparoscopy #1 and Laparoscopy #2 health-states)		
Febrile event	0.00%	7.50%
Wound infection	0.00%	0.00%
Urinary tract infection	0.00%	5.00%
Impact on other organs	3.00%	0.00%
Fistula	0.00%	0.00%
Hysterectomy and oophorectomy complications (Radical surgery #1 and Radical surgery #2 health-states)		

Febrile event	0.00%	1.32%
Wound infection	0.00%	0.66%
Bleeding or haematoma	0.00%	0.66%
Ileus	0.00%	0.66%
Urinary retention	1.42%	0.66%
Urinary tract infection	1.42%	0.00%
Fistula	0.04%	0.00%
Impact on other organs	3.00%	0.00%
Anastomotic leakage	0.00%	10.00%

Abbreviations: STA, single technology appraisal

C 3. Table 79 of the CS presents the costs for surgery-related complications. The values for the costs of the wound infection following laparoscopy and ablation and the respective costs following hysterectomy and oophorectomy are reversed in the electronic model. Please clarify what should be the correct cost value for wound infection for each type of surgery. Please explain which are correct, and if necessary, please provide a revised model and updated results.

The costs for surgery-related complications, specifically the costs of the wound infection following laparoscopy and ablation and the respective costs following hysterectomy and oophorectomy are correct in the electronic model. However the correction is required in Table 79 of the CS. The cost of wound infection for the laparoscopy procedure should be WH07G (Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1), while the costs for this particular complication following hysterectomy and oophorectomy should be the weighted average of codes: WH07A (Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+), WH07B (Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1), WH07C (Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+), WH07D (Infections or Other Complications of Procedures, with

Single Intervention, with CC Score 0-1), WH07E (Infections or Other Complications of Procedures, without Interventions, with CC Score 4+), WH07F (Infections or Other Complications of Procedures, without Interventions, with CC Score 2-3) , WH07G (Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1). The corrected table is presented below (Table 20).

Table 20: Complication costs

Type of complication	Unit cost per complication	Source
Laparoscopy and ablation complications (Laparoscopy #1 and Laparoscopy #2 health-states)		
Febrile event	£850.09	Code LA04S
Wound infection	£1,118.39	Code: WH07G
Urinary tract infection	£2,219.67	Weighted average of codes: LA04H, LA04J, LA04K, LA04L, LA04M, LA04N, LA04P, LA04Q, LA04R, LA04S
Impact on other organs	£1,159.31	Code: FE32Z, Non-Elective Inpatient - Long Stay
Fistula	£3,294.49	Code: YQ42Z
Hysterectomy and oophorectomy complications (Radical surgery #1 and Radical surgery #2 health-states)		
Febrile event	£850.09	Code: LA04S
Wound infection	£2,209.49	Weighted average of codes: WH07A, WH07B, WH07C, WH07D, WH07E, WH07F, WH07G
Bleeding or hematoma	£1,768.59	Weighted average of codes: WH07C, WH07D [
Ileus	£7,842.15	Weighted average of codes: FF33A, FF33B, FF34A, FF34B, FF34C
Urinary retention	£2,036.71	Code LA04Q
Urinary tract infection	£2,219.67	Weighted average of codes: LA04H, LA04J, LA04K, LA04L, LA04M, LA04N, LA04P, LA04Q, LA04R, LA04S
Fistula	£3,294.49	Code YQ42Z
Impact on other organs	£1,159.31	Code FE32Z, Non-Elective Inpatient - Long Stay
Anastomic leakage	£4,973.78	Weighted average of codes: WH07C, WH07D, WH07E, WH07F, WH07G

C 4. Table 61 of the CS presents an overview of the frequencies of adverse reactions. For GnRH agonists, these are set at 0.47%, 1.71%, 0.40%, and 0.24%, for depression, headache, hot flushes, and increased blood pressure, respectively. This does not correspond with the probabilities included in the electronic model, which are 0.40%, 0.47%, 1.71%, and 0.24% for depression, headache, hot flushes, and increased blood pressure, respectively. Please explain which are correct, and if necessary, please provide a revised model and updated results.

Two values for the frequencies of adverse reactions for GnRH agonists applied in the electronic model, namely: 0.47% for headache and 1.71% for hot flushes are not correct and have been changed according to values sourced from NICE STA Relugolix: 1.71%, and 0.47% for headache and hot flushes. Since the costs associated with adverse events are identical for the AEs which frequencies erroneously switched in the model (The cost for all included AEs was assumed to be the same as the cost of a general practitioner consultation), correcting these frequencies had no impact on the results. Therefore, there is no need to include recalculated model outcomes. The revised model has been provided. Table 61 has been also corrected (depression: changed for 0.40% and hot flushes changed for 0.47%). The values in table 76 from CS has been changed accordingly to the corrected model and table 61 from the CS. The revised tables in which values for Relugolix CT (not used in the model) were also revised and corrected are shown in Table 21 and Table 22.

Table 21: Frequency of adverse reactions sourced from the literature

AE	Linzagolix 200 mg plus ABT	Source	Relugolix CT	Source	GnRH agonist	Source
Depression	0.00%	EDELWEISS 3; month 6	0.00%	NICE STA Relugolix ⁸	0.40%	NICE STA Relugolix ⁸
Headache	0.00%		1.67%		1.71%	
Hot flushes	0.00%		0.24%		0.47%	

AE	Linzagolix 200 mg plus ABT	Source	Relugolix CT	Source	GnRH agonist	Source
Increased blood pressure	0.00%		0.24%		0.24%	

Abbreviations: ABT, add-back therapy; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate); STA, single technology appraisal

Table 22: Adverse events probabilities

Adverse event	Probabilities				
	Linzagolix 200 mg plus ABT	Relugolix CT	Leuprorelin acetate	Goserelin	Triptorelin
Headache	0.00%	1.67%	1.71%	1.71%	1.71%
Hot flush	0.00%	0.24%	0.47%	0.47%	0.47%
Depression	0.00%	0.00%	0.40%	0.40%	0.40%
Increased blood pressure	0.00%	0.24%	0.24%	0.24%	0.24%

Abbreviations: ABT, add-back therapy; relugolix CT, relugolix combined therapy (relugolix-oestradiol-norethisterone acetate)

C 5. Table 87 of the CS provides an overview of the results of the scenario analyses. Regarding the scenario that adopts a 1.5 years time horizon, it is mentioned that linzagolix is “less costly, equal effective”. According to the electronic model, however (sheet “Scenario analysis”), linzagolix is “less costly and less effective” than leuprorelin in this scenario. Please explain this discrepancy.

The electronic model contained an error in which scenarios categorized as "less costly, equal effective" were incorrectly classified as "less costly and less effective." This issue was limited to the labelling of outcomes and did not affect the underlying results or calculations. The error has been corrected.

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**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Single technology appraisal

**Linzagolix for treating symptoms of
endometriosis**

[ID6357]

**Addendum to clarification response –
Comparison with relugolix**

03 December 2024

File name	Version	Contains confidential information	Date
[ID6357] Linzagolix Endometriosis – Addendum to clarification response 03Dec2024 [noCON]	1.0	No	03 December 2024

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Abbreviations

ABT	Add-back therapy
BMD	Bone mineral density
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
EAP	Endometriosis-associated pain
EHP-30	Endometriosis health profile-30
GnRH	Gonadotropin-releasing hormone
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
LYG	Life years gained
MAIC	Match-adjusted indirect comparison
NMB	Net marginal benefit
NMPP	Non-menstrual pelvic pain
NRS	Numeric rating scale
OPP	Overall pelvic pain
OWSA	One-way deterministic sensitivity analysis
PICOS	Population, intervention, outcomes, study design
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
Relugolix CT	Relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)
RoB 2	Risk-of-bias tool 2
SLR	Systematic literature review
STA	Single technology appraisal
TEAE	Treatment-emergent adverse event

1 Clinical effectiveness

1.1 Indirect treatment comparisons vs. relugolix combination therapy

In the absence of head-to-head data, an indirect treatment comparison (ITC) was performed using the Bucher analysis method to compare the efficacy and safety of linzagolix 200 mg plus add-back therapy (ABT) with relugolix 40 mg plus ABT (relugolix combination therapy [relugolix-oestradiol-norethisterone acetate] [relugolix CT]), a pharmacological comparator of relevance to the decision problem using published evidence from the clinical systematic literature review (SLR; see Section B.2.1 and Appendix D; an ITC comparing linzagolix and leuprorelin was presented in the company submission, section B2.9). The efficacy outcomes analysed in the ITC (Table 1) were based on those specified in the final scope issued by NICE and the availability of data reported in the literature.

Table 1: Outcomes assessed in the ITC for linzagolix 200 mg plus ABT vs. relugolix CT

Outcome	Analyses	Output statistics
Efficacy outcomes: • Dysmenorrhoea • NMPP • OPP • EHP-30 (pain dimension) Safety outcomes: • BMD at lumbar spine • BMD at total hip • TEAEs	Logistic regression	Risk difference, mean difference or odds ratios with 95% CIs

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; CI, confidence interval; EHP-30, Endometriosis Health Profile-30; ITC, indirect treatment comparison; NMPP, non-menstrual pelvic pain; OPP, overall pelvic pain; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate); TEAE, treatment-emergent adverse event.

1.1.1 Identification and selection of relevant studies from the clinical SLR

As described in Section B.2.1 and Appendix D, an SLR was conducted in September 2024. Of the 22 studies identified for the intervention (n=2) and comparators (n=20), only two studies relating to linzagolix and relugolix CT were eligible according to the

scope for this submission. The population, intervention, outcomes, study design (PICOS) criteria used for the ITC are presented in Appendix D.

1.1.2 Risk of bias

The methodological quality of each trial was assessed independently by two reviewers using the Cochrane Collaboration's revised risk-of-bias tool for randomised trials (RoB 2).¹ Disagreements were resolved by consensus. The risk of bias was defined as low for all the trials included in the Bucher analysis. Further details can be found in Appendix D.

1.1.3 Overview of the selected studies

The SLR identified the EDELWEISS² and EDELWEISS 3³ studies for linzagolix in endometriosis-associated pain (EAP) and 20 comparator trials (described in 18 publications). The studies considered to be suitable for inclusion in the ITC Bucher analysis are presented in Table 2.

The SLR for the comparators searched for trials that could be compared with the trials found in the review for the intervention (linzagolix 200 mg plus ABT). Therefore, only studies with 12 or 24 weeks of follow-up were included in the ITC for the efficacy analysis. Safety was assessed using the longest available follow-up period of 24 weeks.

Although two linzagolix studies (EDELWEISS 3, EDELWEISS) were identified from the SLR, only the EDELWEISS 3 trial was included in the ITC. The EDELWEISS study² was a dose-ranging phase 2b study that included a dose of linzagolix 200 mg alone (without ABT) and was not included in the ITC for the efficacy analysis due to a lack of alignment of clinically relevant endpoints for inclusion in the treatment comparison. In addition, safety in the EDELWEISS study was only assessed for 12 weeks, so this study could not be included in the ITC for the safety analysis.

Reasons for exclusion of other studies from the ITC included: comparator therapy not relevant to the scope of this submission; no placebo group for comparison with the

intervention arm; data displayed only graphically, without detailed breakdown for analysis; outcomes data did not include standard deviation/standard error; lack of clarity of scale used. Further details regarding the rationale for inclusion/exclusion of individual comparator trials on the basis of heterogeneity can be found in Appendix D.

Table 2: Trials included in the Bucher analysis

Study name	Intervention	N	Phase	Study design
EDELWEISS 3 (Donnex et al 2024) ³	Linzagolix 200 mg plus ABT Placebo	162 162	3	RCT, double-blind, placebo-controlled, parallel-group, multi-centre, multinational study
SPIRIT 1 (Giudice et al 2022) ⁴	Relugolix 40 mg plus ABT in fixed combination (relugolix CT) Placebo	212 212	3	RCT, double-blind, placebo-controlled, multi-centre, multinational study
SPIRIT 2 (Giudice et al 2022) ⁴	Relugolix 40 mg plus ABT in fixed combination (relugolix CT) Placebo	206 204	3	RCT, double-blind, placebo-controlled, multi-centre, multinational study

Abbreviations: ABT, add-back therapy; RCT, randomised controlled trial; relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)

1.1.4 Heterogeneity assessment of trials included

Consistently reported inclusion/exclusion criteria were age, diagnosis of endometriosis, menstrual cycle, presence of dysmenorrhoea and pelvic pain, history of surgery, and need for treatment.

No trials were excluded from the Bucher analysis because of their inclusion/ exclusion criteria. The effect of different inclusion/exclusion criteria was assessed by reviewing the baseline characteristics. The included trials used similar inclusion criteria for age, endometriosis diagnosis and interval between menstrual cycles. Although the trials all included adult premenopausal women with moderate to severe endometriosis-associated pain (EAP) as measured by dysmenorrhoea and non-menstrual pelvic pain (NMPP), the scales used to measure dysmenorrhoea and NMPP scores differed between trials. The heterogeneity assessment confirmed the feasibility of an ITC

between linzagolix vs. relugolix CT. Further details regarding heterogeneity are presented in Appendix D.

1.1.5 Methods

An ITC was conducted using the Bucher method performed in R version 4.3.2. The Bucher method can only be applied to two-arm trials. The main assumption is that the relative efficacy of a treatment is the same in all trials included in the ITC to allow the indirect comparison of A vs. C when direct evidence of A vs. B and B vs. C is available.

The results of the included trials were analysed to determine whether it was possible to construct a network of relationships between the different arms of the trials. The methodology of each study and patient baseline characteristics were also analysed to identify differences between the trials that might impact the health outcomes. SPIRIT 1 and SPIRIT 2 were two replicate, phase 3 studies which evaluated similar endpoints over the same observation periods, had the same study design and included patients with similar baseline characteristics. It was, therefore, possible to perform a meta-analysis of the SPIRIT 1/SPIRIT 2 studies and to include the results of the meta-analysis in the ITC.

The EDELWEISS 3 linzagolix study and the relugolix CT studies SPIRIT 1 and SPIRIT 2 differed in their definitions of the co-primary efficacy endpoints dysmenorrhoea and NMPP, in terms of the rating scale used for the pain assessment (verbal rating scale vs. numeric rating scale), magnitude of significant clinical change and the assessment timepoint. Of note, the primary endpoint of EDELWEISS 3 was assessed at 3 months [week 12], whereas the primary endpoint of SPIRIT 1 and SPIRIT 2 was assessed at 6 months [week 24]; early pain control in patients is of utmost importance, hence the 3-month assessment was prioritised in the EDELWEISS studies. As patient-level data were available from the EDELWEISS 3 study, reconstruction of the endpoints was performed according to the definitions from the SPIRIT studies to reduce these differences and increase the ITC's validity. Logistic regression modelling was performed using the reconstructed endpoints to obtain outcomes (risk differences) to compare linzagolix with relugolix in an anchored ITC. As the SPIRIT and EDELWEISS 3 studies were generally well-balanced in terms of characteristics, an additional match-adjusted

indirect comparison (MAIC) was performed using the reconstructed endpoints as a sensitivity analysis. Non-inferiority was defined based on p-values of >0.05 for the ITC and >0.1 for the MAIC (to select prognostic factors or treatment effect modifiers), indicating no statistically significant difference between the treatments.

Detailed methods for the ITC are presented in Appendix D.

1.1.6 ITC results

1.1.6.1 Efficacy of linzagolix vs. relugolix CT

The ITC and MAIC revealed no significant difference between linzagolix 200 mg plus ABT and relugolix CT for efficacy at 24 weeks (Table 3 and Table 4).

Table 3: Bucher ITC for the efficacy of linzagolix 200 mg plus ABT vs. relugolix CT at week 24

Outcome	Linzagolix 200 mg plus ABT vs. placebo	Relugolix 40 mg plus ABT vs. placebo ^a	Indirect comparison	
	Risk difference (95% CI)		Risk difference (95% CI)	p-value
Dysmenorrhoea response (NRS)	0.52 (0.42, 0.6)	0.46 (0.4, 0.52)	0.06 (-0.05, 0.16)	0.28
NMPP response (NRS)	0.2 (0.1, 0.3)	0.21 (0.14, 0.28)	-0.01 (-0.13, 0.11)	0.87
	Mean difference (95% CI)		Mean difference (95% CI)	p-value
Dysmenorrhoea (NRS)	-3.5 (-4.08, -2.92)	-3.2 (-3.59, -2.81)	-0.3 (-1.00, 0.40)	0.40
NMPP (NRS)	-0.96 (-1.46, -0.46)	-0.8 (-1.19, -0.41)	-0.16 (-0.79, 0.47)	0.62
OPP	-1.2 (-1.7, -0.7)	-1.06 (-1.44, -0.68)	-0.14 (-0.77, 0.49)	0.66
EHP-30 pain dimension	-16.13 (-20.59, -11.67)	-13.62 (-17.05, -10.19)	-2.51 (-8.14, 3.12)	0.38

^aMeta-analysis of the SPIRIT 1 and SPIRIT 2 studies

Abbreviations: ABT, add-back therapy; CI, confidence interval; EHP, endometriosis health profile; ITC, indirect treatment comparison; NRS, numeric rating scale; OPP, overall pelvic pain; relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)

All outcomes showed no statistically significant difference between linzagolix vs. relugolix (p>0.05).

Table 4: MAIC for the efficacy of linzagolix 200 mg plus ABT vs. relugolix CT at week 24

Outcome	Linzagolix 200 mg plus ABT vs. placebo	Relugolix 40 mg plus ABT vs. placebo ^a	Indirect comparison	
	Risk difference (95% CI)		Risk difference (95% CI)	p-value
Dysmenorrhoea response (NRS) MAIC scenario 1	0.48 (0.38, 0.59)	0.46 (0.4, 0.52)	0.02 (-0.1, 0.14)	0.75
Dysmenorrhoea response (NRS) MAIC scenario 2	0.39 (0.22, 0.56)	0.46 (0.4, 0.52)	-0.07 (-0.25, 0.12)	0.45
Dysmenorrhoea response (NRS) MAIC scenario 3	0.39 (0.22, 0.57)	0.46 (0.4, 0.52)	-0.07 (-0.25, 0.12)	0.46
NMPP response (NRS) MAIC scenario 2	0.2 (0, 0.35)	0.21 (0.14, 0.28)	-0.01 (-0.19, 0.18)	0.92
Scenario 1 – based on treatment effect modifiers and prognostic factors identified by logistic regression or forest plots analysis <u>and</u> imbalance between the EDELWEISS 3 and the pooled SPIRIT 1 and SPIRIT 2 studies Scenario 2 – based on imbalance between the EDELWEISS 3 and the pooled SPIRIT 1 and SPIRIT 2 studies Scenario 3 – based on treatment effect modifiers and prognostic factors indicated within logistic regression or forest plots analysis <u>and</u> the parameter with the highest deviation - analgesic use at baseline (non-opioids use)				

^aMeta-analysis of the SPIRIT 1 and SPIRIT 2 studies

Abbreviations: ABT, add-back therapy; CI, confidence interval; MAIC, match-adjusted indirect comparison; NRS, numeric rating scale; relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)

All outcomes showed no statistically significant difference between linzagolix vs. relugolix (p>0.1).

1.1.6.2 Safety of linzagolix 200 mg plus ABT vs. relugolix CT

The safety of linzagolix 200 mg plus ABT was comparable to relugolix CT (Table 5). Although the ITC results indicate that adverse changes in lumbar spine bone mineral density (BMD) were statistically significantly increased with linzagolix vs. relugolix (Table 5), there was no significant difference between treatments for total hip BMD and the difference for lumbar spine BMD was not considered large enough to be clinically meaningful.⁵⁻⁹ It is likely that the lumbar spine BMD result was affected by differences in the placebo arms across both trials, which served as a reference point for the ITC. The least squares mean percentage change from baseline to month 6 (measured by dual-energy X-ray absorptiometry) in lumbar spine BMD was comparable for linzagolix 200 mg plus ABT (-0.80 in EDELWEISS 3¹⁰; Section B.10.8) and relugolix CT (-0.70 in

SPIRIT1, -0.78 in SPIRIT2⁴), however results for the placebo groups differed between the EDELWEISS 3 and SPIRIT studies (0.78 in EDELWEISS 3; 0.21 in SPIRIT1, 0.02 in SPIRIT2).

BMD was also assessed using Z-scores, which provide information on the BMD of the study population by comparing it with a reference group of women of the same age. In pre-menopausal women, Z-scores below -2.0 indicate a BMD 'below the expected range for age' and Z-scores above -2.0 indicate a BMD 'within the expected range for age'.⁵⁻⁹ In EDELWEISS 3, there was a greater numerical difference between mean lumbar spine Z-score at baseline in the linzagolix 200 mg plus ABT arm vs the placebo arm (0.25 vs 0.49, respectively; Section B.2.4.4), compared with smaller differences for relugolix CT vs. placebo groups in the SPIRIT1 and SPIRIT2 studies (0.17 vs 0.18, and 0.23 vs 0.35 for lumbar spine in SPIRIT1 and SPIRIT2, respectively).⁴

Further reassurance that the lumbar spine BMD changes observed under treatment with linzagolix 200 mg plus ABT are not clinically meaningful was provided from longer-term follow-up data after 12 months of treatment in EDELWEISS 6 which indicated that small fluctuations in the median Z-score values between baseline and month 12 were observed in all groups, with no defined pattern, and that minimum Z-scores at month 12 did not decrease below -2.0 at the lumbar spine, -1.4 at the femoral neck, and -1.5 at the total hip, femoral neck, and total hip (Section B.2.10.8). BMD Z-scores, therefore, remained 'within the expected range for age' despite 12 months of exposure to linzagolix 200 mg plus ABT. Median Z-scores at month 12 for the linzagolix 200 mg plus ABT group were 0.09 at the lumbar spine, -0.03 at the femoral neck and 0.03 at the total hip.

Table 5: Bucher ITC for the safety of linzagolix 200 mg plus ABT vs. relugolix CT at week 24

Outcome	Linzagolix 200 mg plus ABT vs. placebo	Relugolix 40 mg plus ABT vs. placebo ^a	Indirect comparison	
	Mean difference (95% CI)		Mean difference (95% CI)	p-value
Lumbar spine BMD	-1.58 (-2.12, -1.04)	-0.85 (-1.33, -0.37)	-0.73 (-1.45, -0.01)	0.048*
Total hip BMD	-0.69 (-1.14, -0.23)	-0.37 (-0.78, 0.03)	-0.32 (-0.93, 0.29)	0.30
	Risk difference (95% CI)		Risk difference (95% CI)	p-value
TEAEs	0.1 (-0.01, 0.21)	0.05 (-0.01, 0.11)	0.05 (-0.08, 0.18)	0.43
Severe TEAEs	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.04)	0 (-0.04, 0.04)	1.00
Serious TEAEs	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0 (-0.01, 0.03)	1.00
TEAEs leading to permanent discontinuation of study drug	0.01 (-0.03, 0.04)	0.02 (-0.01, 0.04)	-0.01 (-0.05, 0.03)	0.65
Incidence of hot flushes	0.04 (-0.002, 0.09)	0.05 (0.01, 0.09)	-0.01 (-0.07, 0.05)	0.75
Incidence of headaches	0.02 (-0.04, 0.09)	0.07 (0, 0.13)	-0.05 (-0.14, 0.04)	0.29

^aMeta-analysis of the SPIRIT 1 and SPIRIT 2 studies; *Lumbar spine BMD loss was statistically significantly greater with linzagolix vs. relugolix, although the difference between groups was not considered large enough to be clinically meaningful; all other outcomes showed no statistically significant difference between treatments (p>0.05). Abbreviations: ABT, add-back therapy; BMD, bone mineral density; CI, confidence interval; ITC, indirect treatment comparison; relugolix combination therapy (relugolix-oestradiol-norethisterone acetate); TEAE, treatment-emergent adverse event

1.1.7 ITC conclusions

The ITC and MAIC suggest no significant difference in efficacy between linzagolix 200 mg plus ABT and relugolix CT at week 24.

Although the ITC results indicate that adverse changes in lumbar spine BMD were statistically significantly increased with linzagolix vs. relugolix, it should be noted that the result was likely affected by the differences in the placebo arms across both trials as the

difference was not considered large enough to be clinically meaningful. There was no significant difference between these treatments for total hip BMD.

2 Cost effectiveness

2.1 *Economic analysis*

The patient population, model structure and features are identical to that described in the company submission, sections B3.2.1, B3.2.2 and B3.2.3.

2.1.1 Intervention and comparators

The intervention evaluated in the model is linzagolix 200 mg plus ABT, administered orally once daily. Linzagolix 200 mg is designed to address endometriosis symptoms by reducing EAP, while adding ABT preserves BMD. As a result, this regimen can be used continuously without a predefined treatment duration, except for cessation at the onset of menopause.

The comparators in the model are:

- Gonadotropin-releasing hormone (GnRH) agonists; with the licensed agents in the UK of leuprorelin acetate, goserelin, and triptorelin. All are administered via intramuscular or subcutaneous injection and are available monthly and three-monthly formulations. All GnRH agonists were assumed to have equal efficacy and safety [see company submission section B.2.9.7]
- Laparoscopic surgery (excision and ablation)
- Relugolix CT (40 mg relugolix, 1 mg oestradiol, and 0.5 mg norethisterone acetate), administered orally, once daily

2.2 *Clinical parameters and variables*

The clinical parameters are identical to those described in the company submission, section B3.3. Based on the results of the ITC, the efficacy of linzagolix and relugolix are assumed to be the same, therefore the probabilities used for relugolix in the model for response after 3 and 6 months, and transitions to and between pain-related health states are identical to those used for linzagolix and GnRH agonists (Table 6 to Table 8).

Similarly, the proportion of patients taking analgesics during relugolix treatment was assumed to be the same as with linzagolix and GnRH agonists (Table 9).

All other clinical parameters outlined in the company submission Document B, section 3.3, remain the same.

Table 6: Probabilities of response after three and six months

Response type	Linzagolix 200 mg plus ABT	GnRH agonist	Relugolix CT	Source
Complete response all patients after three months	38.27%	38.27%	38.27%	EDELWEISS 3, individual patient-level data
Partial response all patients after three months	39.51 %	39.51 %	39.51 %	
Complete response from partial response after six months	34.38%	34.38%	34.38%	
Partial response from partial response after six months	50.00%	50.00%	50.00%	

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

Table 7: Probabilities of transition to a specific pain state after 6 months

Transition	Linzagolix 200 mg plus ABT	GnRH agonist	Relugolix CT	Source
Complete response to no pain/mild	87.88%	87.88%	87.88%	EDELWEISS 6, individual patient-level data
Complete response to moderate	12.12%	12.12%	12.12%	
Complete response to severe	0.00%	0.00%	0.00%	
Partial response to no pain/mild	41.67%	41.67%	41.67%	
Partial response to moderate	58.33%	58.33%	58.33%	
Partial response to severe	0.00%	0.00%	0.00%	

Abbreviations: GnRH, gonadotropin-releasing hormone

Table 8: Probabilities of transitions between pain-related health states

Transition	Linzagolix 200 mg plus ABT	GnRH agonist	Relugolix CT	Source
No pain/mild to no pain/mild	94.52%	94.52%	94.52%	EDELWEISS 6, individual patient-level data
No pain/mild to moderate	5.48%	5.48%	5.48%	
No pain/mild to severe	0.00%	0.00%	0.00%	
Moderate to no pain/mild	31.03%	31.03%	31.03%	
Moderate to moderate	65.52%	65.52%	65.52%	
Moderate to severe	3.45%	3.45%	3.45%	

Abbreviations: GnRH, gonadotropin-releasing hormone

Table 9: Proportion of patients using analgesics during the treatment of linzagolix 200 mg plus ABT and comparators

Treatment	Before response	After response	Source
Linzagolix 200 mg plus ABT	90.00%	28.90%	NICE STA Relugolix ¹¹
GnRH agonist	90.00%	28.90%	
Surgery	90.00%	28.90%	
Relugolix	90.00%	28.90%	

Abbreviations: ABT, add-back therapy; GnRH, gonadotropin-releasing hormone; STA, single technology appraisal

2.3 Measurement and valuation of health effects

The methods and inputs for measuring and valuing health effects are identical to those described in the company submission section B3.4, except for the frequency of adverse reactions used in the scenario analysis (company submission section B3.4.4).

The frequency of adverse events (AEs) used in the scenario analysis were sourced from EDELWEISS 3 (for the intervention), and the Relugolix NICE appraisal (for GnRH agonists and relugolix CT; Table 10). This table has been updated versus the original CS based on the response to clarification question C4.

Table 10: Frequency of adverse reactions sourced from the literature

AE	Linzagolix 200 mg plus ABT	Source	Relugolix CT	Source	GnRH agonist	Source
Depression	0.00%	EDELWEISS 3; month 6	0.00%	NICE STA Relugolix ¹¹	0.40%	NICE STA Relugolix ¹¹
Headache	0.00%		1.67%		1.71%	
Hot flushes	0.00%		0.24%		0.47%	
Increased blood pressure	0.00%		0.24%		0.24%	

Abbreviations: ABT, add-back therapy; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate); STA, single technology appraisal

2.4 Cost and healthcare resource use identification, measurement and valuation

A cost and resources SLR was conducted to identify any relevant cost or healthcare resource use data relevant to the model. Full details of the SLR and results are presented in the company submission Appendix I.

The model includes several cost categories to reflect the key cost components related to drug therapies, surgical procedures, disease management, the natural course of pregnancy, and management of fertility issues in patients with endometriosis. These remain the same in the model, including relugolix, except the addition of drug acquisition costs for relugolix CT, as detailed below.

2.4.1.1 Drug acquisition costs

The costs of medical therapy (linzagolix 200 mg plus ABT, relugolix CT and GnRH agonists) were applied in model cycles relating to patients on treatment, i.e., within a decision tree in the initial response states and whilst in No pain/mild or Moderate pain states thereafter. The duration of therapy for the intervention and comparator was assumed to be fixed (1.5 years for GnRH agonists) or without restriction (linzagolix and

relugolix CT). Drug acquisition costs were not applied for treatment breaks (in the Off-treatment, No pain/mild and Pregnancy health-states).

A 50:50 split was assumed between patients treated with the short- (1-month) and long- (3-month) acting GnRH agonists - leuprorelin acetate, goserelin and triptorelin. This assumption was based on the equivalent parameter in the NICE STA for relugolix and indicated by expert opinion.^{11,12}

No wastage or compliance was considered in the base case analysis. However, compliance for linzagolix, relugolix CT and ABT for linzagolix was used in the scenario analysis, based on data from the EDELWEISS 6 study and relugolix CT long-term study.^{13,14}

The calculation of drug costs is shown in Table 11.

Table 11: Drug costs and dosing

Drug therapy	Cost per pack	Doses per package	Administrations		Cost per cycles	
			1&2	3+	1&2	3+
Linzagolix 200 mg	£80.00	28	91	183	£260.00	£522.86
Leuprorelin acetate, 1-month	£75.24	1	3	6	£225.72	£451.44
Leuprorelin acetate, 3-month	£225.72	1	1	2		
Other GnRH						
Goserelin, 1-month	£70.00	1	3	6	£222.50	£445.00
Goserelin, 3-month	£235.00	1	1	2		
Triptorelin, 1-month	£81.69	1	3	6	£226.04	£452.07
Triptorelin, 3-month	£207.00	1	1	2		
Relugolix CT	£72.00	28	91	183	£234.00	£470.57

Abbreviations: GnRH, gonadotropin-releasing hormone; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)

For relugolix CT, no administration cost was included as it is administered orally.

2.5 Summary of base-case analysis inputs

Table 12: List of additional parameters used in cost effectiveness model

#	Parameter label	Value	Distribution	Lower	Upper	Use in OWSA?	Use in PSA?
1	Partial responder's (DYS or NMPP) discontinuation rate between 3 rd and 6 th month relugolix %	0.0062	Beta	0.005022	0.00744	Yes	Yes
2	Complete responder's discontinuation rate between 3 and 6 months relugolix %	0.0123	Beta	0.010044	0.014878	Yes	Yes
3	Complete responder's discontinuation after 6 th month relugolix %	0.0303	Beta	0.024648	0.036514	Yes	Yes
4	Partial responder's discontinuation after 6 th month relugolix %	0	Beta	0	0	No	No
5	Maximum time of relugolix treatment (years)	15.1	N/A			No	No
6	Cost per relugolix administration	2.5714	Gamma	2.09222	3.09932	No	No
7	Compliance for relugolix	1	Gamma	0.81364	1.205289	No	No
8	relugolix - Probability of AE 1	0,0170	Beta	0	0	Yes	Yes
9	relugolix - Probability of AE 2	0,0024	Beta	0	0	Yes	Yes
10	relugolix - Probability of AE 3	0,0000	Beta	0	0	Yes	Yes
11	relugolix - Probability of AE 4	0,0024	Beta	0	0	Yes	Yes
12	relugolix - Probability of AE 5	0,0000	Beta	0	0	Yes	Yes
13	relugolix - Probability of AE 6	0,0000	Beta	0	0	Yes	Yes
14	relugolix - Probability of AE 7	0,0000	Beta	0	0	Yes	Yes
15	relugolix - Probability of AE 8	0,0000	Beta	0	0	Yes	Yes
16	relugolix - Probability of AE 9	0,0000	Beta	0	0	Yes	Yes

Abbreviations: AE, adverse event, DYS, dysmenorrhea, NMPP, non-menstrual pelvic pain; OWSA, one way sensitivity analysis; PSA, probabilistic sensitivity analysis

Parameters 1-4 and 8-16 are used in scenario analysis only. Other parameters in the model remained the same as outlined in the company submission, Appendix N.

2.5.1 Assumptions

Assumptions in the model remained the same as outlined in the company submission, section B.3.9.1.

2.6 Base-case results

2.6.1 Base-case incremental cost-effectiveness analysis results

The base-case cost-effectiveness model results are presented in Table 13 and Table 14. Compared with relugolix CT, linzagolix 200 mg plus ABT is associated with incremental costs of £835 and is therefore dominated.

Table 13: Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Linzagolix 200 mg plus ABT	14,897	11.76	9.33	-	-	-	-
Relugolix CT	14,062	11.76	9.33	835	0.00	0.00	Dominated*

Abbreviations: ABT, add-back therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

*Linzagolix was associated with additional costs and dominated by Relugolix CT

Table 14: Net marginal benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NMB at £20,000	NMB at £30,000
Linzagolix 200 mg plus ABT	14,897	9.33	-	-	-	-
Relugolix CT	14,062	9.33	835	0.00	0.00	-835

Abbreviations: ABT, add-back therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net marginal benefit; QALYs, quality-adjusted life years

2.7 Exploring uncertainty

Sensitivity analyses explored the underlying uncertainty in the base-case cost-effectiveness results. These include deterministic sensitivity analyses, probabilistic sensitivity analyses, and scenario analyses. The results for net marginal benefit are presented only for the base-case scenario but are available within the cost-effectiveness model. For comparison with laparoscopic surgery, no probabilistic or deterministic cost-

effectiveness analyses were conducted as this is an additional comparator only. However, two alternative scenarios on surgery efficacy were performed.

2.7.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to explore the uncertainty around key model parameters. PSA was conducted by varying these parameters using their upper and lower bound values based on an assigned distribution. 1,000 simulations were run for the PSA, by which time the incremental results converged to a stable mean, represented by the probabilistic incremental costs. The probabilistic result (£822) is close to the base case (£835), indicating that the cost-effectiveness results are robust (see Table 13 and Table 15).

Output from the PSA iterations is presented as scatter points on the cost-effectiveness plane for linzagolix vs. relugolix (Figure 1). All scatter points representing the simulated incremental costs and QALYs are in the northeast quadrant for linzagolix vs. relugolix. This indicates that linzagolix plus ABT is associated with higher costs compared to relugolix and has comparable QALY.

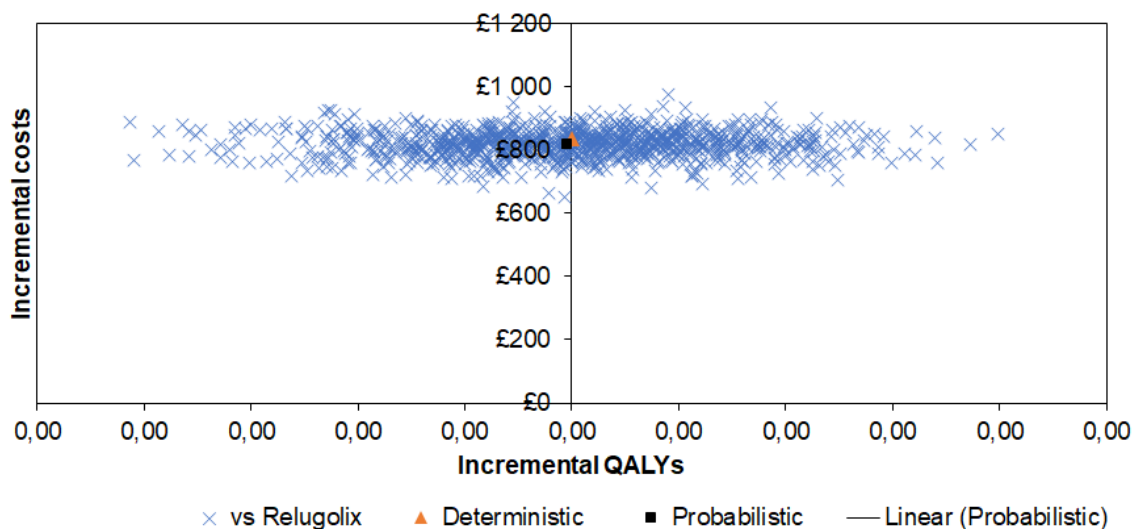
The PSA results were not plotted as a cost-effectiveness acceptability curve (CEAC), as the QALY difference between compared therapies is equal to 0 or close to 0 in all iterations.

Table 15: Probabilistic cost-effectiveness results – linzagolix 200 mg plus ABT vs. relugolix CT

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	CER incremental (£/QALY)
Linzagolix 200 mg plus ABT	14,902	11.76	9.32	-	-	-	-
Relugolix CT	14,081	11.76	9.32	822	0.00	0.00	N/A

Abbreviations: ABT, add-back therapy; LYG, life years gained; QALYs, quality-adjusted life years; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)

Figure 1: PSA output on the cost-effectiveness plane, linzagolix 200 mg plus ABT vs. relugolix CT



Abbreviations: ABT, add-back therapy; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)

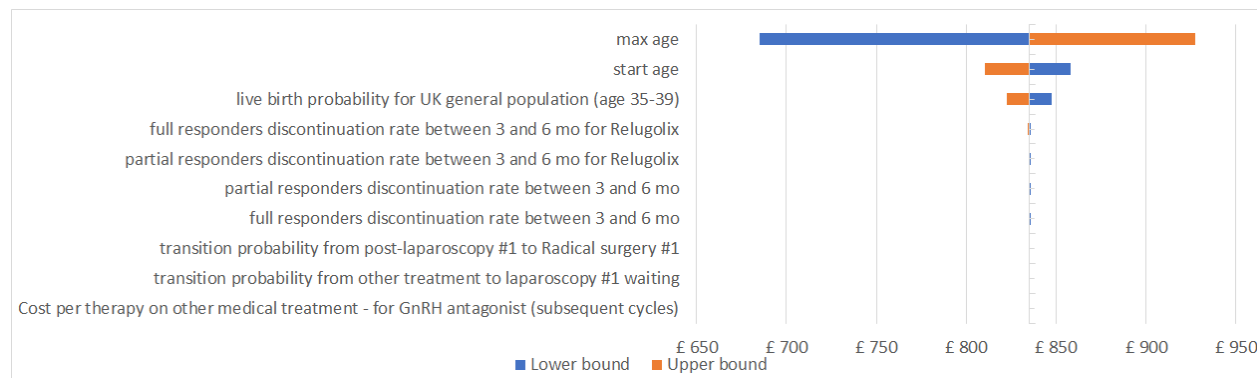
2.7.2 Deterministic sensitivity analysis

One-way deterministic sensitivity analyses (OWSAs) were conducted to examine the sensitivity of the model result to lower and upper estimates of parameter values.

The results from the OWSA are presented in the form of a tornado diagram where the ten parameters with the largest influence on the ICER are presented in Figure 2 for linzagolix vs. relugolix.

The tornado diagram below shows that the maximum age of patients with endometriosis has the largest impact on the incremental costs. Overall, the results appear robust, and none of the parameters considerably impact the incremental costs, as all results are within the range of £650 – £950 in any of the OWSAs.

Figure 2: Tornado diagram – linzagolix 200 mg plus ABT vs. relugolix CT



Abbreviations: ABT, add-back therapy; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)

2.7.3 Scenario analysis

The sensitivity of the model results to changes in key assumptions or parameters was explored through several scenario analyses. The scenario analysis results are presented below, with pairwise ICERs presented (Table 16). The most impactful scenarios are related to the time horizon parameters: different time horizons, or alternative starting age of patients with the disease. Other significant scenarios included treatment discontinuation assumptions, alternative rules for continuing initial treatment (i.e., minimum health benefit required to continue therapy), and discount rates for costs.

The overall conclusion did not change for any of the alternative scenarios.

Alternative approaches to obtaining health state transitions in the model remained the same as outlined in the company submission, section B.3.11.3.

Table 16: Results of scenario analyses – linzagolix 200 mg plus ABT vs. relugolix CT

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Base-case			£835	0.00	0.00	Dominated
Comparators discontinuation based on clinical studies	Assumed as linzagolix	Clinical studies	£74	0.00	0.00	Dominated
Time horizon	15.1 years	1.5 year	£133	0.00	0.00	Dominated
Time horizon	15.1 years	5 years	£409	0.00	0.00	Dominated
Response criteria for continuing treatment after 6 months	Dysmenorrhoea or NMPP responders	Only complete responders and NMPP responders	£553	0.00	0.00	Dominated
Start age	34.9	18	£1,034	0.00	0.00	Dominated
Response criteria for continuing treatment after 6 months	Dysmenorrhoea or NMPP responders	Only complete responders	£651	0.00	0.00	Dominated
Discount rates	Discount rates: 3.5%	Discount rates: 0%	£1,019	0.00	0.00	Dominated
Time horizon	15.1 years	10 years	£665	0.00	0.00	Dominated
Partial response definition	NMPP or DYS reduction	Only DYS reduction	£764	0.00	0.00	Dominated
Response criteria for continuing treatment after 6 months	Dysmenorrhoea or NMPP responders	Only complete responders and DYS responders	£764	0.00	0.00	Dominated

Abbreviations: ABT, add-back therapy; DYS, dysmenorrhoea; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMPP, non-menstrual pelvic pain; QALYs, quality-adjusted life years; relugolix CT, relugolix combination therapy (relugolix-oestradiol-norethisterone acetate)

2.8 Interpretation and conclusions of economic evidence

Compared with the potential future second-line medical treatment (relugolix CT), linzagolix 200 mg plus ABT is associated with incremental costs of £835. The results are stable across all types of sensitivity analyses.

The limitations remained the same as outlined in the company submission, section B.3.15.

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Single technology appraisal

Linzagolix Endometriosis ID6357

Clarification questions: Response to A13c

9 December 2024

File name	Version	Contains confidential information	Date
[ID6357] Linzagolix endometriosis response to qA13c [NoCON]	1.0	No	6 December 2024

Response A13C

An in-depth analysis of the GnRH agonist trials excluded due to missing variability measures, or the data being presented graphically (with no numerical values provided) revealed that only one additional study could potentially be included in a comparison (Acs et al. 2015). However, the process has further limitations, and we believe the study should not be included in a hypothetical NMA. With limitations, it could be tested in a simple ITC by comparing the results from Acs et al. 2015 with those from the EDELWEISS 3 study. The analysis is presented in a dedicated paragraph below. The list of studies presenting data graphically and the reasons for not including them in the comparison are specified below.

Table 1: Studies presenting data in graphs and the reasons for not including them in an ITC and/or NMA

Study	Reasons for not including the study in ITC and/or NMA
Acs 2015	The baseline characteristics presented in the publication are limited, encompassing only mean age, BMI, mean time since diagnosis, and race. Consequently, the assessment of heterogeneity and risk of bias in the comparison is not feasible due to these constraints in baseline data. Dysmenorrhoea and non-menstrual pelvic pain (NMPP) are assessed on the modified Biberou-Bergman scale (mB&B), and the data is provided on graphs. Assuming mB&B is comparable with VRS (as assumed for the Osuga studies), it would be possible to extract the mean values of dysmenorrhoea and NMPP. While it is feasible to derive the mean values for dysmenorrhoea and NMPP, the standard errors of the mean cannot be derived from the graphs, and the imputation of variability measures would be necessary. Implementing data extraction from graphs and the imputation of variability measures poses a considerable risk of bias. Aside from the data presented on dysmenorrhoea and NMPP, data for endometriosis-associated pelvic pain assessed on a numerical rating scale (NRS) is available. However, the endpoint definition is not provided (it is inconclusive whether the authors analysed NMPP or overall pelvic pain, OPP).
Bergqvist 1998	The pain was assessed on a visual analogue scale (VAS) instead of a verbal rating scale (VRS), NRS or mB&B scale. The endometrisis pain score was not defined properly, and it is impossible to state whether the definition of the endometriotic pain score overlaps with the endpoints assessed in the linzagolix studies (i.e., it is inconclusive, whether the authors analysed NMPP or OPP). Moreover, newer, more up-to-date trials were identified in the systematic literature review (Company Submission, Appendix D).
Cheung 2000	The publication does not report pain-related data.

Dlugi 1990	Authors used only the B&B scale in the assessments of dysmenorrhoea, pelvic pain and dyspareunia. The descriptions of the grading of symptoms do not overlap with VRS or mB&B scales, which makes the comparison unfeasible. Newer, more up-to-date trials (Osuga 2021a/Osuga 2021b) were identified in the SLR (Company Submission, Appendix D). The imputation of variability measures would be necessary, which might introduce additional risk of bias to the analysis.
Hornstein 1997	According to the Expert Elicitation Reports August / October 2024, intranasal nafarelin is not a relevant comparator^{1,2}. The authors used the B&B scale to assess dysmenorrhoea, pelvic pain and dyspareunia. The descriptions of grading of symptoms do not overlap with the VRS or mB&B scale, which makes the comparison unfeasible. Additionally, the analysis of pain scores was combined for dysmenorrhoea, pelvic pain and dyspareunia.
Ling 1999	The pain was assessed on an analogue scale instead of a VRS, NRS or mB&B scale. The baseline characteristics provided in the publication are limited (only age, race, and percentage of patients using oral contraceptives were provided), so the heterogeneity and risk of bias assessment in the comparison would not be possible.
Loverro 2008	No endpoints matching with those identified in the trials for linzagolix were found.
Osuga 2021a	The data identified that might be extracted from graphs are reported on a VAS instead of VRS, NRS or mB&B scale.
Osuga 2021b	The data identified that might be extracted from graphs are reported on a VAS instead of VRS, NRS or mB&B scale.
Parazzini 1994	According to Expert Elicitation Reports August / October 2024, intranasal nafarelin is not a relevant comparator^{1,2}. No endpoints matching with those identified in the trials on linzagolix were identified.

In conclusion, potential (pairwise) comparisons based on the studies mentioned above would not add additional value to the analysis. It is important to underline that the comparisons provided in the original submission are of higher credibility, and including any of these additional trials would introduce uncertainty.

Indirect treatment comparison of the results from Acs et al. (2015) with those from the EDELWEISS 3 study

To compare results reported by Acs (2015) for leuprorelin with those from the EDELWEISS 3 study, it was assumed that dysmenorrhea and non-menstrual pelvic pain (NMPP) scores measured using the verbal rating scale (VRS) could be compared with those assessed using the

¹ Theramex. Single technology appraisal: Linzagolix for treating symptoms of endometriosis [ID6357] – Expert Elicitation Report. 2024 Aug.

² Theramex. Single technology appraisal: Linzagolix for treating symptoms of endometriosis [ID6357] – Expert Elicitation Report. 2024 Oct.

modified Biberoglu-Behrman scale (mB&B). Both scales are four-point measures (ranging from 0 – no pain to 3 – severe pain) with similar pain level descriptions provided in the forms completed by patients to indicate their level of pain³. The comparison of those scales can be seen in table 1 below.

Table 1 Descriptive categorisation in VRS and modified Biberoglu-Behrman scale

Numeric value	Pain level description modified Biberoglu-Behrman scale	Pain level description VRS
0	None	No pain
1	Mild pain: almost no impact on daily life.	Mild pain: I was easily able to do things I usually do.
2	Moderate pain: some impact on daily life.	Moderate pain: I had some difficulty doing the things I usually do.
3	Severe pain: great impact on daily life.	Severe pain: I had great difficulty doing the things I usually do.

The monthly mean dysmenorrhea and NMPP scores (mB&B scale) for the leuprorelin 3.75mg treatment arm and placebo arm were extracted from graphs (Figure 1 B and C) using a data digitisation tool⁴ The extracted values can be found in the table 2.

Table 2 Dysmenorrhoea and NMPP scores extracted from Acs (2015)

Outcome	Leuprorelin 3.75 mg baseline	Leuprorelin 3.75 mg after 12 weeks	Placebo baseline	Placebo after 12 weeks
Dysmenorrhoea (mB&B)	1.29	0.13	1.40	0.94
NMPP (mB&B)	0.94	0.40	0.96	0.67

After calculating the mean differences between baseline and week 12 for dysmenorrhoea and NMPP scores in the leuprorelin 3.75 mg and placebo arms, these values were compared to obtain the mean differences (MD) in dysmenorrhoea and NMPP scores for leuprorelin 3.75 mg versus placebo. The confidence intervals (CI) for those MDs were derived using a proportional method based on the CIs reported for linzagolix 200 mg plus add-back therapy (ABT) versus placebo. The lower (CIL) and upper (CIU) bounds of the CIs for linzagolix 200 mg plus ABT

³ Supplement to: Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. N Engl J Med 2017;377:28-40. DOI: 10.1056/NEJMoa1700089

⁴ Plotdigitizer [Internet]. Available from: <https://plotdigitizer.com/app>. Accessed 2024 Dec 4.

versus placebo were expressed as percentages (k for CIL and l for CIU) of its MDs, using the following formulas (**method 1**):

$$CIL_{linzagolix} = k\% \cdot MD_{linzagolix}$$

$$k\% = \frac{CIL_{linzagolix}}{MD_{linzagolix}}$$

$$CIU_{linzagolix} = l\% \cdot MD_{linzagolix}$$

$$l\% = \frac{CIU_{linzagolix}}{MD_{linzagolix}}$$

These proportional values were then applied to the MDs calculated for leuprorelin 3.75 mg versus placebo, resulting in confidence intervals for leuprorelin that maintained the same relative width as those of linzagolix.

In addition to deriving confidence intervals for leuprorelin 3.75 mg versus placebo mean differences using the method described above, an approach based on scaling the standard deviation (SD) of linzagolix 200 mg versus placebo MDs was also applied (**method 2**)⁵. This scaling utilised the relationship between variance and sample size, adjusting linzagolix SDs using the effective sample size (n_{eff})⁶ ratio for the Acs et al. 2015 study. With the scaled SD (SD_{scaled}) and standard error ($SE_{leuprorelin}$), the confidence intervals for leuprorelin 3.75 mg versus placebo MDs were calculated by the following steps:

$$n_{eff} = \frac{n_{intervention}}{n_{placebo}}$$

$$SD_{scaled} = SD_{linzagolix} \cdot \sqrt{\frac{n_{efflinzagolix}}{n_{effleuprorelin}}}$$

$$SE_{leuprorelin} = SD_{scaled} \cdot \sqrt{n_{effleuprorelin}}$$

$$CI_{leuprorelin} = MD_{leuprorelin} \pm t \cdot SE_{leuprorelin}, t = 1.96 \text{ for } CI95\%$$

⁵ Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol. 2006 Jan;59(1):7-10. doi: 10.1016/j.jclinepi.2005.06.006. PMID: 16360555.

⁶ Thorlund, K., Mills, E.J. Sample size and power considerations in network meta-analysis. Syst Rev 1, 41 (2012). <https://doi.org/10.1186/2046-4053-1-41>

To explore the broader range of imputation methods for missing confidence intervals, a third approach was applied (**method 3**), assuming the same standard error (SE) for both MDs. The known SE for linzagolix 200 mg plus ABT was used for calculating the CI for leuporelin by applying the following formula:

$$CI_{leuporelin} = MD_{leuporelin} \pm t \cdot SE_{linzagolix}, t = 1.96 \text{ for } CI95\%$$

The resulting comparison for the efficacy of linzagolix 200mg plus ABT versus leuporelin at week 12 is presented in table 3 below.

Table 3 Bucher ITC for the efficacy of linzagolix versus leuporelin at week 12

Outcome	Linzagolix 200 mg plus ABT versus placebo	Leuprorelin 3.75 mg versus placebo	Indirect comparison	
	Mean difference (95% CI)		Mean difference (95% CI)	p-value
Method 1 of imputing CIs				
Dysmenorrhoea (VRS/mB&B)	-1.06 (-1.25, -0.87)	-0.71 (-0.84, -0.58)	-0.35 (-0.58, -0.12)	<0.01
NMPP (VRS/mB&B)	-0.24 (-0.38, -0.1)	-0.25 (-0.39, -0.1)	-0.01 (-0.19, 0.21)	0.92
Method 2 of imputing CIs				
Dysmenorrhoea (VRS/mB&B)	-1.06 (-1.25, -0.87)	-0.71 (-1.40; -0.01)	-0.35 (-1.07; 0.37)	0.34
NMPP (VRS/mB&B)	-0.24 (-0.38, -0.1)	-0.25 (-0.76; 0.27)	-0.01 (-0.52; 0.54)	0.97
Method 3 of imputing CIs				
Dysmenorrhoea (VRS/mB&B)	-1.06 (-1.25, -0.87)	-0.71 (-0.9; -0.52)	-0.35 (-0.62; -0.08)	0.01
NMPP (VRS/mB&B)	-0.24 (-0.38, -0.1)	-0.25 (-0.39; -0.1)	-0.01 (-0.19; 0.21)	0.92

A significant limitation of this comparison is the substantially lower baseline values reported by Acs et al. 2015 for the leuporelin 3.75 mg and placebo arms compared to those observed in the EDELWEISS 3 study. Specifically, baseline dysmenorrhea scores for the leuporelin and placebo arms were 1.29 and 1.40, respectively, as reported by Acs (2015), whereas, in the EDELWEISS 3 study, both arms recorded baseline dysmenorrhoea scores of 2.29. Similarly, baseline NMPP scores were markedly lower in the Acs (2015) study, with values of 0.94 and 0.96 for the leuporelin and placebo arms, respectively, compared to 1.80 and 1.78 in the

EDELWEISS 3 study. These pronounced differences in baseline values limit the comparability of the results and must be carefully considered when interpreting the findings.

The supplemented results do not change conclusions regarding the relative efficacy of linzagolix 200 mg plus ABT vs leuprorelin 3.75 mg, as presented in the company submission Section B2.

The heterogeneity assessment between the EDELWEISS 3 and Acs 2015 study is presented in table 4 below.

Table 4: Heterogeneity assessment

	Acs 2015	EDELWEISS 3 trial	Conclusions
Inclusion and exclusion criteria	<u>Inclusion criteria:</u> - women aged 18-45 years with laparoscopically confirmed endometriosis within 60 weeks of screening - total Composite Pelvic Signs and Symptoms Score (CPSSS) ≥ 6 with a score of ≥ 2 for dysmenorrhoea and a score of ≥ 1 for NMPP⁷	<u>Inclusion criteria:</u> - women of reproductive age with surgically confirmed pelvic endometriosis in the previous 10 years. - prior to screening, the subjects needed to exhibit moderate-to-severe endometriosis-associated pain, defined as a score of at least two for dysmenorrhoea and at least two for NMPP over the previous month according to the mB&B scale - during the screening period, over the course of two full menstrual cycles, subjects had to show a mean overall pelvic pain score of at least four (0–10 numeric rating scale [NRS]) for 5 days, with the highest score for each cycle separately, and at least 2 days of moderate-to-severe pelvic pain (0–3 verbal rating scale [VRS]) on bleeding days and non-bleeding days - BMI of $\geq 18\text{kg/m}^2$.	- authors in the Acs 2015 study state that the classic Biberoglu-Behrman scale was used to assess the pain level required for inclusion instead of mB&B scale - even assuming that mB&B was used to assess eligibility, the inclusion criterion related to NMPP score were different in the trials (i.e., ≥ 1 points in Acs 2015 and ≥ 2 points in EDELWEISS 3 trial) - patients regardless of BMI were included in the Acs 2015 trial compared to a prespecified criterion in the EDELWEISS 3 trial
	<u>Exclusion criteria:</u> Patients who were administered a GnRH agonist or antagonist, or danazol within 6 months of screening, depot medroxyprogesterone acetate within 3 months of screening or had used hormonal contraception or other hormonal therapy within 1 month of screening, or if they had a history of unresponsiveness to GnRH agonist or antagonist treatment.	<u>Exclusion criteria:</u> Liver enzyme anomalies, osteoporosis, or other metabolic bone disease or if they had taken specific medications like combined oral contraceptives, GnRH agonists, or systemic glucocorticoids, within a specified wash-out period for each based on the time period these medications were expected.	
Baseline characteristics	- age, mean: 31.7 years - BMI, mean: 22.6 kg/m²	- age (around 35 years in each group) - race – mostly white patients	- the baseline data available in the Acs 2015 are scarce, and it limits the

⁷ CPSSS (Composite Pelvic Signs and Symptoms Score) is based on the Biberoglu-Behrman monthly recall scale addressing dysmenorrhoea, dyspareunia, NMPP, pelvic tenderness, and pelvic induration.

	- time since diagnosis of endometriosis, mean: 21.9 months - only white patients were included	- BMI (24–25 kg/m²) - time since first seeking medical diagnosis / treatment - pain scores (overall pelvic pain on VRS and NRS, NMPP on VRS, dysmenorrhoea on VRS, dyspareunia on VRS, EHP-30 pain dimension) - analgesic use on bleeding days - analgesic use on non-bleeding days - dyschezia on NRS - lipid levels (LDL cholesterol, triglycerides) - baseline BMD (femoral neck, lumbar spine, total hip).	- possibility of comparing the populations of interest - the BMI was higher in the EDELWEISS 3 trial compared to the Acs 2015 study in the Acs 2015 study, <u>time since the diagnosis</u> was reported, and in the EDELWEISS 3 trial – <u>time since seeking medical diagnosis/treatment</u> - no data related to baseline lipid levels, baseline BMD, or analgesic use were provided in the Acs 2015 trial - specific data on baseline pain was provided in the EDELWEISS 3 trial. The data in the Acs 2015 might be extracted from the graphs. However, the approach introduces bias to the comparison of baseline characteristics.
Intervention	Patients were randomised (on day 2-5 of menses) equally to receive oral elagolix 150 mg once daily, elagolix 250 mg once daily, placebo or LA 1-month depot 3.75 mg intramuscularly for 12 weeks. Thereafter, patients originally randomised to placebo or LA were re-randomised to one of the elagolix doses, and patients originally randomised to elagolix continued their dose assignment for an additional 12 weeks. Patients were required to use 2 forms of nonhormonal contraception during screening, treatment and follow-up periods.	Subjects were randomised at a 1:1:1 ratio to one of the three study groups: 75mg linzagolix alone, 200mg linzagolix in combination with ABT (1.0mg E2/ 0.5mg NETA), or a placebo. Treatment was administered orally once a day for up to 6 months. All enrolled participants were instructed to use non-hormonal, double-barrier contraception, such as condoms or a diaphragm, each combined with a spermicide.	The interventions applied might be compared.
Outcomes	There was <u>no prespecified primary efficacy endpoint</u> for this phase 2 study. Efficacy measures included daily assessment of pelvic pain using an 11-point numerical rating scale (NRS) and daily assessment of dysmenorrhoea and NMPP using a 4-point mB&B (0 = none, 1 = mild, 2 = moderate, 3 = severe) adapted for daily use. Assessments occurred at approximately the same time each day using an e-Diary which was also used to record the daily use of analgesics for endometriosis-associated pain. Additional efficacy assessments	The primary objective was to demonstrate the efficacy and safety of linzagolix administered orally once daily for up to 3 months (12 weeks) at a dose of 75 mg alone or 200 mg with ABT versus placebo in the management of moderate-to-severe endometriosis-associated pain in women with surgically confirmed endometriosis. The two co-primary efficacy endpoints were a clinically meaningful reduction of dysmenorrhoea and NMPP over the last 28 days of randomised treatment up to Month 3, along with stable or decreased use	- the dysmenorrhoea and NMPP results at 12 weeks might be compared - in the Acs 2015 study, the outcomes were not prespecified to be primary or secondary as opposed to the EDELWEISS 3 trial, which might introduce bias - no meaningful reduction thresholds were specified in the Acs 2015 trial while it is feasible to derive the mean values for dysmenorrhea and NMPP, the standard errors of the mean remain inconclusive, and the imputation of variability measures would be

	included the dyspareunia component of the CPSSS, which was completed at baseline and at the end of weeks 4, 8, 12, 16, 20 and 24 and at the follow-up visit (or early termination). Quality of life was assessed using the Endometriosis Health Profile-5 (EHP-5) core questionnaire, which assesses pain, control and powerlessness, emotional well-being, social support and self-image on a 5-point scale (0 = never, 25 = rarely, 50 = sometimes, 75 = often, 100 = always). The questionnaire was administered at baseline and at the end of weeks 4, 8, 12, 16, 20 and 24 and at the follow-up visit (or early termination). No specified meaningful reduction thresholds.	of analgesics for endometriosis-associated pain. The clinically meaningful reduction thresholds for the primary analysis of dysmenorrhoea and NMPP were determined on blinded Month 3 data using appropriate anchors and were defined as a reduction of at least 1.10 and 0.8 points on the VRS for dysmenorrhea and non-menstrual pelvic pain, respectively, as measured using an electronic diary (eDiary).	necessary in the Acs 2015 trial. In contrast, the data available from EDELWEISS 3 trial are very detailed.

ABT, add-back therapy; BMD, bone mineral density; CPSSS, Composite Pelvic Signs and Symptoms Score; EHP-30, endometriosis health profile questionnaire; GnRH, gonadotrophin releasing hormone; LDL, low-density lipoprotein; NETA, norethisterone acetate; NMPP, non-menstrual pelvic pain; NRS, numerical rating scale; mB&B, modified Biberoglu-Behrman scale; VRS, verbal rating scale

Risk of Bias

An assessment of the risk of bias for the Acs 2015 study raised 'some concerns' due to not identifying the trial protocol. Therefore, it was not possible to assess the risk of bias related to the selection of the reported result (domain 5 of RoB 2 tool).

Table 5: Risk of bias assessment of trials included in the Bucher analysis using the Cochrane Collaboration's revised risk-of-bias tool for randomised trials (RoB 2)

Nr	Signalling questions	<i>Acs 2015 study</i>
Domain 1: Risk of bias arising from the randomisation process		
1.1	Was the allocation sequence random?	Yes
1.2	Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes
1.3	Did baseline differences between intervention groups suggest a problem with the randomisation process?	Probably no
Risk-of-bias judgement		Low risk of bias
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		
2.1	Were participants aware of their assigned intervention during the trial?	No
2.2	Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No
2.3	If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Not applicable
2.4	If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Not applicable
2.5	If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	Not applicable
2.6	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes
2.7	If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	Not applicable
Risk-of-bias judgement		Low risk of bias
Risk of bias due to missing outcome data		
3.1	Were data for this outcome available for all, or nearly all, participants randomised?	Yes
3.2	If N/PN/NI to 3.1 Is there evidence that the result was not biased by missing outcome data?	Not applicable

Nr	Signalling questions	<i>Acs 2015 study</i>
3.3	<i>If N/PN to 3.2</i> <i>Could missingness in the outcome depend on its true value?</i>	Not applicable
3.4	<i>If Y/PY/NI to 3.3:</i> <i>Is it likely that missingness in the outcome depended on its true value?</i>	Not applicable
Risk-of-bias judgement		Low risk of bias
Risk of bias in measurement of the outcome		
4.1	Was the method of measuring the outcome inappropriate?	No
4.2	Could measurement or ascertainment of the outcome have differed between intervention groups?	No
4.3	<i>If N/PN/NI to 4.1 and 4.2:</i> Were outcome assessors aware of the intervention received by study participants?	No
4.4	<i>If Y/PY/NI to 4.3:</i> Could assessment of the outcome have been influenced by knowledge of intervention received?	Not applicable
4.5	<i>If Y/PY/NI to 4.4:</i> Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Not applicable
Risk-of-bias judgement		Low risk of bias
Risk of bias in selection of the reported result		
5.1	Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	No information
5.2	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No information
5.3	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No information
Risk-of-bias judgement		Some concerns
Overall risk-of-bias judgement		Some concerns

*The study was designed as open-label, but study drug randomisation information was only broken after testing and observation at Week 24 for the last patient in this study. To maintain blinding during the double-blind and extension phases, test results were concealed by the laboratory that conducted the drug concentration and pharmacodynamic analyses until the randomisation schedule was broken.

Low risk of bias: The study is judged to be at low risk of bias for all domains for this result.

Some concerns: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.

High risk of bias: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Linzagolix Endometriosis ID6357

Clarification questions: Response to B24, B25, B28

10 December 2024

File name	Version	Contains confidential information	Date
[ID6357] Linzagolix endometriosis response to B24, B25, B28 [NoCON]	1.0	No	10 December 2024

B.24. Priority question: In the model, it is not feasible to switch to all the regression models for the estimation of quality of life utilities. Furthermore, a regression model that excludes any covariates except for the different health states have not been described in the CS and the model.

a) Please also perform a regression analyses excluding any other covariates except the covariates for the health states and the report the AIC and the BIC for these models. Please also include that regression model in the electronic model.

b) Please add the other regression models to the model, to enable the EAG to explore the impact of the other regression models

Response B24a

The utility regression model, including only covariates for health states (excluding all other covariates), was performed and evaluated using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) (see Table B.24.1 below). The pain-based model (for no pain/mild, moderate and severe health states), which excluded additional covariates, was already included in the original electronic model (Regression model 1) and described in section B.3.4.1 of the company submission (CS), as it demonstrated the best performance according to AIC and BIC (see Table 52 of CS). Consequently, only the response-based model (no response, partial response and complete response health states) was performed and tested under the no-covariate condition.

Table B 24.1: Response-based models with no covariates

Model	AIC	BIC
Partial response status, complete response status, no response status	-680	-656

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian information criterion

All variables in the model retained their statistical significance at the level of 0.05. The estimates for health states with the requested model are presented in Table B.24.2.

Table B 24.2: Utility values derived from response-based model for health-states: no response, partial response and complete response

Health state	Utility value
Complete response	0.873
Partial response	0.776
No response	0.715

The regression model, as described above, has been incorporated into the electronic model as Regression model 3. The revised model has been provided.

Response B24b

The revised model incorporates three additional sets of utility values: two derived from newly developed regression models addressing clarification questions (CQs) B.24 and B.25, and one directly extracted from the EDELWEISS 3 study (CQ B28). Users can switch between the previous and newly added utility sets via the controls tab.

Predictions generated by all regression models are listed in the "Utility Values" tab, while detailed outputs of the regression models are available in the "Utility Regression" tab.

The newly added utility sets have also been integrated into an additional scenario analysis, with results in the "Scenario Analysis" tab. A summary of the utility value sets available for use in the model is provided in the table below.

Table B.24.3 Utility values sets available for use in the electronic model

Utility values set	No response utility	Partial response utility	Complete response utility	No pain/mild utility (£)	Moderate pain utility	Severe pain utility
Regression model 1 (described in CS, B.3.4.1)	0.713	0.775	0.876	0.876	0.741	0.477

Regression model 2 (described in CS, B.3.4.1)	0.661	0.779	0.888	0.874	0.739	0.554
Regression model 3 (without any other covariates except health states; described in the B24b answer)	0.714	0.776	0.873	0.876	0.741	0.477
Regression model 4 (base EQ-5D included as a covariate)	0.711	0.775	0.877	0.876	0.741	0.477
EDELWEISS 3 6 th month utility values (according to clarification question B.28)	0.708	0.783	0.892	0.878	0.747	0.489
NICE STA relugolix model*	0.719	0.801	0.884	0.884*	0.884*	0.719*

*Relugolix model had only response health states and no pain states (NICE STA Relugolix). We assumed values for pain states based on response states.

B.25 Priority question: On page 143 of the CS, it is stated that the baseline observations were excluded from response regression models because patients in the no-response state showed higher utility values at the 3-month mark compared with baseline. At the other hand, it is shown in Table 50 of the CS that base EQ-5D-5L is associated with higher utility score.

a) Please reflect on the validity of excluding base EQ-5D-3L although it is associated with a better HRQoL at later time points

b) Please also include base EQ-5D-3L as covariate in the quality of life regression models and allow the use of these regression models in the estimation of health-related quality of life utilities.

Response B25a

For the pain regression model, only 6-month observations were included, while for the response regression model, 3- and 6-month data were deemed suitable. During the early feasibility process, we considered the impact of baseline EQ-5D-3L as potentially significant, but due to potential autocorrelation, these baseline data were not included in favour of baseline pain scores (avoiding a potential collinearity problem). In both models, with and without baseline EQ-5D-3L, the covariates related to model states were statistically significant, thus supporting the conclusion that there is minimal impact on regression outputs and conclusions.

Response B25b

We acknowledged the request of NICE and included the base EQ-5D-3L as a covariate for selecting the best fitted models. We built two requested regression models:

1. pain-based for health states: no pain/mild, moderate, severe.
2. response-based for health states: no response, partial response, complete response.

Predictions of the newly developed regression models can be used in the cost-effectiveness model (see Response B.24b) and have also been integrated into an additional scenario analysis (see response B.28).

1) Pain-based model with base EQ-5D covariate

A utility regression model was developed for pain-related health states, incorporating baseline EQ-5D-3L as a binary covariate (1 for patients with baseline EQ-5D-3L below the median and 0 for those above the median). The model's performance was assessed using the AIC and BIC criteria. (see Table B.25.1 below).

Table B 25.1: The best pain-based model according to AIC with the inclusion of baseline EQ-5D-3L

Model structure	AIC	BIC
Base pain level*, dyschezia*, OPP no pain/mild, OPP moderate, OPP severe, Base EQ-5D-3L level*	-890	-850

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian information criterion, OPP, overall pelvic pain

* Variables introduced as binary ones with groups defined by median

To evaluate pain-related health state utility values incorporating base EQ-5D-3L as a covariate, two predictive approaches with distinct weighting techniques were applied. The first approach, used in prior models (Regression model 1 and 2 described in section B.3.4.1 of the CS), weighted results based on the study population distribution. The second weighting method uses a uniform scheme assigning equal weights (0.5) to both patient profiles within each health state. The two weighting approaches are summarised in tables (B.25.2 and B.25.3) below.

Table B 25.2: The first weighting method for the pain-based, newly developed regression model

Health states	Predicted utility	Base utility binary variable	Proportion	Weighted utility
No pain/mild	0.900	0	0.538	0.484
No pain/mild	0.849	1	0.462	0.392
Moderate	0.766	0	0.517	0.396
Moderate	0.715	1	0.483	0.345
Severe	0.519	0	0.189	0.098
Severe	0.467	1	0.811	0.379

Table B 25 3: The second weighting method for the pain-based, newly developed regression model

Health states	Predicted utility	Base utility binary variable	Proportion	Weighted utility
No pain/mild	0.900	0	0.5	0.450
No pain/mild	0.849	1	0.5	0.424
Moderate	0.766	0	0.5	0.383
Moderate	0.715	1	0.5	0.357
Severe	0.519	0	0.5	0.259
Severe	0.467	1	0.5	0.234

The final model utilised weighting method 1, as it simplifies the influence of the binary variable by standardising its impact across health states. This approach ensures that each utility contributes equally to the result, regardless of distribution. The predictions of the pain-based regression model resulting from different weighting methods are presented in Table B.25.4. below.

Table B 25.4: Predictions of the pain-based regression model for different weighting methods

Health state	Base case model (no weighting)	Newly developed model with the first weighting method	Newly developed model with the second, 0.5 weighting method
No pain/mild	0.876	0.876	0.874
Moderate	0.741	0.741	0.740
Severe	0.477	0.477	0.493

2) Response-based model with baseline EQ-5D-3L as covariate

A utility regression model including baseline EQ-5D-3L as a binary covariate (1 for patients with base EQ-5D-3L below the median, 0 for those above the median) for response-

related health states was also performed and evaluated using AIC and BIC criteria (see Table B.25.5 below).

Table B 25.5: The best response-based model according to AIC with inclusion of baseline EQ-5D-3L

Model structure	AIC	BIC
Baseline pain +dyschezia+ partial response+ complete response+ baseline EQ-5D-3L	-866	-825

The two weighting methods described above were also applied to response-based utility regression models. Both approaches are summarised in tables B25.6 and B25.7 below.

Table B 25.6: The first weighting method for the response-based, newly developed regression model

Response-related health states	Predicted utility	Base utility binary variable	Base pain binary variable	Dyschezia binary variable	Proportion	Weighted utility
CR	0.842	0	0	0	0.061	0.0515
CR	0.760	1	0	0	0.054	0.0410
CR	0.896	0	1	0	0.018	0.0161
CR	0.814	1	1	0	0.014	0.0117
CR	0.912	0	0	1	0.126	0.1148
CR	0.829	1	0	1	0.353	0.2924
CR	0.965	0	1	1	0.234	0.2256
CR	0.883	1	1	1	0.140	0.1239
NR	0.694	0	0	0	0.090	0.0623
NR	0.612	1	0	0	0.220	0.1345

NR	0.748	0	1	0	0.211	0.1575
NR	0.666	1	1	0	0.121	0.0804
NR	0.764	0	0	1	0.025	0.0189
NR	0.682	1	0	1	0.053	0.0359
NR	0.817	0	1	1	0.170	0.1392
NR	0.736	1	1	1	0.111	0.0820
PR	0.749	0	0	0	0.115	0.0861
PR	0.667	1	0	0	0.172	0.1151
PR	0.803	0	1	0	0.073	0.0585
PR	0.721	1	1	0	0.046	0.0332
PR	0.818	0	0	1	0.073	0.0596
PR	0.737	1	0	1	0.161	0.1185
PR	0.873	0	1	1	0.249	0.2174
PR	0.790	1	1	1	0.111	0.0878

CR, complete response; NR, no response; PR, partial response

Table B 25 7: The second weighting method for the response-based, newly developed regression model

Response-related health states	Predicted utility	Base utility binary variable	Base pain binary variable	Dyschezia binary variable	Proportion	Weighted utility
CR	0.842	0	0	0	0.125	0.105
CR	0.760	1	0	0	0.125	0.095
CR	0.896	0	1	0	0.125	0.112
CR	0.814	1	1	0	0.125	0.102
CR	0.912	0	0	1	0.125	0.114
CR	0.829	1	0	1	0.125	0.104
CR	0.965	0	1	1	0.125	0.121
CR	0.883	1	1	1	0.125	0.110
NR	0.694	0	0	0	0.125	0.087
NR	0.612	1	0	0	0.125	0.076
NR	0.748	0	1	0	0.125	0.094
NR	0.666	1	1	0	0.125	0.083
NR	0.764	0	0	1	0.125	0.095
NR	0.682	1	0	1	0.125	0.085
NR	0.817	0	1	1	0.125	0.102
NR	0.736	1	1	1	0.125	0.092
PR	0.749	0	0	0	0.125	0.094
PR	0.667	1	0	0	0.125	0.083

PR	0.803	0	1	0	0.125	0.100
PR	0.721	1	1	0	0.125	0.090
PR	0.818	0	0	1	0.125	0.102
PR	0.737	1	0	1	0.125	0.092
PR	0.873	0	1	1	0.125	0.109
PR	0.790	1	1	1	0.125	0.099

CR, complete response; NR, no response; PR, partial response

The final response-based model is also based on the first weighting method (as was the case for the final pain-based model). Model predictions, depending on the weighting method applied, are presented in the table B.25.8 below.

Table B 25.8: Predictions for different response-based models and weighting

Health state	Base case model with the first weighting method	Base case model with the second, 0.5 weighting method	New model with the EQ-5D-3L included and first weighting method	New model with the EQ-5D-3L included and second, 0.5 weighting method
Complete response	0.876	0.861	0.877	0.863
Partial response	0.775	0.771	0.775	0.770
No response	0.713	0.713	0.711	0.715

B.28 Priority question: Please provide a scenario analysis in which the quality of life utilities were based upon the observed utility values of the EDELWEISS 3 trial.

Response B28:

The scenario in which the quality of life utilities are based upon the observed utility values of the EDELWEISS 3 trial has been added to the model. The revised model has

been provided. The results of the scenario analyses are presented in the tables B.28.1-B.28.3 below.

Table 28 1: Results of scenario analyses – linzagolix 200 mg plus abb-back therapy (ABT) vs. leuprorelin

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Base-case			£2,252	0.00	0.41	£5,554
Utility estimates	Regression model 1	Utility values based on regression model 2	£2,252	0.00	0.39	£5,767
Utility estimates	Regression model 1	Utility values based on regression model 3	£2,252	0.00	0.40	£5,563
Utility estimates	Regression model 1	Utility values based on regression model 4	£2,252	0.00	0.41	£5,543
Utility estimates	Regression model 1	Utility values based on EDELWEISS 3, 6th month	£2,252	0.00	0.40	£5,574
Utility estimates	Regression model 1	Utility values based on relugolix regression model	£2,252	0.00	0.29	£7,635

Table 28 2: Results of scenario analyses – linzagolix 200 mg plus ABT vs. laparoscopic surgery

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Base-case			£421	0.00	0.61	£693
Utility estimates	Regression model 1	Utility values based on regression model 2	£421	0.00	0.59	£717
Utility estimates	Regression model 1	Utility values based on regression model 3	£421	0.00	0.61	£694
Utility estimates	Regression model 1	Utility values based on regression model 4	£421	0.00	0.61	£691
Utility estimates	Regression model 1	Utility values based on EDELWEISS 3, 6th month	£421	0.00	0.60	£699

Utility estimates	Regression model 1	Utility values based on relugolix regression model	£421	0.00	0.28	£1,522

Table 28 3: Results of scenario analyses – linzagolix 200 mg plus ABT vs. relugolix combination treatment

Structural assumption	Base-case scenario	Other scenarios considered	Incremental costs (£)	Incremental LYGs	Incremental QALYs	ICER (£/QALY)
Base-case			£835	N/A	N/A	N/A
Utility estimates	Regression model 1	Utility values based on regression model 2	£835	N/A	N/A	N/A
Utility estimates	Regression model 1	Utility values based on regression model 3	£835	N/A	N/A	N/A
Utility estimates	Regression model 1	Utility values based on regression model 4	£835	N/A	N/A	N/A
Utility estimates	Regression model 1	Utility values based on EDELWEISS 3, 6th month	£835	N/A	N/A	N/A
Utility estimates	Regression model 1	Utility values based on relugolix regression model	£835	N/A	N/A	N/A

As there is no difference between linzagolix 200 mg plus ABT and relugolix combination treatment in terms of modelled health benefit, Table 28.3 presents only incremental costs, with N/A (not available) filled in the other columns dedicated to incremental life years gained (LYG), quality adjusted life years (QALY) and incremental cost-effectiveness ratio (ICER).

Conclusions

Utilising different regression models based on data from the EDELWEISS 3 study does not yield different QALY or ICER outputs, regardless of the comparator. Similarly, the

results generated with observed mean utility estimates (no regression modelling) from the EDELWEISS 3 study are close to the base case.

The only utility scenario with markedly different results is based on the relugolix STA utility estimates, where the linzagolix QALY gain is lower, and the ICER is higher. In such a scenario, linzagolix remains cost-effective with an ICER below the defined threshold of £20,000 per QALY. The difference arises because the relugolix model and utility analysis did not define pain states; instead, they only defined response states. Additionally, it was assumed that all patients would experience the marginal benefits of treatment with initial GnRH analogues, even after the therapy had ended.

Single Technology Appraisal
Linzagolix for treating symptoms of endometriosis [ID6357]
Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	Endometriosis UK
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Endometriosis UK is the leading UK endometriosis charity. As well as raising much-needed awareness and supporting research, we provide support and information for those living with the disease, their partners, and families. We are the only UK organisation providing endometriosis support through a Helpline, web chat, online moderated community (Health Unlocked) and 54 local support groups. Over 200 volunteers with personal lived experience of the disease are trained to provide support through our services. Endometriosis UK delivers a range of projects including supporting employers around Womens Menstrual Wellbeing. The organisation also delivers an Endometriosis Friendly Employer Scheme. Support and services reached over 70,000 people impacted by endometriosis last year. Funding is received from a range of sources including through voluntary income donations and community fundraising. Grants and donations are also received from a range of funders including statutory, corporates and charitable trusts and foundations.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	We have received £15,000 donation from Gedeon Richter in the last 12 months. This was through the company sponsoring a group of Surgeons raising funds for Endometriosis UK through a sponsored bike ride.

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gathered information from 10 detailed feedback sessions specifically focused on gonadotropin releasing hormone (GnRH) antagonist with individuals from our community. In addition, we cross referenced the questions with our previous surveys which have between 2,000 and 10,000 responses.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patients describe the condition as debilitating, with daily pain and an overall lower quality of life. They said that they often feel like their life is on hold, and struggle with daily tasks particularly if they have a high pain day. Respondents described living with endometriosis as extremely challenging and the detrimental impact that the condition's symptoms can have upon their day-to-day lives both logistically and in terms of quality of life and general physical and mental wellbeing requires exhaustive resilience. None of our respondents were caring for someone with the condition.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients said that the overall treatment on the NHS currently is inadequate. They expressed finding the process of getting a diagnosis and also receiving treatments and aftercare with follow up appointments a very long-winded struggle. Despite these lengthy processes that are currently in place, patients said that they often don't find they get a lot of out of their appointments unless they really advocate for themselves and fight in appointments in order not to be dismissed by medical professionals. Patients expressed that the options available as treatments at the moment can all have considerable side effects and expressed how they were often being prescribed a type of contraceptive for their pain without any real investigation as to what the pain might be or were not given enough information about the effects of hormonal contraceptives can have on them. All medical treatment options are also currently all hormonal which are not suitable for those wishing to conceive.
8. Is there an unmet need for patients with this condition?	All of our respondents believe that there is an unmet need for patients with endometriosis. Patients described there being a lack of basic understanding about endometriosis as a condition, and a need for better treatment pathways or referrals once diagnosed. Patients also described their condition not being a priority, with appointments being repeatedly cancelled and long waiting times for those appointments and surgeries. One respondent suggested that endometriosis needs to be approached in a way that is similar to how the NHS approached diabetes, with every clinician having a basic training in endometriosis symptoms, the condition's treatments and the side effects of those treatments. Many of our respondents have been through multiple surgeries, countless different hormonal treatments and often describe feeling 'like their life is on hold waiting for next steps and appointments' all whilst they are still suffering in their day-to-day life. Our respondents stated that this can be very draining and should be something to consider, should patients seem unenthusiastic about trying another hormonal drug.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients described having a GnRH antagonist in a tablet form as a positive step, current comparators – GnRH agonists are injectables which require administration via a healthcare practitioner. Oral medication is attractive as it leads to reduced GP/Hospital attendances for administration. Tablets are also short acting, so treatment can be discontinuing immediately, whereas comparators have an effect for 1-3 months. Quicker symptom control without the risk of experiencing a flare of pain/endometriosis symptoms which is often experienced when commencing GnRH agonists. Patients say that there will be flexibility in adjuvant HRT regimes, HRT can dosing/routes of administration can be altered. Patients also praised about new treatments coming out for endometriosis, believing it to be a positive step for the future of endometriosis care.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Some respondents had concerns about the lack of information into why this drug is being proposed as a treatment for endometriosis. Would this be a short term treatment option for those where HRT is contraindicated (6 months). Patients want to understand more about what tests have been done and how potential side effects are assessed. Patients also spoke of their concern about the lack of information that is currently known about the long-term side effects of this drug, including potential conditions such as cardiovascular disease, osteoporosis in later life for patients who've spent years being prescribed GnRH Analogues/Agonists. Patients also spoke of their want of treatments or drugs that are not hormonal to try and limit potential side effects

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Some respondents said that they were not able to take GnRH Analogue treatments due to the side effects of the drug, therefore this would not be a beneficial treatment option for this group. People who want to conceive will also not be able to take this drug as a form of treatment. Bone density was also raised as a concern for people who will be undergoing this type of treatment. Respondents reported the importance of having bone density scans to monitor bone mineral density alongside treatment. Endometriosis UK would like to know if this drug would be licensed for those with confirmed endometriosis or could it also be used where endometriosis is suspected.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	At the moment, what treatments and drugs are offered are based on the knowledge/speciality of individual medical professionals as well as what is currently available in certain areas and different NHS Trusts. This means the choices of treatments can vary depending on healthcare providers and location of patients.

Other issues

13. Are there any other issues that you would like the committee to consider?	Nothing more to add.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There was positive feedback regarding having tablet/oral GnRH antagonist as an option of treatment as comparators are injectables, gives patient more control in administration of treatment. • Quicker symptom control without the risk of experiencing a flare of pain/endometriosis symptoms which is often experienced when commencing GnRH agonists. • Respondents were also positive at the prospect of being able to have this treatment with flexibility in the adjuvant HRT regime. • Respondents were reluctant to take another hormonal drug as they feel that there is currently not enough evidence to show what long terms effects might be caused by long term use of the drug. • This drug is not suitable for those who are wanting to conceive.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Single Technology Appraisal

Linzagolix for treating symptoms of endometriosis

Clinical expert response

1. We understand that relugolix CT is a combination therapy and linzagolix can be used with or without add-back therapy. For people with endometriosis, would you expect them to always take linzagolix with add-back therapy?

Theoretically, studies indicate Linzagolix can be taken safely without add-back therapy (Edelweiss 3 study). If taken alone, patients can have significant reduction in dysmenorrhoea and are beneficial for patients not wishing to take hormonal medications or have contraindications such as thromboembolic and cerebrovascular diseases. Studies have shown only up to 3 months.

Having to administer Linzagolix without add-back therapy is largely related to the dose and time duration in taking Linzagolix.

Linzagolix doses between 75mg and 125mg in Caucasian women were safe enough to keep oestrogen levels between 20-50pg/ml. This was deemed the best balance between a reduction in endometriosis symptoms and safety end points. If these levels are maintained and patient symptom-free, then there will be no need for add-back therapy. However it would be prudent to check bone mineral density levels.

Beyond these doses, levels of oestrogen will drop to levels which will increase the risk of bone mineral density reduction and increase in menopausal symptoms such as hot-flushes.

If women fail to respond to the lower dose then higher doses of Linzagolix (up to 200mg) may be warranted as a suggested management plan. This will inevitably reduce oestrogen levels beyond safety endpoints in which case add-back therapy would be recommended to avoid safety risks.

But whether Linzagolix can always be taken with add-back therapy will largely depend on if they have symptoms, if they have significant risk factors against add-back therapy and medical history.

2. What, if any, are substantial differences in the administration and monitoring between relugolix CT use and linzagolix ABT for symptoms of endometriosis?

The administration of Linzagolix with ABT and Relugolix-CT will be the same. They both have similar pharmacokinetics and can safely be taken orally and given once a day. They both come in tablet form with Linzagolix being manufactured for studies in the 50mg, 75mg, 100mg and 200mg dosages but commercially come in 100 and 200mg tablets. Linzagolix would need to be taken with a separate ABT tablets in the form of estradiol 1mg and norethisterone 0.5mg.

Monitoring patients while on either Relugolix CT or Linzagolix ABT would be more or less the same. These would include bone mineral density assessments, blood pressure monitoring as both require hormone replacement. If however there is any doubt on adherence that Linzagolix is being taken without ABT then there is more risk of a drop in BMD, in which closer monitoring may be required.

3. What, if any, are substantial differences in the safety and tolerability profiles between relugolix CT or linzagolix ABT for symptoms of endometriosis?

Measurements for parameters of safety have largely been in relation to its pharmacokinetics, vasomotor side-effects, and its anti-oestrogen effects. Its effects in its metabolism and blocking GnRH receptors with ABT will lead to a less dose-dependent hypooestrogenic state with menopausal symptoms and a reduction in bone mineral density.

Studies show that Linzagolix-ABT can have a small increase in lipid profile with a 15% rise in total cholesterol and 20% increase in LDL. These changes were not seen with Relugolix-CT. So patients with hypercholesterolaemia taking Linzagolix-ABT may require lipid profile monitoring. There was also an initial transient increase in AST but this level normalised whilst participants were still on treatment within the 52 week extended study.

For menopausal side-effects, the most common was hot-flushes which were reported in both studies with Relugolix CT and Linzagolix ABT. Both were of similar rates but neither higher than 15% of patients. (Relugolix-CT up to 11% and Linzagolix-ABT up to 13%).

BMD levels decline for Relugolix CT, Linzagolix ABT 100mg and Linzagolix ABT 200mg when given up to 52 weeks to -0.8%, -1.5% and -2% from their baseline respectively. So use beyond 1 year could suggest levels will continue to decline with continued use.

I reiterate that Relugolix studies, Linzagolix-ABT extension studies do not exceed beyond 52 weeks so long term effects of these symptoms cannot yet be objectively determined.

4. In terms of clinical outcomes, do you consider relugolix CT and linzagolix ABT to be comparable treatments for the symptoms of endometriosis?

There are no direct studies comparing both together Relugolix-CT and Linzagolix-ABT for the treatment of endometriosis however, in terms of their pharmacokinetics, mechanism of action and tolerability they compare. There is comparisons in the LIBERTY and ELARIS extension studies showing that significant reduction in blood loss (less than 80mls) were seen in 77% in Relugolix CT and between 76% and 94% in patients who received 200mg Linzagolix amenorrhoea was established. This could be extrapolated for dysmenorrhoea (as no menstrual bleeding means no dysmenorrhoea). The 200mg Linzagolix-ABT showed complete amenorrhoea in as high as 81% of patients after 52 weeks of the trial drug. However both treatments reduce to similar degrees endometriosis associated pains and non menstrual pelvic pains.

5. Do you have any other comments on the comparison of relugolix CT and linzagolix ABT for symptoms of endometriosis?

Comparative studies for these two drugs were mainly in women at the average age being in their mid thirties to mid forties. Many of the studies were for management of uterine fibroid and heavy menstrual bleeding. Consideration for treatment for endometriosis may be for patients at a younger cohort with fertility considerations.

Quality of life, Visual Analogue Scores (VAS) and Endometriosis Health Profile 30 (EHP-30) data for Relugolix, Relugolix CT Linzagolix and Linzagolix ABT all show a comparable improvement in scores when given over the selected period of time.

Lastly, deciding whether relugolix CT or Linzagolix ABT would largely be patient specific and patients who may require treatment without hormone replacement may initially benefit with Linzagolix only.



in collaboration with:

Erasmus School of
Health Policy
& Management



Maastricht University

Linzagolix for treating symptoms of endometriosis [ID6357]

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Abbreviations

ABT	Add-back therapy
AdViSHE	Assessment of the Validation Status of Health-Economic decision models tool
AE	Adverse event
AIK	Akaike information criterion
ANCOVA	Analysis of covariance
BIA	Budget impact analysis
BIC	Bayesian information criterion
B&B	Biberoglu-Behrman
BMD	Bone mineral density
BMI	Body mass index
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CE	Cost-effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CiC	Commercial in confidence
COVID-19	Coronavirus disease 2019
CRD	Centre for Reviews and Dissemination
CS	Company submission
CT	Combination therapy (relugolix-oestradiol-norethisterone acetate)
DP	Decision problem
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
DYS	Dysmenorrhea
EAG	Evidence Assessment Group
EAP	Endometriosis-associated pain
eCRF	Electronic case report form
EHP-30	Endometriosis health profile-30
eMIT	electronic Market Information Tool
EMRS	Endometriosis Market Research Survey
EQ-5D	European Quality of Life-5 dimensions
EQ-5D-3L	European Quality of Life-5 dimensions 3 levels
EQ-5D-5L	European Quality of Life-5 dimensions 5 levels
ESAF	Extension safety analysis set
ESHPM	Erasmus School of Health Policy & Management
ESHRE	European Society of Human Reproduction and Embryology
EUR	Erasmus University Rotterdam
FAC	Factual accuracy check
FAS	Full analysis set
FU EAS	Follow-up extension analysis set
FU SAF	Follow-up safety analysis set
GnRH	Gonadotropin-releasing hormone
GnRHa	Gonadotropin-releasing hormone agonist
GP	General Practitioner
HR	Hazard ratio
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
iMTA	Institute for Medical Technology Assessment

Incr	Incremental
ITC	Indirect treatment comparison
KM	Kaplan-Meier
KOL	Key opinion leader
KSR	Kleijnen Systematic Reviews Ltd
LARC	Long-acting reversible contraception
LDL	Low-density lipoprotein
LGX	Linzagolix
LNG-IUS	Levonorgestrel-releasing intrauterine system
LSM	Least squares mean
LYs	Life years
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MAR	Missing at random
max	Maximum
MCT	Meaningful change threshold
MD	Mean difference
MeSH	Medical Subject Headings
Mg	milligram
MRI	Magnetic resonance imaging
N/A	Not applicable
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NL	The Netherlands
NMA	Network meta-analysis
NMB	Net monetary benefit
NMPP	Non-menstrual pelvic pain
NR	Measure relevant to study outcomes but not recorded
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
OPP	Overall pelvic pain
OR	Odds ratio
OWSA	One-way sensitivity analysis
PP	Per-protocol
PP EAS	Per-protocol extension analysis set
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PSA	Probabilistic sensitivity analysis
PSIQ	Physician Surgery Intention Question
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
Q	Quartile
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RGX	Relugolix
RR	Risk ratio
SAE	Serious adverse events
SAF	Safety analysis set
SARC	Short-acting reversible contraception
SD	Standard deviation
SE	Standard error

SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SSIQ	Subject Surgery Intention Question
STA	Single Technology Appraisal
TAs	Technology Appraisals
TEAE	Treatment-emergent adverse event
TEAS	Treatment extension analysis set
TSD	Technical Support Document
Tx	Treatment
UK	United Kingdom
US	United States
VAS	Visual analogue scale
VRS	Verbal rating scale
WHO	World Health Organization
WTP	Willingness-to-pay

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1. Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, 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 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relate to the clinical effectiveness, and Section 1.5 issues related to the cost-effectiveness (CE). A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem [DP]), 3 (clinical effectiveness) and 4 (CE) for more details.

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

Table 1.1: Summary of key issues

ID6357	Summary of issue	Report Sections
1	Uncertainty as to the precise nature of the population in terms of treatment history, line of therapy and in relation to menopause	2.1, 3.3, 3.4, and 4
2	The effectiveness of linzagolix 200 mg plus ABT as estimated from the trial might not be applicable to clinical practice due variation in ABT	2.3, 3.2, 3.4, and 4
3	Lack of justification for the exclusion of comparators	2.3, 3.3, 3.4, and 4
4	Potential lack of applicability of the trial data	3.2, 3.3, and 4
5	Exclusion of studies to complete a NMA, which might have prevented an understanding of the uncertainty in effectiveness	3.3, 3.4, and 4
6	Lack of full details for the MAIC analysis	3.3, 3.4, and 4
7	Transition probabilities between surgery related health states lack validity	4.2 and 6.4
8	Utilities of post-initial treatment health states lack validity	4.2 and 6.2
9	Inclusion of infertility in the model lacks validity	4.2 and 6.4
10	Cut-off point for pain-related health states	4.2.6
ABT = add-back therapy; EAG = Evidence Assessment Group; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis		

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, linzagolix 200 mg + ABT is modelled to affect QALYs by:

- Increasing the number of QALYs in the no pain/mild state on initial treatment because treatment can be continued until menopause (when compared with leuporelin) or because a larger proportion of patients experiences no pain/mild symptoms (when compared with surgery).
- Decreasing the number of QALYs in the no response state (when compared with surgery) because surgery patients wait 18 months in no response before they receive the surgery.
- Decreasing the number of QALYs in the health states associated with other medical treatment or surgery as fewer patients need these other treatment options.

Overall, linzagolix 200 mg + ABT is modelled to affect costs by:

- Increasing the drug acquisition costs on initial treatment due to the higher unit costs and the longer treatment duration
- Increasing the resource use costs on initial treatment (in comparison with leuporelin) due to the longer treatment duration
- Increasing the treatment costs for other medical treatment, laparoscopic waiting and post-laparoscopic treatment (in comparison with leuporelin), because GnRH agonists, which are more expensive, are part of the treatment baskets for other medical treatment after linzagolix.
- Decreasing the treatment costs for the surgery states as fewer patients need surgery in the linzagolix arm.
- Decreasing the resource use costs for the other medical treatment and surgery states as fewer patients enter these health states.

The modelling assumptions that have the greatest effect on the ICER are:

- The transition probabilities between health states after patients have stopped their initial treatment;
- Excluding the disutility for infertility (weighted for percentage of women with a child wish) after a radical surgery or including the disutility for infertility (weighted for percentage of women with a child wish) also in other health states;
- Using an alternative data source for estimates relating to infertility and pregnancy (Soliman et al. 2017);¹
- The utility values for the health states after the initial treatment;
- Only continuing treatment in complete responders after 6 months.

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there was uncertainty as to the precise nature of the population in terms of treatment history and line of therapy (Table 1.2). It should be noted that the effectiveness of linzagolix 200 mg plus add-back therapy (ABT) as estimated from the trial might not be applicable to clinical practice due variation in ABT (Table 1.3). There was also a lack of justification for the exclusion of comparators (Table 1.4).

Table 1.2: Key issue 1: Uncertainty as to the precise nature of the population in terms of treatment history and line of therapy, and in relation to menopause

Report Sections	2.1, 3.3, 3.4 and 4
Description of issue and why the EAG has identified it as important	The company is not ruling out any treatment history in the DP population, whether medical or surgical, or in terms of line of therapy, which is at least 2 nd , and that all patients in this population might be eligible for either medical or surgical treatments. There are also no restrictions regarding age or menopausal status in the DP, although restriction to reproductive age does apply to the anticipated marketing authorisation.
What alternative approach has the EAG suggested?	A more precise description of patient history.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	No further evidence or analyses would seem to be helpful. Uncertainty in treatment history does, however, raise a question of appropriate comparators as well as applicability of the evidence (see key issues 3 and 4). This issue regarding menopausal status can be resolved by limiting the DP to reproductive age only.
CE = cost-effectiveness; DP = decision problem; EAG = Evidence Assessment Group	

Table 1.3: Key issue 2: The effectiveness of linzagolix 200 mg plus ABT as estimated from the trial might not be applicable to clinical practice due variation in ABT

Report Sections	2.2, 3.2, 3.4 and 4
Description of issue and why the EAG has identified it as important	In clinical practice there is large array of different forms of HRT that could be used as ABT, to which linzagolix 200 mg is added. There is therefore a concern that the effectiveness of linzagolix as estimated from the trial might not be the same as in clinical practice.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Evidence as to the effect of variation in ABT type on effectiveness might be useful.
ABT = add-back therapy; CE = cost effectiveness; EAG = Evidence Assessment Group; HRT = hormone replacement therapy	

Table 1.4: Key issue 3: Lack of justification for the exclusion of comparators

Report Sections	2.3, 3.3, 3.4 and 4
Description of issue and why the EAG has identified it as important	There continues to be a lack of justification for the exclusion of GnRH agonists other than leuprorelin as separate comparators in the CS, and specifically the ITC and the CEA. The company stated in the response to clarification that surgery should not be a comparator, but on grounds that seemed to suggest that the population in the DP would need to be redefined to exclude it. Note that in the factual inaccuracy check (FAC) the company have informed the EAG that neither of two comparators for which there is trial evidence, opigolix and elagolix, is licensed in the UK.

Report Sections	2.3, 3.3, 3.4 and 4
	However, the EAG understand that they might still be used in clinical practice.
What alternative approach has the EAG suggested?	Include all comparators in the NICE scope, including all types of GnRH agonists separately and all types of surgery.
What is the expected effect on the CE estimates?	Depends on relative effectiveness of other GnRH agonists versus leuprorelin.
What additional evidence or analyses might help to resolve this key issue?	The inclusion of all comparators would require a new systematic literature review, NMA and CEA. Surgery might be ruled out by an explicit adaptation of the DP population.
CE = cost effectiveness; CEA = cost effectiveness analysis; CS = company submission; DP = decision problem; EAG = Evidence Assessment Group; GnRH = gonadotropin-releasing hormone; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Table 1.5: Key issue 4: Potential lack of applicability of the trial data

Report Sections	3.2, 3.3 and 4
Description of issue and why the EAG has identified it as important	The population in the scope and the DP does not rule out any age or women who are post-menopausal, although the EDELWEISS trials are limited to women of reproductive age. Also, there were no UK patients in these trials.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The population would be defined to exclude women who are post-menopausal. Otherwise, the company should provide evidence that outcomes are applicable to the post-menopausal population. The company should also provide evidence to support the applicability of the trial data to the UK.
CE = cost effectiveness; DP = decision problem; EAG = Evidence Assessment Group; UK = United Kingdom	

Table 1.6: Key issue 5: Exclusion of studies to complete a NMA, which might have prevented an understanding of the uncertainty in effectiveness

Report Sections	3.3, 3.4 and 4
Description of issue and why the EAG has identified it as important	The justification for excluding studies on the basis of having to form a NMA using common comparators other than placebo is questionable. The EAG do accept that there is some risk associated with including data from graphs or imputation of missing variance data, as well as missing baseline characteristics or full outcome definitions. The company stated in the FAC that one of the studies, D'Hooghe 2019, was excluded erroneously and one, Harada 2021, was excluded for reasons that were incorrectly reported in the CS. The latter should have been excluded due to lack of accompanying ABT in the relugolix arm, which the EAG considers to be reasonable.
What alternative approach has the EAG suggested?	Include all studies in a full NMA.

Report Sections	3.3, 3.4 and 4
What is the expected effect on the CE estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	A full NMA using at least all studies that can be connected by some set of common comparators (and not only placebo) with full numerical data, regardless of availability of baseline characteristics or information on outcome definition. This would also enable the comparison with GnRH agonists in addition to leuporelin. It could also include evidence from D’Hooghe 2019.
CE = cost effectiveness; EAG = Evidence Assessment Group; GnRH = gonadotropin-releasing hormone; NMA = network meta-analysis	

Table 1.7: Key issue 6: There was a lack of full details of the MAIC analysis, which may have introduced the uncertainty in the results of MAIC analysis

Report Sections	3.3 and 3.4
Description of issue and why the EAG has identified it as important	Due to the availability of patient-level data in the EDELWEISS 3 study, the company conducted the MAIC analysis to estimate the relative efficacy of linzagolix 200 mg plus ABT versus relugolix 40 mg plus ABT at week-24 follow-up. However, there was a lack of full details of the MAIC analysis. It was unclear about the number of important prognostic variables, which were adjusted for in the MAIC analysis. Therefore, given that there was a lack of full details of the MAIC analysis, this issue may have introduced the uncertainty in the results of MAIC analysis.
What alternative approach has the EAG suggested?	Full details of the MAIC analysis should be provided.
What is the expected effect on the CE estimates?	The effect on the CE estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends that full details of the MAIC analysis should be provided. The number of important prognostic variables, which were adjusted for in the MAIC analysis, should be provided.
ABT = add-back therapy; CE = cost effectiveness; EAG = Evidence Assessment Group; MAIC = matching-adjusted indirect comparison	

1.5 The CE evidence: summary of the EAG’s key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The EAG’s summary and detailed critique can be found in Section 4, the company’s cost effectiveness results are presented in Section 5, and the EAG’s amendments to the company’s model and results are in Section 6. The key issues in the cost effectiveness evidence are discussed below in Table 1.8 to 1.10.

Table 1.8: Key issue 7: Transition probabilities between surgery related health states

Report Sections	4.2. and 6.4
Description of issue and why the EAG has identified it as important	Transition probabilities between surgery related health states were estimated based on data collected in a market research survey. ² The EAG did not understand the logic applied in deriving the transition probabilities, and appeared wrong at several instances. As many women will receive at least one

Report Sections	4.2. and 6.4
	operation at some point, it was assumed that these estimates might have a relevant impact on the ICER.
What alternative approach has the EAG suggested?	The EAG has suggested an alternative calculation of the transition probabilities, using the same market research survey data as source.
What is the expected effect on the cost effectiveness estimates?	When changing these transition probabilities, the ICER versus leuprorelin increases from £5,554 to £7,014 and versus surgery from £693 to £1,018
What additional evidence or analyses might help to resolve this key issue?	It might be good to validate the model outcomes, to assess if the percentage women having had radical surgery is reflective of what is seen in this population. The model input for these transition probabilities could be validated against literature that reports on this for the UK.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.9: Key issue 8: Utilities of post-initial treatment health states

Report Sections	4.2.and 6.2
Description of issue and why the EAG has identified it as important	All the utilities for the post-initial treatment health states are derived as some weighted average of the utilities for the response health states and the pain-based health states. At several points the EAG does not agree with the logic applied in these calculations: 1) For the EAG, there is no reason to include the no response health state in the estimation of the average utility for other medical treatment and surgery health states, these should be based only on the pain-based health states; 2) utility for the post-laparoscopic health states is estimated using incorrect weights. This issue is important as the health-related quality of life in these subsequent health states is a driving factor for the difference in QALYs between the treatment alternatives as the proportion of patients who need subsequent treatment differ between linzagolix and leuprorelin or surgery. Unfortunately, empirical evidence is missing with respect to the health-related quality of life in these health states. Therefore, there is a large uncertainty regarding these input parameters.
What alternative approach has the EAG suggested?	For the first issue, the EAG has removed the utility of non-responders from the estimation of utility values for other medical treatment and surgery health states. For the second issue, the EAG applied weights for no pain/mild, moderate and other medical treatments that are derived from the proportion of patients who were classified as no pain/mild, moderate or other medical treatment in the (laparoscopic) surgery comparator arm.
What is the expected effect on the cost effectiveness estimates?	When changing these utilities, the ICER versus leuprorelin increases from £5,554 to £6,092 when issue 1 is addressed and £6,205 when issue 2 is addressed. The impact on the ICERs compared to surgery is negligible.
What additional evidence or analyses might help to resolve this key issue?	The model input for these utilities could be validated against literature that reports on the health-related quality of life and utilities in these health states.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio	

Table 1.10: Key issue 9: Inclusion of infertility in the model

Report Sections	4.2 and 6.4
Description of issue and why the EAG has identified it as important	Endometriosis impacts the fertility of women, both through the disease itself and through the impact of treatments, such as the use of hormones or having a hysterectomy. In addition, a potential benefit of treatment with linzagolix is the option to control the endometriosis to such an extent that women stop the treatment to become pregnant. In the current model the impact on fertility is included in two ways: 1) patients in the linzagolix arm of the model are more likely to become pregnant than patients treated with leuporelin or surgery (though this does not lead to an increased health-related quality of life in the model), and 2) patients who enter the post-hysterectomy state get a disutility applied for infertility, weighted by the percentage of women with a child wish. The question is whether this is a sufficient reflection of the impact (in)fertility plays on the health-related quality of life in women with moderate to severe endometriosis. The company motivates the choice to only apply a disutility after hysterectomy by stating that the impact of not being able to conceive was captured by the EQ-5D values collected during the trials as patients were aware of the fact that they could not get pregnant while receiving treatment. However, treatment with linzagolix can last up to 15 years and it is unknown whether this longer time of infertility is fully captured by the EQ-5D values in the first 6 months of treatment.
What alternative approach has the EAG suggested?	In the response to the clarification letter, the company provided two scenarios in which either infertility was applied to none of the health states or to all health states. According to the EAG, both scenarios are incorrect representations of the reality. However, the evidence is missing to accurately reflect infertility in any of the other health states.
What is the expected effect on the cost effectiveness estimates?	When applying these 2 scenarios, the ICER versus leuporelin increases from £5,554 to £7,722 when the disutility is excluded from all health states and to 10,175 when it is included in all health states. There was very little impact on the ICERS versus surgery.
What additional evidence or analyses might help to resolve this key issue?	It is difficult to say what type of evidence might resolve this issue, so the best option might be a set of scenario analyses, for different subgroups of patients for example, to reduce the heterogeneity of the population.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio	

1.6 Summary of the EAG's view

The company's base-case deterministic results for linzagolix 200 mg plus ABT compared to leuporelin and surgery showed ICERs of £5,554 and £693 per QALY gained, respectively. Linzagolix was around £835 more expensive than relugolix, whilst yielding the same number of QALYs.

After implementing the EAG preferred assumptions and estimates, these ICERs increased to £8,638 (linzagolix compared to leuprorelin) and £1,082 per QALY gained (linzagolix compared to surgery,) respectively. The incremental costs for linzagolix versus relugolix remained the same as in the company base case.(see Table 1.10).

The probabilistic results both for the company and the EAG base case were very similar to the deterministic results. The PSA results show for both base cases that the probability of linzagolix being cost-effective at thresholds of £20,000 and £30,000 per QALY gained is 100% compared to leuprorelin and 100% compared to surgery. In the comparison between linzagolix and relugolix, linzagolix is more expensive yielding the same QALYs in all iterations.

The company defined a large range of scenarios, with were also applied to the EAG preferred base case. In the comparison between linzagolix versus leuprorelin the ICER did not go above £13,000, with various scenarios yielding an ICER around £10,000. In the comparison between linzagolix and surgery the highest ICER was almost £10,000, when a time horizon of 1.5 years was applied. For all other scenarios the ICER remained below £3,000.

Of the EAG defined exploratory scenario analyses, most had little impact on the results, only using the health state utilities as reported by Wang et al. led to a small increase in the ICERs versus leuprorelin and surgery.³ In all scenarios considered, linzagolix remained more expensive and equally effective as relugolix, as was the case in the EAG base-case analysis.

Table 1.11: Deterministic EAG base-case compared to company base-case, with step-by-step impact

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case					
Linzagolix 200 mg plus ABT	£14,897	9.33	-		
Leuprorelin	£12,646	8.93	£2,252	0.41	£5,554
Surgery	£14,476	8.73	£421	0.61	£693
Relugolix	£14,062	9.33	£835	0.00	Dominated
Alternative transition probabilities for the surgery health states					
Linzagolix 200 mg plus ABT	£14,276	9.34			
Leuprorelin	£11,465	8.94	£2,811	0.40	£7,014
Surgery	£13,660	8.74	£616	0.61	£1,018
Relugolix	£13,441	9.34	£835	0.00	Dominated
Regression model for the response-based states excluding additional covariates					
Linzagolix 200 mg plus ABT	£14,897	9.33			
Leuprorelin	£12,646	8.93	£2,252	0.41	£5,554
Surgery	£14,476	8.73	£421	0.61	£693
Relugolix	£14,062	9.33	£835	0.00	Dominated
Regression model for the pain-based states estimated from baseline, 3-month and 6-month observations					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Linzagolix 200 mg plus ABT	£14,897	9.34			
Leuprorelin	£12,646	8.95	£2,252	0.39	£5,767
Surgery	£14,476	8.75	£421	0.59	£719
Relugolix	£14,062	9.34	£835	0.00	Dominated
Estimation of utilities for other medical treatment and surgery					
Linzagolix 200 mg plus ABT	£14,897	9.31			
Leuprorelin	£12,646	8.90	£2,252	0.42	£5,411
Surgery	£14,476	8.64	£421	0.67	£628
Relugolix	£14,062	9.31	£835	0.00	Dominated
Estimation of utilities for post-laparoscopic surgery					
Linzagolix 200 mg plus ABT	£14,897	9.38			
Leuprorelin	£12,646	9.00	£2,252	0.38	£5,972
Surgery	£14,476	8.78	£421	0.60	£705
Relugolix	£14,062	9.38	£835	0.00	Dominated
All HRQoL changes combined					
Linzagolix 200 mg plus ABT	£14,897	9.42			
Leuprorelin	£12,646	9.07	£2,252	0.34	£6,564
Surgery	£14,476	8.84	£421	0.57	£733
Relugolix	£14,062	9.42	£835	0.00	Dominated
Inclusion of adverse events					
Linzagolix 200 mg plus ABT	£14,898	9.33	-		
Leuprorelin	£12,647	8.93	£2,251	0.41	£5,552
Surgery	£14,477	8.73	£420	0.61	£692
Relugolix	£14,063	9.33	£835	0.00	Dominated
EAG base-case					
Linzagolix 200 mg plus ABT	£14,276	9.44			
Leuprorelin	£11,466	9.12	£2,810	0.33	£8,638
Surgery	£13,661	8.88	£615	0.57	£1,082
Relugolix	£13,442	9.44	£835	0.00	Dominated
ABT = Add-back therapy; EAG = External Assessment Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years					

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
Population	Adults with symptoms of endometriosis	Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis	The submission is aligned with the intended indication for linzagolix in women with endometriosis	The precise history was unclear in the CS, with the possibility of multiple permutations of pharmacological and surgical therapies, and line of therapy being referred to as second (see Comparator(s)).
Intervention	Linzagolix 200 mg plus ABT	Linzagolix 200 mg plus ABT	Linzagolix 200 mg plus ABT	The nature of ABT in the CS, including as implemented in the key trial EDELWEISS 3.
Comparator(s)	Where hormone-based therapy is suitable Established clinical management without linzagolix, including: - analgesics or NSAID alone or in combination - neuromodulators - relugolix-oestradiol-norethisterone acetate (relugolix CT; subject to NICE evaluation) - other hormonal treatment such as combined hormonal contraception (off-label for some combined hormonal	- Leuprorelin, as a representative of all GnRH agonists - Surgery - specific surgical procedure(s) to be explored as relevant comparators based on UK clinical practice and types of surgeries undertaken in second line	As linzagolix would be expected to be used as a second-line treatment (in accordance with the indication), the comparators are based on those potentially used at the same point of the treatment pathway. Relugolix CT has not yet been approved by NICE.	Surgery was included in the DP and the economic analysis, but not in the clinical effectiveness section. Also, surgical comparators in the surgical SLR were limited to minimally invasive procedures only, excluding hysterectomy. Only one type of GnRH, leuprorelin, was included in the DP and the clinical effectiveness section, but three types were included in the costing (see Table 65, CS). Table 65 also refers to short- (1-month) and long-

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	contraceptives), oral progestogens, GnRH agonists • surgery such as excision/ablation with or without hysterectomy Where hormone-based therapy is not suitable Established clinical management without linzagolix, including: • analgesics or NSAID alone or in combination • neuromodulators • surgery such as excision/ablation with or without hysterectomy			(3- month) acting GnRH agonists, but no such distinction was made in the indirect treatment comparison.
Outcomes	Pain Opioid use Analgesic use Recurrence, progression and regression of endometriosis Admission to hospital Subsequent surgical treatment Fertility Adverse effects of treatment Complications of treatment HRQoL	Pain Opioid use Analgesic use Adverse effects of treatment HRQoL	The company provided comments on the draft scope, proposing that the following outcomes should be excluded from the scope: Admission to hospital Recurrence of endometriosis Subsequent surgical treatment Fertility Complications of treatment The exclusion of ‘admission to hospital’ is due to an absence of relevant outcome data from the pivotal trials. In the EDELWEISS 3 and 6	The EAG considers that admission to hospital should have been included even if only occurring in fewer than 2% of patients. The EAG considers that it might be reasonable to exclude endometriosis outcomes if the treatments being compared only affect symptoms and not the course of the disease. However, this would not apply to at least some surgical procedures.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
			studies, fewer than 2% of patients required hospitalisation at any time, or in any treatment arm. The other excluded outcomes were not collected in the key studies and, therefore, cannot be included in the analysis for this evaluation.	
Economic analysis	The reference case stipulates that the CE of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and CE 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 PSS 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	A CE analysis of linzagolix versus leuprorelin and relevant surgical procedures, from an NHS and PSS perspective. CE is expressed in terms of incremental cost per QALY.	Not applicable.	As per the reference case except that the time horizon of the model is approximately 15 years, which is the time from the starting age in the model until the average age the menopause starts. According to the company, with a very small proportion of women who experience post-menopausal endometriosis and a high discount factor after 15 years, the impact of extending the time horizon would be marginal and not affect the overall conclusions.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE scope	EAG comment
	products should be taken into account.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • people having short-term treatment of 6 months or less, with hormone-based therapy • people having short-term treatment of 6 months or less, without hormone-based therapy • people having longer-term treatment, with hormone-based therapy • people having longer-term treatment, without hormone-based therapy	Subgroups have not been considered in the submission. In this indication, linzagolix will always be administered with concomitant ABT. There is no set time duration (specified course) for this treatment and treatment may continue for as long as patients continue to benefit. If the risks of BMD decrease exceed the potential benefit of treatment with linzagolix, treatment should be discontinued.	The submission is aligned with the intended indication for linzagolix in women with endometriosis which does not include the use of linzagolix without hormone-based therapy.	The EAG agrees with the company that this subgroup analysis appears to be inappropriate.
Based on Table 1 of the CS.⁴ ABT = add-back therapy; BMD = bone mineral density; CE = cost effectiveness; CS = company submission; CT = combination therapy (relugolix-oestradiol-norethisterone acetate); EAG = Evidence Assessment Group; GnRH = gonadotropin-releasing hormone; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for health and Care Excellence; NSAID = non-steroidal anti-inflammatory drug; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review; UK = United Kingdom				

2.1 Population

The population in the Scope is “*Adults with symptoms of endometriosis*”, but in the decision problem (DP) it is described as: “*Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis*” (see Table 1).⁴ It is also referred to as “second-line” in Table 1, which would seem to be more limited. Figure 2 of the company submission (CS) shows that first-line treatment can be any of non-steroidal anti-inflammatory drugs (NSAIDs)/analgesics, hormonal treatment or surgery.⁴

EAG comment: The Evidence Assessment Group (EAG) requested clarification as to the precise nature of the medical and surgical treatments mentioned in Table 1 to which the company responded that the Summary of Product Characteristics (SmPC) reported that EDELWEISS 3 “...*previous medical treatments consisted of analgesics for pelvic pain, including opioids. The most frequently reported other pharmacotherapies for endometriosis treatment included dienogest, hormonal oral contraceptives and GnRH agonists.*”⁵ They went on to state that these prior therapies are those that would be received in United Kingdom (UK) clinical practice prior to receiving linzagolix 200 mg plus add-back therapy (ABT), according to clinical expert opinion and National Institute for Health and Care Excellence (NICE)/European Society of Human Reproduction and Embryology (ESHRE) guidelines.

The EAG also requested clarification as to whether patients where the comparator would be leuprorelin would have a different treatment history and/or be considered to form a different subgroup to those where the comparator would be some form of surgery. The company responded that this was not the case: “*For patients treated with leuprorelin, other GnRH agonists or conservative surgery at this point in the treatment pathway, a similar mix of previous treatments to linzagolix would be expected.*”⁵ They went on to state that women who had already undergone surgery might also be eligible for further surgery.

In conclusion, it seems that the company is not ruling out any treatment history in the DP population, whether medical or surgical, or in terms of line of therapy, which is at least second, and that all patients in this population might be eligible for either medical or surgical treatments. This creates substantial uncertainty as to the precise nature of this population in clinical practice and is therefore a key issue.

It is also worth noting that there is no age limit nor any mention of menopause in the population description. Although the anticipated marketing authorisation (MA)⁶ and the key trial of linzagolix, EDELWEISS 3, limits eligibility to those of reproductive age (see Section 3.2.2), endometriosis can still require management post-menopause.⁷ This therefore increases the uncertainty associated with the population, as well as one regarding the applicability of the trial data if the population is broader than women of reproductive age.

2.2 Intervention

The intervention in the DP is linzagolix 200 mg plus ABT, which is as in the NICE scope.⁴

EAG comment: The precise nature of ABT was not found in the CS, so the EAG requested that this be provided as would be received in clinical practice in the National Health Service (NHS), to which the company responded that for EDELWEISS 3, ABT comprised oestradiol (E2) 1 mg/norethisterone acetate 0.5 mg.⁵ They went on to state that in clinical practice there is large array of different forms of hormone replacement therapy (HRT) that could be used as ABT, providing a large table listing many doses of oestradiol and progesterone either as monotherapy or in combination. There is therefore a

concern that the effectiveness of linzagolix 200 mg plus ABT as estimated from the trial might not be the same as in clinical practice, which implies that this is a key issue.

2.3 Comparators

The comparators in the NICE scope were:

Where HRT is suitable, established clinical management without linzagolix plus ABT, including:

- analgesics or NSAID alone or in combination
- neuromodulators
- relugolix-oestradiol-norethisterone acetate (relugolix combination therapy [CT]; subject to NICE evaluation)
- other hormonal treatment such as combined hormonal contraception (off-label for some combined hormonal contraceptives), oral progestogens, gonadotropin-releasing hormone (GnRH) agonists
- surgery such as excision/ablation with or without hysterectomy

Where hormone-based therapy is not suitable, established clinical management without linzagolix plus ABT, including:

- analgesics or NSAID alone or in combination
- neuromodulators
- surgery such as excision/ablation with or without hysterectomy

Those in the DP were only:⁴

- leuprorelin, as a representative of all GnRH agonists
- surgery, limited to minimally invasive procedures only, excluding hysterectomy

Relugolix was excluded on the basis that it is not currently part of NHS clinical practice, given that it is currently subject to a NICE appraisal.⁴

EAG comment: Only one type of GnRH agonist, leuprorelin, was included in the DP and the clinical effectiveness section, but three types were included in the costing (see Table 65, CS). Table 65 also refers to short- (1-month) and long- (3-month) acting GnRH agonists, but no such distinction was made in the indirect treatment comparison (ITC). Therefore, the EAG requested that the company include all GnRH agonists that might be used in clinical practice, differentiating between short- and long- acting forms of leuprorelin as required, as comparators in both analysis of clinical effectiveness and CE. The EAG also noted that, although surgery was included in the DP and the cost effectiveness analysis (CEA), it was not included in the clinical effectiveness evidence. The EAG therefore requested adequate justification for the exclusion of comparators including surgery other than minimally invasive, and the inclusion of all comparators in the NICE scope, including in the clinical effectiveness section and the ITC and the CEA. The company responded that: *“Based on clinical expert opinion in the UK, and in line with European clinical guidelines, gonadotropin-releasing hormone (GnRH) antagonists (including linzagolix) will be used as second-line hormonal treatment options, as an alternative to GnRH agonists.”*⁵ On this basis they rule out analgesics, neuromodulators and any hormonal contraception, stating that the latter are only used first-line. They emphasise this by stating: *“GnRH agonists are reserved as second-line hormonal treatment, and are therefore considered to be*

appropriate comparators. The following GnRH agonists are indicated for the treatment of endometriosis: goserelin (depot injection), leuprorelin (depot injection), nafarelin (nasal spray), buserelin (nasal spray), and triptorelin (depot injection). Intranasal GnRH agonists (nafarelin and buserelin) are rarely prescribed, with all surveyed clinical experts reporting a preference for intramuscular or subcutaneous formulations, therefore only leuprorelin acetate, goserelin, and triptorelin were considered comparators in the model. Leuprorelin, as a representative of all GnRH agonists, is included in the base case... However, the EAG notes that it is misleading to state that more than one GnRH was included in the CEA: inclusion of the costs for more than one is not the same as including each of several as separate comparators given that there might be variation in the effectiveness between these comparators. Note that the company did not provide any other types of GnRH agonist in the ITC, which could have shed light on this. Indeed, the EAG clinical expert stated that there were several options for the population as described in the DP: *“GnRH agonists are a common choice for this group. It depends on what is available in the formulary ranging from Prostag [leuprorelin], Decapeptyl [triptorelin], Zoladex [goserelin]. Generally, im or subcutaneous preparations are used and not nasal.”*

In relation to surgery, the company stated:⁵ *“Surgery is not considered to be a direct comparator to linzagolix because:*

- 1) Linzagolix would be used in situations where GnRH agonists are currently prescribed, and where medical therapy is preferred over surgical intervention.*
- 2) Treatment decisions are guided by the need to balance treatment priorities regarding fertility and pain management. Women who do not wish to take hormonal therapy due to priorities regarding fertility would not be suitable for linzagolix treatment and would be prioritised for surgical treatment.*
- 3) Clinical experts suggest that when included in the overall pathway, GnRH analogues impact when and how surgery might be used. GnRH analogues may be used as a complementary treatment to reduce the risk of symptom recurrence post-surgery or to provide symptom relief whilst women are waiting for surgery, and in this case, do not directly replace surgical treatment.”*

The company seem to be suggesting that the population in the DP and for those eligible for linzagolix would rule out surgery as a comparator, according to some preference (point 1), according to fertility priorities (point 2), and because GnRH analogues in some way accompany surgery (either before or after). However, the population as expressed in the DP and subject to clarification, as described in Section 2.1, does not explicitly recognised a population that precludes surgery. It is also not expressed in relation to the timing of surgery, either before or after. In addition, the company have provided a comparison with surgery in the CS. This means that unless the population is redefined in a more precise way, surgery, both less and more invasive might still be a comparator or comparators. Indeed, for the population as currently described in the DP, the EAG clinical expert stated: *“The commonly used treatments for this group is GnRH agonist with add back HRT, alternative hormonal treatment that they may not have tried, Dienogest or repeat surgery.”* With regards to the nature of the surgery, the clinical expert went on to state: *“The options include both repeat laparoscopic surgery to excise/ablate endometriosis or hysterectomy depending on patients wishes, future desire for fertility, coexisting symptoms or pathology such as heavy menstrual bleeding or adenomyosis.”* Given that the population as currently described in the DP would be subdivided into those eligible for surgery and those not eligible for surgery, the EAG asked how patients might differ, to which the clinical expert stated: *“This is largely governed by informed choice and patient preference. In the group that is trying to conceive,*

surgery is the preferred option as all other hormonal treatments are contraceptive in nature. GnRHa may also be prescribed to those who have multiple co-morbidities and are not fit for surgery or repetitive surgery has not been particularly beneficial.” The EAG concludes from this that it might be reasonable to define a population for the DP i.e. those eligible for linzagolix in terms of eligibility for surgery i.e. those who either:

- express a preference to not have surgery
- are not fit for surgery
- have not benefited previously from laparoscopic surgery

However, this would need to be explicitly acknowledged if surgery were to be ruled out as a comparator.

With regards to forms of pharmacological treatment other than GnRH agonists and specifically analgesics or neuromodulators, the EAG clinical expert stated: *“Yes, this is in conjunction with analgesics and neuromodulators for pain management where required.”* The EAG interprets this response as indicating that analgesics and neuromodulators would not be an alternative to GnRH agonists or surgery but used adjunctively.

The company also did not include relugolix CT as a comparator on the basis that it is still the subject of a NICE appraisal. However, the NICE technical team asked the company to consider its inclusion on the basis that it might soon receive a positive recommendation by NICE. The company have responded by providing an addendum with an ITC, both an unadjusted Bucher and a matching adjusted indirect comparison (MAIC), and a CEA of a comparison with relugolix CT (see Sections 3.3, 3.4 and 4).

Lack of justification for the exclusion of pharmacological comparators, particularly GnRH agonists other than leuprorelin, and the lack of presentation of clinical effectiveness evidence for surgery unless surgery can be ruled out, implies a key issue.

2.4 Outcomes

The company included the following outcomes, which were specified in the NICE scope:⁴

- Pain
- Opioid use
- Analgesic use
- Adverse effects of treatment
- Health-related quality of life (HRQoL)

They excluded:

- Recurrence, progression and regression of endometriosis
- Admission to hospital
- Subsequent surgical treatment
- Fertility
- Complications of treatment

EAG comment: The EAG considers that admission to hospital should have been included even if only occurring in 2% of patients. Also, the EAG considers that it might be reasonable to exclude

endometriosis outcomes if the treatments being compared only affect symptoms and not the course of the disease. However, this would not apply to at least some surgical procedures.⁸

2.5 Other relevant factors

None.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.⁴ The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.^{9, 10} The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the systematic literature review (SLR) conducted to identify relevant clinical evidence regarding the safety and efficacy of linzagolix 200 mg (the intervention) and other therapies (comparators) for the treatment of endometriosis.¹¹ The searches were conducted in December 2023 and updated in September 2024.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review: search 1: intervention (as reported in CS)

Resource	Host/Source	Date ranges	Last date searched
Electronic databases			
Embase	Embase.com	ALL (1975-C)	02.09.2024
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	PubMed	ALL	02.09.2024
CENTRAL	Cochrane Library (Wiley)	ALL	02.09.2024
CDSR	Cochrane Library (Wiley)	ALL	02.09.2024
Other searching			
Reference checking of bibliographies			
CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission			

Table 3.2: Data sources for the clinical effectiveness systematic review: search 2: comparators (as reported in CS)

Resource	Host/Source	Date ranges	Last date searched
Electronic databases			
Embase	Embase.com	ALL (1975-C)	03.09.2024
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	PubMed	ALL	10.09.2024
CENTRAL	Cochrane Library	ALL	03.09.2024
Other searching			
Reference checking of bibliographies			
CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission			

EAG comment:

- Searches were undertaken in two stages in order to identify clinical evidence on safety and efficacy of linzagolix 200 mg (the intervention) and other therapies (comparators) for the treatment of endometriosis. The searches were conducted in December 2023 and updated in September 2024. Initially the search searches were presented in two tables which combined results of the three databases (MEDLINE, Embase and the Cochrane Library) and provided the hits for each resource in separate columns. This approach hindered the EAG's ability to fully critique the search methods therefore the EAG requested that the company supply the search strategies in their original format as recommended by best practice "... *bibliographic database search strategies should be copied and pasted into an appendix exactly as run and in full, together with the search set numbers and the total number of records retrieved by each search strategy. The search strategies should not be re-typed, because this can introduce errors.*"¹² The EAG was grateful to the company for their prompt response and the revised searches combined with the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{5, 13}
- The revised searches were well structured, transparent and reproducible.
- Whilst searches were performed on an adequate number of bibliographic databases, other than reference checking, no grey literature searching was conducted. Best practice recommends the searching of grey literature in order to minimise publication bias.¹⁴ Without running their own searches, the EAG is unable to say what impact this may have had on the overall recall of results.
- The EAG noticed that whilst the Cochrane Database of Systematic Reviews (CDSR) was mentioned in Section D2.2.1 (Appendix D) line #35 of the comparators search in the Cochrane Library appeared to remove all Cochrane records except for those in the Cochrane Central Register of Controlled Trials (CENTRAL).¹³ The company confirmed that whilst CDSR was searched, the records were not screened due to the scope of the SLR.⁵ For this reason, the EAG have removed CDSR from the list of searched resources above.
- The first search for the intervention used a broad search strategy combining facets for endometriosis and linzagolix, no limits were applied. The second search for comparators combined facets for endometriosis and named GnRH analogues. In the Embase and MEDLINE searches, this was then combined with a study design filter for clinical trials.
- At the time of requesting the revised searches, the EAG also queried if the strategies had included both subject headings and free text terms. The company confirmed that whilst Medical Subject Headings (MeSH) and Emtree had been consulted to identify relevant synonyms, they had not been included in the strategies. The company went on to say "*Not all databases have indexing terms and some contain records that have not yet been indexed. It was decided that a search strategy based on free-terms and synonyms would be sufficient to cover relevant publications.*"¹³ The EAG would point out that in this case all three resources searched in the clinical effectiveness SLR contained subject headings and that Cochrane best practice states that "*Both free-text and subject headings (e.g. Medical Subject Headings (MeSH) and Emtree) should be used.*"¹² A brief comparison of the company's own search facets for endometriosis in PubMed demonstrate the potential impact:

Intervention Search facet for endometriosis (All fields including MeSH) = 131,507

Comparators Search facet for endometriosis (limited to free text in title and abstract) = 121,040

Although the difference displayed in final numbers when combined with the other facets will be much smaller, and key papers with the relevant terms in their title and abstracts where available, should have been retrieved, the EAG feels it possible that relevant studies may have been missed.

Table 3.3: Data sources for feasibility assessment – ITC of linzagolix and minimally invasive surgical procedures for treatment of endometriosis-associated pain (as reported in CS, Appendix M)

Resource	Host/Source	Date ranges	Last date searched
Electronic databases			
Embase	Ovid	2019-2024/08	29.08.2024
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	Ovid	2019-2024/08	29.08.2024
CENTRAL	Cochrane Library (Wiley)	ALL	29.08.2024
CDSR	Cochrane Library (Wiley)	ALL	29.08.2024
Other searching			
Reference checking of bibliographies			
CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; ITC = indirect treatment comparison			

EAG comment:

- An additional SLR was conducted in August 2024, to identify relevant evidence assessing the efficacy and safety of minimally invasive surgical procedures recommended in guidelines for patients with endometriosis.¹⁵
- Search facets combined both free text terms and relevant subject headings for endometriosis and minimally invasive surgical techniques, along with study design filters to limit to randomised controlled trials (RCTs) and systematic reviews.
- At clarification, the company confirmed that the MEDLINE/Embase search was run simultaneously for both databases on the Ovid search platform and that the search strategy implemented both Emtree and MeSH subject headings.⁵

3.1.2 Inclusion criteria

A SLR was conducted in a stepwise manner to identify clinical evidence for intervention, comparators and surgery. The SLR was divided into three parts: a SLR for the intervention, a SLR for the comparators and an additional SLR was conducted for minimally invasive surgical procedures.⁴

The eligibility criteria used for the intervention (linzagolix plus ABT 200 mg, with or without ABT) is presented in Table 3.4.

Table 3.4: Inclusion and exclusion criteria for the intervention

	Inclusion criteria	Exclusion criteria
Population	Patients with endometriosis	• Healthy volunteers • Disease other than endometriosis
Interventions	Linzagolix at a dose of 200 mg	• All non-pharmacological interventions • Other interventions
Comparators	• Placebo • Any pharmacological intervention	No exclusion on comparators

	Inclusion criteria	Exclusion criteria
Outcomes	• Treatment response (e.g. change in NMPP, OPP, dyspareunia, dyschezia score) • HRQoL • Safety	• Pharmacokinetics/pharmacodynamics • Economic outcomes
Study design	• RCTs • Non-RCTs • Single-arm studies for intervention • Observational studies (both prospective and retrospective) • Long-term follow-up (RCTs extension studies)	• Preclinical studies • Comments, letters, editorials • Case reports, case-series^a • Narrative review • Conference abstracts • Systematic reviews
Language restrictions	English	Other than English
Based on Table 1 of Appendix D.¹¹ ^a studies involving more than 10 patients from the target population in the cohort will be included HRQoL = health-related quality of life; NMPP = non-menstrual pelvic pain; OPP = overall pelvic pain; RCT = randomised controlled trial		

The eligibility criteria used for the comparators is presented in Table 3.5.

Table 3.5: Inclusion and exclusion criteria for the comparators

	Inclusion criteria	Exclusion criteria
Population	Patients with endometriosis	• Healthy volunteers • Disease other than endometriosis
Interventions	GnRH analogues other than linzagolix	• All non-pharmacological interventions • Other interventions
Comparators	• Placebo • Other GnRH analogues	No exclusion on comparators
Outcomes^a	• Treatment response (e.g. change in NMPP, OPP, dyspareunia, dyschezia score) • HRQoL • Safety	• Pharmacokinetics/pharmacodynamics • Economic outcomes
Study design	• RCTs^b	• Preclinical studies • Comments, letters, editorials • Case reports, case-series^c • Narrative review • Conference abstracts • Systematic reviews • Observational studies
Language restrictions	English	Other than English
Based on Table 2 of Appendix D.¹¹ ^a assessed at 12 or 24 weeks to allow comparison with studies for linzagolix ^b the broad SLR for the intervention found EDELWEISS 3, a placebo controlled RCT study. The aim of the SLR for comparators was therefore to find RCTs allowing for anchored ITCs ^c studies involving more than 10 patients from the target population in the cohort will be included GnRH = gonadotropin-releasing hormone; HRQoL = health-related quality of life; ITC = indirect treatment comparison; NMPP = non-menstrual pelvic pain; OPP = overall pelvic pain; RCTs = randomised controlled trials; SLR = systematic literature review		

The eligibility criteria used for the minimally invasive surgical procedures is presented in Table 3.6.

Table 3.6: Inclusion and exclusion criteria for surgery

	Inclusion criteria	Exclusion criteria
Population	Patients with endometriosis	• Healthy volunteers • Disease other than endometriosis
Interventions	Minimally invasive surgical procedures, including excision and ablation*	Interventions other than specified in the inclusion criteria, studies in which concomitant hormonal therapies or devices*** were used, studies on hysterectomies*
Comparators	Diagnostic laparoscopy, placebo, no treatment, sham procedures	Comparators other than specified in the inclusion criteria
Outcomes^a	Any outcomes allowing the comparison with the trial assessing the efficacy and safety of linzagolix**	Outcomes other than specified in the inclusion criteria
Study design	RCTs [^]	Study designs other than specified in the inclusion criteria, conference abstracts ^{^^}
Based on Table 1 of Appendix M.¹⁵ * Trials assessing hysterectomies were excluded as hysterectomy is recommended only if other surgical options have been offered, failed or are inappropriate ** In the review on linzagolix, the EDELWEISS 3 study was identified as adequate to perform an ITC *** Prohibited concomitant therapies and devices in the EDELWEISS 3 study, including GnRH antagonists, GnRH agonist injections, danazol, oral contraceptives and other sex hormones, selective progesterone receptor modulators, selective oestrogen receptor modulators, aromatase inhibitors, copper intrauterine devices and intrauterine devices with progestogen [^] additionally, SLRs published in the last 5 years (from 2019 onwards) were found and revised to identify any further evidence ^{^^} conference abstracts were excluded due to substantially limited description of methodology and results GnRH = gonadotropin-releasing hormone; RCT = randomised controlled trial; SLR = systematic literature review		

EAG comment: The EAG noted that the DP includes a broad set of comparators representing established clinical management without linzagolix. However, the company's SLR appears to limit the scope of comparators in several areas. The company was asked to provide a detailed justification when comparators deviate from the NICE scope e.g. are listed in the NICE scope but were not used in the CS and provide clarification on the following points:⁵

- The scope includes a variety of hormone-based treatments, such as combined hormonal contraception and oral progestogens, as potential comparators. The company were asked to clarify why these additional hormonal treatments were not included in the GnRH analogue SLR. The company responded that, *"As described in response to question A2a, combined hormonal contraception and oral progestogens are used as first line hormonal therapies in UK practice and were therefore not considered to be comparators in the submission."*
- The scope specifies surgical comparators as *"excision/ablation with or without hysterectomy."* The company were asked to explain the rationale for limiting surgical comparators in the surgical SLR to minimally invasive procedures only, excluding hysterectomy. The company responded that, *"In the NICE endometriosis guideline (published in 2017 and updated in 2024)*

the suggested surgical approaches involve laparoscopic excision or ablation plus adhesiolysis and laparoscopic ovarian cystectomy, depending on the location of the lesions. Hysterectomy is advised only if other surgical options have been offered, failed or are inappropriate, and research with clinical experts indicated that hysterectomy tends to be a last resort rather than considered early in the treatment pathway. Additionally, hysterectomy is indicated if treatment-resistant adenomyosis or heavy menstrual bleeding is present. Linzagolix is a treatment indicated for the treatment of adult women of reproductive age - in this population it might be a priority to maintain fertility. When performing a hysterectomy, the fertility is not maintained. Therefore, it was decided not to include it in the feasibility analysis."

- b. The scope lists analgesics, NSAIDs, and neuromodulators as part of established clinical management without linzagolix. The company were asked to clarify why these treatments were not included as comparators in the SLRs. The company responded that, *"Analgesics and NSAIDs are routinely prescribed as first-line therapies in endometriosis (often before a formal diagnosis has been made). Expert elicitation revealed an expectation that once GnRH agonists (or antagonists) are introduced, there is a clinical expectation that the need for such treatments should reduce or cease. Neuromodulators are reserved for patients with exceptionally difficult-to-manage pain secondary to endometriosis. Prescription would be started after referral to a specialist pain service rather than as part of routine supportive care. As such, the proportion of patients prescribed neuromodulators is limited and not part of routine practice."*

In conclusion, the EAG eligibility criteria might be appropriate if either GnRH agonists and minimally invasive (laparoscopic) surgery are the only comparators (see Section 2.3).

3.1.3 Critique of data extraction

According to the CS, two reviewers independently screened the titles, abstracts, and full texts for eligibility based on the predefined selection criteria. Any disagreements were resolved in consultation with a third reviewer.⁴

No details of the process of data extraction were provided.

EAG comment: The EAG asked the company to describe the process used for data extraction and risk of bias assessment of the included studies (for intervention and comparator data). The company responded that, *"Data extraction was performed by one reviewer and quality-checked by the other reviewer. The extraction was performed in tables. Additionally, if available in the identified publications, graphs were provided. Data from graphs was not extracted if specific values were not provided, due to the possibility of introducing bias to the analysis."* The EAG is satisfied with this response.

3.1.4 Quality assessment

The Company conducted the quality assessment of trials included in the Bucher analysis. The assessment covers six key domains of methodological quality, including randomisation, blinding, and the handling of missing data.

3.1.5 Evidence synthesis

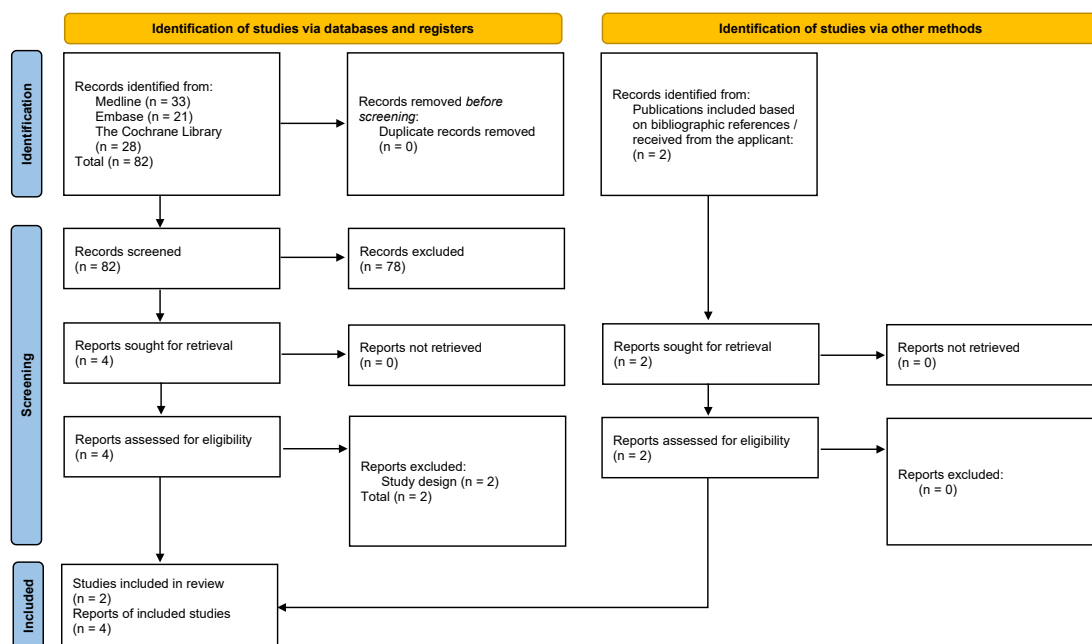
Not applicable – see Sections 3.3 and 3.4 for the ITC.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Study retrieval

The SLR was conducted to identify relevant clinical studies in support of this submission. The CS appendices detail this process¹¹. Eighty-two records were identified via databases and registers while two records were identified via other methods. With further exploration, 80 records were then deemed irrelevant and excluded. Therefore, the SLR ends with four reports of two included studies in total. Further details can be found in Table 3.2.

Figure 3.1: PRISMA diagram showing the publication selection process for the intervention



Based on Figure 1 of the CS, Appendix D¹¹

CS = company submission

3.2.2 Summary of EDELWEISS 3, EDELWEISS 6

The Phase 3 EDELWEISS 3 study (N=484) and its extension study EDELWEISS 6 (N=353 for the treatment extension analysis set/356 in the extension safety analysis set) designed to access the efficacy and safety of linzagolix 200 mg plus ABT for the treatment of Moderate to Severe endometriosis-associated pain (EAP) in women of reproductive age.⁴ The trials are briefly summarised below in Table 3.7.

Table 3.7: Overview of study characteristics

Study	EDELWEISS 3	EDELWEISS 6
Study design	Randomised, double-blind, placebo-controlled, multicentre phase 3 trial (NCT03992846)	Extension study of patients who completed the 6-month treatment period of EDELWEISS 3 (NCT04335591)
Study geography	91 centres across Europe	45 centres across Europe

Study	EDELWEISS 3	EDELWEISS 6
	(65 centres [Austria (5), Bulgaria (8), Czech Republic (5), France (6), Hungary (6), Poland (12), Romania (6), Spain (6), Ukraine (11)]) and the US (26 centres) There were no UK trial centres.	(36 centres [Austria (1), Bulgaria (4), Czech Republic (2), Poland (11), Romania (6), Spain (1), Ukraine (11)] and the US (9 centres) There were no UK trial centres.
Population	Women of reproductive age with Moderate to Severe EAP	Women of reproductive age with Moderate to Severe EAP who completed the 6-month treatment period of EDELWEISS 3
Intervention(s)	Once daily linzagolix 75 mg (plus ABT placebo) Once daily linzagolix 200 mg plus ABT	Once daily linzagolix 75 mg (plus ABT placebo) Once daily linzagolix 200 mg plus ABT (Patients who received placebo in EDELWEISS 3 were randomised to linzagolix 75 mg [plus ABT placebo] or linzagolix 200 mg plus ABT. Patients who received active treatment in EDELWEISS 3 continued with the same treatment).
Comparator(s)	Placebo	None
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	N/A	N/A
Reported outcomes specified in the decision problem	Pain Opioid use Analgesic use Adverse effects of treatment (only Grade 3/4 TEAEs) HRQoL	Pain Opioid use Analgesic use Adverse effects of treatment HRQoL
All other reported outcomes	Dyschezia Intention for surgery Number of days in hospital Time to post-treatment menses	Dyschezia Intention for surgery Number of days in hospital Time to post-treatment menses
Based on Table 3 of the CS ⁴ ABT = add-back therapy; CS = company submission; EAP = endometriosis-associated pain; HRQoL = health-related quality of life; N/A = not applicable; TEAE = treatment-emergent adverse event; UK = United Kingdom; US = United States		

Note that adverse event (AE) data were also obtained from another phase 3 study, EDELWEISS 2 (NCT03986944; 18-OBE2109-002), which was included in the SmPC, and with its extension

(EDELWEISS 5; NCT04372121; 19-OBE2109-005) were planned as replicate pivotal trials to EDELWEISS 3 and 6, but were discontinued early.⁴ This was reported to be due to challenges in patient screening and recruitment affected by the coronavirus disease 2019 (COVID-19) pandemic, and meant that no efficacy analyses were performed due to insufficient numbers of randomised patients. See Section 3.2.7 for the AE data.

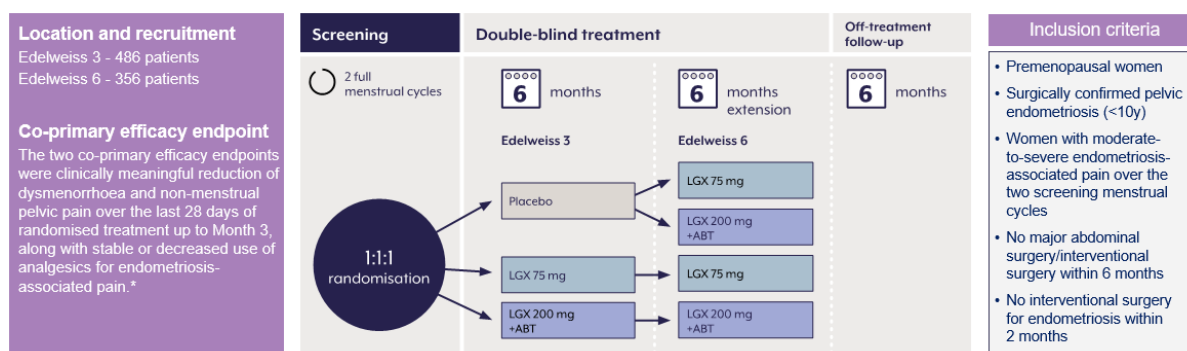
3.2.2.1 EDELWEISS 3 overview

EDELWEISS 3 was a randomised, double-blind, placebo-controlled, multicentre phase 3 trial of linzagolix in women of reproductive age with Moderate to Severe EAP⁴.

The trial comprised a 3-month screening period, a 6-month treatment period, a 6-month extension and a 6-month drug-free follow-up period.⁴ Please see Figure 3.2 for an overview of EDELWEISS 3 trial process.

The CS⁴ clarifies that the EDELWEISS 3 co-primary efficacy endpoints were a clinically meaningful reduction from baseline of dysmenorrhoea (reduction of ≥ 1.10 points on the verbal rating scale [VRS]) and NMPP (reduction of ≥ 0.8 points on the VRS) to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP. Secondary endpoints were changes from baseline to month 6 in dysmenorrhoea, NMPP, dyschezia, overall pelvic pain, interference of pain with the ability to perform daily activities (using the Endometriosis health profile 30 [EHP-30] pain dimension) and dyspareunia, and no analgesic/no opiate use for EAP during the preceding 4-week period at month 6. Other secondary endpoints included analgesic and opioid use for EAP, number of days in hospital, Physician Surgery Intention Question (PSIQ)/Subject Surgery Intention Question (SSIQ) and HRQoL.

Figure 3.2: EDELWEISS 3 (NCT03992846) and EDELWEISS 6 (NCT04335591) trial design



Based on Figure 6 of CS⁴

ABT = add-back therapy; CS = company submission; LGX = linzagolix; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale

* The clinically meaningful reduction thresholds for the primary analysis of dysmenorrhoea and NMPP were based on blinded month 3 data using appropriate anchors and were defined as a reduction of ≥ 1.10 and ≥ 0.8 points from baseline on the VRS for dysmenorrhoea and NMPP, respectively, as measured using an electronic diary (eDiary)

3.2.2.1.1 EDELWEISS 3 Eligibility criteria

The following criteria applied for inclusion of participants in the study:⁴

- Women of reproductive age with surgically confirmed endometriosis in the past 10 years

- Moderate to Severe EAP over the month prior to screening and over two menstrual cycles during screening
- Body mass index (BMI) ≥ 18 kg/m²
- Practice birth control if of childbearing potential

The following criteria applied for exclusion of participants in the study:⁴

- Liver enzyme anomalies
- Osteoporosis or other metabolic bone disease
- Use of certain medications (e.g. COC, GnRH agonists or systemic glucocorticoids) within a specified wash-out period

3.2.2.1.2 EDELWEISS 3 Baseline characteristics

Table 3.8 describes the baseline characteristics of both arms of the EDELWEISS 3 as presented in the CS.⁴ Demographic and baseline characteristics were generally well balanced among treatment groups in the EDELWEISS 3.

Table 3.8: EDELWEISS 3 | Baseline characteristics (FAS)

EDELWEISS 3 Characteristics	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Total (N=484)
Age, years, mean (SD)	34.9 (6.8)	35.1 (6.4)	34.6 (6.8)	34.9 (6.6)
Race, n (%)				
White	160 (98.8)	158 (98.8)	159 (98.1)	477 (98.6)
Black or African-American	2 (1.2)	1 (0.6)	1 (0.6)	4 (0.8)
Asian	0	1 (0.6)	0	1 (0.2)
American Indian or Alaska Native	0	0	1 (0.6)	1 (0.2)
Multiple	0	0	1 (0.6)	1 (0.2)
BMI, kg/m ² , mean (SD)	24.14 (4.44)	24.60 (5.23)	24.09 (5.17)	24.27 (4.95)
Weight, kg, mean (SD)	65.81 (11.96)	67.73 (14.45)	65.75 (14.75)	66.42 (13.77)
Time since seeking medical diagnosis / treatment, years, mean (SD)	4.94 (4.51)	5.15 (4.38)	5.50 (4.74)	5.20 (4.54)
Baseline pain scores, mean (SD)				
Overall pelvic pain VRS ^a	1.90 (0.40)	1.87 (0.41)	1.92 (0.42)	1.90 (0.41)
NMPP VRS ^a	1.78 (0.44)	1.73 (0.46)	1.80 (0.46)	1.77 (0.45)
Dysmenorrhoea VRS ^a	2.29 (0.43)	2.25 (0.40)	2.29 (0.43)	2.28 (0.42)
Overall pelvic pain NRS	6.18 (1.51)	5.84 (1.65)	6.12 (1.60)	6.05 (1.59)
Dyspareunia VRS	1.95 (0.87)	1.92 (0.86)	2.09 (0.84)	1.99 (0.86)

EDELWEISS 3 Characteristics	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Total (N=484)
EHP-30 pain dimension	51.77 (14.43)	51.46 (14.28)	52.37 (15.14)	51.87 (14.60)
Baseline analgesic use on bleeding days ^a , pill count/day, mean (SD)	1.65 (1.45)	1.88 (1.69)	2.01 (1.95)	1.85 (1.71)
Baseline analgesic use on non-bleeding days ^a , pill count/day, mean (SD)	0.78 (0.98)	1.00 (1.23)	1.08 (1.26)	0.95 (1.17)
Baseline dyschezia NRS, mean (SD)	4.46 (2.51)	3.73 (2.60)	4.07 (2.79)	4.09 (2.65)
Baseline lipids and BMD data [SAF]	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Total (N=484)
Baseline lipid levels, mg/dL, mean (SD) [SAF]				
LDL cholesterol	114.3 (31.8)	117.4 (39.4)	115.4 (32.1)	115.7 (34.5)
Triglycerides	91.9 (46.8)	92.0 (48.5)	90.0 (43.2)	91.3 (46.2)
Baseline BMD, g/cm ² , mean (SD) [SAF]				
Femoral neck	1.002 (0.132)	0.995 (0.141)	0.980 (0.144)	0.992 (0.139)
Lumbar spine	1.214 (0.140)	1.197 (0.150)	1.169 (0.134)	1.193 (0.143)
Total hip	1.031 (0.116)	1.026 (0.127)	1.015 (0.125)	1.024 (0.123)
Baseline BMD, Z-scores, mean (SD) [SAF]				
Femoral neck	0.25 (0.88)	0.35 (0.96)	0.14 (0.93)	0.25 (0.93)
Lumbar spine	0.49 (1.01)	0.51 (1.15)	0.25 (0.93)	0.41 (1.04)
Total hip	0.40 (0.90)	0.44 (0.99)	0.30 (0.97)	0.38 (0.96)
Based on Table 8 of CS ⁴ ^a Based on the two selected screening menstrual cycles ABT = add-back therapy; BMD = bone mineral density; BMI = body mass index; CS = company submission; EHP-30 = endometriosis health profile-30; FAS = full analysis set; LDL = low-density lipoprotein; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; SAF = safety analysis set; SD = standard deviation; VRS = verbal rating scale				

3.2.2.2 EDELWEISS 6 overview

Patients who completed the 6-month treatment period in the EDELWEISS 3 study were invited to enter the EDELWEISS 6 extension study. In EDELWEISS 6, patients who received placebo in EDELWEISS 3 were randomised 1:1 to linzagolix 75 mg or linzagolix 200 mg plus ABT. Patients who received active treatment in EDELWEISS 3 continued with the same treatment.⁴ Please see Figure 3.2 above for an overview of EDELWEISS 6 trial process.

In line with EDELWEISS 3, the co-primary endpoints of EDELWEISS 6 were clinically meaningful reduction of dysmenorrhoea (reduction of ≥ 1.10 points on the VRS) and NMPP (reduction of ≥ 0.8 points on the VRS) from baseline to the last 28 days preceding the month 12 visit, along with stable or decreased use of analgesics for EAP. Secondary endpoints of EDELWEISS 6 included changes from baseline to month 12 in dysmenorrhoea, NMPP, dyschezia, OPP, interference of pain with the ability to perform daily activities (using the EHP-30 pain dimension) and dyspareunia. Other secondary

endpoints included analgesic and opioid use for EAP, number of days in hospital, PSIQ/SSIQ and HRQoL⁴.

3.2.2.2.1 EDELWEISS 6 Eligibility criteria

The following criteria applied for inclusion of participants in the study:⁴

- Patients who completed the 6-month treatment period in EDELWEISS 3

The following criteria applied for exclusion of participants in the study:⁴

- Liver enzyme anomalies reaching discontinuation levels
- BMD decrease of >8% from EDELWEISS 3 baseline or a Z-score ≤ 2.5 at either the femoral neck, hip or spine at EDELWEISS 3 month 6

3.2.2.2.2 EDELWEISS 6 Baseline characteristics

The baseline characteristics of both arms of the EDELWEISS 6 are presented in Table 3.9 below. Generally, the arms are well balanced.

Table 3.9: EDELWEISS 6 | Baseline characteristics (TEAS)

EDELWEISS 6 Characteristics	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)	Total (N=353)
Age, years, mean (SD)	34.2 (6.6)	35.0 (7.7)	35.0 (6.3)	34.9 (6.8)	34.8 (6.7)
Race, n (%)					
White	57 (100.0)	56 (98.2)	116 (98.3)	119 (98.3)	348 (98.6)
Black or African-American	0	1 (1.8)	1 (0.8)	1 (0.8)	3 (0.9)
Asian	0	0	1 (0.8)	0	1 (0.3)
Multiple	0	0	0	1 (0.8)	1 (0.3)
BMI, kg/m ² , mean (SD)	23.41 (4.04)	24.77 (5.06)	24.83 (5.55)	23.83 (4.59)	24.25 (4.94)
Weight, kg, mean (SD)	63.93 (11.19)	68.03 (13.83)	65.59 (15.13)	65.26 (13.55)	66.61 (13.87)
Time since seeking medical diagnosis / treatment, years, mean (SD)	5.76 (5.20)	4.56 (4.22)	5.13 (4.49)	5.36 (3.99)	5.22 (4.40)
Baseline pain scores, mean (SD)					
Overall pelvic pain VRS ^a	1.84 (0.41)	1.93 (0.41)	1.90 (0.40)	1.90 (0.39)	1.89 (0.40)
NMPP VRS ^a	1.70 (0.45)	1.82 (0.47)	1.76 (0.45)	1.77 (0.43)	1.76 (0.45)
Dysmenorrhoea VRS ^a	2.27 (0.41)	2.30 (0.45)	2.27 (0.39)	2.28 (0.40)	2.28 (0.41)

EDELWEISS 6 Characteristics		Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)	Total (N=353)
Overall pelvic pain NRS		5.97 (1.53)	6.37 (1.60)	6.00 (1.62)	6.16 (1.53)	6.11 (1.57)
Dyspareunia VRS		1.93 (0.87)	2.00 (0.83)	1.94 (0.87)	2.12 (0.84)	2.01 (0.86)
EHP-30 pain dimension		50.56 (15.40)	52.92 (13.45)	51.83 (14.30)	52.08 (15.00)	51.88 (14.55)
Baseline analgesic use on bleeding days ^a , pill count/day, mean (SD)		1.80 (1.49)	1.36 (1.17)	1.96 (1.83)	2.11 (1.79)	1.89 (1.68)
Baseline analgesic use on non-bleeding days ^a , pill count/day, mean (SD)		0.85 (1.03)	0.60 (0.74)	1.05 (1.27)	1.11 (1.12)	0.97 (1.12)
Baseline dyschezia NRS, mean (SD)		4.38 (2.22)	4.57 (2.76)	3.78 (2.70)	3.94 (2.75)	4.06 (2.66)
Baseline lipids and BMD data [ESAF]	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)		Total (N=356)
Baseline lipid levels, mg/dL, mean (SD) [ESAF]						
LDL cholesterol		110.6 (33.3)	116.7 (32.6)	115.5 (33.5)	116.4 (31.9)	115.2 (32.7)
Triglycerides		88.3 (39.2)	93.0 (51.5)	97.3 (53.9)	90.6 (42.2)	92.9 (47.4)
Baseline BMD, g/cm ² , mean (SD) [ESAF]						
Femoral neck		1.000 (0.121)	1.002 (0.148)	1.009 (0.141)	0.987 (0.143)	0.999 (0.139)
Lumbar spine		1.224 (0.135)	1.194 (0.140)	1.210 (0.153)	1.179 (0.128)	1.199 (0.140)
Total hip		1.034 (0.106)	1.029 (0.121)	1.041 (0.127)	1.022 (0.124)	1.031 (0.122)
Baseline BMD, Z-scores, mean (SD) [ESAF]						
Femoral neck		0.245 (0.831)	0.251 (0.930)	0.437 (1.008)	0.195 (0.920)	0.293 (0.940)
Lumbar spine		0.600 (0.973)	0.313 (0.987)	0.576 (1.153)	0.257 (0.911)	0.428 (1.027)
Total hip		0.430 (0.854)	0.379 (0.904)	0.529 (1.025)	0.347 (0.973)	0.427 (0.962)
Based on Table 9 of CS ⁴						
^a Based on the two selected screening menstrual cycles.						
ABT = add-back therapy; BMD = bone mineral density; BMI = body mass index; CS = company submission; EHP-30 = endometriosis health profile-30; ESAF = extension safety analysis set; LDL = low-density						

EDELWEISS 6 Characteristics	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)	Total (N=353)
lipoprotein; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; SD = standard deviation; TEAS = treatment extension analysis set; VRS = verbal rating scale					

EAG comment: As already mentioned in Section 2.1, limiting the trial to women of reproductive age might limit the applicability of the trial data if the population is broader than women of reproductive age. Also, the lack of UK patients might also limit generalisability. Together these imply a key issue.

3.2.3 Statistical analysis for the EDELWEISS 3 and EDELWEISS 6

A summary of the analysis sets in the EDELWEISS 3 is provided in Table 3.10.

Table 3.10: EDELWEISS 3 | Analysis sets

Analysis set	Definition	Number of patients			
		Linzagolix 75 mg	Linzagolix 200 mg plus ABT	Placebo	Total
FAS	All randomised patients who received ≥ 1 dose of study drug, irrespective of the treatment received. Patients were analysed according to randomised treatment.	160	162	162	484
Per-protocol	All randomised patients who completed the 6 months of treatment, excluding those with major protocol deviations that could potentially affect efficacy assessments up to month 6. Patients were analysed according to randomised treatment.	134	139	133	406
Safety analysis set	All randomised patients who received ≥ 1 dose of study drug, irrespective of the treatment received. Patients were analysed according to the treatment received.	160	162	162	484
Based on Table 6 of CS ⁴ ABT = add-back therapy; CS = company submission; FAS = full analysis set					

A summary of the analysis sets in the EDELWEISS 6 is provided in Table 3.11.

Table 3.11: EDELWEISS 6 | Analysis sets

Analysis set	Definition	Number of patients				
		Placebo/ linzagolix 75 mg	Placebo/ linzagolix 200 mg plus ABT	Linzagolix 75 mg	Linzagolix 200 mg plus ABT	Total
Treatment extension	All patients from the EDELWEISS 3 study	57	57	118	121	353

Analysis set	Definition	Number of patients				
		Placebo/ linzagolix 75 mg	Placebo/ linzagolix 200 mg plus ABT	Linzagolix 75 mg	Linzagolix 200 mg plus ABT	Total
analysis set	who entered the EDELWEISS 6 extension study and received ≥ 1 dose of study drug, with the exception of patients whose month 6 assessments subsequently met any of the protocol discontinuation criteria. Patients were analysed according to randomised treatment.					
Follow-up extension analysis set	All patients from the main study who entered the extension study and received ≥ 1 dose of study drug, with the exception of patients whose month 6 assessment subsequently met any of the discontinuation criteria, and who entered the post-treatment follow-up period. Patients were analysed according to randomised treatment.	53	50	111	112	326
Per-protocol extension analysis set	All patients from the treatment extension analysis set, excluding those with major protocol deviations that could potentially affect efficacy assessments up to month 12. Patients were analysed according to randomised treatment.	54	55	112	115	336
Extension safety analysis set	All patients randomised into the extension study who received ≥ 1 dose of study drug irrespective of the treatment received. Patients were analysed according to treatment received.	58	57	119	122	356

Analysis set	Definition	Number of patients				
		Placebo/ linzagolix 75 mg	Placebo/ linzagolix 200 mg plus ABT	Linzagolix 75 mg	Linzagolix 200 mg plus ABT	Total
Follow-up safety analysis set	All subjects randomised into the extension study who received ≥ 1 dose of study drug irrespective of the treatment received, and who entered the post-treatment follow-up period. Patients were analysed according to treatment received.	54	50	112	113	329
Based on Table 7 of CS ⁴ ABT = add-back therapy; CS = company submission						

Statistical methods used in the EDELWEISS 3 and 6 trials are summarised in Table 3.12.

Table 3.12: Clinical effectiveness studies | Summary of statistical analyses

	EDELWEISS 3	EDELWEISS 6
Trial name/number	NCT03992846	NCT04335591
Hypothesis objective	The primary objective was to demonstrate the efficacy and safety of once daily linzagolix at a dose of 75 mg alone or 200 mg with ABT, versus placebo, in the management of Moderate to Severe EAP in women with surgically confirmed endometriosis.	The primary objective was to assess the maintenance of efficacy of once daily linzagolix for up to an additional 6 months (for up to 12 months of treatment in total) in women who had already completed 6 months of linzagolix treatment (in EDELWEISS 3) at a dose of 75 mg alone or of 200 mg plus ABT in the management of Moderate to Severe EAP in women with surgically confirmed endometriosis.
Statistical analysis	Statistical analyses were performed using SAS statistical software. Efficacy analyses were performed using the FAS (primary analysis) and PP populations. Responder threshold analyses for co-primary endpoints and ranked secondary endpoints were performed based on MCTs estimated from blinded data using anchor-based methods. Co-primary endpoints: analysed using a logistic regression model, with the treatment group as the main effect (three values) and the baseline pain score as a covariate. Estimated	Statistical analyses were performed using SAS statistical software. Efficacy analyses were performed using the TEAS (primary analysis), the FU EAS and the PP EAS. Efficacy endpoints were derived in the same way as for EDELWEISS 3 although results were summarised using descriptive statistics.

	EDELWEISS 3	EDELWEISS 6
	proportions of responders were reported based on the overall mean baseline pain score and differences between the linzagolix groups versus placebo were reported using Bonferroni-corrected p-values. Ranked secondary endpoints: A fixed-sequence testing strategy within individual groups was used for ranked secondary endpoints, to maintain the family-wise type I error rate. Comparisons for each linzagolix group versus placebo for each ranked endpoint only reached a statistically significant difference if the doubled raw p-value was ≤ 0.05 for that particular endpoint and all preceding endpoints for that linzagolix dose versus placebo. Changes from baseline in dysmenorrhoea, NMPP, dyschezia, OPP, EHP-30 pain dimensions and dyspareunia were analysed using ANCOVA, with treatment group as the main effect and baseline and pain scores as covariates. Other secondary endpoint analyses used Bonferroni correction for p-values of comparison of treatment groups. The analyses did not form part of the fixed-sequence strategy being used for the co-primary and ranked secondary endpoints and were not fully controlled for an overall type I error rate.	
Sample size, power calculation	The planned sample size was 150 patients per treatment group (450 patients in total). This considered the hierarchical, fixed sequence testing of the ranked secondary endpoints as well as the co-primary endpoints. The assumptions used for the sample size calculations were informed by response rates from the Phase 2b EDELWEISS study (NCT02778399).^{46, 57} The inclusion of 150 patients per treatment group provided a power >95% to reject the null hypothesis for both co-primary endpoints for	With 150 subjects in each of the three treatment groups in the main study (450 patients in total), the power was >95% to reject the null hypothesis for both co-primary endpoints and 85% to reject all the null hypotheses for the ranked secondary endpoints. All patients who had completed the full 6-month treatment period in the main study and who met the inclusion criteria were invited to enter the extension study. It was estimated that up to 288 subjects would enter the extension study,

	EDELWEISS 3	EDELWEISS 6
	either treatment group, assuming (based on EDELWEISS study results), a placebo response rate of 14.6% and an active treatment response rate of 48.6% (75 mg) or 64.7% (200 mg) for dysmenorrhoea, and a placebo response rate of 18.8% and an active treatment response rate of 42.1% (75 mg) for NMPP; the response rate for 200 mg in EDELWEISS was lower but was inconsistent with the other doses and other timepoints for the same dose so was not used for NMPP. Including 150 patients per treatment group also provided 85% power to reject the null hypotheses for all the ranked secondary endpoints based on the observed results from the placebo and 200 mg treatment group in the EDELWEISS study. The values used for the sample size calculations assumed that these response rates are what would be seen on average when on treatment including taking into account any possible early withdrawals; therefore, no further adjustment for dropouts was needed.	assuming that 80% of the patients randomised in the main study would complete the study (namely 360 subjects) and that up to 80% of these would enter the extension study.
Data management, patient withdrawals	Summary statistics were based primarily on non-missing values. The planned statistical analyses aimed to estimate the efficacy of linzagolix versus placebo while under randomised treatment and therefore lack of data after treatment discontinuation were not considered as missing for these analyses. Patients whose response could not be assessed for the co-primary efficacy endpoints, e.g. due to lack of on treatment pain data (i.e. subjects who received less than 28 days of treatment), were considered as non-responders (and assigned a change from baseline of zero). For any missing data during the screening or treatment periods (e.g. missed days of completing the eDiary), the primary analyses used observed data only in such cases	Summary statistics were based primarily on non-missing values. As the planned analyses aimed to estimate the efficacy of linzagolix versus placebo while under randomised treatment, lack of data after treatment discontinuation were not considered as missing for these analyses. For any missing data (e.g. missed days of completing the eDiary) during the screening period (from EDELWEISS 3) and treatment periods, the primary analyses used observed data only in such cases that a minimum number of completed daily eDiary entries were available. This effectively assumed that the individual values such as daily eDiary assessments (observed or not) were independent of being missing.

	EDELWEISS 3	EDELWEISS 6
	where a minimum number of completed daily eDiary entries were available. This effectively assumed that the individual values such as daily eDiary assessments (observed or not) were independent of being missing. Patients with less than the minimum number of days available were excluded from the analysis. This is valid under the assumption that such data were MAR, conditional on the baseline value. Imputation of missing adverse event and concomitant medication data was only done to identify TEAEs.	Imputation of missing adverse event and concomitant medication data was only done to identify TEAEs.
Statistical analysis timepoints	The co-primary endpoint analyses were based on the 28 days preceding the month 3 visit. Ranked secondary endpoint analyses were based on the 28 days preceding the month 6 visit.	The co-primary endpoint and main secondary endpoint analyses were based on the 28 days preceding the month 12 visit.
Based on Table 5 of CS ⁴ ABT = add-back therapy; ANCOVA = analysis of covariance; CS = company submission; EAP = endometriosis-associated pain; EHP-30 = Endometriosis Health Profile-30; FAS = full analysis set; FU EAS = follow-up extension analysis set; MAR = missing at random; MCT = meaningful change threshold; NMPP = non-menstrual pelvic pain; OPP = overall pelvic pain; OR = odds ratio; PP = per-protocol; PP EAS = per-protocol extension analysis set; TEAE = treatment-emergent adverse event; TEAS = treatment extension analysis set		

3.2.4 Risk of bias assessment

According to the CS⁴, “The methodological quality of each trial was assessed independently by two reviewers using the Cochrane Collaboration’s revised risk-of-bias tool for randomised trials (RoB 2). Disagreements were resolved by consensus. The risk of bias was defined as low for all the trials included in the Bucher analysis.” Further details can be found in Table 3.13.

Table 3.13: Risk of bias assessment of trials included in the Bucher analysis using the Cochrane Collaboration’s revised risk-of-bias tool for randomised trials (RoB 2)

No	Signalling questions	<i>EDELWEISS 3</i>	<i>SPIRIT 1</i>	<i>SPIRIT 2</i>	<i>Osuga 2021a/2021b</i>
Domain 1: Risk of bias arising from the randomisation process					
1.1	Was the allocation sequence random?	Yes	Yes	Yes	Yes
1.2	Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	Yes	Yes	Yes
1.3	Did baseline differences between intervention groups suggest a problem with the randomisation process?	No	No	No	No

No	Signalling questions	<i>EDELWEISS 3</i>	<i>SPIRIT 1</i>	<i>SPIRIT 2</i>	<i>Osuga 2021a/2021b</i>
Risk-of-bias judgement		Low risk	Low risk	Low risk	Low risk
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)					
2.1	Were participants aware of their assigned intervention during the trial?	No	No	No	No*
2.2	Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No	No	No	No*
2.3	If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	N/A	N/A	N/A	N/A
2.4	If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	N/A	N/A	N/A	N/A
2.5	If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	N/A	N/A	N/A	N/A
2.6	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes	Yes	Yes
2.7	If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	N/A	N/A	N/A	N/A
Risk-of-bias judgement		Low risk	Low risk	Low risk	Low risk
Risk of bias due to missing outcome data					
3.1	Were data for this outcome available for all, or nearly all, participants randomised?	Yes	Yes	Yes	Yes
3.2	If N/PN/NI to 3.1 Is there evidence that the result was not biased by missing outcome data?	N/A	N/A	N/A	N/A
3.3	If N/PN to 3.2 Could missingness in the outcome depend on its true value?	N/A	N/A	N/A	N/A
3.4	If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	N/A	N/A	N/A	N/A
Risk-of-bias judgement		Low risk	Low risk	Low risk	Low risk
Risk of bias in measurement of the outcome					

No	Signalling questions	<i>EDELWEISS 3</i>	<i>SPIRIT 1</i>	<i>SPIRIT 2</i>	<i>Osuga 2021a/2021b</i>
4.1	Was the method of measuring the outcome inappropriate?	No	No	No	No
4.2	Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No	No	No
4.3	If N/PN/Ni to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No	No	No	No
4.4	If Y/PY/Ni to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N/A	N/A	N/A	N/A
4.5	If Y/PY/Ni to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	N/A	N/A	N/A	N/A
Risk-of-bias judgement		Low risk	Low risk	Low risk	Low risk
Risk of bias in selection of the reported result					
5.1	Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes	Yes	Yes	Yes
5.2	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	No	No	No	No
5.3	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	No	No	No	No
Risk-of-bias judgement		Low risk	Low risk	Low risk	Low risk
Overall risk-of-bias judgement		Low risk	Low risk	Low risk	Low risk
Based on Table 31 of CS Appendix D ¹¹ CS = company submission; N/A = not applicable					

EAG comment: It appears that the key trial of the intervention, as well as those in the ITC included in the CS are of low risk of bias. Note that patients in the placebo arm of EDELWEISS 3 received placebo capsules for both linzagolix and ABT.¹⁶

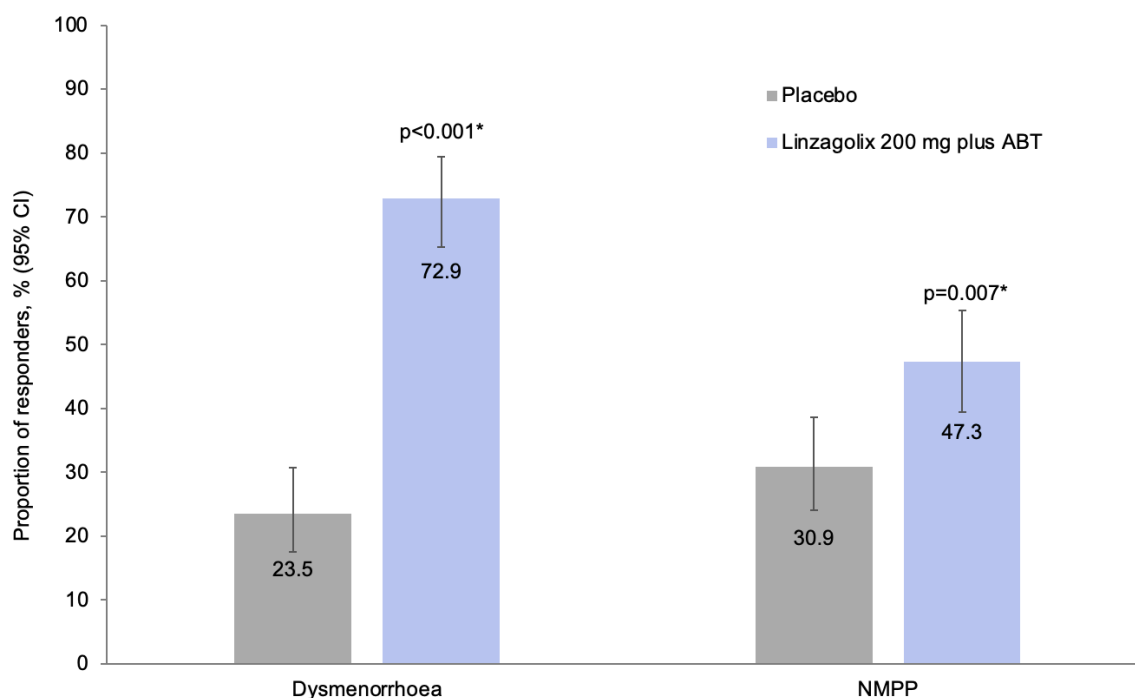
3.2.5 Efficacy results of the EDELWEISS 3

3.2.5.1 Co-primary endpoints of EDELWEISS 3

According to the CS⁴, the co-primary endpoint for the group of patients receiving a daily dose of linzagolix 200 mg plus ABT shown that at month 3, the estimated percentage of responders for dysmenorrhoea was 72.9% (95% confidence interval [CI]: 65.3–79.4) in the linzagolix 200 mg plus ABT group versus 23.5% (95% CI: 17.5–30.7) in the placebo group (odds ratio [OR] 8.80 [97.5% CI: 4.86–15.91]; $p < 0.001$); the proportions for NMPP were 47.3% (95% CI: 39.5–55.3) with linzagolix 200 mg plus ABT versus 30.9% (95% CI: 24.1–38.6) with placebo (OR 2.01 [97.5% CI: 1.18–3.42]; $p = 0.007$). Further details can be found in the Figure 3.3 below.

The company noticed that the linzagolix 75 mg alone dose demonstrated a clinically meaningful and statistically significant reduction in dysmenorrhoea versus placebo at month 3, but the reduction in NMPP at month 3 versus placebo was not statistically significant.⁴

Figure 3.3: EDELWEISS 3 | Pain and analgesia | Dysmenorrhoea and NMPP responders at month 3 (co-primary endpoints; FAS)



Based on Figure 9 of CS⁴

Responders for the co-primary endpoint were defined as patients who met the clinically meaningful reduction thresholds for the primary analysis of dysmenorrhoea and NMPP as a reduction of ≥ 1.10 and ≥ 0.8 points on the VRS for dysmenorrhoea and NMPP, respectively, from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for endometriosis-associated pain.

* Clinically significant value

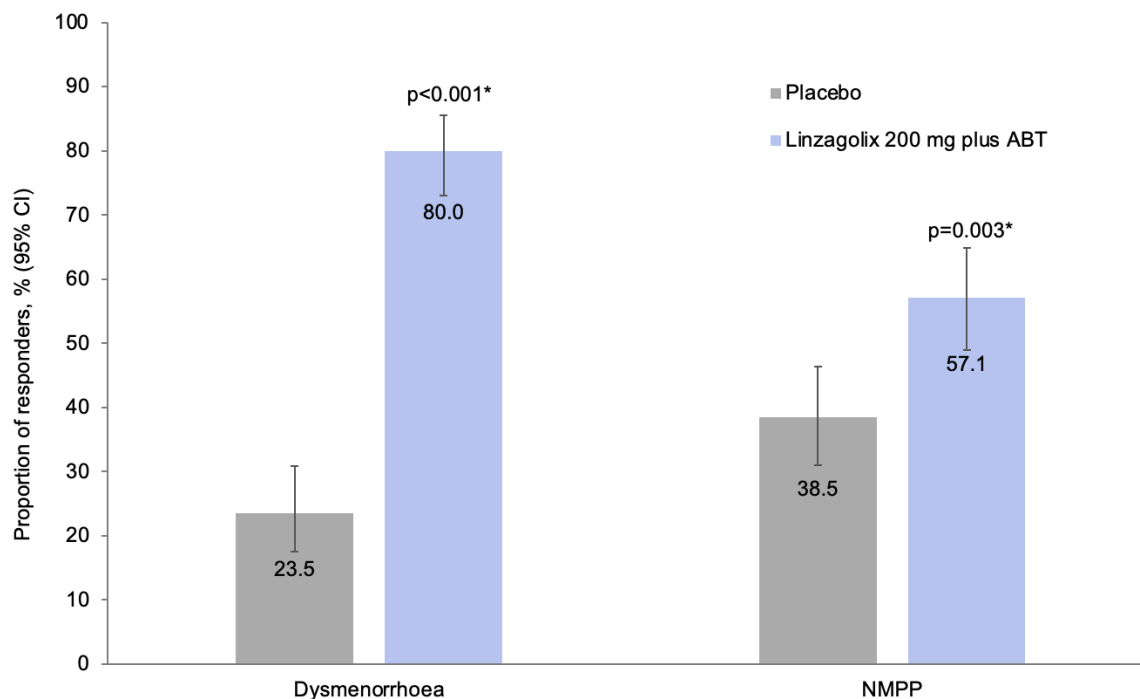
ABT = add-back therapy; CI = confidence interval; CS = company submission; FAS = full analysis set; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale

3.2.5.2 Secondary endpoints

3.2.5.2.1 Pain and analgesia

According to the CS⁴, the proportions of responders for both dysmenorrhoea and NMPP were significantly greater for linzagolix 200 mg plus ABT than placebo at EDELWEISS 3 month 6. Details can be found in Figure 3.14.

Figure 3.4: EDELWEISS 3 | Pain and analgesia | Dysmenorrhoea and NMPP responders at month 6 (secondary endpoints; FAS)



Based on Figure 12 of CS⁴

* Clinically significant value

ABT = add-back therapy; CI = confidence interval; CS = company submission; FAS = full analysis set; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale

The company also reported the statistically significant and clinically meaningful improvements from baseline to month 6 with linzagolix 200 mg plus ABT versus placebo were dysmenorrhoea, NMPP, dyschezia, OPP and ability to participate in daily activities (based on pain dimensions listed in the EHP-30).

Table 3.14: EDELWEISS 3 | Ranked secondary endpoints at month 6 (FAS)

EDELWEISS 3 Endpoint	Placebo (N=162)	Linzagolix 75 mg (N=160)			Linzagolix 200 mg plus ABT (N=162)		
Change from baseline to month 6 in:							
	LSM (95% CI)	LSM (95% CI)	Difference versus placebo (97.5% CI)	p- value ^a	LSM (95% CI)	Difference versus placebo (97.5% CI)	p-value ^a
Dysmenorrhoea (VRS)	−0.66 (−0.79, −0.53)	−1.10 (−1.23, −0.97)	−0.44 (−0.65, −0.23)	<0.001	−1.83 (−1.96, −1.70)	−1.17 (−1.38, −0.97)	<0.001
NMPP (VRS)	−0.66 (−0.79, −0.56)	−0.84 (−0.95, −0.73)	−0.17 (−0.35, 0.00)	0.048	−0.92 (−1.03, −0.82)	−0.26 (−0.43, −0.09)	0.002
Dyschezia (NRS)	−1.41 (−1.71, −1.12)	−1.98 (−2.28, −1.69)	−0.57 (−1.05, −0.09)	0.015	−1.99 (−2.29, −1.70)	−0.58 (−1.05, −0.11)	0.012
OPP (NRS)	−2.19 (−2.55, −1.84)	−2.84 (−3.20, −2.48)	−0.65 (−1.23, −0.07)	0.024	−3.39 (−3.74, −3.03)	−1.19 (−1.77, −0.62)	<0.001
EHP-30 Pain dimension	−19.47 (−22.66, −16.28)	−27.37 (−30.50, −24.25)	−7.90 (−13.01, −2.79)	0.001	−35.60 (−38.73, −32.48)	−16.13 (−21.24, −11.02)	<0.001
Dyspareunia (VRS)	−0.82 (−0.97, −0.66)	−1.04 (−1.21, −0.88)	−0.23 (−0.49, 0.03)	0.100	−1.01 (−1.18, −0.85)	−0.20 (−0.46, 0.07)	0.184
No analgesic/opiate use for EAP during the preceding 4-week period at month 6							
	% of responders (95% CI)	% of responders (95% CI)	OR ^{b,c} (97.5% CI)	p-value ^{a,c}	% of responders (95% CI)	OR ^{b,c} (97.5% CI)	p-value ^{a,c}
No analgesic use for EAP	13.2 (8.9, 19.2)	30.9 (23.8, 39.1)	2.95 (1.58, 5.50)	<0.001	44.5 (36.3, 52.9)	5.27 (2.83, 9.82)	<0.001
No opiate use for EAP	97.0 (92.5, 98.9)	93.8 (88.5, 96.8)	0.47 (0.12, 1.82)	0.420	97.0 (92.7, 98.8)	0.99 (0.22, 4.51)	1.000
Based on Table 12 of CS ⁴							
^a Bonferroni-corrected p-value. A fixed-sequence testing strategy was used to account for multiplicity. The linzagolix 200 mg plus ABT group demonstrated statistically significant differences versus placebo for both co-primary endpoints. The linzagolix 75 mg group was not statistically significantly different from placebo for the non-menstrual pelvic pain co-primary endpoint.							
^b ORs and 97.5% CIs were estimated using a logistic regression model with no analgesic use/no opiate use in the last 28 days on treatment prior to month 6 as the response variable, treatment group as the main effect and including the baseline analgesic use/opiate use as a covariate.							
^c The statistical analysis hierarchy was interrupted as the change from baseline to month 6 in dyspareunia with linzagolix did not differ significantly from that observed with placebo. Therefore, statistical significance cannot be confirmed for the proportions of patients reporting no analgesic use in the 4 weeks to month 6 with linzagolix versus placebo.							

EDELWEISS 3 Endpoint	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)
ABT = add-back therapy; CI = confidence interval; EAP = endometriosis-associated pain; EHP-30 = Endometriosis Health Profile-30; FAS = full analysis set; LSM = least squares mean; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; OPP = overall pelvic pain; OR = odds ratio; VRS = verbal rating scale. Scores were computed as means of daily assessments on the last 28 days prior to month 6 or discontinuation. Analysis of covariance with change from baseline as response variable, and baseline value, treatment as covariates.			

3.2.5.2.2 Number of days in hospital

According to the CS⁴, hospitalisations were infrequent throughout the EDELWEISS 3 studies, with <2% of patients hospitalised at any measured time point (and most time points having 0% hospitalisation).

3.2.5.2.3 Physician/Subject Surgery Intention Question

The company explained the reductions in EAP resulted in a reduced intention for surgery after 6 months in EDELWEISS 3 based on both the PSIQ and SSIQ with linzagolix versus placebo.⁴ Further details can be found in Table 3.15.

Table 3.15: EDELWEISS 3 | Change from baseline in intention for surgery: analysis of covariance (FAS)

EDELWEISS 3	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)
PSIQ			
Baseline, mean (SD)	4.1 (2.7)	4.0 (2.8)	4.4 (2.7)
Month 6			
LSM (95% CI)	-0.8 (-1.2, -0.5)	-1.5 (-1.8, -1.1)	-1.5 (-1.9, -1.2)
LSM difference versus placebo (97.5% CI)		-0.6 (-1.2, 0.0) p=0.037 ^a	-0.7 (-1.3, -0.1) p=0.017 ^a
SSIQ			
Baseline, mean (SD)	5.2 (3.2)	5.2 (3.1)	5.5 (3.3)
Month 6			
LSM (95% CI)	-0.7 (-1.1, 0.3)	-1.5 (-1.9, -1.1)	-1.6 (-2.1, -1.2)
LSM difference versus placebo (97.5% CI)		-0.8 (-1.5, -0.1) p=0.022 ^a	-0.9 (-1.6, -0.2) p=0.005 ^a
Based on Table 16 of CS ⁴ Answers ranged from 0-Not at all to 10-Very likely. Analysis of covariance at each timepoint or discontinuation with change from baseline as response variable, baseline value and treatment as covariates. ^a Bonferroni-corrected p-value. ABT = add-back therapy; CI = confidence interval; CS = company submission; FAS = full analysis set; LSM = least squares mean; PSIQ = Physician Surgery Intention Question; SD = standard deviation; SSIQ = Subject Surgery Intention Question			

3.2.5.2.4 Health-related quality of life

The company reported improvements in broader HRQoL aspects: “The EHP-30 dimensions of ‘control and powerlessness’, ‘emotional wellbeing’, ‘social support’ and ‘self-image’ also showed statistically

significant improvements (score reductions) from baseline to month 6 in the linzagolix 200 mg plus ABT group versus placebo, although improvement in the ‘modular sexual relationship’ dimension was not statistically significant versus placebo. The improvement (increase) in EQ-5D-5L Index and VAS scores from baseline to month 6 was also significantly greater with linzagolix 200 mg plus ABT versus placebo.”⁴ Further details can be found in Table 3.16.

Table 3.16: EDELWEISS 3 | Change from baseline in HRQoL (FAS)

EDELWEISS 3	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)
EHP-30 Pain^a			
Baseline, mean (SD)	51.77 (14.43)	51.46 (14.28)	52.37 (15.14)
Change from baseline to month 6			
LSM (95% CI)	-19.47 (-22.66; -16.28)	-27.37 (-30.50, -24.25)	-35.60 (-38.73, -32.48)
LSM difference versus placebo (97.5% CI)		-7.90 (-13.01, -2.79) p=0.001 ^b	-16.13 (-21.24, -11.02) p<0.001 ^b
EHP-30 Control and powerlessness^a			
Baseline, mean (SD)	58.36 (19.47)	55.53 (20.92)	60.65 (19.93)
Change from baseline to month 6			
LSM (95% CI)	-21.75 (-25.63, -17.88)	-28.12 (-31.93, -24.31)	-37.38 (-41.19, -33.58)
LSM difference versus placebo (97.5% CI)		-6.36 (-12.59, -0.14) p=0.044 ^b	-15.63 (-21.84, -9.42) p<0.001 ^b
EHP-30 Emotional wellbeing^a			
Baseline, mean (SD)	46.18 (19.51)	46.50 (20.32)	47.27 (20.58)
Change from baseline to month 6			
LSM (95% CI)	-12.57 (-16.13, -9.01)	-19.04 (-22.52, -15.57)	-22.03 (-25.52, -18.54)
LSM difference versus placebo (97.5% CI)		-6.47 (-12.17, -0.78) p=0.022 ^b	-9.46 (-15.17, -3.76) p<0.001 ^b
EHP-30 Social support^a			
Baseline, mean (SD)	45.21 (25.10)	44.79 (25.33)	47.05 (25.42)
Change from baseline to month 6			
LSM (95% CI)	-13.82 (-17.69, -9.95)	-18.48 (-22.25, -14.70)	-25.89 (-29.68, -22.10)
LSM difference versus placebo (97.5% CI)		-4.65 (-10.85, 1.54) p=0.183 ^b	-12.07 (-18.27, -5.87) p<0.001 ^b

EHP-30 Self-image ^a			
Baseline, mean (SD)	41.56 (25.76)	42.57 (23.96)	43.97 (25.79)
Change from baseline to month 6			
LSM (95% CI)	-9.57 (-13.31, -5.84)	-16.43 (-20.07, -12.78)	-20.69 (-24.34, -17.03)
LSM difference versus placebo (97.5% CI)		-6.86 (-12.83, -0.88) p=0.020 ^b	-11.11 (-17.10, -5.13) p<0.001
EHP-30 Modular sexual relationship ^a			
Baseline, mean (SD)	56.90 (25.08)	53.63 (24.86)	59.96 (23.43)
Change from baseline to month 6			
LSM (95% CI)	-20.55 (-24.96, -16.14)	-22.59 (-27.00, -18.18)	-26.79 (-31.14, -22.44)
LSM difference versus placebo (97.5% CI)		-2.04 (-9.18, 53.10) p=1.000 ^b	-6.24 (-13.33, 0.86) p=0.097 ^b
EQ-5D-5L Index value ^c			
Baseline, mean (SD)	0.72 (0.16)	0.74 (0.16)	0.74 (0.15)
Change from baseline to month 6			
LSM (95% CI)	0.08 (0.06, 0.10)	0.11 (0.08, 0.13)	0.12 (0.10, 0.15)
LSM difference versus placebo (97.5% CI)		0.03 (-0.01, 0.06) p=0.190 ^b	0.05 (0.01, 0.08) p=0.009 ^b
EQ-5D-5L VAS score ^d			
Baseline, mean (SD)	61.9 (19.6)	63.8 (19.7)	62.0 (19.8)
Change from baseline to month 6			
LSM (95% CI)	5.4 (1.9, 8.8)	9.4 (6.0, 12.7)	14.6 (11.2, 18.0)
LSM difference versus placebo (97.5% CI)		4.0 (-1.5, 9.5) p=0.209 ^b	9.2 (3.7, 14.7) p<0.001 ^b
Based on Table 17 of CS⁴ ^a EHP-30 scale score was computed as the sum of each scale question score/(number of items*4)*100 and ranges from 0 (best possible health status) to 100 (worst possible health status). ^b Bonferroni-corrected p-value. ^c The index score ranges from -0.109 to 1. A higher index value indicates a better QoL. ^d The VAS score ranges from 0 to 100. A higher VAS score indicates a better QoL. Scores were computed as mean of daily assessments on the last 28 days prior to each visit or discontinuation. Analysis of covariance at each timepoint with change from baseline as response variable, baseline value and treatment as covariates. Subjects with less than 43% of daily diary data completed were excluded. ABT = add-back therapy; CI = confidence interval; CS = company submission; EHP-30 = endometriosis health Profile-30; EQ-5D-5L = European Quality of Life-5 dimension 5 levels; FAS = full analysis set; HRQoL = health-related quality of life; QoL = quality of life; SD = standard deviation; VAS = visual analogue scale			

EAG comment: There was a statistically significant advantage to linzagolix 200 mg plus ABT versus placebo in all outcomes except for dyspareunia (VRS) and EHP-30 Modular sexual relationship where there was only a numerical advantage.

3.2.6 Efficacy results of the EDELWEISS 6

3.2.6.1 Co-primary endpoints of EDELWEISS 6

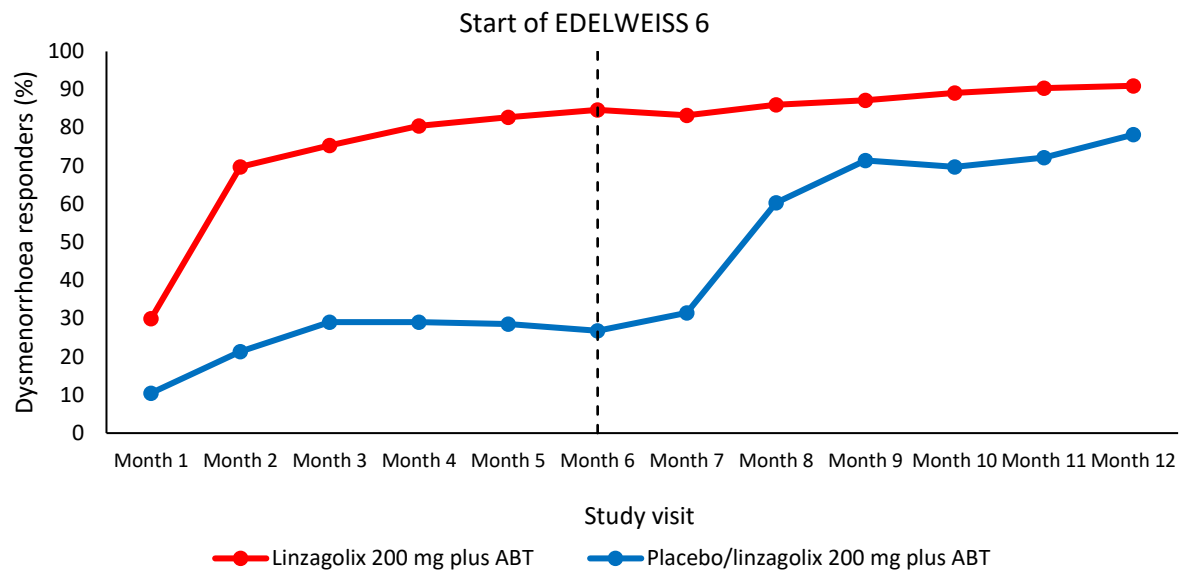
The company observed further improvements in the linzagolix 200 mg plus ABT group at month 12 in EDELWEISS 6 ⁴. Further details are shown in the Table 3.17 below.

There is an apparently reduction in dysmenorrhoea and an increment in the proportion of responders for NMPP following the start of EDELWEISS 6 since Month 6. Further details can be found in the following Figures 3.5 and 3.6.

Table 3.17: EDELWEISS 6 | Pain and analgesia co-primary endpoint | Dysmenorrhoea and NMPP responders at month 12 (TEAS)

EDELWEISS 6 Endpoint	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
Proportion of responders for dysmenorrhoea, n (%)	32 (56.1)	43 (78.2)	62 (55.9)	101 (91.0)
Proportion of responders for non-menstrual pelvic pain, n (%)	34 (59.6)	27 (49.1)	66 (59.5)	75 (67.6)
Based on Table 11 of CS⁴ Responders at month 12 were defined as patients who met the clinically meaningful reduction thresholds of a reduction of ≥ 1.10 and ≥ 0.8 points on the VRS for dysmenorrhoea and NMPP, respectively, from EDELWEISS 3 baseline to the last 28 days of randomised treatment up to month 12, along with stable or decreased use of analgesics for endometriosis-associated pain. Scores were computed as means of daily assessments on the last 28 days prior to month 12 or discontinuation. ABT = add-back therapy; CS = company submission; NMPP = non-menstrual pelvic pain; TEAS = treatment extension analysis set; VRS = verbal rating scale				

Figure 3.5: EDELWEISS 6 | Pain and analgesia co-primary endpoint | Dysmenorrhoea responders up to month 12 (TEAS)



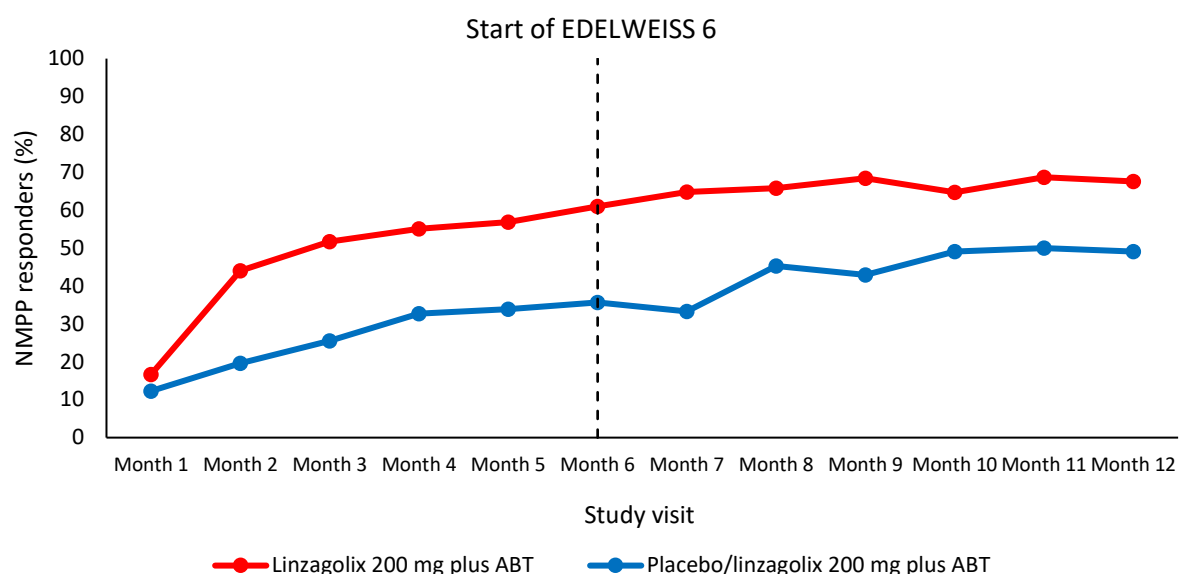
Based on Figure 10 of CS⁴

Patients who received placebo for 6 months in EDELWEISS 3 were then randomised to receive either linzagolix 75 mg or linzagolix 200 mg ABT for 6 months in EDELWEISS 6.

Dysmenorrhoea responders were defined as patients who met the clinically meaningful reduction threshold of a reduction of ≥ 1.10 on the VRS for dysmenorrhoea from EDELWEISS 3 baseline to the last 28 days of randomised treatment, along with stable or decreased use of analgesics for endometriosis-associated pain.

ABT = add-back therapy; CS = company submission; TEAS = treatment extension analysis set; VRS = verbal rating scale

Figure 3.6: EDELWEISS 6 | Pain and analgesia co-primary endpoint | NMPP responders up to month 12 (TEAS)



Based on Figure 11 of CS⁴

Patients who received placebo for 6 months in EDELWEISS 3 were then randomised to receive either linzagolix 75 mg or linzagolix 200 mg ABT for 6 months in EDELWEISS 6.

NMPP responders were defined as patients who met the clinically meaningful reduction thresholds of a reduction of ≥ 0.8 points on the VRS for NMPP from EDELWEISS 3 baseline to the last 28 days of randomised treatment, along with stable or decreased use of analgesics for endometriosis-associated pain.

ABT = add-back therapy; CS = company submission; NMPP = non-menstrual pelvic pain; TEAS = treatment extension analysis set; VRS = verbal rating scale

3.2.6.2 Secondary endpoints

3.2.6.2.1 Pain and analgesia

According to the CS⁴, steady improvements were observed with linzagolix 200 mg plus ABT throughout the treatment period of EDELWEISS 6. Further details can be found in Table 3.18.

The company also mentioned that patients in the EDELWEISS 6 follow-up extension analysis set (FU EAS) were still experiencing lingering treatment benefits at the end of treatment, as the proportions of responders for NMPP (with stable or reduced use of analgesics) remained relatively stable after the end of the treatment period. Further details can be found in Table 3.19.

Table 3.18: EDELWEISS 6 | Pain and analgesia secondary endpoints at month 12 (TEAS)

EDELWEISS 6 Endpoint	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
Mean (SD) change from baseline to month 12 in:				
Dysmenorrhoea (VRS)	-1.26 (0.93)	-1.79 (0.93)	-1.32 (0.90)	-2.02 (0.71)
NMPP (VRS)	-0.85 (0.62)	-0.96 (0.81)	-1.03 (0.72)	-1.16 (0.64)
Dyschezia (NRS)	-2.52 (2.26)	-2.47 (2.50)	-2.11 (2.43)	-2.72 (2.36)
OPP (NRS)	-3.44 (2.14)	-3.56 (2.42)	-3.46 (2.37)	-4.35 (2.14)
EHP-30 pain dimension	-29.68 (20.91)	-33.04 (21.69)	-31.65 (22.88)	-41.89 (20.21)
Dyspareunia (VRS)	-0.99 (1.05)	-1.00 (1.11)	-1.24 (1.04)	-1.29 (1.07)
No analgesic/opiate use for EAP during the preceding 4-week period at month 12, n (%)				
No analgesic use for EAP	19 (33.3)	27 (48.2)	52 (45.2)	62 (56.1)
No opiate use for EAP	54 (94.7)	54 (98.2)	107 (95.5)	109 (98.2)
Based on Table 13 of CS ⁴ ABT = add-back therapy; CS = company submission; EAP = endometriosis-associated pain; EHP-30 = Endometriosis Health Profile-30; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; OPP = overall pelvic pain; SD = standard deviation; TEAS = treatment extension analysis set; VRS = verbal rating scale Scores were computed as means of daily assessments on the last 28 days prior to month 12 or discontinuation. Patients with <43% of daily diary data completed were excluded.				

Table 3.19: EDELWEISS 6 | Pain and analgesia | Dysmenorrhoea and NMPP responders at month 12 (end of treatment) and at month 6 after the end of treatment (FU EAS)

EDELWEISS 6 Endpoint	Placebo/ linzagolix 75 mg (N=53)	Placebo/ linzagolix 200 mg plus ABT (N=50)	Linzagolix 75 mg (N=111)	Linzagolix 200 mg plus ABT (N=112)
Proportion of responders for dysmenorrhoea, n (%)				
Month 12 (end of treatment)	29 (54.7)	39 (79.6)	59 (56.2)	94 (90.4)
Month 6 extension follow-up (month 6 after end of treatment)	18 (41.9)	15 (35.7)	36 (40.9)	51 (54.3)
Proportion of responders for NMPP, n (%)				
Month 12 (end of treatment)	32 (60.4)	24 (49.0)	61 (58.1)	68 (65.4)
Month 6 extension follow-up (month 6 after end of treatment)	17 (39.5)	18 (42.9)	49 (55.7)	63 (67.0)
Based on Table 14 of CS ⁴ ABT = add-back therapy; CS = company submission; FU EAS = follow-up extension analysis set; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale Scores were computed as means of daily assessments on the last 28 days prior to month 12 or discontinuation.				

3.2.6.2.2 Number of days in hospital

According to the CS⁴, hospitalisations were infrequent throughout the EDELWEISS 6 studies, with <2% of patients hospitalised at any measured time point (and most time points having 0% hospitalisation).

3.2.6.2.3 Physician/Subject Surgery Intention Question

The company demonstrated that the longer patients received linzagolix, the lower the desire of physicians to recommend surgery and, as “*The reduction from baseline to EDELWEISS 3, month 6, on the PSIQ in the linzagolix 200 mg plus ABT group became more pronounced at EDELWEISS 6, month 12, while the previous reduction on the SSIQ remained stable*”. For patients themselves, the desire for surgery was reduced at month 6 after introducing linzagolix but this did not change further at month 12.⁴

Further details are shown in Table 3.20.

Table 3.20: EDELWEISS 6 | Change from baseline in intention for surgery (TEAS)

EDELWEISS 6	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
PSIQ				
Baseline, mean (SD)	4.5 (2.4)	4.0 (2.6)	4.0 (2.7)	4.6 (2.7)
Mean (SD) change from baseline				
Month 6	-1.1 (3.0)	-0.7 (2.4)	-1.5 (2.1)	-2.0 (2.8)
Month 12	-1.5 (2.8)	-1.6 (2.8)	-1.8 (2.6)	-2.7 (2.8)
SSIQ				
Baseline, mean (SD)	5.7 (2.9)	5.1 (3.1)	5.4 (3.0)	5.5 (3.2)
Mean (SD) change from baseline				
Month 6	-1.0 (2.9)	-0.6 (2.8)	-1.4 (2.7)	-1.9 (3.4)
Month 12	-2.1 (3.0)	-1.7 (3.7)	-1.6 (3.5)	-1.9 (3.7)
Based on Table 14 of CS ⁴ ABT = add-back therapy; CS = company submission; PSIQ = Physician Surgery Intention Question; SD = standard deviation; SSIIQ = Subject Surgery Intention Question; TEAS = treatment extension analysis set Answers ranged from 0-not at all to 10-very likely.				

3.2.6.2.4 Health-related quality of life

The company observed improvements from baseline in the EHP-30 dimensions of pain, control and powerlessness, emotional wellbeing, social support, self-image and sexual relationship and European Quality of Life-5 dimensions 5 levels (EQ-5D-5L) index and visual analogue scale (VAS) scores with linzagolix 200 mg plus ABT up to month 12 in EDELWEISS 6 ⁴.

EAG comment: There was a continued improvement with linzagolix 200 mg plus ABT in all outcomes during the 6-month extension to the 6-month double blind randomised period, with plateauing towards the end of the 12-month follow-up period.

3.2.7 Adverse events

3.2.7.1 Treatment compliance and exposure

3.2.7.1.1 EDELWEISS 3 and EDELWEISS 2

The company states that the median treatment duration in EDELWEISS 3 was 24 weeks for each group, while in EDELWEISS 2, the median treatment duration and time on study were longer for patients in the linzagolix groups versus the placebo group as higher dropout rates from approximately month 2 in the placebo versus linzagolix groups.⁴ Further details can be found in Table 3.21.

The company also mentioned that “Treatment compliance was high in EDELWEISS 3 and EDELWEISS 2, with a median in all treatment groups of 100% in EDELWEISS 3 and >90% in EDELWEISS 2. Approximately 75% of patients in EDELWEISS 3 had a compliance of ≥98%.”⁴

Table 3.21: EDELWEISS 3 and EDELWEISS 2 | Exposure to study treatment (EDELWEISS 3 FAS; EDELWEISS 2 SAF)

	EDELWEISS 3			EDELWEISS 2		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Placebo (N=27)	Linzagolix 75 mg (N=28)	Linzagolix 200 mg plus ABT (N=29)
Treatment duration, weeks ^a						
Mean (SD)	22.22 (4.93)	22.18 (5.32)	22.72 (4.24)	14.50 (9.30)	18.34 (7.64)	15.76 (8.93)
Median (Q1, Q3)	24.00 (23.57, 24.14)	24.00 (23.57, 24.21)	24.00 (23.71, 24.14)	14.57 (4.29, 24.14)	23.64 (12.21, 24.07)	18.14 (8.00, 24.14)
Range	1.1–25.9	0.1–26.1	1.6–27.9	0.1–25.0	1.4–25.3	0.1–25.0
Time on study, weeks ^b						
Mean (SD)	25.68 (11.66)	25.13 (10.35)	26.41 (9.84)	18.51 (11.90)	20.43 (8.66)	17.46 (8.39)
Median (Q1, Q3)	24.00 (23.71, 24.57)	24.00 (23.71, 24.29)	24.00 (23.86, 24.57)	14.86 (9.71, 24.84)	23.86 (14.50, 24.29)	19.86 (10.14, 24.29)
Range	1.4–84.3	0.1–78.0	1.7–72.1	3.1–50.9	4.1–46.4	0.1–29.0
Based on Table 23 of CS ⁴ ^a Duration of treatment (weeks) was defined as: [(date of last treatment administration) - (date of first administration as collected in the eCRF) +1] /7 ^b The time on study (weeks) was defined as: [(end of study date) – (date of first dose) +1]/7. ABT = add-back therapy; CS = company submission; eCRF = electronic case report form; FAS = full analysis set; Q = quartile; SAF = safety analysis set; SD = standard deviation						

3.2.7.1.2 EDELWEISS 6

The median treatment duration for each treatment group was 24 weeks and the median time on study was 49 weeks in the extension study period (EDELWEISS 6); meanwhile, median treatment duration was 48 weeks and the median time on study was 73 weeks in the overall study period (EDELWEISS 3 and EDELWEISS 6).⁴ The details are summarised in Table 3.22.

Table 3.22: EDELWEISS 6 | Exposure to study treatment (TEAS)

	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
Treatment duration in extension study, weeks ^a				
Mean (SD)	22.29 (5.20)	23.12 (2.89)	22.41 (4.65)	23.02 (3.53)
Median (Q1, Q3)	24.00 (23.71, 24.29)	24.00 (23.86, 24.29)	24.00 (23.71, 24.14)	24.00 (23.71, 24.14)
Range	4.0–24.9	9.3–25.4	3.3–27.1	4.0–27.0

	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=57)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=118)	Linzagolix 200 mg plus ABT (N=121)
Treatment duration overall, weeks^b				
Mean (SD)	46.43 (4.92)	47.37 (2.45)	46.49 (4.51)	47.17 (3.39)
Median (Q1, Q3)	48.00 (47.71, 48.29)	48.00 (47.86, 48.43)	48.00 (47.57, 48.29)	48.00 (47.86, 48.29)
Range	28.3–49.3	39.0–49.9	27.6–50.9	31.9–51.4
Time on extension study, weeks^c				
Mean (SD)	47.55 (13.38)	48.21 (12.78)	49.32 (13.40)	50.47 (13.27)
Median (Q1, Q3)	48.43 (47.29, 50.29)	48.86 (47.71, 50.29)	48.79 (47.29, 51.29)	49.14 (47.86, 52.43)
Range	4.3–75.1	5.0–78.4	4.0–82.4	4.1–82.0
Time on study overall, weeks^d				
Mean (SD)	71.69 (13.18)	72.46 (12.53)	73.40 (13.31)	74.62 (13.16)
Median (Q1, Q3)	72.86 (71.29, 74.14)	72.46 (71.71, 74.57)	72.57 (71.43, 75.14)	73.29 (71.71, 77.00)
Range	28.4–99.3	34.7–103.4	27.9–106.6	32.0–105.4
Based on Table 24 of CS ⁴				
^a Duration of treatment in extension (weeks) was defined as: [(date of last treatment administration in extension) - (date of first administration in extension as collected in the eCRF) +1] /7				
^b Duration of treatment overall (weeks) was defined as: [(date of last treatment administration in extension) - (date of first administration in EDELWEISS 3 as collected in the eCRF) +1] /7				
^c The time on study in extension (weeks) was defined as: [(end of extension study date) – (date of first dose in extension) +1]/7				
^d The time on study overall (weeks) was defined as: [(end of extension study date) – (date of first dose in EDELWEISS 3) +1]/7				
ABT = add-back therapy; CS = company submission; eCRF = electronic case report form; Q = quartile; SD = standard deviation; TEAS = treatment extension analysis set				

3.2.7.2 Treatment-emergent adverse events

3.2.7.2.1 EDELWEISS 3 and EDELWEISS 2

The company states that linzagolix was well tolerated. Similar percentages of patients reported TEAEs in the linzagolix 75 mg and placebo groups (46.9% in each group) during the 6-month treatment period in EDELWEISS 3, while slightly higher rates of TEAEs were observed in the linzagolix 200 mg plus ABT group (56.8%). In EDELWEISS 2, the percentages of patients reporting TEAEs were similar between placebo and linzagolix groups. ⁴ Details are summarised in Table 3.23.

The company also mentioned, “In both studies, most TEAEs were mild or moderate in intensity, and the incidence of Severe TEAEs was low and comparable between groups.” ⁴

Table 3.23: EDELWEISS 3 and EDELWEISS 2 | Summary of adverse events up to month 6 (SAF)

TEAEs, n (%)	EDELWEISS 3			EDELWEISS 2		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Placebo (N=27)	Linzagolix 75 mg (N=28)	Linzagolix 200 mg plus ABT (N=29)
Any TEAE	76 (46.9)	75 (46.9)	92 (56.8)	14 (51.9)	14 (50.0)	15 (51.7)
Severe TEAEs	2 (1.2)	5 (3.1)	3 (1.9)	2 (7.4)	0	0
TEAEs related to linzagolix	40 (24.7)	45 (28.1)	56 (34.6)	4 (14.8)	4 (14.3)	7 (24.1)
TEAEs related to ABT	33 (20.4)	33 (20.6)	45 (27.8)	4 (14.8)	4 (14.3)	5 (17.2)
Serious AEs	0	2 (1.3)	2 (1.2)	0	0	0
Serious TEAEs	0	1 (0.6)	2 (1.2)	0	0	0
Serious TEAEs related to linzagolix	0	0	0	0	0	0
Serious TEAEs related to ABT	0	0	0	0	0	0
TEAEs leading to permanent discontinuation of study drug	4 (2.5)	9 (5.6)	5 (3.1)	2 (7.4)	1 (3.6)	2 (6.9)
Fatal TEAEs	0	0	0	0	0	0
Based on Table 25 of CS ⁴ ABT = add-back therapy; AEs = adverse events; CS = company submission; SAF = safety analysis set; TEAE = treatment-emergent adverse event						

3.2.7.2.2 EDELWEISS 6

The company states that linzagolix continued to be well tolerated during EDELWEISS 6. No additional safety signals were observed during the extension study treatment period or post-treatment follow-up period (follow-up safety analysis set [FU SAF]). Also, more than 40% of patients reported TEAEs between month 6 and the end of the treatment period at month 12. Most TEAEs (approximately 99% overall) were mild or Moderate in intensity.⁴ Details are summarised in Table 3.24.

Table 3.24: EDELWEISS 6 | Summary of adverse events from month 6 to month 12 (ESAF)

TEAEs, n (%)	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)
Any TEAE	27 (46.6)	27 (47.4)	53 (44.5)	49 (40.2)

TEAEs, n (%)	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)
Severe TEAEs	1 (1.7)	2 (3.5)	1 (0.8)	1 (0.8)
TEAEs related to linzagolix	13 (22.4)	14 (24.6)	19 (16.0)	23 (18.9)
TEAEs related to ABT	10 (17.2)	8 (14.0)	14 (11.8)	13 (10.7)
Serious TEAEs	0	1 (1.8)	3 (2.5)	0
Serious TEAEs related to linzagolix	0	0	0	0
Serious TEAEs related to ABT	0	0	1 (0.8)	0
TEAEs leading to permanent discontinuation of study drug	2 (3.4)	2 (3.5)	3 (2.5)	2 (1.6)
Fatal TEAEs	0	0	0	0
Based on Table 26 of CS ⁴ ABT = add-back therapy; CS = company submission; ESAF = extension safety analysis set; TEAE = treatment-emergent adverse event				

3.2.7.3 Most common treatment-emergent adverse events

3.2.7.3.1 EDELWEISS 3 and EDELWEISS 2

The company stated that “The most common TEAEs were headaches, which were reported for similar proportions of patients in each group. Hot flushes were more common in the linzagolix groups than the placebo group in EDELWEISS 3. Rates of fatigue were similar in the linzagolix 75 mg and placebo groups, but slightly higher in the linzagolix 200 mg plus ABT group in EDELWEISS 3.”⁴

The company also reported “Data from EDELWEISS 2 were generally in line with those from EDELWEISS 3, but interpretability was limited by the low patient numbers.”⁴

Further details can be found in Table 3.25.

Table 3.25: EDELWEISS 3 and EDELWEISS 2 | TEAEs reported up to month 6 by $\geq 5\%$ of patients in any group in EDELWEISS 3 (SAF)

TEAEs, n (%)	EDELWEISS 3			EDELWEISS 2		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Placebo (N=27)	Linzagolix 75 mg (N=28)	Linzagolix 200 mg plus ABT (N=29)
Headache	13 (8.0)	13 (8.1)	17 (10.5)	2 (7.4)	2 (7.1)	2 (6.9)
Hot flush	4 (2.5)	12 (7.5)	11 (6.8)	1 (3.7)	1 (3.6)	1 (3.4)
Fatigue	4 (2.5)	6 (3.8)	11 (6.8)	1 (3.7)	2 (7.1)	0
Anaemia	10 (6.2)	5 (3.1)	4 (2.5)	0	0	0
Mood swings	3 (1.9)	8 (5.0)	5 (3.1)	1 (3.7)	0	0
Arthralgia	2 (1.2)	8 (5.0)	3 (1.9)	0	0	0

Based on Table 27 of CS⁴
 ABT = add-back therapy; CS = company submission; SAF = safety analysis set; TEAE = treatment-emergent adverse event

3.2.7.3.2 EDELWEISS 6

The company stated that “Headache and hot flushes were also among the most commonly reported TEAEs from month 6 to month 12 in EDELWEISS 6, along with COVID-19 and anaemia.”⁴

The company also noted that “Hot flushes were not reported for any patients in the placebo/linzagolix 200 mg plus ABT group and anaemia was not reported in the linzagolix 200 mg plus ABT group.”⁴ Further details can be found in Table 3.26.

Table 3.26: EDELWEISS 6 | TEAEs reported from month 6 to month 12 by $\geq 5\%$ of patients in any group (ESAF)

TEAEs, n (%)	EDELWEISS 6			
	Placebo/linzagolix 75 mg (N=58)	Placebo/linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)
COVID-19	1 (1.7)	2 (3.5)	6 (5.0)	6 (4.9)
Headache	3 (5.2)	3 (5.3)	5 (4.2)	3 (2.5)
Hot flush	4 (6.9)	0	4 (3.4)	5 (4.1)
Anaemia	3 (5.2)	2 (3.5)	7 (5.9)	0
Vaginal haemorrhage	1 (1.7)	3 (5.3)	3 (2.5)	3 (2.5)

Based on Table 28 of CS⁴
 ABT = add-back therapy; COVID-19 = coronavirus disease 2019; CS = company submission; ESAF = extension safety analysis set; TEAE = treatment-emergent adverse event

3.2.7.4 Most common treatment-related adverse events

3.2.7.4.1 EDELWEISS 3 and EDELWEISS 2 | Most common linzagolix-related AEs up to month 6

The company stated that “The most common TEAEs related to linzagolix treatment were hot flushes and headache.”⁴ Further details can be found in Table 3.27.

Table 3.27: EDELWEISS 3 and EDELWEISS 2 | TEAEs related to linzagolix treatment reported up to month 6 by $\geq 5\%$ of patients in any group in EDELWEISS 3 (SAF)

TEAEs, n (%)	EDELWEISS 3			EDELWEISS 2		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)	Placebo (N=27)	Linzagolix 75 mg (N=28)	Linzagolix 200 mg plus ABT (N=29)
Headache	6 (3.7)	12 (7.5)	10 (6.2)	0	1 (3.6)	1 (3.4)
Hot flush	4 (2.5)	12 (7.5)	11 (6.8)	1 (3.7)	1 (3.6)	1 (3.4)
Mood swings	2 (1.2)	8 (5.0)	4 (2.5)	1 (3.7)	0	0
Based on Table 29 of CS ⁴ ABT = add-back therapy; CS = company submission; SAF = safety analysis set; TEAE = treatment-emergent adverse event						

3.2.7.4.2 EDELWEISS 3 and EDELWEISS 2 | Most common ABT-related AEs up to month 6

The company stated that “22.9% of patients in the EDELWEISS 3 safety analysis set reported TEAEs considered related to ABT. The percentage of patients reporting TEAEs related to ABT was similar in the placebo (20.4%) and linzagolix 75 mg (20.6%) groups and slightly higher in the linzagolix 200 mg ABT group (27.8%).”⁴

The company also reported that “The most common ABT-related TEAEs included headache (5.8%), fatigue (2.9%), nausea (2.9%), and hot flushes (2.7%). Nausea was observed with similar frequency in the placebo and linzagolix groups. Headache, fatigue and hot flushes were reported more frequently in the linzagolix groups compared with placebo.”⁴

Also, “In EDELWEISS 2, the number of patients reporting ABT-related TEAEs was similar between the placebo (n=4 patients), linzagolix 75 mg (n=4) and linzagolix 200 mg plus ABT (n=5) groups.”⁴

3.2.7.4.3 EDELWEISS 6 | Most common linzagolix-related AEs from month 6 to month 12

The company stated that “The most common linzagolix-related TEAEs included decreased bone density, hot flush and mood swings.”⁴ Further details can be found in Table 3.28.

Table 3.28: EDELWEISS 6 | TEAEs related to linzagolix treatment reported from month 6 to month 12 by $\geq 2\%$ of patients in any group (ESAF)

TEAEs, n (%)	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)
Bone density decreased	2 (3.4)	2 (3.5)	5 (4.2)	2 (1.6)
Hot flush	3 (5.2)	0	4 (3.4)	4 (3.3)
Mood swings	2 (3.4)	1 (1.8)	1 (0.8)	3 (2.5)
Headache	1 (1.7)	2 (3.5)	1 (0.8)	1 (0.8)
Nausea	2 (3.4)	2 (3.5)	1 (0.8)	1 (0.8)
Vaginal haemorrhage	0	2 (3.5)	1 (0.8)	1 (0.8)
Vulvovaginal dryness	0	2 (3.5)	0	1 (0.8)
Increased appetite	0	2 (3.5)	0	1 (0.8)
Alopecia	2 (3.4)	0	0	0
Based on Table 30 of CS ⁴ ABT = add-back therapy; CS = company submission; ESAF = extension safety analysis set; TEAE = treatment-emergent adverse event				

3.2.7.4.4 EDELWEISS 6 | Most common ABT-related AEs from month 6 to month 12

The company reported that “The percentage of patients reporting ABT-related TEAEs was slightly higher in the placebo/linzagolix 75 mg group (17.2%, compared with placebo/linzagolix 200 mg plus ABT: 14.0%; linzagolix 75 mg: 11.8%; linzagolix 200 mg plus ABT: 10.7%).”⁴

Also, “The most common (i.e., in at least 1% of the ESAF overall) ABT-related TEAEs included vaginal haemorrhage (1.7%), hot flush (1.4%) and nausea (1.4%).”⁴

3.2.7.5 Treatment discontinuation due to adverse events

3.2.7.5.1 EDELWEISS 3 and EDELWEISS 2

In EDELWEISS 3, the treatment discontinuation rate due to TEAEs in the linzagolix 200 mg plus ABT group (3.1%) was similar to that for the placebo group (2.5%), although the rate was slightly higher for the linzagolix 75 mg group (5.6%); While, in EDELWEISS 2, treatment discontinuation rates due to TEAEs were comparable between the placebo and linzagolix groups.⁴

3.2.7.5.2 EDELWEISS 6

Nine patients discontinued treatment due to TEAEs from month 6 to month 12, with rates comparable across treatment groups (placebo/linzagolix 75 mg: 3.4%; placebo/linzagolix 200 mg plus ABT: 3.5%; linzagolix 75 mg: 2.5%; linzagolix 200 mg plus ABT: 1.6%).⁴

3.2.7.6 Serious adverse events

3.2.7.6.1 EDELWEISS 3 and EDELWEISS 2

Serious adverse events (SAEs) were comparable across all groups in EDELWEISS 3, with none reported in EDELWEISS 2, indicating good tolerability for linzagolix. In EDELWEISS 3, serious TEAEs included pneumonia and abdominal pain (n=1 each) in the 200 mg group, and peritonitis and endometriosis (in the same patient) in the 75 mg group, none of which were treatment-related.⁴

3.2.7.6.2 EDELWEISS 6

Four patients experienced serious TEAEs from month 6 to 12, none related to linzagolix. These included genital tract bleeding (n=1, placebo/linzagolix 200 mg plus ABT), exacerbation of cholelithiasis (n=1, placebo/linzagolix 75 mg), acute anxiety (n=1, linzagolix 75 mg), and vaginal bleeding (n=1, linzagolix 75 mg). The vaginal bleeding was linked to ABT, though this patient received an ABT placebo.⁴

3.2.7.7 EDELWEISS 3 and EDELWEISS 6 | Bone mineral density

Bone mineral density (BMD) was largely unaffected by linzagolix treatment at month 6 (EDELWEISS 3) and month 12 (EDELWEISS 6). Some BMD increases were noted at 6 months after end of treatment (EDELWEISS 6 month 6 ExFU), indicating partial recovery.⁴

Most patients in the linzagolix groups had either an increase, no change or $\leq 3\%$ decrease in BMD at month 6 in the lumbar spine (84.5%), femoral neck (88.2%) and total hip (94.3%).⁴ Further details can be found in Table 3.29.⁴

Table 3.29: EDELWEISS 3 | Percentage change in BMD by category from baseline at month 6 (SAF)

BMD, g/cm ² , % change from baseline	EDELWEISS 3		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)
Lumbar spine			
n (missing)	123 (39)	132 (28)	132 (30)
No change, increase, or decrease $\leq 3\%$, n (%)	118 (95.9)	109 (82.6)	114 (86.4)
Decrease $> 3\%$, n (%)	5 (4.1)	6 (4.5)	18 (13.6)
Decrease $> 8\%$, n (%)	0	1 (0.8)	0
Femoral neck			
n (missing)	121 (41)	130 (30)	132 (30)
No change, increase, or decrease $\leq 3\%$, n (%)	109 (90.1)	117 (90.0)	114 (86.4)
Decrease $> 3\%$, n (%)	12 (9.8)	13 (9.8)	18 (13.6)
Decrease $> 8\%$, n (%)	1 (0.8)	0	3 (2.3)
Total hip			
n (missing)	121 (41)	130 (30)	132 (30)

BMD, g/cm ² , % change from baseline	EDELWEISS 3		
	Placebo (N=162)	Linzagolix 75 mg (N=160)	Linzagolix 200 mg plus ABT (N=162)
No change, increase, or decrease ≤3%, n (%)	114 (94.2)	122 (93.8)	125 (94.7)
Decrease >3%, n (%)	7 (5.8)	8 (6.2)	7 (5.3)
Decrease >8%, n (%)	0	0	1 (0.8)
Based on Table 31 of CS ⁴ ABT = add-back therapy; BMD = bone mineral density; CS = company submission; SAF = safety analysis set			

Changes in BMD during EDELWEISS 6 were also minimal, with most patients having an increase, no change or ≤3% decrease in BMD at each measured site from baseline to month 12.⁴ Further details can be found in Table 3.30.⁴

Some BMD increases were noted at 6 months after end of treatment (EDELWEISS 6 Month 6 ExFU), indicating partial recovery. Up to month 6 ExFU, most patients registered either no change or increase, or decrease ≤3% in BMD at the lumbar spine (75.3%), femoral neck (78.0%) and total hip (90.2%). Decreases >8% in BMD were observed at the femoral neck (four patients in total) and at the total hip (one patient in the linzagolix 75 mg group).⁴

Table 3.30: EDELWEISS 6 | Percentage change in BMD from baseline at month 12 (ESAF)

BMD, g/cm ² , percentage change from baseline	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)
Lumbar spine				
n (missing)	39 (19)	42 (15)	78 (41)	86 (36)
Mean (SD) [95% CI] change	-0.74 (2.93) [-1.69, 0.21]	-0.45 (3.26) [-1.47, 0.56]	-1.10 (2.52) [-1.67, -0.53]	-1.10 (3.22) [-1.79, -0.41]
No change, increase, or decrease ≤3%, n (%)	31 (79.5)	31 (73.8)	60 (76.9)	63 (73.3)
Decrease >3%, n (%)	8 (20.5)	11 (26.2)	18 (23.1)	23 (26.7)
Decrease >8%, n (%)	0	0	1 (1.3)	2 (2.3)
Femoral neck				
n (missing)	39 (19)	42 (15)	77 (42)	85 (37)
Mean (SD) [95% CI] change	-0.93 (2.78) [-1.83, -0.03]	-0.93 (2.75) [-1.79, -0.08]	-0.57 (3.42) [-1.35, 0.20]	-0.70 (3.00) [-1.35, -0.06]
No change, increase, or	32 (82.1)	34 (81.0)	56 (72.7)	69 (81.2)

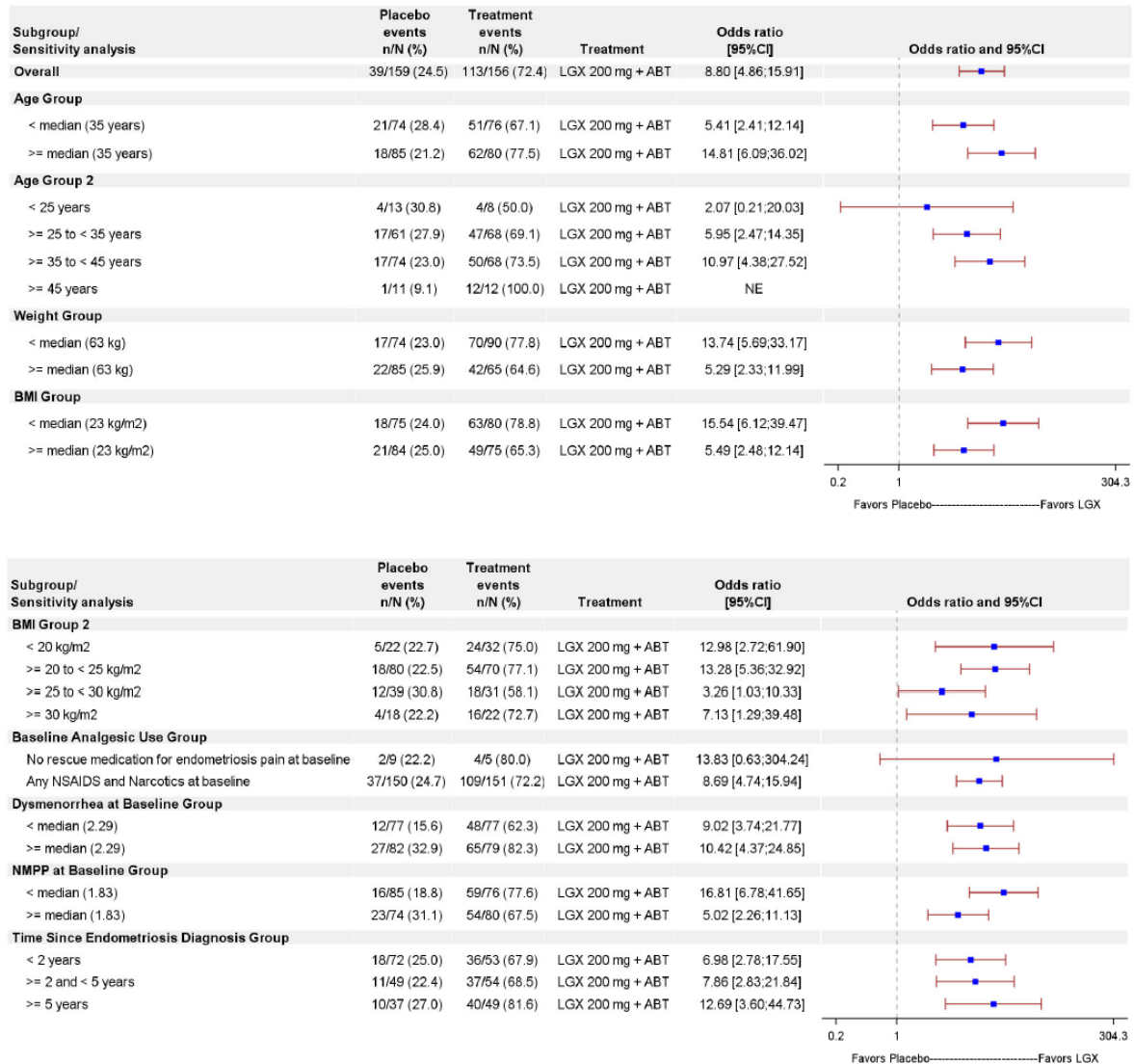
BMD, g/cm ² , percentage change from baseline	EDELWEISS 6			
	Placebo/ linzagolix 75 mg (N=58)	Placebo/ linzagolix 200 mg plus ABT (N=57)	Linzagolix 75 mg (N=119)	Linzagolix 200 mg plus ABT (N=122)
decrease $\leq 3\%$, n (%)				
Decrease $> 3\%$, n (%)	7 (17.9)	8 (19.0)	21 (27.3)	16 (18.8)
Decrease $> 8\%$, n (%)	1 (2.6)	0	2 (2.6)	1 (1.2)
Total hip				
n (missing)	39 (19)	42 (15)	77 (42)	85 (37)
Mean (SD) [95% CI] change	-0.41 (2.16) [-1.11, 0.29]	0.58 (1.77) [0.03, 1.13]	-0.37 (2.51) [-0.94, 0.20]	-0.52 (2.13) [-0.98, -0.06]
No change, increase, or decrease $\leq 3\%$, n (%)	35 (89.7)	42 (100.0)	67 (87.0)	76 (89.4)
Decrease $> 3\%$, n (%)	4 (10.3)	0	10 (13.0)	9 (10.6)
Decrease $> 8\%$, n (%)	0	0	0	1 (1.2)
Based on Table 32 of CS ⁴ ABT = add-back therapy; BMD = bone mineral density; CI = confidence interval; CS = company submission; ESAF = extension safety analysis set; SD = standard deviation				

EAG comment: AE rates appear to have been similar between the placebo and linzagolix 200 mg plus ABT with higher rates for headache, hot flush and mood swings, which were regarded as treatment related. Decrease in BMD, albeit appearing to be uncommon, was also more common with linzagolix 200 mg plus ABT.

3.2.8 Subgroup analysis

Subgroup analyses were provided for co-primary endpoints (dysmenorrhea and NMPP). The CS states that the treatment effect was consistent across various prespecified subgroups.⁴

Figure 3.7: Forest plots of ORs of reduction of dysmenorrhea* at month 3 overall and by subgroup (FAS)



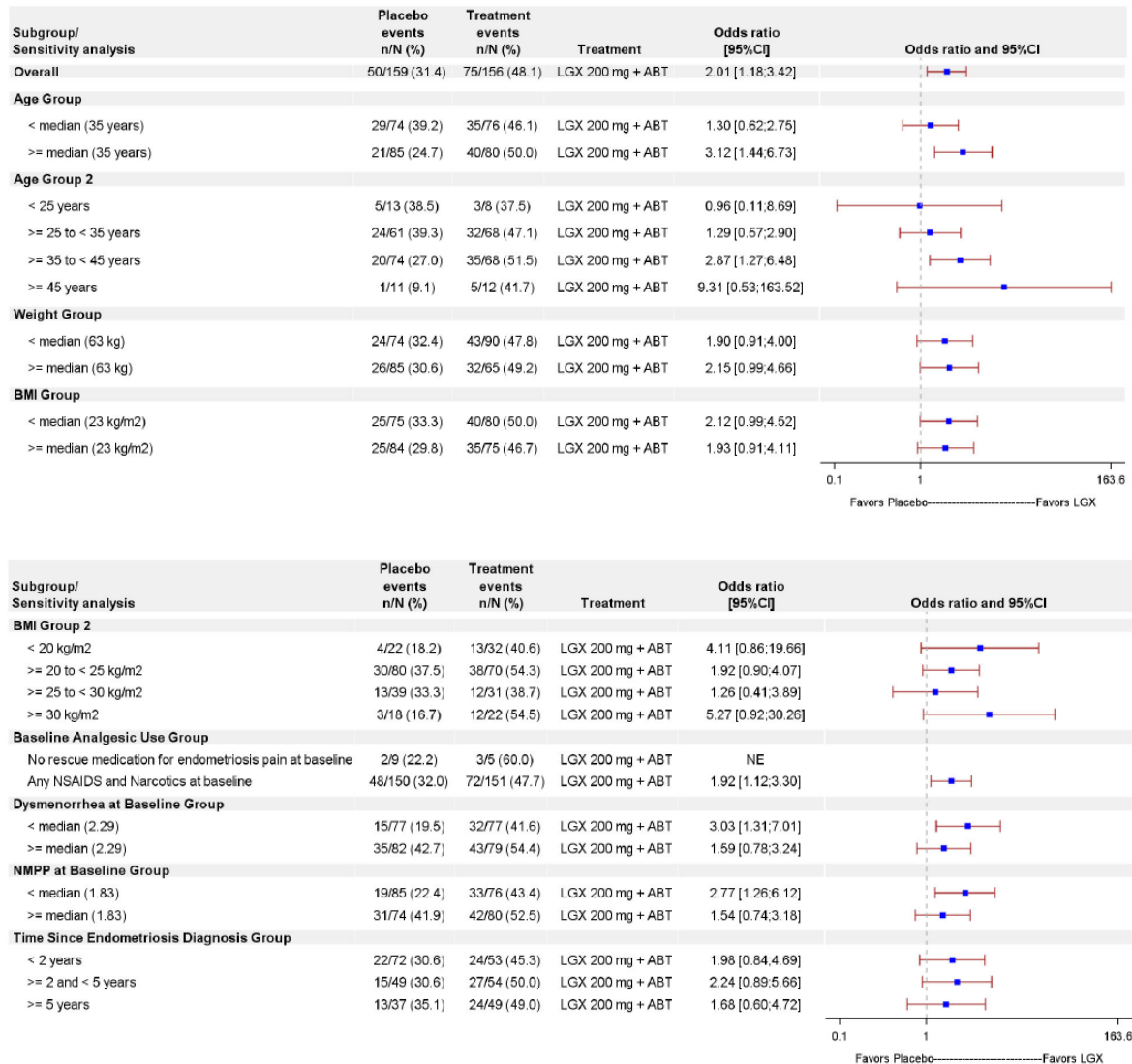
Based on Figure 1 of Appendix E¹⁷

* Reduction of ≥ 1.1 of DYS in mean pelvic pain score from baseline to the last 28 days prior to month 3 or discontinuation, and stable or decreased use of analgesics for EAP within the same calendar year

N is the number of subjects with non-missing response per treatment arm

Subjects with less than 43% of daily diary data completed were excluded

ABT = add-back therapy; BMI = body mass index; CI = confidence interval; EAP = endometriosis associated pain; FAS = full analysis set; LGX = linzagolix; NE = not estimable; NSAIDs = non-steroidal anti-inflammatory drugs; NMPP = non-menstrual pelvic pain; ORs = odds ratios

Figure 3.8: Forest plots of ORs of reduction of NMPP* at month 3 overall and by subgroup (FAS)

Based on Figure 2 of Appendix E ¹⁷

*Reduction of ≥ 0.8 for NMPP in mean pelvic pain score from baseline to the last 28 days prior to Month 3 or discontinuation, and stable or decreased use of analgesics for EAP within the same calendar days

N is the number of subjects with non-missing response per treatment arm

Subjects with less than 43% of daily diary data completed were excluded

ABT = add-back therapy; BMI = body mass index; CI = confidence interval; EAP = endometriosis associated pain; FAS = full analysis set; LGX = linzagolix; NE = not estimable; NSAIDs = non-steroidal anti-inflammatory drugs; NMPP = non-menstrual pelvic pain; ORs = odds ratios

EAG comment: The EAG agrees that the treatment effect seemed to be consistent across the subgroups that were examined. However, there seems to be a trend of increasing treatment effect with increasing age for both outcomes, which might indicate that linzagolix is more effective in older women at least amongst those of reproductive age. This might have implications for applicability to UK clinical practice as already identified in Section 3.2.2.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

An ITC was carried out to compare the safety and efficacy of linzagolix 200 mg plus ABT with other GnRH analogues. A SLR was used to select appropriate studies for inclusion in the analysis. Inclusion and exclusion criteria for the intervention treatment (linzagolix) are provided as Table 3.4, and for the comparator treatments (other GnRH analogues) as Table 3.5. The review considered efficacy, safety and quality of life (QoL) outcomes in patients with diagnosed endometriosis. For linzagolix, eligible studies were randomised or non-RCTs, single arm studies, observational studies, and long-term follow up to RCTs; for GnRH analogues only RCTs were included. For linzagolix, included comparators were placebo or any pharmacological intervention; for GnRH analogues included comparators were placebo or any other GnRH analogue. Only studies written in the English language were included in the review.

One study (EDELWEISS 3¹⁸) was identified for inclusion as a part of the intervention SLR. As no head-to-head trials comparing linzagolix to comparators were identified, the SLR for comparators was narrowed down to only include studies that could be compared to the intervention as part of an anchored ITC. This limited studies to those with 12- and 24- week follow-up for efficacy outcomes, and 24 weeks of follow-up for safety and QoL outcomes. Studies were also excluded from the SLR for other reasons, listed in Appendix D of the CS, Section 3.2.1, page 28:

“It should be noted that the studies D’Hooghe 2019, Harada 2021, Bergqvist 2000 were not included in the indirect comparison for the following reasons:

D’Hooghe 2019 – no comparison of leuprorelin vs placebo, study includes results for comparison of elagolix vs placebo;

Harada 2021 [relugolix versus leuprorelin] and Bergqvist 2000 [goserelin versus nafarelin] – no placebo group in the study.

Other studies included as a result of the systematic review for the comparator were not included in the analysis because the relevant outcomes/endpoints were not matched to the EDELWEISS 3 study:

- *studies with data on graph: Acs 2015 (for NMPP and DYS) [elagolix versus leuprorelin versus placebo], Elaris EM1 (for EHP-30 pain dimension only) [elagolix versus placebo], Elaris EM2 (for EHP-30 pain dimension only) [elagolix versus placebo]*
- *studies with data without standard deviation/standard error (SD/SE): Dlugi 1990 [leuprorelin versus placebo], Ling 1999 [leuprorelin versus placebo]; Elaris EM1 (for lumbar spine only), Elaris EM2 (for lumbar spine only) [elagolix versus placebo]*
- *studies with unreadable data: Acs 2015 (for dyspareunia – unclear which scale was used) [elagolix versus leuprorelin versus placebo].”*

Three studies were identified for the comparator; the SPIRIT 1 and 2 studies, and Osuga 2021a¹⁹/2021b²⁰. The SPIRIT studies compare relugolix CT with placebo; Appendix D of the CS (page 28) includes data for these studies, but states that:

“Relugolix plus ABT has been included in this report, since it was listed in the final scope for this submission (subject to NICE evaluation). However, since it has not yet been approved by NICE, results comparing linzagolix to relugolix have not been presented in the company submission (Document B)”

Therefore, the ITC for linzagolix and relugolix was not included in Document B of the CS.

One study was identified comparing a GnRH agonist, leuporelin, to placebo with two papers included in the ITC: Osuga 2021b, and Osuga 2021a (a long-term extension to Osuga 2021b). Details of these studies are presented as Table 3.31.

Table 3.31: Studies included in the ITC

Study name	Intervention	N	Phase	Study design
EDELWEISS 3 (Donnez et al 2024) ⁵⁸	Linzagolix 200 mg plus ABT Placebo	162 162	3	RCT, double-blind, placebo-controlled, parallel-group, multi-centre, multinational study
Osuga et al 2021a/Osuga et al 2021b ^{74,74,75}	Leuporelin 3.75 mg Placebo	69 77	2	RCT and open-label ^a , multi-centre, parallel-group, long-term extension
Source: adapted from Table 20 of Document B of the CS. ⁴ ABT = add-back therapy; CS = company submission; ITC = indirect treatment comparison; RCT = randomised controlled trial Further detail from the CS: <i>"^bThis study was designed as an open-label study but randomisation information for the study drug was not broken until the last patient in the study was assessed and observed at week 24"</i>				

Osuga 2021a/2021b also included treatment arms for varying doses of relugolix; as this is not being used as a comparator, this data was not included in the ITC. However, it is worth noting, as this affects the context of the study.

The studies vary from each other in several respects. The number of participants is higher in EDELWEISS 3 than in Osuga 2021a/2021b (162 in either arm for EDELWEISS 3, 82 and 99 for treatment and placebo groups in Osuga 2021a/2021b, respectively). The placebo used in each study also differs; EDELWEISS 3 uses an oral placebo, whereas Osuga 2021a/2021b administered two placebos concurrently: an oral placebo and an injected placebo. This was due to the different administration methods of the study drugs; relugolix was given orally, and leuporelin as a subcutaneous injection. In order to maintain blinding, all participants received a daily oral tablet (relugolix or placebo), and a subcutaneous injection (leuporelin or placebo) every 4 weeks.

EAG comment: Given that only one trial of one comparator was included, the EAG requested that consideration be given to the inclusion of more studies. Specifically, the EAG recommended a network meta-analysis (NMA) in order to include non-placebo-controlled trials, as well as including data from graphs and imputing measures of variance, which potentially could have permitted the inclusion of further studies, and more comparators i.e. opigolix and elagolix. Note that in the factual inaccuracy check (FAC) the company have informed the EAG that neither of these comparators is licensed in the UK, but the EAG understand that they might still be used in clinical practice.²¹ The company restated reasons that included heterogeneity, and stated that: *"...many studies are outdated, methodology and population descriptions are not provided in certain instances and are unclear when reported, with some results only presented graphically (with no numerical values provided) and/or without variability measures (like standard deviation)."*⁵ They also cited a lack of common comparators as a reason: *"Finally, as we were only able to link linzagolix with leuporelin (EDELWEISS 3 and Osuga studies), it can be assumed that including trials comparing GnRH agonists vs active treatments would not offer any benefits to the ITC. To address this, studies comparing different GnRH agonists with placebo, and studies linking different GnRH agonists vs other GnRH agonists, directly or indirectly, are required. We have only one GnRH agonist which we can compare with linzagolix via placebo."* The company stated that: *"Introducing any additional studies would result in further limitations, making conclusions more difficult to interpret and results more prone to bias... Building an NMA would not be credible in*

this therapeutic area for the reasons already mentioned above.” However, none of the studies listed above were excluded explicitly because of heterogeneity, and the only study that could not be connected in an NMA using common comparators of either placebo, leuprorelin or relugolix CT seems to be Bergqvist 2000 (goserelin versus nafarelin). Not that the company stated in the FAC that one of the studies, D’Hooghe 2019, was excluded erroneously and one, Harada 2021, was excluded for reasons that were incorrectly reported in the CS.²¹ D’Hooghe 2019 could therefore be included in any ITC or NMA. Harada 2021 should have been excluded because of the lack of accompanying ABT in the relugolix arm, which the EAG considers to be reasonable. The company did include an additional ITC (EDELWEISS 3 versus Ács 2015), using imputed 95% CIs in answer to Question A13c.²² Efficacy outcomes (dysmenorrhoea and NMPP) were reported in this study and were compared in the ITC. A consideration of clinical heterogeneity is reported in Section 3.4.1 and the results are reported in Sections 3.4.2 and 3.4.3.

The company also provided an addendum with an ITC versus relugolix.²³ A consideration of clinical heterogeneity is reported in Section 3.4.1 and the results are reported in Section 3.4.2.

The full set of studies for these two additional ITCs are listed as Table 3.32.

Table 3.32: Studies included in the additional ITCs

Study name	Intervention	N	Phase	Study design
SPIRIT 1 (Giudice et al 2022)	Relugolix 40 mg plus ABT in fixed combination (relugolix CT) Placebo	212 212	3	RCT, double-blind, placebo-controlled, multi-centre, multinational study
SPIRIT 2 (Giudice et al 2022)	Relugolix 40 mg plus ABT in fixed combination (relugolix CT) Placebo	206 204	3	RCT, double-blind, placebo-controlled, multi-centre, multinational study
Ács 2015 (Ács et al 2015)	Leuprorelin 3.75mg Placebo	44 43	2	RCT, double-blind, placebo-controlled, multi-centre, multinational study
Source: CS, Addendum to clarification response: Table 2. ²³ ABT = add-back therapy; CS = company submission; RCT = randomised controlled trial; CT = combination therapy (relugolix-oestradiol-norethisterone acetate)				

3.4 Critique of the indirect comparison and/or multiple treatment comparison

Bucher analyses were performed to compare the efficacy of linzagolix, oral once-daily dose of 200 mg in combination with ABT with leuprorelin, 3.75 mg subcutaneous injection every 4 weeks for the following outcomes:⁴

- Week 12:
 - Dysmenorrhoea (VRS)
 - NMPP (VRS)
- Week 24
 - Dysmenorrhoea (VRS)
 - NMPP (VRS)
 - EHP-30 pain dimension

- Dyspareunia (VRS)

3.4.1 Assessment of clinical heterogeneity

An analysis of heterogeneity was carried out by comparing the baseline characteristics for each study. Comparisons were made using data from the Osuga 2021a paper, as it has a longer observation period than Osuga 2021b, but as the 2021a paper is a long term extension of Osuga 2021b, refer to the same population.⁴ A summary of baseline characteristics recorded for EDELWEISS 3 and Osuga 2021a is presented in Table 3.33.

EAG comment: Table 3.28 also contains the trials for the two additional ITCs provided in response to clarification.^{22, 23}

3.4.1.1 Age

The mean age of participants in the two trials from the original CS was similar, varying between 34.6 years (linzagolix plus ABT, EDELWEISS 3) and 36.6 years (placebo, Osuga 2021a).

The mean age of participants differed between the two trials in the response to clarification; 31.4 for both treatment arms in the Ács 2015 trial, and 34.6 and 34.9 for the linzagolix 200 mg plus ABT and placebo arms in the EDELWEISS 3 trial, respectively. Age in the relugolix trials was somewhere in the middle.

3.4.1.2 Ethnicity

The vast majority of participants in the EDELWEISS 3 study were White (98.1 and 98.8% of participants in the linzagolix plus ABT and placebo arms, respectively). This was similar to the populations in Ács 2015 (100% White, both arms), SPIRIT 1 (91.5 and 91.0% White for relugolix plus ABT and placebo, respectively) and SPIRIT 2 (90.3 and 89.7% white for relugolix plus ABT and placebo, respectively).

Osuga 2021a was markedly different to the other studies; all participants in the trial were Asian. This is acknowledged in Appendix D, page 51: “*Significant heterogeneity was observed in Osuga 2021a. This study included only Japanese women, whereas the remaining studies included mostly Caucasian women.*”

3.4.1.3 Body Mass Index

Mean body mass index (BMI) differs between participants in each study. The mean BMI for participants in EDELWEISS 3 was 24.1 for both treatment arms. Osuga 2021a and Ács 2015 were lower; 21.7 in the leuprorelin arm, and 21.2 in the placebo arm for Osuga 2021a, and 22.6 for all participants in Ács 2015 (BMI for each treatment arm was not recorded). Mean BMI was higher in SPIRIT 1 and SPIRIT 2, ranging from 25.6 (SPIRIT 1, relugolix plus ABT arm) to 26.1 (SPIRIT 1, placebo arm and SPIRIT 2, relugolix plus ABT arm).

3.4.1.4 Pain assessment

Baseline pain scale scores were provided for all studies except Ács 2015.

3.4.1.4.1 EHP-30 scores

EHP-30 pain scale scores were provided in EDELWEISS 3, Osuga 2021a, SPIRT 1 and SPIRT 2. EHP-30 scores were slightly higher in SPIRT 1 and SPIRT 2 than in EDELWEISS 3, ranging from 51.8 (EDELWEISS 3, placebo arm) to 58.3 (SPIRT 1, relugolix plus ABT).

Baseline pain scores were far lower in Osuga 2021a (27.0 for the leuprorelin arm, 23.7 for the placebo arm) than in EDELWEISS 3 (52.4 for the linzagolix plus ABT arm, 51.8 for the placebo arm). This is addressed on page 47 of Appendix D, where the CS postulates that differences in baseline pain measures are due to differences in pain tolerance between different ethnicities:

“Therefore, the difference in mean pain scores between Osuga 2021a and other studies may be due to differences in pain tolerance between the Asian and Caucasian populations”

The authors also note that: *“No studies were identified on perception of endometriosis-related pain in relation to race”*.

3.4.1.4.2 VRS pain scale scores

VRS pain scale scores for dysmenorrhoea and NMPP were reported in EDELWEISS 3 and Osuga 2021a. Measures were lower in Osuga 2021a for both dysmenorrhoea (1.2 for both treatment arms) and NMPP (0.7 for both treatment arms) than in EDELWEISS 3 (dysmenorrhoea = 2.29 and NMPP = 1.2 for both treatment arms).

Table 3.33: Baseline characteristics for studies compared by ITC

Parameter		EDELWEISS 3		Osuga 2021a		Ács 2015		SPIRIT 1		SPIRIT 2	
		LGX 200 mg plus ABT	PLC	LEU 3.75 mg	PLC	LEU 3.75 mg	PLC	RGX 40 mg plus ABT	PLC	RGX 40 mg plus ABT	PLC
N		162	162	69	77	44	43	212	212	206	204
Age, mean (SD) [years]		34.6 (6.8)	34.9 (6.8)	36.6 (6.14)	35.9 (5.99)	31.4 (0.7)	31.4 (0.8)	33.9 (6.3)	34.2 (6.6)	33.8 (6.7)	33.6 (6.5)
Race, n (%)	White	159 (98.1)	160 (98.8)	0 (0.0)	0 (0.0)	44 (100.0)	43 (100.0)	194 (91.5)	193 (91.0)	186 (90.3)	183 (89.7)
	Black or African-American	1 (0.6)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (6.1)	12 (5.7)	14 (6.8)	12 (5.9)
	Other	2 (1.2)	0 (0.0)	69 (100.0)	69 (100.0)	0 (0.0)	0 (0.0)	5 (2.4)	7 (3.3)	6 (2.9)	9 (4.4)
BMI, mean (SD) [kg/m ²]		24.1 (5.17)	24.1 (4.44)	21.7 (3.34)	21.2 (2.88)	22.6 (NR)		25.6 (6.0)	26.1 (6.4)	26.1 (6.5)	25.8 (6.0)
Pain scores, mean (SD) [0–3 VRS]	DYS	2.3 (0.43)	2.29 (0.43)	1.2 (0.48)	1.2 (0.48)	N/A	N/A	N/A	N/A	N/A	N/A
	NMPP	1.8 (0.46)	1.78 (0.44)	0.7 (0.56)	0.7 (0.56)	N/A	N/A	N/A	N/A	N/A	N/A
Pain scores, mean (SD) [0–10 NRS]	DYS	7.1 (1.52)	7.2 (1.40)	N/A	N/A	N/A	N/A	7.2 (1.7)	7.1 (1.7)	7.1 (1.6)	7.0 (1.6)
	NMPP	5.8 (1.74)	5.8 (1.66)	N/A	N/A	N/A	N/A	5.9 (2.0)	5.8 (1.8)	5.8 (1.9)	5.5 (1.9)
EHP-30 pain scale, mean (SD)		52.4 (15.14)/ N=160	51.8 (14.43)/ N=158	27.0 (20.15)	23.7 (18.77)	N/A	N/A	58.3 (16.7)	55.5 (16.0)	56.2 (17.1)	55.0 (16.2)
LDL cholesterol (mg/dL)		115.4 (32.1)	114.3 (31.8)	N/A	N/A	N/A	N/A	101.3 (29.6)*	101.9 (27.1)*	100.5 (29.5)*	98.9 (28.9)*
Triglycerides (mg/dL)		90.0 (43.2)	91.9 (46.8)	N/A	N/A	N/A	N/A	89.7 (45.0)*	95.0 (51.2)*	96.3 (49.4)*	102.8 (64.9)*
BMD z-score, mean (SD)	Total hip	0.30 (0.97)	0.40 (0.91)/ N=161	N/A	N/A	NR	NR	-0.01 (0.9)	0.05 (0.9)	0.1 (1.0)	0.12 (1.0)

Parameter		EDELWEISS 3		Osuga 2021a		Ács 2015		SPIRIT 1		SPIRIT 2	
		LGX 200 mg plus ABT	PLC	LEU 3.75 mg	PLC	LEU 3.75 mg	PLC	RGX 40 mg plus ABT	PLC	RGX 40 mg plus ABT	PLC
	Lumbar spine	0.20 (0.93)	0.50 (1.01)	N/A	N/A	NR	NR	0.17 (1.1)	0.18 (1.1)	0.23 (1.1)	0.35 (1.0)
Time since surgical diagnosis of endometriosis, mean (SD) [years]		4.1 (3.77)	3.5 (3.40)/ N=161	3.1 (3.97)	3.8 (4.69)	1.8 (NR)		3.8 (3.2)	3.8 (3.3)	4.1 (3.5)	3.8 (3.0)
Use of analgesic agents at baseline, n (%)	Overall analgesic agents use	157 (96.9)	153 (94.4)	N/A	N/A	N/A	N/A	192 (90.6)	189 (89.2)	197 (95.6)	192 (94.1)
	Opioids	20 (12.3)	9 (5.6)	N/A	N/A	N/A	N/A	64 (30.2)	52 (24.5)	100 (48.5)	95 (46.6)
Appendix D, Table 12. ¹¹ ABT = add-back therapy; BMD = bone mineral density; BMI = body mass index; EHP-30 = endometriosis health profile-30; ITC = indirect treatment comparison; LDL = low-density lipoprotein; LGX = linzagolix; N/A = not applicable, measure not related to study outcomes; NMPP = non-menstrual pelvic pain; NR = measure relevant to study outcomes but not recorded; RGX = relugolix; SD = standard deviation; VRS = verbal rating scale											

3.4.1.4.3 *NRS pain scale scores*

Numeric rating scale (NRS) pain scale scores were reported for EDELWEISS 3, SPIRIT 1 and SPIRIT 2 for dysmenorrhoea and NMPP. Dysmenorrhoea scores were similar between studies, ranging from 7.1 (SPIRIT 2, placebo arm) to 7.2 (EDELWEISS 3, placebo and SPIRIT 1, relugolix plus ABT). Baseline NMPP scores were also similar, ranging from 5.5 (SPIRIT 2 placebo arm) to 5.9 (SPIRIT 1, relugolix plus ABT arm).

3.4.1.5 *Lipid profile*

Blood lipid profile measures were reported in EDELWEISS 3, SPIRIT 1 and SPIRIT 2. LDL cholesterol was slightly lower in SPIRIT 1 and SPIRIT 2, ranging from 98.9 mg/dL (SPIRIT 2, placebo arm) to 101.9 mg/dL (SPIRIT 1, placebo arm) than in EDELWEISS 3 (115.4 mg/dL for placebo, 114.3 mg/dL for linzagolix plus BT).

A broader range of values for baseline triglyceride values was seen between SPIRIT 1 and SPIRIT 2, ranging from 89.7 mg/dL (SPIRIT 1, relugolix plus ABT) to 102.8 mg/dL (SPIRIT 2, placebo); mean triglyceride values for EDELWEISS 3 were 90.0 mg/dL and 91.9 mg/dL for linzagolix plus ABT and placebo arms, respectively.

3.4.1.6 *Bone mineral density*

Bone mineral density (BMD) z-scores were reported in EDELWEISS 3, SPIRIT 1 and SPIRIT 2 for total hip and lumbar spine. Scores for total hip were slightly lower in SPIRIT 1 and SPIRIT 2 than EDELWEISS 3; the range of values for SPIRIT 1 and SPIRIT 2 was -0.01 (SPIRIT 1, relugolix plus ABT arm) to 0.12 (SPIRIT 2, placebo arm), whereas values for EDELWEISS 3 were 0.30 and 0.40 for the linzagolix plus ABT arm and placebo arm, respectively.

Scores for lumbar spine were similar across the studies, ranging from 0.20 (EDELWEISS 3, linzagolix 200 mg plus ABT) to 0.50 (EDELWEISS 3, placebo arm).

3.4.1.7 *Time since surgical diagnosis of endometriosis*

Mean time since surgical diagnosis of endometriosis was similar in EDELWEISS 3, Osuga 2021a, SPIRIT 1 and SPIRIT 2, ranging from 3.1 years in Osuga 2021a (leuprorelin arm) to 4.1 years in SPIRIT 2 (relugolix plus ABT arm). Ács 2015 was markedly different to the other studies, with a mean of 1.82 years for all participants (mean time since surgical diagnosis of endometriosis by treatment arm was not recorded).

Definitions of duration of disease also varied between the studies; Osuga 2021a reports mean disease duration, EDELWEISS 3 reports time since first surgical diagnosis.

“Due to the lack of a definition of disease duration in Osuga 2021a, it is difficult to determine the timeframe for this variable, although the mean is similar across the included studies.” (Appendix D of the CS, Section 3.3.3.4, page 45).

Inclusion criteria for Osuga 2021a state: *“a diagnosis of endometriosis in the previous 5 years (confirmed by laparotomy, laparoscopy, or magnetic resonance imaging detection of ovarian chocolate cyst[s])”*²⁰

3.4.1.8 Use of analgesic agents

Use of analgesic agents at baseline is reported in EDELWEISS 3, SPIRIT 1 and SPIRIT 2. Overall analgesic use was similar across the studies, ranging from 89.2% of participants (SPIRIT 1, placebo arm) to 96.9% of participants (EDELWEISS 3, linzagolix 200 mg plus ABT).

Use of opioids differs markedly between studies; the lowest opioid usage is in EDELWEISS 3 (12.3 and 5.6% of participants in the linzagolix plus ABT and placebo arms, respectively), then SPIRIT 1 (30.2 and 24.5% of participants, relugolix plus ABT and placebo arms, respectively), with the highest usage in SPIRIT 2 (48.5 and 36.6% of participants, relugolix plus ABT and placebo arms, respectively).

3.4.2 Efficacy outcomes

3.4.2.1 Linzagolix plus ABT (EDELWEISS 3) and leuporelin (Osuga 2020a)

Efficacy outcomes were compared at 12 and 24 weeks by Bucher ITC; results are presented as Table 3.34. No significant differences were found between linzagolix 200 mg plus ABT and leuporelin by indirect comparison.

Table 3.34: Bucher ITC for the efficacy of linzagolix 200 mg plus ABT versus leuporelin at weeks 12 and 24 (Osuga 2020a)

Outcome	Linzagolix 200 mg plus ABT versus placebo	Leuprorelin 3.75 mg versus placebo	Indirect comparison	
			MD (95% CI)	MD (95% CI)
Week 12				
Dysmenorrhoea (VRS)	-1.06 (-1.25, 0.87)	-1 (-1.15, -0.85)	-0.06 (-0.30, 0.18)	0.63
NMPP (VRS)	-0.24 (-0.38, -0.1)	-0.2 (-0.32, -0.08)	-0.04 (-0.22, 0.14)	0.67
Week 24				
Dysmenorrhoea (VRS)	-1.22 (-1.41, -1.03)	-1 (-1.17, -0.83)	-0.22 (-0.47, 0.03)	0.09
NMPP (VRS)	-0.27 (0.43, 0.11)	-0.3 (-0.44, -0.16)	0.03 (-0.18, 0.24)	0.78
EHP-30 pain dimension	-16.93 (-21.9, -11.96)	-21 (-27.72, -14.28)	4.07 (-4.29, 12.43)	0.34
Dyspareunia (VRS)	-0.26 (-0.52, 0.0013)	-0.2 (-0.55, 0.15)	-0.06 (-0.50, 0.38)	0.79
Source: Table 21, Document B of CS. ⁴ ABT = add-back therapy; CI = confidence interval; CS = company submission; EPH-30 = endometriosis health profile-30; ITC = indirect treatment comparison; MD = mean difference; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale				

3.4.2.2 Linzagolix plus ABT (EDELWEISS 3) and leuporelin (Ács 2015)

Efficacy outcomes (dysmenorrhoea and NMPP) were compared at 12 weeks via Bucher ITC, using 95% CIs for Ács 2015 that were imputed by three different methods: a proportional method (assume same ratio of mean difference (MD) to either upper or lower CI limit for both studies) based on the CI reported in EDELWEISS 3 (method 1), a scaling of standard deviations (SDs) from EDELWEISS 3 (method 2) and a method assuming equal standard errors for both studies (method 3). Details of these methods are provided in the response to question A13c.²² A significant improvement was found for

dysmenorrhoea using methods 1 and 3, with a MD from baseline pain measures of -1.06 for linzagolix 200 mg plus ABT, and -0.71 for leuporelin. No difference in efficacy could be found between the two treatments for NMPP by any method.

Table 3.35: Bucher ITC for the efficacy of linzagolix plus ABT versus leuporelin at week 12 (Ács 2015)

Outcome	Linzagolix 200 mg plus ABT versus placebo	Leuporelin 3.75 mg versus placebo	Indirect comparison	
	MD (95% CI)		MD (95% CI)	p-value
Method 1 of imputing CIs				
Dysmenorrhoea (VRS/mB&B)	-1.06 (-1.25, -0.87)	-0.71 (-0.84, -0.58)	-0.35 (-0.58, -0.12)	<0.01*
NMPP (VRS/mB&B)	-0.24 (-0.38, -0.1)	-0.25 (-0.39, -0.1)	-0.01 (-0.19, 0.21)	0.92
Method 2 of imputing CIs				
Dysmenorrhoea (VRS/mB&B)	-1.06 (-1.25, -0.87)	-0.71 (-1.40; -0.01)	-0.35 (-1.07; 0.37)	0.34
NMPP (VRS/mB&B)	-0.24 (-0.38, -0.1)	-0.25 (-0.76; 0.27)	-0.01 (-0.52; 0.54)	0.97
Method 3 of imputing CIs				
Dysmenorrhoea (VRS/mB&B)	-1.06 (-1.25, -0.87)	-0.71 (-0.9; -0.52)	-0.35 (-0.62; -0.08)	0.01*
NMPP (VRS/mB&B)	-0.24 (-0.38, -0.1)	-0.25 (-0.39; -0.1)	-0.01 (-0.19; 0.21)	0.92
Source: Table 3, Response to request for clarification part 2: response to Question A13c. ²² ABT = add-back therapy; B&B = Biberoglu-Behrman; CI = confidence interval; ITC = indirect treatment comparison; MD = mean difference; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale				

3.4.2.3 Linzagolix plus ABT (EDELWEISS 3) and relugolix plus ABT (SPIRIT 1/SPIRIT 2)

A Bucher ITC was carried out to compare the efficacy of linzagolix plus ABT versus relugolix plus ABT. In order to compare EDELWEISS 3, SPIRIT 1 and SPIRIT 2 by this method, a meta-analysis of the SPIRIT 1 and SPIRIT 2 trials was carried out. Justification for this decision is provided in the addendum to clarification response:

“SPIRIT 1 and SPIRIT 2 were two replicate, phase 3 studies which evaluated similar endpoints over the same observation periods, had the same study design and included patients with similar baseline characteristics. It was, therefore, possible to perform a meta-analysis of the SPIRIT 1/SPIRIT 2 studies and to include the results of the meta-analysis in the ITC.”²³

This allowed the results of the meta-analysis to be compared to EDELWEISS 3; results of the Bucher ITC are presented as Table 3.36. No significant differences were found between linzagolix plus ABT and relugolix plus ABT for any of the outcomes.

Table 3.36: Bucher ITC for the efficacy of linzagolix 200 mg plus ABT versus relugolix + ABT at week 24

Outcome	Linzagolix 200 mg plus ABT versus placebo	Relugolix 40 mg plus ABT versus placebo ^a	Indirect comparison	
	Risk difference (95% CI)		Risk difference (95% CI)	p-value
Dysmenorrhoea response (NRS)	0.52 (0.42, 0.6)	0.46 (0.4, 0.52)	0.06 (-0.05, 0.16)	0.28
NMPP response (NRS)	0.2 (0.1, 0.3)	0.21 (0.14, 0.28)	-0.01 (-0.13, 0.11)	0.87
	Mean difference (95% CI)		Mean difference (95% CI)	p-value
Dysmenorrhoea (NRS)	-3.5 (-4.08, -2.92)	-3.2 (-3.59, -2.81)	-0.3 (-1.00, 0.40)	0.40
NMPP (NRS)	-0.96 (-1.46, -0.46)	-0.8 (-1.19, -0.41)	-0.16 (-0.79, 0.47)	0.62
OPP	-1.2 (-1.7, -0.7)	-1.06 (-1.44, -0.68)	-0.14 (-0.77, 0.49)	0.66
EHP-30 pain dimension	-16.13 (-20.59, -11.67)	-13.62 (-17.05, -10.19)	-2.51 (-8.14, 3.12)	0.38
Source: Table 3, Addendum to clarification response ²³ ABT = add-back therapy; CI = confidence interval; EHP-30 = endometriosis health profile-30; ITC = indirect treatment comparison; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; OPP = overall pelvic pain; VRS = verbal rating scale				

The addendum to clarification response acknowledges that differences were present between the SPIRIT studies and EDELWEISS 3:

“The EDELWEISS 3 linzagolix study and the relugolix CT studies SPIRIT 1 and SPIRIT 2 differed in their definitions of the co-primary efficacy endpoints dysmenorrhoea and NMPP, in terms of the rating scale used for the pain assessment (verbal rating scale vs. numeric rating scale), magnitude of significant clinical change and the assessment timepoint. Of note, the primary endpoint of EDELWEISS 3 was assessed at 3 months [week 12], whereas the primary endpoint of SPIRIT 1 and SPIRIT 2 was assessed at 6 months [week 24]; early pain control in patients is of utmost importance, hence the 3-month assessment was prioritised in the EDELWEISS studies.”²³

Due to the availability of patient-level data in the EDELWEISS 3 study, reconstructed endpoints were generated based upon the definitions in the SPIRIT studies. Risk differences were calculated by logistic regression modelling of these reconstructed endpoints, and a MAIC was carried out. The results of this MAIC are presented as Table 3.37. According to the addendum to clarification response:

“As the SPIRIT and EDELWEISS 3 studies were generally well-balanced in terms of characteristics, an additional match-adjusted indirect comparison (MAIC) was performed using the reconstructed endpoints as a sensitivity analysis. Non-inferiority was defined based on p-values of >0.05 for the ITC and >0.1 for the MAIC (to select prognostic factors or treatment effect modifiers), indicating no statistically significant difference between the treatments.”²³

Table 3.37: MAIC for the efficacy of linzagolix 200 mg plus ABT versus relugolix 40 mg plus ABT at week 24

Outcome	Linzagolix 200 mg plus ABT versus placebo	Relugolix 40 mg plus ABT versus placebo ^a	Indirect comparison	
	Risk difference (95% CI)		Risk difference (95% CI)	p-value
Dysmenorrhoea response (NRS) MAIC scenario 1	0.48 (0.38, 0.59)	0.46 (0.4, 0.52)	0.02 (-0.1, 0.14)	0.75
Dysmenorrhoea response (NRS) MAIC scenario 2	0.39 (0.22, 0.56)	0.46 (0.4, 0.52)	-0.07 (-0.25, 0.12)	0.45
Dysmenorrhoea response (NRS) MAIC scenario 3	0.39 (0.22, 0.57)	0.46 (0.4, 0.52)	-0.07 (-0.25, 0.12)	0.46
NMPP response (NRS) MAIC scenario 2	0.2 (0, 0.35)	0.21 (0.14, 0.28)	-0.01 (-0.19, 0.18)	0.92
Source: Table 4, addendum to clarification response ²³ Scenario 1 - based on treatment effect modifiers and prognostic factors identified by logistic regression or forest plots analysis <u>and</u> imbalance between the EDELWEISS 3 and the pooled SPIRIT 1 and SPIRIT 2 studies. Scenario 2 - based on imbalance between the EDELWEISS 3 and the pooled SPIRIT 1 and SPIRIT 2 studies. Scenario 3 - based on treatment effect modifiers and prognostic factors indicated within logistic regression or forest plots analysis <u>and</u> the parameter with the highest deviation - analgesic use at baseline (non-opioids use) ^a Meta-analysis of the SPIRIT 1 and SPIRIT 2 studies. ABT = add-back therapy; CI = confidence interval; MAIC = match-adjusted indirect comparison; NRS = numeric rating scale; CT = combination therapy (relugolix-oestradiol-norethisterone acetate) All outcomes showed no statistically significant difference between linzagolix versus relugolix (p>0.1).				

3.4.3 Safety outcomes

3.4.3.1 Linzagolix plus ABT (EDELWEISS 3) and leuprorelin (Osuga 2020a)

The safety outcomes from the ITC comparing the EDELWEISS 3 and Osuga 2020a studies are shown in Table 3.38.

Significant differences were found between lumbar spine BMD (p<0.001), rate of serious treatment-emergent adverse events (TEAEs) (p=0.03) and incidence of hot flushes (p<0.001). Loss of BMD at the lumbar spine and incidence of hot flushes were higher for leuprorelin compared to linzagolix plus ABT (MD: 4.18, 95% CI: -3.56, 4.80 for lumbar spine BMD; MD: -0.34, 95% CI: -0.47, -0.31 for hot flushes). It is likely that this difference is due to the use of ABT with linzagolix.

Serious TEAEs were found to be significantly more prevalent for linzagolix plus ABT compared to leuprorelin (MD: 0.06, 95% CI: 0.01, 0.11). The serious TEAEs reported were [REDACTED]; these were not considered by investigators to be related to linzagolix or ABT.

Table 3.38: Bucher ITC for the safety of linzagolix versus leuprorelin at week 24

Outcome	Linzagolix 200 mg plus ABT versus placebo	Leuprorelin 3.75 mg versus placebo	Indirect comparison	
			MD (95% CI)	p-value
Lumbar spine BMD	-0.02 (-0.03, -0.01)	-4.2 (-4.82, -3.58)	4.18 (3.56; 4.80)	<0.001*
	Risk difference (95% CI)		Risk difference (95% CI)	p-value
TEAEs	0.1 (-0.01, 0.21)	0.16 (0.08, 0.25)	-0.06 (-0.20, 0.08)	0.40
Severe TEAEs	0.01 (-0.02, 0.03)	-0.02 (-0.06, 0.01)	0.03 (-0.01, 0.07)	0.17
Serious TEAEs	0.01 (-0.01, 0.03)	-0.05 (-0.1, -0.003)	0.06 (0.01, 0.11)	p=0.03*
TEAEs leading to permanent discontinuation of study drug	0.01 (-0.03, 0.04)	0.05 (-0.03, 0.13)	-0.04 (-0.13, 0.05)	0.37
Incidence of hot flushes	0.04 (-0.002, 0.09)	0.38 (0.26, 0.5)	-0.34 (-0.47, -0.21)	<0.001*
Incidence of headaches	0.02 (-0.04, 0.09)	0.03 (-0.06, 0.13)	-0.01 (-0.13, 0.11)	0.86
Source: Table 22, Document B of CS. ⁴ ABT = add-back therapy; BMD = bone mineral density; CI = confidence interval; CS = company submission; ITC = indirect treatment comparison; MD = mean difference; TEAEs = treatment-emergent adverse event				

3.4.3.2 Linzagolix plus ABT (EDELWEISS 3) and leuprorelin (Ács 2015)

No safety outcomes were presented in the company response to request for clarification. AEs were reported in Ács 2015, but not at timepoints that are comparable to EDELWEISS 3.

3.4.3.3 Linzagolix plus ABT (EDELWEISS 3) and relugolix plus ABT (SPIRIT 1/SPIRIT 2)

The safety outcomes from the ITC comparing the EDELWEISS 3 and SPIRIT 1/SPIRIT 2 studies are presented in Table 3.39. Results of the two SPIRIT trials were combined by meta-analysis. Significant differences were found between lumbar spine BMD change between the two treatments compared to placebo, with linzagolix plus ABT associated with a greater loss in BMD than relugolix plus ABT (-1.58 versus -0.85, respectively; p value= 0.048).

Table 3.39: Bucher ITC for the safety of linzagolix 200 mg plus ABT versus relugolix CT at week 24

Outcome	Linzagolix 200 mg plus ABT versus placebo	Relugolix 40 mg plus ABT versus placebo ^a	Indirect comparison	
			MD (95% CI)	p-value
Lumbar spine BMD	-1.58 (-2.12, -1.04)	-0.85 (-1.33, -0.37)	-0.73 (-1.45, -0.01)	0.048*

Outcome	Linzagolix 200 mg plus ABT versus placebo	Relugolix 40 mg plus ABT versus placebo ^a	Indirect comparison	
	MD (95% CI)		MD (95% CI)	p-value
Total hip BMD	-0.69 (-1.14, -0.23)	-0.37 (-0.78, 0.03)	-0.32 (-0.93, 0.29)	0.30
	Risk difference (95% CI)		Risk difference (95% CI)	p-value
TEAEs	0.1 (-0.01, 0.21)	0.05 (-0.01, 0.11)	0.05 (-0.08, 0.18)	0.43
Severe TEAEs	0.01 (-0.02, 0.03)	0.01 (-0.02, 0.04)	0 (-0.04, 0.04)	1.00
Serious TEAEs	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)	0 (-0.01, 0.03)	1.00
TEAEs leading to permanent discontinuation of study drug	0.01 (-0.03, 0.04)	0.02 (-0.01, 0.04)	-0.01 (-0.05, 0.03)	0.65
Incidence of hot flushes	0.04 (-0.002, 0.09)	0.05 (0.01, 0.09)	-0.01 (-0.07, 0.05)	0.75
Incidence of headaches	0.02 (-0.04, 0.09)	0.07 (0, 0.13)	-0.05 (-0.14, 0.04)	0.29
Source: Table 5 CS, Addendum to clarification response ²³ Further information from the CS: ^a Meta-analysis of the SPIRIT 1 and SPIRIT 2 studies * lumbar spine BMD loss was statistically significantly greater with linzagolix versus relugolix, although the difference between groups was not considered large enough to be clinically meaningful; all other outcomes showed no statistically significant difference between treatments (p>0.05). ABT = add-back therapy; BMD = bone mineral density; CI = confidence interval; CS = company submission; CT = relugolix combination therapy (relugolix-oestradiol-norethisterone acetate); ITC = indirect treatment comparison; MD = mean difference; TEAE = treatment-emergent adverse event				

EAG comment: It does appear to be the case that there is little difference between linzagolix 200 mg plus ABT and leuprorelin in efficacy using the CS ITC with Osuga 2020a. This was to some extent confirmed using the ITC provided in response to clarification i.e. with Ács 2015. However, for dysmenorrhoea this depends on the method used to impute the missing CIs with methods 1 and 2 showing a statistically significant difference in favour of linzagolix. The EAG questions the validity of method 1, which assumes that each CI limit (upper or lower) is proportional to the point estimate, providing no evidence for this assumption. The EAG also questions the validity of method 2 given that the paper cited for the methodology does not seem to describe a method of imputing CIs, but instead how to estimate the precision of indirect comparisons. Finally, method 3 simply assumes that the CIs (and, by implication, the same standard errors (SEs) in both trials are identical, but this seems unlikely given that the sample size of EDELWEISS is about four times that of Ács 2015 (n=362 versus 87). The EAG considers that a more valid method would be one that assumes the same SD, as mentioned in the Cochrane Handbook. This means that the SE is calculated as SD/sqrt(n). The EAG does not have access to the original means for each arm from Ács 2015, but it seems clear that, if the sample size is approximately four times smaller then the SEs would be approximately twice as large and therefore the CI, which are proportional to SE, would also be twice as large. This is likely to increase the CI in the indirect estimate.

However, loss of BMD at the lumbar spine and incidence of hot flushes were higher for leuporelin compared to linzagolix 200 mg plus ABT. The EAG considers that this is probably related to the addition of ADT to linzagolix 200 mg.

The same appears to be the case from the ITC with relugolix CT, in terms of efficacy i.e. little difference, whether using the Bucher method or the MAIC. However, the greater loss in lumbar spine BMD with linzagolix 200 mg cannot be attributed to the use of ABT because it was combined with both interventions. The company argued that: “...the difference was not considered large enough to be clinically meaningful.” (page 12).²³ However, no reference was cited to support this. It should also be noted that there was a lack of full details of the MAIC analysis: it was unclear about the number of important baseline characteristics, which were adjusted for in the MAIC analysis. Therefore, given that there was a lack of full details of the MAIC analysis, this issue may have introduced the uncertainty in the results of MAIC analysis.

In conclusion, the EAG considers that it is reasonable on the basis of these ITCs to consider that the efficacy of linzagolix 200 mg plus ABT is similar to that of leuporelin and relugolix CT. However, it still remains uncertain how it might compare to other GnRH agonists such as goserelin or triptorelin, as mentioned by the EAG clinical expert.

3.5 Additional work on clinical effectiveness undertaken by the EAG

None.

3.6 Conclusions of the clinical effectiveness Section

The CS^{4, 11} and response to clarification⁵ provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence on safety and efficacy of linzagolix 200 mg (the intervention) and other therapies (comparators) for the treatment of endometriosis. Searches were conducted in December 2023 and updated in September 2024. The revised searches provided by the company were clear and reproducible.¹³ The EAG noted some limitations regarding the lack of additional searches beyond key databases and the failure to include MeSH/Emtree terms. Without rerunning the searches, the EAG is unable to say what impact this may have had on the overall recall of results, but it is possible that some relevant papers may have been missed.

There was one key trial, the Phase 3 EDELWEISS 3 study (N=484) and its extension study EDELWEISS 6 (N=353 for the treatment extension analysis set/356 in the extension safety analysis set) designed to assess the efficacy and safety of linzagolix 200 mg plus ABT for the treatment of Moderate to Severe EAP in women of reproductive age. The trial comprised a 3-month screening period, a 6-month treatment period and a 6-month extension. The EAG identified that limiting to reproductive age and lack of UK patients might limit the applicability of the trial to UK clinical practice.

In EDELWEISS 3, there was a statistically significant advantage to linzagolix 200 mg plus ABT versus placebo in all outcomes, except for dyspareunia (VRS) and EHP-30 modular sexual relationship where there was only a numerical advantage. This advantage included the co-primary endpoints of clinically meaningful reduction of dysmenorrhoea (reduction of ≥ 1.10 points on the VRS) and NMPP (reduction of ≥ 0.8 points on the VRS) from baseline to the last 28 days preceding the month 6 visit. In EDELWEISS 6, there was a continued improvement with linzagolix 200 mg plus ABT in all outcomes during the 6-month extension to the 6-month double blind randomised period, with plateauing towards the end of the 12-month follow-up period. AE rates appear to have been similar between the placebo and linzagolix 200 mg plus ABT with higher rates for headache, hot flush and mood swings, which

were regarded as treatment related. Decrease in BMD, albeit appearing to be uncommon, was also more common with linzagolix 200 mg plus ABT. The treatment effect on the co-primary endpoints of dysmenorrhoea and NMPP seemed to be consistent across the subgroups that were examined. However, there seems to be a trend of increasing treatment effect with increasing age for both outcomes, which might indicate that linzagolix is more effective in older women at least amongst those of reproductive age, which might have implications for UK clinical practice, as stated above.

An ITC using the Bucher method was carried out to compare the safety and efficacy of linzagolix 200 mg plus ABT with other GnRH analogues. A SLR was used to select appropriate studies for inclusion in the analysis. Three studies were identified for the comparator: the SPIRIT 1 and 2 studies to compare with relugolix CT, and Osuga 2021a to compare with leuprorelin. Although an ITC with relugolix CT was not included in the CS because it had not been approved by NICE, it was included in response to a request by the NICE technical team in the clarification letter, and the company also performed a MAIC. The EAG requested a NMA to include all comparators, including all GnRH agonists and relugolix CT. However, the company did not comply with this request, citing heterogeneity, availability of data only graphically, lack of measures of variance and lack of common comparators to form a network as reasons. The EAG notes that none of the GnRH agonist trials were excluded explicitly because of heterogeneity. Lack of common comparator was cited as a reason for three trials:

- D'Hooghe 2019 – opigolix versus placebo
- Harada 2021 - relugolix versus leuprorelin
- Bergqvist 2000 - goserelin versus nafarelin

Data only available graphically was cited for:

- Ács 2015 (for NMPP and dyspareunia) - elagolix versus leuprorelin versus placebo
- Elaris EM1 (for EHP-30 pain dimension only) - elagolix versus placebo
- Elaris EM2 (for EHP-30 pain dimension only) - elagolix versus placebo

Lack of SD/SE was cited for:

- Dlugi 1990 - leuprorelin versus placebo
- Ling 1999 leuprorelin versus placebo
- Elaris EM1 (for lumbar spine only) - elagolix versus placebo
- Elaris EM2 (for lumbar spine only) - elagolix versus placebo

Therefore, given that placebo, leuprorelin or relugolix CT were available as common comparators, it seems that only Bergqvist 2000 (goserelin versus nafarelin) could not be connected in a NMA. The company stated in the FAC that one of the studies, D'Hooghe 2019, was excluded erroneously and one, Harada 2021, was excluded for reasons that were incorrectly reported in the CS.²¹ The latter should have been excluded due to lack of accompanying ABT in the relugolix arm, which the EAG considers to be reasonable, but D'Hooghe 2019 could have been included. The company did in fact include Ács 2015 for NMPP and dyspareunia, which also required an assumption regarding missing SD/SE. A comparison of baseline characteristics did in fact show women substantial clinical heterogeneity, most notably in that Osuga 2021a only included women who were Asian, and the company postulated that this might also explain lower pain scores.

Results from the CS ITC using Osuga 2020a showed that there is little difference between linzagolix 200 mg plus ABT and leuprorelin in efficacy by any outcome including dysmenorrhoea and NMPP, which was to some extent confirmed using the ITC provided in response to clarification i.e. with Ács 2015. However, for dysmenorrhoea this depends on which of the three methods used to impute the missing CIs, two of which showed a statistically significant advantage to linzagolix 200 mg plus ABT. The EAG questions the validity of all three methods and considers that a more valid method would be one that assumes the same SD for Ács 2015 as EDELWEISS 3, as mentioned in the Cochrane Handbook. Given that the sample size is approximately four times larger for EDELWEISS 3, the SEs would be approximately twice as large and therefore the CI, which is proportional to SE, would also be twice as large, which is likely to increase the CI in the indirect estimate. However, loss of BMD at the lumbar spine and incidence of hot flushes were higher for leuprorelin compared to linzagolix 200 mg plus ABT. The EAG considers that this is probably related to the addition of ADT to linzagolix 200 mg.

The same appears to be the case from the ITC with relugolix CT, in terms of efficacy i.e. little difference, whether using the Bucher method of the MAIC. However, the greater loss in lumbar spine BMD with linzagolix 200 mg cannot be attributed to the use of ABT because it was combined with both interventions. However, it should be noted that there was a lack of full details of the MAIC analysis: it was unclear about the number of important baseline characteristics, which were adjusted for in the MAIC analysis. Therefore, given that there was a lack of full details of the MAIC analysis, this issue may have introduced the uncertainty in the results of MAIC analysis.

In conclusion, the EAG considers that it is reasonable on the basis of these ITCs to consider that the efficacy of linzagolix 200 mg plus ABT is similar to that of leuprorelin and relugolix CT. However, it still remains uncertain how it might compare to other GnRH agonists such as goserelin or triptorelin, as mentioned by the EAG clinical expert. It should also be noted that no data to inform a comparison with surgery were presented in the clinical effectiveness section, the relevance of which is to be determined depending on whether or not surgery can be ruled out as a comparator.

4. Cost effectiveness (CE)

4.1 EAG comment on company's review of CE evidence

This Section pertains mainly to the review of CEA studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to CE presented in the CS.⁴ Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for CE Section

The following paragraphs contain summaries and critiques of all searches related to CE, HRQoL and resource use identification presented in the CS. The CADTH evidence-based checklist for the PRESS, was used to inform this critique.⁹ The EAG has presented only the major limitations of each search strategy in the report.

Appendix G of the CS provides details of an SLR conducted in July 2024 to identify relevant studies on CE in adult patients with endometriosis.²⁴

A summary of the sources searched is provided in Tables 4.1 to 4.3.

Table 4.1: Data sources searched for economic evaluations (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-2024/07	10.7.24
MEDLINE	PubMed	ALL	11.7.24

EAG comment:

- A search for relevant published CE data was undertaken in July 2024 on the Embase and MEDLINE databases. The CS, Appendix G and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{5, 24}
- The searches contained a number of limitations - only two databases MEDLINE and Embase were searched, no grey literature searches were reported. Further to this, the EAG noted that the strategies contained the same lack of subject headings as observed in the clinical effectiveness searches. Again the company responded that the decision was made to use keywords rather than subject headings in order to "avoid potential limitations associated with controlled vocabulary indexing".⁵ However, the EAG does not accept this rationale and refers the company to Cochrane best practice which states that "Both free-text and subject headings (e.g. Medical Subject Headings (MeSH) and Emtree) should be used."¹² Whilst the EAG recognises that costs searches tend to be more pragmatic, it remains possible that the limitations described above may have resulted in relevant papers being missed.

Table 4.2: Data sources searched for HRQoL studies (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-2024/07	10.7.24
MEDLINE	PubMed	ALL	10.7.24
CS = company submission; HRQoL = health-related quality of life			

EAG comment:

- A search for relevant HRQoL, utility/disutility data was undertaken in July 2024 on the Embase and MEDLINE databases. The CS, Appendix H and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{5, 25}
- As with the CE Section the searches provided contained some limitations. As before, only MEDLINE and Embase were searched. The EAG did note the inclusion of 10 additional records found through 'other sources' reported on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart, and the company later clarified that this referred to records identified through reference checking.⁵ As noted in the previous Section, the strategies contained the same lack of subject headings as observed in the clinical and CE searches. Therefore, the same limitations will apply.

Table 4.3: Data sources searched for Cost and healthcare resource identification, measurement and valuation (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	2013-2024/09	6.9.24
MEDLINE	Ovid	2013-2024/09	6.9.24
CS = company submission			

EAG comment:

- A search for relevant studies on resource use in relation to endometriosis was undertaken in September 2024 on the Embase and MEDLINE databases. The CS, Appendix I and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.^{5, 26}
- Unlike the previous Sections, only a single strategy on the Ovid database was reported for both resources, the company confirmed at clarification that the Ovid search strategy was run simultaneously across both databases.⁵
- As with the CE Section, the searches contained a number of limitations. Only MEDLINE and Embase were searched, no additional grey literature searches were reported and strategy contained the same lack of subject headings as observed in the clinical and CE searches. Therefore, the same limitations will apply.

4.1.2 Inclusion/exclusion criteria

The inclusion and exclusion criteria used in the company's reviews of CE, HRQoL, and resource use/costs evidence can be found in Table 4.4.

Table 4.4: Inclusion and exclusion criteria for the SLRs

	SLR of studies on CE		SLR of studies on HRQoL		SLR of studies on resource use/costs	
	Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria	Inclusion criteria	Exclusion criteria
Study population	Adult (age ≥ 18 years) patients with endometriosis	- Healthy volunteers - Children only (<18 years) - Disease other than endometriosis	Patients with endometriosis	- Healthy volunteers - Disease other than endometriosis	Adult (age ≥ 18 years) patients with endometriosis	- Healthy volunteers - Children only (<18 years) - Disease other than endometriosis
Study design	Full economic evaluations - Cost-consequence - Cost-minimisation - CE - Cost-utility - Cost-benefit	Studies other than economic evaluations	Studies reporting utility/disutility data, HRQoL	Studies not reporting utility/disutility data, HRQoL	- Cost and resource use studies - Cost studies - Resource use studies - Economic evaluations and BIA reporting costs or resource use	Studies not reporting cost and resource use data
Interventions/comparators	No restrictions	None	No restrictions	None	No restrictions	None
Outcomes			HRQoL, utility/disutility data	Outcome different than HRQoL, utility/disutility data		
Language	English	Other than English	English	Other than English	English	Other than English
Time limits	2000 onwards	Publications prior to 2000	1990 onwards	Publications prior to 1990	2013 onwards	Publications prior to 2013

Based on Table 1 of Appendix G, Table 1 of Appendix H, and Table 1 of Appendix I of the CS^{4, 24-26}

BIA = budget impact analysis; CE = cost effectiveness; CS = company submission; HRQoL = health-related quality of life; SLR = systematic literature review

EAG comment: The selection criteria were broad, permitting the inclusion of any type of economic evaluation or HRQoL study for any intervention targeting endometriosis. The decision to restrict the searches to studies conducted in adult patients and those published after specific years (1990, 2000, or 2013) appears appropriate. Though in general a restriction on language might exclude relevant papers, in this instance only one study in the CE search and one study in the HRQoL search were excluded due to language. Based on their abstracts, the EAG considers it unlikely that these studies contained relevant information.

So, overall, the EAG considers the in- and exclusion criteria suitable for capturing all relevant evidence.

4.1.3 Findings of the CE review

The PRISMA flow diagram for the SLR of CE studies is presented in Figure 1 of Appendix G.²⁴ The search, conducted on 11 July 2024, identified 16 CE studies that were included in the final review (i.e., references 84 up to 99 of the CS),⁴ all of which were published after 2011. These studies originated from different countries, including the UK, US, China, Colombia, Argentina, Brazil, Turkey and Russia, and consisted of seven full articles and nine conference abstracts. Among the 16 studies, two were cost-utility studies, four were cost-minimisation studies, and 10 were CE studies. They analysed a range of treatment options for endometriosis, including dienogest, (combined) oral contraceptives, goserelin, elagolix, leuprolide acetate, NSAIDs, short-acting reversible contraception (SARC), and long-acting reversible contraception (LARC). So, none of the studies focused on evaluating the CE of linzagolix. Most of the studies employed either a Markov model or a decision tree model (see Table 33 of the CS for an overview of the study characteristics). The SLR did not identify any previous NICE Technology Appraisals (TAs) for endometriosis treatment.

Furthermore, the company did an SLR aimed to identify relevant studies on HRQoL in relation to endometriosis, with searches completed on 10 July 2024. As can be seen in Figure 1 of Appendix H, this review identified 11 studies. Publications reporting results from EQ-5D questionnaires were prioritised, as the SLR aimed to gather HRQoL data for an economic model and given the guidelines set forth by NICE. Consequently, all 11 included studies used the EQ-5D questionnaire to measure HRQoL. The studies assessed HRQoL in adults with endometriosis undergoing a variety of medical procedures (primarily surgical treatments), none of them with a specific focus on linzagolix. Selected studies were conducted in Australia (2), New Zealand (2), United Kingdom (2), United States (1), Ireland (1), France (1), Turkey (1), and Japan (1).

Finally, an SLR conducted on 6 September 2024, aimed to identify relevant studies on resource use and/or costs in relation to endometriosis. This review identified 15 studies (Figure 1 of Appendix I). In addition, a search of grey literature identified three more studies, including the NICE STA for relugolix.²⁷ The selected studies originated from the UK (2), the US (10), Australia (1), Israel (1), and Spain (1). Again, the selected studies covered a wide range of medical procedures.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.5: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	As per the reference case
Perspective on costs	NHS and PSS	As per the reference case
Type of economic evaluation	Cost utility analysis with fully incremental analysis	As per the reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The time horizon of the model is approximately 15 years, which is the time from the starting age in the model until the average age the menopause starts. According to the company, with a very small proportion of women who experience post-menopausal endometriosis and a high discount factor after 15 years, the impact of extending the time horizon would be marginal and not affect the overall conclusions.
Synthesis of evidence on health effects	Based on systematic review	Evidence from EDELWEISS 3 and 6 was used for linzagolix. SLRs were done to search for evidence on the comparators.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects are expressed in QALYs. HRQoL measured using the EQ-5D-5L (mapped to EQ-5D-3L).
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	HRQoL was measured during the EDELWEISS 3 and 6 trials.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	As per the reference case
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	As per the reference case. QALY weighting due to disease severity is not applicable.
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	As per the reference case

Element of HTA	Reference case	EAG comment on CS
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per the reference case
CS = company submission; EAG = Evidence Assessment Group; EQ-5D = EuroQoL-5 Dimensions; EQ-5D-3L = EuroQoL-5 Dimensions, 3 levels; EQ-5D-5L = EuroQoL-5 Dimensions, 5 levels; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; HTA = Health Technology Assessment; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom		

4.2.2 Model structure

The company developed a de novo semi-Markov model in Microsoft Excel® to assess the CE of linzagolix 200 mg plus ABT compared to alternative treatment options for UK adult pre-menopausal patients with Moderate to Severe EAP who have a history of previous medical or surgical treatment for their endometriosis. The model consists of 17 mutually exclusive health states that reflect the varied responses of patients to both medical therapies and surgical interventions.

To capture clinically and economically significant aspects of managing symptomatic endometriosis, the company divided the model into two main components. The first component is a decision tree, wherein health states are determined by treatment response, defined as a meaningful reduction in pain levels. This part consists of two 3-month cycles followed by a 6-month period during which the decision to continue treatment is made. The 3-month cycles align with the EDELWEISS 3 primary endpoints, which include a clinically meaningful reduction of dysmenorrhoea and NMPP to the last 28 days of randomised treatment up to month 3. The 6-month period is consistent with clinical practice, where specialist consultations for treatment continuation typically occur biannually and allowed flexibility to build the tunnel-state pregnancy. Additionally, the Markov transitions during initial treatment at month 6 were based on EDELWEISS 6 data. Due to the relatively long cycle length, a half-cycle correction has been applied.

The second component of the model focuses on health states contingent upon the level of pain experienced by the patient. The model structure is based on reviews of the study designs for EDELWEISS 3, as well as prior economic models for the treatment of symptomatic endometriosis identified through a targeted SLOR (see Section 4.1 of this report and Appendix G of the CS)²⁴ and established clinical practice guidelines.^{2, 28} Additionally, the company had the model structure and patient pathway validated by clinical experts.^{29, 30} The various conditions or stages through which the model can transition over time are presented in Figure 4.1.

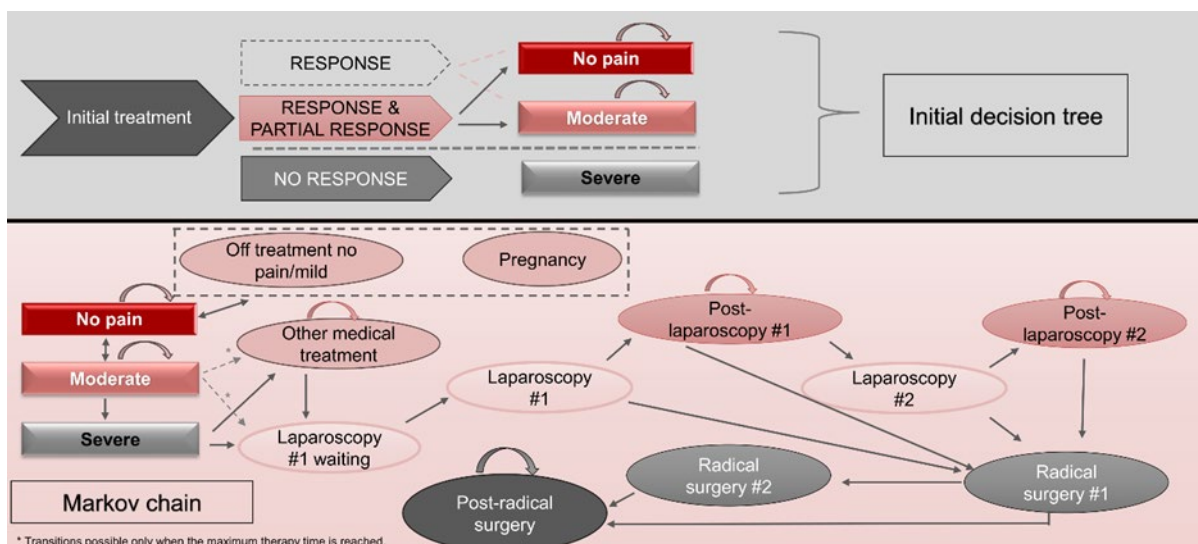


Figure 4.1: Model structure

Based on Figure 4 of the response to the clarification letter⁵

The first two cycles of the model last 3 months each. During this time, patients are categorised into one of three (relative) health-states based on their treatment responses:

- No response: in this state, patients show no clinically relevant improvement in NMPP or dysmenorrhoea compared to baseline
- Partial response: in this state, patients experience a clinically relevant reduction in NMPP or dysmenorrhoea, indicating a partial therapeutic effect
- Complete response: in this state, patients exhibit a dual response, with clinically relevant reductions in both NMPP and dysmenorrhoea, reflecting an optimal treatment outcome

After each of the two 3-month cycles of initial treatment, patients who do not respond to treatment (No Response) are transitioned to subsequent treatment options, which may include the Other Medical Treatment health state or the Laparoscopy #1 Waiting health state. Patients remain in the Laparoscopy #1 Waiting state for one cycle of the model (6 months) before progressing to the Laparoscopy #1 state. After the first 3 months, partial responders may move in the next 3 months to either No Response or Complete response or may remain in Partial response. Complete responders remain in that state in the next 3 months.

Following the two initial cycles, a new phase in the model starts (Markov model), where treatment cycles extend to 6 months. Patients who responded to the treatment (Complete response and Partial response) are categorised into three pain-related health states based on OPP: No pain/mild, Moderate, or Severe. Patients can transition between pain states until they transition into the Severe state (dependent on treatment waning assumption applied), until the maximal duration of therapy is reached (in the case of GnRH agonists) or until moving to the Pregnancy tunnel state.

- Patients entering the Severe pain state are transitioned to Other Medical Treatment or Laparoscopy #1 Waiting.
- When the maximum therapy time is reached, patients remaining in No pain/mild are transitioned to Off-treatment No pain/mild, and those remaining in the Moderate pain state transition to Other Medical Treatment or Laparoscopy #1 Waiting.
- Patients can enter the Pregnancy state from No pain/mild pain state (fixed probability per model cycle).

If symptoms recur whilst in the Other Medical Treatment state, patients transition to the Laparoscopy #1 Waiting state and subsequently to the Laparoscopy #1 state. Laparoscopy #1 is a temporary state, and patients remain in it for one cycle of the model. This pathway assumes timely surgical intervention for patients experiencing symptom resurgence.

After conservative surgery is performed in Laparoscopy #1, patients enter a postoperative care phase in the Post-Laparoscopy #1 state, aimed at maintaining the benefits of the surgical procedure. From this state, they may proceed to another surgical intervention, either conservative surgery Laparoscopy #2 or a radical procedure - Radical surgery #1. Notably, patients who experience a recurrence of symptoms within three months of their initial surgery bypass the Post-Laparoscopy #1 state and move directly to the second surgical procedure. Following Laparoscopy #2, patients may enter the Post-Laparoscopy #2 state, analogous to the Post-Laparoscopy #1 state, or proceed to a radical surgical intervention, specifically Radical surgery #1. After this intervention, patients transition to the Post-Radical surgery state. Alternatively, if they still have disease symptoms, they undergo a second radical surgery, Radical surgery #2. Post Radical surgery #2 they will also transition to the Post-Radical surgery state (for a description of the treatment applied in this health-state see Section 4.2.9 or CS Section B.3.5.7).⁴

Similar to Laparoscopy #1, the states Laparoscopy #2, Radical surgery #1, and Radical surgery #2 are temporary. Patients remain in these states for one model cycle, subsequently transitioning either to the next surgical intervention state or post-surgical intervention state.

Patients can only enter the Pregnancy state from the No pain/mild pain state (fixed probability per model cycle). Pregnancy is a tunnel state with three sub-states, each with one cycle duration. It was assumed that 18 months would be the minimum time for conception, pregnancy and breastfeeding. After three cycles (18 months) spent in this health state, patients move back to the No pain/mild pain state (with active initial treatment) or to the Off-treatment, No pain/mild state if the maximal therapy time of the initial treatment has been reached.

It is important to note that patients may transition to the "Dead" state from any health state within the model and the same mortality rate is applied across all states.

EAG comment: The EAG is much in favour of the company's approach to use response status only as health states in the first 2 cycles, and then after 6 months translating response status into pain health states, since response status is relative to starting situation of patient, i.e. patient may have Complete response but may still have more pain than a patient with Partial response who was in a better position at baseline.

However, it is unfortunate that this classification based on pain state was not used for all other treatments after the initial treatment, such as Other Medical Treatment or the surgery health states. Instead, patients now enter for example into a post-surgery state without separating patients based on their pain levels. As a consequence, for instance, utilities for these surgical treatments were derived as some (weighted) average of utilities estimated for the No pain/mild, Moderate pain, and Severe pain health states. This means that implicitly some distribution over pain health states is assumed, but this approach lacks transparency.

4.2.3 Population

The patient population considered in the CEA consisted of adult pre-menopausal women with Moderate to Severe EAP and a history of previous medical or surgical treatment for their endometriosis (Section B.3.2.1 of the CS⁴). The patient demographics used in the base-case model, which were taken from the

EDELWEISS 3 trial, are shown in Table 4.6. The EDELWEISS 3 trial,¹⁸ which randomised 484 women into three study groups (placebo, 75 mg linzagolix alone or 200 mg linzagolix in combination with ABT) was conducted in 91 centres (65 in Europe and 26 in the US), with none located in the UK.

Table 4.6: Patient population demographics

Table 10: Patient population demographics		
Baseline characteristics	Value (mean)	Source
Age, years	34.9	EDELWEISS 3 ¹⁸
BMI, kg/m ²	24.27	
Time since seeking medical diagnosis/treatment, years	5.20	
Overall pelvic pain, VRS	1.90	
Non-menstrual pelvic pain, VRS	1.77	
Dysmenorrhoea, VRS	2.28	
Based on Table 35 of the CS ⁴		
BMI = body-mass index; CS = company submission; VRS = verbal rating scale		

EAG comment: The EAG observed that the EDELWEISS 3 trial, which served as the basis for the patient characteristics in the model, did not include any patients from the UK. It can be questioned, therefore, to which extent the population demographics in the economic model are generalisable to the patient population in England and Wales. In their response to the clarification questions, the company argued that the EDELWEISS 3 trial population is generalisable to the patient population in England and Wales, based on the assumption that there are no clinically relevant differences between the overall patient populations in Europe and the US compared to the UK (apart from the underrepresentation of non-white ethnic groups in the EDELWEISS 3 population). The EAG agrees with this reasoning and considers that the absence of UK participants in the EDELWEISS 3 trial is unlikely to introduce significant bias.

Furthermore, it appeared to the EAG that the population defined by the NICE scope was “adults with symptoms of endometriosis”, whereas the population considered in the CS was “women with a history of previous medical or surgical treatment for their endometriosis” (see Table 1 of the CS⁴). The company clarified this apparent discrepancy by explaining that the wording used for the population (i.e., “symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis”) reflects the expected indication for linzagolix in the UK and its position in the treatment pathway. According to the expected indication, linzagolix would not be used as a first-line therapy in adults with symptoms of endometriosis and would only be indicated when other treatments (medical, surgical or both) have been tried. This means that linzagolix is intended for second- or later-line therapy after conventional hormone therapy. The company further explained that the majority of the EDELWEISS 3 study population had undergone previous surgeries/procedures for endometriosis treatment before inclusion into the study, including treatments such as analgesics for pelvic pain, dienogest, hormonal oral contraceptives, and GnRH agonists (see response B2d of the response to the clarification letter).⁵ As indicated in Section 2.1 of this report, there appears to be substantial uncertainty as to the precise nature of this population in clinical practice and is therefore a key issue.

4.2.4 Interventions and comparators

The intervention evaluated in the model is linzagolix 200 mg plus ABT, administered orally once daily. In principle, this treatment can be used continuously without a predefined treatment duration, except for cessation at the onset of menopause. The comparators in the model are: 1) GnRH agonists, with the

licensed agents in the UK of leuprorelin acetate, goserelin, and triptorelin, and 2) laparoscopic surgery (Section B.3.2.4 of the CS⁴). In the base-case analysis, leuprorelin acetate was selected as primary comparator, as all GnRH agonists are considered to have equivalent efficacy in this population, and leuprorelin acetate has the largest market share in the UK. Intranasal GnRH agonists (nafarelin and buserelin) were not included as comparator due to their limited clinical use. Laparoscopic surgery is an additional comparator included in the analysis, at the request of NICE and the EAG, as expressed during the decision problem meeting for linzagolix.

Initially, relugolix (i.e., relugolix-oestradiol-norethisterone acetate, or relugolix combination therapy) was not included as a comparator, as it had not yet been approved by NICE. However, after the clarification phase, the company provided comparative data on relugolix at NICE's request and incorporated it into the economic analysis.⁵

EAG comment: The main EAG concerns related to the intervention and relevant comparators are discussed in Section 2.3 of this report.

4.2.5 Perspective, time horizon, and discounting

The CEA was performed from an NHS perspective. Therefore, the analysis accounted for expenses associated with the healthcare sector. In term of outcomes, the direct health effects experienced by the patients were included. Health effects on carers were excluded.

The study's time horizon in the base-case was 15.1 years, spanning the period from a starting age of 34.9 years (i.e., the mean age of women included in the EDELWEISS 3 study) to the average age of menopause in the UK, set at 50 years.

Both costs and outcomes were discounted at an annual rate of 3.5%.

EAG comment: The analysis was done from the perspective of the NHS, aligning with the NICE reference case. The decision to ignore health effects on carers can be justified in the context of this disease.

The discount rates applied in the analysis were also consistent with the NICE reference case.

The base-case analysis used a 15.1-year time horizon, reflecting the period between the expected age at initiation of linzagolix treatment and the age at which women typically reach menopause in the UK. The latter was sourced from the National Health Service website: <https://www.nhs.uk/conditions/menopause/>. As such, a life-time horizon was not adopted. The question is whether the chosen time horizon is long enough to reflect all important differences in costs or outcomes between the technologies being compared, as required by the NICE reference case. In response to the clarification letter, the company argued that the selected time horizon was indeed sufficient to capture all significant differences in costs and outcomes between the compared technologies. The company further stated that extending the time horizon to account for cases of post-menopausal endometriosis would have a marginal impact and not affect the overall conclusions. This is because post-menopausal endometriosis affects only a small proportion of patients and because of the high discount rate after 15 years. Furthermore, the expected impact on the CE results of using a lifetime time horizon should be marginal, according to the company.

The EAG agrees that only a small proportion of women (~2–5%) experience post-menopausal endometriosis (as mentioned in Section B.1.3.1.1 of the CS⁴), and also supported by a report from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) on the quality of care

provided to women diagnosed with endometriosis³¹) and that, generally, adopting a life-time horizon is expected to have a minimal impact on the CE results. To confirm this expectation, the EAG performed an exploratory scenario analysis, extending the time horizon with 10 years (see Section 6.1.2).

4.2.6 Treatment effectiveness and extrapolation

As mentioned in Section 4.2.2, the company's model consists of two parts, i.e. a part describing the initial 6 months of treatment through a response-based decision tree followed by a long-term Markov model with health states based on OPP. Event and transition probabilities were derived by the company from individual patient-level data from EDELWEISS 3.¹⁸ These will be presented in Section 4.2.6.1 and 4.2.6.2, respectively.

Then, the company's approach to estimating the rate of treatment discontinuation is discussed in Section 4.2.6.3. When patients fail on the intervention or comparator, they will receive other medical treatment or surgery. The estimated proportions of patients for these events are presented in Section 4.2.6.4. Finally, Section 4.2.6.5 presents the data the company used for the comparator 'laparoscopic surgery'.

4.2.6.1 Treatment response first 6 months

For the first part of the model, the company divided treatment response into Complete response, Partial response, and non-response, where response was assessed at 3 months and 6 months.

Complete response was defined as a clinically meaningful reduction in both dysmenorrhoea (i.e., a reduction of ≥ 1.10 points on the VRS) and NMPP (i.e., a reduction of ≥ 0.8 points on the VRS), from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP.

For Partial response, the company submission presents three different definitions:

1. **Dysmenorrhoea- or NMPP-based definition** (company base-case): A clinically meaningful reduction in either dysmenorrhoea (as above) or NMPP (as above) from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP.
2. **Dysmenorrhoea-based definition:** A clinically meaningful reduction in dysmenorrhoea (i.e., a reduction of ≥ 1.10 points on the VRS) from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP.
3. **NMPP-based definition:** A clinically meaningful reduction in NMPP (i.e., a reduction of ≥ 0.8 points on the VRS) from baseline to the last 28 days of randomised treatment up to month 3, along with stable or decreased use of analgesics for EAP.

It is assumed that patients with No response at 3 months switch to a different treatment.

Treatment continues for another 3 months for the complete and partial responders; those patients with a Partial response at 3 months may either lose their response, maintain a Partial response or achieve a Complete response (by month 6) whereas patients with Complete response retain that Complete response. Patients who have moved from Partial response to No response at 6 months are assumed to switch to a different treatment.

Based on the results of the ITC (Section 3.4.2) the company assumed that response rates for GnRH agonists are equal to those derived for linzagolix 200 mg plus ABT. Furthermore, at the request of NICE, the company also added relugolix to the model as a comparator. Based on an ITC the company

concluded that there was no evidence that there was a difference in efficacy between linzagolix 200 mg plus ABT versus relugolix CT (40 mg relugolix, 1 mg oestradiol, and 0.5 mg norethisterone acetate). Thus, all three treatments have the same probability of response.

The probabilities of response used in the model are presented in Table 4.7.

Table 4.7: Probabilities of response after 3 and 6 months

Response type	Linzagolix 200 mg plus ABT (also applied to GnRH agonist and relugolix) (n/N)	Source
Complete response all patients after three months	38.27% (62/162)	EDELWEISS 3, individual patient-level data ¹⁸
Partial response* all patients after three months	39.51% (64/162)	
No response all patients after three months (move to subsequent treatment)	22.22% (36/162)	
Complete response from Partial response after six months	34.38% (22/64)	
Partial response* from Partial response after six months	50.00% (32/64)	
No response from Partial response after six months	15.62% (10/64)	
Source: Table 38 of the CS ⁴ *Based on dysmenorrhoea- or NMPP-based definition of Partial response, i.e. the base case definition ABT = add-back therapy; CI = company submission; GnRH = gonadotropin-releasing hormone		

4.2.6.2 Long term treatment response (after 6 months)

In the company's model, patients are assigned to pain-based health states after 6 months, based on their OPP score on a VRS as observed in the EDELWEISS 6 study (see Table 4.8). Patients are classified as follows:

1. No/Mild pain: OPP, VRS score < 1
2. Moderate pain: $1 \leq \text{OPP}$, VRS score ≤ 2
3. Severe pain: OPP, VRS score > 2

It is assumed that the distribution over pain-based health states for patients receiving GnRH agonists and relugolix is equal to that derived for linzagolix plus ABT.

Table 4.8: Probabilities to transition to a specific pain state after 6 months

Classification to long term model	Linzagolix 200 mg plus ABT (also applied to GnRH agonist and relugolix) (n/N)	Source
Complete response to No pain/mild	87.88% (58/66)	EDELWEISS 6, individual patient-level data ^{32, 33}
Complete response to Moderate	12.12% (8/66)	
Complete response to Severe	0.00% (0/66)	
Partial response to No pain/mild	41.67% (15/36)	
Partial response to Moderate	58.33% (21/36)	
Partial response to Severe	0.00% (0/36)	
Source: Table 39 of the CS ⁴		

Classification to long term model	Linzagolix 200 mg plus ABT (also applied to GnRH agonist and relugolix) (n/N)	Source
ABT = add-back therapy; CS = company submission; GnRH = gonadotropin-releasing hormone		

In the subsequent 6-month cycles of the model, patients may move between these three pain-based health states. The transition probabilities were estimated using the transitions observed between month 6 and month 12 in the complete and partial responders from EDELWEISS 3 whilst enrolled in the EDELWEISS 6 extension study, see Table 4.9. The company assumed that these transition probabilities can also be applied in all subsequent cycles of the model.

Note that whenever a patient enters the ‘Severe pain’ state (which is only possible from the ‘Moderate pain’ state), the patient is assumed to switch to another treatment.

Table 4.9: Probabilities of transitions between pain-related health states

Transition	Linzagolix 200 mg plus ABT (also applied to GnRH agonist and relugolix) (n/N)	Source
No pain/mild to No pain/mild	94.52% (69/73)	EDELWEISS 6, individual patient-level data ^{32, 33}
No pain/mild to Moderate	5.48% (4/73)	
No pain/mild to Severe	0.00% (0/73)	
Moderate to No pain/mild	31.03% (9/29)	
Moderate to Moderate	65.52% (19/29)	
Moderate to Severe	3.45% (1/29)	
Source: Table 40 of the CS ⁴ ABT = Add-back therapy; CS = company submission; GnRH = gonadotropin-releasing hormone		

4.2.6.3 Treatment discontinuation

The company’s model includes for each cycle a probability that a patient will discontinue the initial treatment.

In the model, treatment discontinuation is interpreted by the company as a loss of efficacy (i.e., patients moving to the Severe pain health-state), intolerability to treatment, a break in the state of No pain/mild symptoms, or due to pregnancy and breastfeeding. The percentage of women discontinuing treatment due to pregnancy was estimated from the live birth rate in the UK,³⁴ whereas the rate of patients who discontinue linzagolix 200 mg plus ABT due to loss of efficacy or intolerability to treatment was estimated based on EDELWEISS 3 and 6.^{18, 32, 33}

In the EDELWEISS 3 and 6 studies, discontinuation was primarily attributed to factors such as COVID-19, political reasons, or the withdrawal of patient consent from the study. Such instances of discontinuation, which were clearly unrelated to the medical intervention, were excluded from the analysis. Following the exclusion of these cases, discontinuation rates were assessed at three and six months of treatment using individual patient-level data, and the resulting discontinuation coefficients were determined and are presented in Table 4.10.

Note that again the assumption is made that patients receiving GnRH agonists and relugolix have the same discontinuation rates as those derived for patients receiving linzagolix plus ABT. Additionally,

the company assumes that the discontinuation rate from ‘No pain/mild’ and ‘Moderate pain’ is applicable to all model cycles as long as the patient still receives the initial treatment.

Table 4.10: Discontinuation rates used in the model

Discontinuation	Probability	Source
From Partial response health-state after 3 months	0.62%	EDELWEISS 3 (patient level data) ¹⁸
From Complete response health-state after 3 months	1.23%	EDELWEISS 3 (patient level data) ¹⁸
From No pain/mild and Moderate health-states	3.03%	EDELWEISS 6 (patient level data) ^{32, 33}
From No pain/mild health-state due to pregnancy	5.8%	Office for National Statistics ³⁴

4.2.6.4 Subsequent medical treatments

The first subsequent treatment following the failure of the intervention or comparator therapy is either conservative surgery (32% of patients) or other medical treatment (68% of patients), which constitutes a weighted basket of potential therapeutic options, as illustrated in Table 4.11. This distribution over subsequent treatments is based on a market research survey amongst 47 gynaecologists.²

Table 4.11: Other medical treatment weighted basket

Therapy	Basket therapy split*	Source
LNG-IUS	13%	Endometriosis Market Research Survey 2024 ²
NSAIDS/Pain killers	3%	
Common oral contraceptives	4%	
Oral progestogen	5%	
Synthetic steroids	4%	
Aromatase inhibitors	4%	
GnRH agonists	25%	
GnRH antagonists	8%	
Source: Table 42 CS * Does not sum to 100% because only medical treatments are shown (i.e., laparoscopic surgery not included). In the model this was recalculated to 100%. CS = company submission; GnRH = gonadotropin-releasing hormone; LNG-IUS = levonorgestrel-releasing intrauterine system; NSAID = non-steroidal anti-inflammatory drug		

When symptoms recur following the first conservative surgery ((post-)Laparoscopy #1 health-state) or failure of subsequent medical therapy (Other medical treatment health-state), patients in the model are assumed to move to the next treatment option in accordance with clinical practice (see Section B.1.3.3 of the company submission).² The probabilities of patients transitioning to various therapeutic options are presented in Table 4.10; presented are both the base-case defined by the company as well as the alternative estimates that were explored in the scenario analyses.

In order to estimate these transition probabilities, one of the elements of information that was used was obtained in the Market Research Survey posing the following question to the 47 gynaecologists: *For your patients first/second surgical procedure to treat endometriosis, can you complete the proportion of different surgical procedures that are carried out: [list of surgery options]*

The resulting distribution across the various surgery options is presented in Table 4.12.

Table 4.12: First and second surgical procedure type for UK women living with endometriosis

Surgical procedure	First surgical procedure	Second surgical procedure
Laparoscopic excision and/or ablation of endometrial tissue	50.00%	36.00%
Ovarian cystectomy	13.00%	15.00%
Bowel resection surgery	4.00%	6.80%
Oophorectomy	6.40%	11.00%
Adhesiolysis	14.00%	14.00%
Partial/total hysterectomy	7.10%	14.00%
Other	4.60%	3.20%
Source: electronic model submitted by company ³⁵		

Table 4.13: Transition probabilities between surgical procedures

Transition	Probability Base-case	Rationale	Probability Scenario 1	Rationale	Probability Scenario 2	Rationale
Other treatment to Laparoscopy #1 waiting	32.00%	Surgery as a second-line treatment after recurrence of symptoms.	32.00%	Surgery as a second-line treatment after recurrence of symptoms	32.00%	
Laparoscopy #1 to Radical surgery #1	2.04%	(Laparoscopy as first surgical type) [†] x (radical surgery as second surgical type) [^] x (% patients in whom recurrence occurs within 0-3 months after unsuccessful surgery) [@]	1.24%	(Annual recurrence rate after laparoscopic surgery) [§] x (fraction immediate recurrence: 0-3 months of 1 st year recurrence) [@] x (treatment decision following recurrence is repeat surgery)* x (adjusted % of radical surgery) [^]	0.75%	(Annual recurrence rate after laparoscopic surgery) [§] x fraction immediate recurrence: 0-3 months of 1 st year recurrence) [@] x treatment decision following recurrence is repeat surgery)* x (unadjusted % of radical surgery) [^]
Laparoscopy #1 to Laparoscopy #2	2.93%	(Laparoscopy as first surgical type) [†] x (laparoscopy as second surgical type) [^] x (% patients in whom recurrence occurs within 0-3 months after unsuccessful surgery) [@]	1.78%	(Annual recurrence rate after laparoscopic surgery) [§] x (fraction immediate recurrence: 0-3 months of 1 st year recurrence) [@] x (treatment decision following recurrence is repeat surgery)* x (adjusted % of conservative surgery) [^]	2.26%	(Annual recurrence rate after laparoscopic surgery) [§] x (fraction immediate recurrence: 0-3 months of 1 st year recurrence) [@] x (treatment decision following recurrence is repeat surgery)* x (unadjusted % of conservative surgery) [^]

Transition	Probability Base-case	Rationale	Probability Scenario 1	Rationale	Probability Scenario 2	Rationale
Post-laparoscopy #1 to Laparoscopy #2	8.10%	(Laparoscopy as first surgical type) [†] x (laparoscopy as second surgical type) [^] x (treatment decision following recurrence is repeat surgery)*	3.08%	(% recurrence after laparoscopic surgery during month 4-12) ^{§@} x (treatment decision following recurrence is repeat surgery)* x (adjusted % of radical surgery) [^]	3.92%	(% recurrence after laparoscopic surgery during month 4-12) ^{§@} x (treatment decision following recurrence is repeat surgery)* x (unadjusted % of radical surgery) [^]
Post-laparoscopy #1 to Radical surgery #1	5.63%	(Laparoscopy as first surgical type) [†] x (radical surgery as second surgical type) [^] x (treatment decision following recurrence is repeat surgery)*	2.14%	(% recurrence after laparoscopic surgery during month 4-12) ^{§@} x (treatment decision following recurrence is repeat surgery)* x (adjusted % of conservative surgery) [^]	1.31%	(% recurrence after laparoscopic surgery during month 4-12) ^{§@} x (treatment decision following recurrence is repeat surgery)* x (unadjusted % of conservative surgery) [^]
Laparoscopy #2 to Radical surgery #1	0.48%	(At least three endometriosis-related surgical procedures over lifetime) [#] x (radical surgery as second surgical type) [^] x (% patients in whom recurrence occurs within 0-3 months after unsuccessful surgery) [@]	1.24%	As Laparoscopy #1 to Radical surgery #1	0.75%	As Laparoscopy #1 to Radical surgery #1

Transition	Probability Base-case	Rationale	Probability Scenario 1	Rationale	Probability Scenario 2	Rationale
Radical surgery #1 to Radical surgery #2	2.79%	Annual recurrence rate following radical surgeries recalculated for 6 months [§]	2.79%	Annual recurrence rate following radical surgeries recalculated for 6 months [§]	2.79%	Annual recurrence rate following radical surgeries recalculated for 6 months [§]
Post-laparoscopy #2 to Radical surgery #1	5.63%	As Post-laparoscopy #1 to Radical surgery #1	2.14%	As Post-laparoscopy #1 to Radical surgery #1	1.31%	As Post-laparoscopy #1 to Radical surgery #1
Source: Table 44 and 88 CS,⁴ electronic model.³⁶ All data from Market research survey.² † 50% of the first surgical procedure are a laparoscopy # 11.74% of women living with endometriosis undergo 3 or more surgeries § Annual recurrence rate is 24.90% for laparoscopy and 5.50% for hysterectomy * 45.00% of patients in whom symptoms recur after surgery will undergo repeat surgery @ In 16.28% of women symptoms recur within 3 months after unsuccessful surgical intervention, in 60.5% within the first year ^ see Table 4.14 CS = company submission						

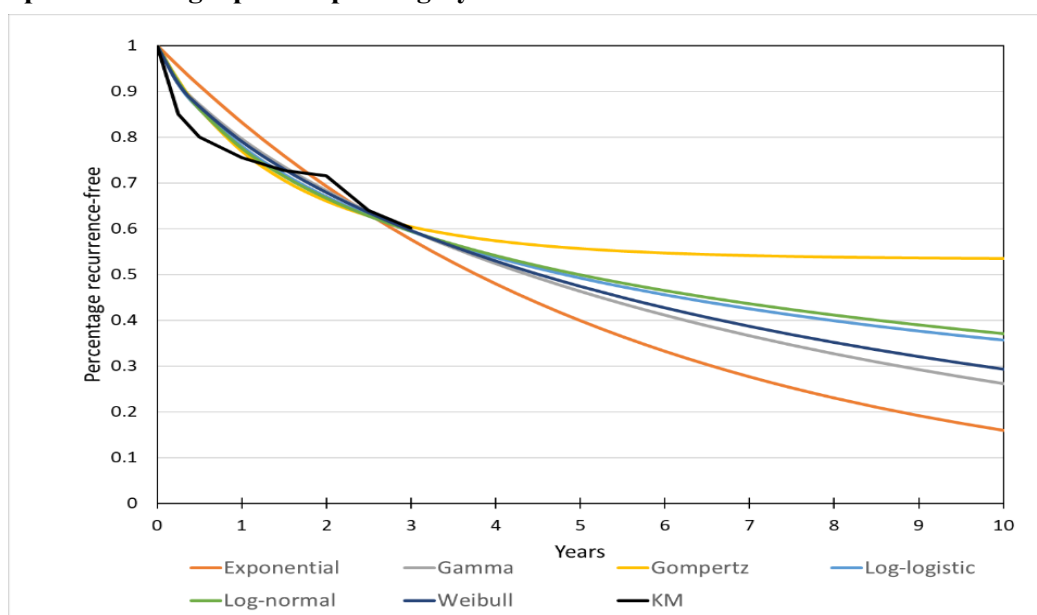
4.2.6.5 Clinical parameters for comparator laparoscopic surgery

For the comparison of linzagolix versus laparoscopic surgery, two additional parameters were required, i.e. the response rate for laparoscopic surgery and pain recurrence following surgery. These parameters were established by the company with studies found in the SLR described in Appendix M of the CS.¹⁵

Response rate for laparoscopic surgery was set to 50% based on Johnson et al. 2004.³⁷ The response definition provided in this study (at least 50% reduction of pain on the VAS) was considered most consistent with the response definition applied for the pharmacological treatments. As different definitions of pain response and timepoints were available in this study, the company opted to select the most conservative (in favour of surgery versus linzagolix), i.e. the highest response rate. The response rate for surgical treatment was validated with clinical expert opinion.^{2, 30} The split between complete and partial responders was assumed similar to the one observed at 3 months after start of pharmacological treatment (see Table 4.8). In the scenario analyses, the company explored the impact of using the higher response rate of 63% as reported by Sutton et al.³⁸

Pain recurrence following surgery was established based on the Kaplan-Meier (KM) curve for the recurrence of Moderate to Severe pain based on the Vercellini et al. 2003 (see Figure 4.2).³⁹

Figure 4.2: Fitted parametric survival curves for recurrence of Moderate to Severe pain following laparoscopic surgery



Source: electronic model.³⁵

Note that Figure 18 in the CS also showed the fitted parametric curves but only included the observed period.

CS = company submission; KM = Kaplan-Meier

According to the company, the recurrence rates that could be extracted based on this study are similar to clinical expert opinion.^{2, 30} The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to assess goodness of fit; based on this a log normal curve was used in the model (see Table 47, CS).

Note that all other transition probabilities for the surgery arm of the model are assumed to be the same as for the linzagolix arm.

EAG comment: The EAG encountered major issues in the estimation of the various transition probabilities, leading to various EAG derived transition probabilities to correct some errors. Three additional, smaller, issues relate to a potential error in the estimation of the number of patients in each pain state after the first 6 months of treatment for the two alternative definitions of partial responders, the probability per cycle of becoming pregnant, and the wait time for a laparoscopy.

Major issues

For the transition probabilities between the various surgery related health states, the company presented three different sets of estimates (see Table 4.10), all based on data collected in a market research survey among 47 gynaecologists.²

The EAG was unable to understand the rationale for the base-case estimates, for example the transition from laparoscopy #1 to Radical surgery #1 is estimated as:

(Laparoscopy as first surgical type) x (radical surgery as second surgical type) x (% patients in whom recurrence occurs within 0-3 months after unsuccessful surgery) = 50% * 25% * 16% = 2.04%

It is unclear why this calculation starts with the 50% of all first surgeries being a laparoscopy, which is then multiplied by the 25% of all second surgeries being a radical surgery. This calculation estimates the probability that a woman who is referred for surgery will first have a laparoscopy and then a radical surgery. However, in the model we are interested in the probability of needing a radical surgery conditional of just having had a laparoscopy. In that regard the alternative defined by the company is more intuitive, i.e.

(Annual recurrence rate after laparoscopic surgery) x (fraction immediate recurrence: 0-3 months of 1st year recurrence) x (treatment decision following recurrence is repeat surgery) x (adjusted % of radical surgery).

Here it is clear for a woman to transition to radical surgery she 1) needs to have a recurrence of pain after her laparoscopy, 2) needs to decide with her doctor that a new surgery is the best option and 3) decide that radical surgery is a better option than a second laparoscopy. In addition, a correction is made to the recurrence rate since the recurrence needs to be in the first 3 months in order to transition immediately from laparoscopy to radical surgery, bypassing the post-laparoscopy state.

However, some of the alternative probabilities also appear to be incorrect. For example, for the transitions from post-laparoscopy #1 to laparoscopy #2 and to radical surgery #1, the adjustment to the annual recurrence to exclude the 0–3-month recurrence also includes the probability that a repeat surgery is required, which is incorrect.

Thus, the EAG has calculated alternative transition probabilities, where the simplifying assumption is made that the probability to go from laparoscopy to radical surgery is the same as from post-laparoscopy to radical surgery. This simplification is made as a) it is not clear why 0-3 months was chosen for the immediate transition to radical surgery after a laparoscopy instead of 0-6 months in line with the cycle length, b) if a distinction is made between 0-3 months versus 3-9 or 3-12 months, we should also consider differences between the first year and subsequent years (which is impossible given the Markov property of the model), and c) the distribution of recurrence over time is only based on expert opinion and thus subject to large uncertainty.

We estimate the transition from any laparoscopy state to radical surgery based on the 6-month recurrence rate after laparoscopy * probability that the treatment decision after recurrence is a new

surgery * probability that the new surgery is a radical surgery, which yields a probability of 2.46%. Similarly, the transition from any laparoscopy state to a next laparoscopy is the 6-month recurrence rate after laparoscopy * probability that the treatment decision after recurrence is a new surgery * probability that the new surgery is a laparoscopy, yielding a probability of 3.54%. As for the probability from first to second radical surgery, the company used the 6-months recurrence rate for this probability. However, the EAG considers this incorrect, as this should be multiplied by the probability of a surgery (45%) in case of recurrence. This adjustment leads to a probability of 1.26% to have a second radical surgery after having already had one.

All these transition probabilities will be implemented in an EAG preferred base-case, which will be presented in Section 6 of this report.

Additional issues

- Table 4.7 shows how the complete and partial responders are classified based on pain score. The percentages presented for the partial responders are based on the base-case definition of a partial responder as having either a dysmenorrhoea or a NMPP response. The electronic model also contains the pain classification when Partial response is 1) defined as patients with only a dysmenorrhoea response and 2) defined as patients with only an NMPP response, and the underlying patient numbers are reproduced in Table 4.14. The number of patients with such Partial response and their distribution over the pain states appear incorrect to the EAG, as for both alternative definitions of Partial response the number of patients should be lower than for the base case definition. The EAG considers it possible that the correct rows for only DYS responders and for only NMPP responders can be found by subtracting the values from the complete responders from the current rows for DYS responders and NMPP responders. However, this cannot be known for sure at this moment, as the EAG has no access to the patient level data. Thus, no corrections have been made, also because such changes would only lead to different results when running a scenario analysis changing the definition of Partial response, for the base-case the error and the corrections have no impact.

Table 4.14: Distribution of patients with (partial) response after 6 months over pain health states

Parameter	No pain/mild	Moderate	Severe	Total
Complete responders after 6 months	58	8	0	64
DYS responders after 6 months	69	28	0	97
NMPP responders after 6 months	62	9	0	71
DYS or NMPP responders after 6 months	15	21	0	36

- In the model a probability of becoming pregnant is incorporated for women with no pain or mild pain. This probability is estimated from the live birth rate in the UK, and, according to the company it assumes that women with endometriosis have similar desires and probability of pursuing pregnancy as the general UK population, as there is no evidence to suggest otherwise. The company states that this approach ensures that the model reflects real-world reproductive intentions without introducing unnecessary bias. The problem however is that the UK live birth rate not only reflects real-world reproductive intentions, but also the success in becoming pregnant and delivering a baby. As the company explains in their submission (Section B.1.3.2.1), while women without endometriosis have a 10%–20% chance of getting pregnant each month, this is reduced to only a 1%–10% chance for patients with endometriosis.⁴⁰ Thus,

the EAG considers that it would be preferable to use a smaller pregnancy rate in the model. However, the company ran a scenario excluding pregnancy from the model which led to a rather modest increase in the ICER. In Section 6, we will apply the same scenario to the EAG base-case to assess the impact.

- Another smaller issue concerns the waiting time for a laparoscopy. In the CS it is stated that the average wait time for a laparoscopy in the UK is 18 months. The company incorporated this into the model for the comparison of linzagolix versus surgery. This means that at the start of the model, the patients in the surgery arm will remain in the No response state for the first 18 month. However, in the modelling of laparoscopy as subsequent treatment, this wait time has been modelled for only 6 months. When queried about this during clarification, the company responded that *“The waiting for laparoscopy health state one cycle of six months was implemented to maintain model simplicity and not introduce additional tunnel states within the CE model. As the health-state utility value of Laparoscopy #1 waiting is lower compared with Post-laparoscopy #1 (0.644 vs 0.758) the solution is conservative regarding impact on the ICER (as patients in comparator arms are assumed to progress quicker to laparoscopy health-states).”*. The EAG concurs with this conclusion.

4.2.7 Adverse events

The company included AEs in the scenario analysis but not in the base-case, due to an absence of significant (grade 3 or 4) AEs, such as depression, headache, hot flushes or increased blood pressure in the EDELWEISS 3 study. Surgical complications were included in the base-case analysis. The company’s approach to incorporate the influence of AEs and surgical complications on HRQoL (i.e., the disutilities associated with them) will be discussed in Section 4.2.8.3 below. The impact on resource use and costs will be discussed in Sections 4.2.9.4 (AEs) and 4.2.9.5 (surgical complications).

EAG comment: Despite the absence of significant AEs for linzagolix, the EAG does not consider it appropriate to exclude AEs from the base-case analysis. Therefore, the AEs are included in the EAG base-case which is presented in Section 6.

4.2.8 Health-related quality of life

In the base-case analysis, the company mainly used HRQoL evidence from the EDELWEISS 3 trial. Only information about the disutility for infertility and surgical complications were taken from the literature as EDELWEISS 3 did not provide relevant HRQoL inputs for these parameters. The systematic literature search also provided alternative HRQoL utility values for some health states. The impact of the use of these HRQoL utilities was explored in the company’s scenario analyses. Both the evidence from the EDELWEISS 3 trial and the literature are described in detail in the subsections of this paragraph.

4.2.8.1 Health-related quality of life from clinical trials

In EDELWEISS 3, the EQ-5D-5L questionnaire was administered to patients at day 1, month 1, month 3 and month 6. Patients had to choose between five levels of difficulty for five different domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) resulting in a five-digit health state. The five-digit health states of the individual patient level-data were mapped to the EQ-5D-3L UK utility score using the NICE Decision Support Unit (DSU) mapping function according to the algorithm presented in Hernández-Alava and Pudney et al. 2017.⁴¹ EQ-5D-3L utilities were based upon the UK value set, which is in accordance with the current NICE guidance.

The EQ-5D-5L was also administered in EDELWEISS 6. However, the company did not incorporate the data from EDELWEISS 6 in the CEA due to possible attrition bias. In the response to the clarification letter, the company explained that patients who completed the 6-month treatment period of the EDELWEISS 3 study were invited to enter the EDELWEISS 6 extension study. Therefore, the patient population of the EDELWEISS 6 study consists of patients who already received 6 months of treatment with linzagolix and who choose to continue. The company state that there is potential risk, that patient who did not perceive therapeutic benefits or who experienced AEs during the initial 6 months were less likely to enrol in EDELWEISS 6. Therefore, EDELWEISS 6 might represent a patient population with more favourable responses to linzagolix, leading to an overestimation of its impact on HRQoL. This assumption of the company was supported by evidence from the EDELWEISS 6 study which showed a slightly larger increase in EQ-5D-5L utility at month 6 for the subgroup of patients who continued in EDELWEISS 6 (see Table 4.15)

Table 4.15: Change from baseline to month 6 in EQ-5D-5L index

	Placebo	Linzagolix 75 mg	Linzagolix 200 mg plus ABT
All patients in EDELWEISS 3			
N	162	160	162
Baseline, mean (SD)	0.72 (0.16)	0.74 (0.16)	0.74 (0.15)
Change from baseline to month 6, mean (95% CI)	0.08 (0.06; 0.10)	0.09 (0.07; 0.11)	0.11 (0.09; 0.13)
Patients who continued in EDELWEISS 6			
	Placebo/ linzagolix 75 mg	Placebo/ linzagolix 200 mg plus ABT	
N	57	57	118
Baseline, mean (SD)	0.73 (0.16)	0.71 (0.18)	0.72 (0.17)
Change from baseline to month 6, mean (SD)	0.08 (0.19)	0.07 (0.19)	0.12 (0.18)
Based on Table 13 of the clarification letter, part I ⁵ ABT = add-back therapy, CI = confidence interval, mg = milligram, N = number of patients, SD = standard deviation			

The patient-level data of EDELWEISS 3 was used to develop two separate regression models: a response model to estimate HRQoL utility values for the states No response, Partial response, and Complete response and a pain model to estimate HRQoL utility values for the states No pain/mild, Moderate, and Severe.

For both regression models, the inclusion of additional patient characteristics was explored to enhance the accuracy of the models. First, a comprehensive literature search was conducted alongside references in a SLR with the aim to identify potentially relevant quality of life predictors for patients with endometriosis. The predictors identified through this search, which matched with available patient characteristics reported in EDELWEISS 3, were subsequently tested using univariate analysis. For this purpose, continuous variables were dichotomized in two groups defined by the median value of these variables. For each patient characteristic, a linear regression was performed with the 6-month EQ-5D

utility score as dependent variable. The results of the univariate analysis are shown in Table 4.16. Variables found to be statistically significant in the univariate analysis were explored in multivariate regression models, except for endometriosis diagnosis between 2 and 5 years.

Table 4.16: Univariate analysis results

Variable	Estimate	P-value
Age	<0.005	0.988
Age*	<0.005	0.812
Base pain*	0.0970	<0.005
BMI*	-0.0464	<0.005
Base EQ-5D-3L*	0.476	<0.005
Pregnancy history*	-0.030	0.698
Opiate use*	-0.108	<0.005
Months to diagnosis*	0.0183	0.286
Dyspareunia*	0.129	<0.005
Dyschezia*	0.143	<0.005
Treatment arm 2 (linzagolix 75 mg)	0.0206	0.237
Treatment arm 3 (linzagolix 200 mg plus ABT)	0.0358	0.0386
No/Mild pain	0.320	<0.005
Moderate pain	0.185	<0.005
Endometriosis diagnosis <2 years	<0.005	0.930
Endometriosis diagnosis ≥ 2 and <5 years	-0.0521	<0.005
Partial response	0.123	<0.005
Complete response	0.234	<0.005
Based on Table 50 of the CS ⁴		
* Variables introduced as binary ones with groups defined by median; in bold if statistically significant at the level of 0.05		
ABT = add-back therapy; BMI = body mass index; CS = company submission; EQ-5D-3L = EuroQoL 5-Dimension 3-Level		

4.2.8.1.1 Response-based regression model

The response categories used in the response-based regression model were based upon to the response criteria used for the co-primary endpoints of EDELWEISS 3 and EDELWEISS 6.

- Complete response = a patient meeting the response criteria for both dysmenorrhoea and NMPP endpoints, indicating a comprehensive improvement in pain management and overall well-being
- Partial response = a patient achieving a response in either dysmenorrhoea or NMPP but not both, potentially reflecting a more limited benefit from the treatment
- No response = a patient who did not meet the criteria for any of the endpoints, indicating a lack of therapeutic effect.

Table 4.17 shows the observed EQ-5D-3L utility in the three response states at 3 months and 6 months for all treatment arms combined. The baseline HRQoL utility for all patients in EDELWEISS 3 was 0.631.

Table 4.17: Observed EQ-5D-3L utility for all treatment arms in the EDELWEISS 3 study categorised by response

Response category	Month 3 (n)	Month 6 (n)
Non responders	0.704 (195)	0.708 (181)

Partial responder	0.768 (147)	0.783 (135)
Complete responders	0.881 (129)	0.892 (155)
Based on Table 51 of the CS ⁴ CS = company submission; n = number of observations		

The company used two different datasets for the estimation of the regression model. The primary dataset consisted of all observations at month 3 and month 6 for patients who could be categorised to any of the response groups (n=862). The second dataset (n=1,325) included the baseline data and classified those observations to the No response category. In the primary dataset, the baseline data were excluded because it was shown that non-responders had a better HRQoL at 3 and 6 months compared to baseline. According to the company, this meant that non-responders had some improvement in overall health and a reduction in EAP was observed, despite the lack of a clinically relevant response. The company stated that the exclusion of baseline HRQoL ensured that the model accurately reflects the HRQoL in the three response states.

Multiple linear mixed-effects regression models with different covariates were tested on the primary dataset for best fit to the data, with the selection based on AIC and BIC criteria. In the initial CS, none of these five models included baseline EQ-5D-3L utility as a covariate despite the significant association with 6-month EQ-5D utility. The EAG asked to perform this analysis as well to assess whether this would improve the statistical fit of the model. Furthermore, the EAG also asked to run a model that only includes the response-based health state and no other covariates. Table 4.18 shows statistical performance of the five best performing response-based models (based on AIC and BIC) as reported in the CS and the two additional models that the EAG requested in the clarification letter.

Table 4.18: Five best-performing (based on AIC and BIC) response-based models

Model	AIC	BIC
1. Base pain level*, dyschezia*, Partial response status, Complete response status, No response status	-691.189	-654.865
2. Base pain level*, opiate use*, dyschezia*, Partial response status, Complete response status, No response status	-688.806	-647.292
3. BMI*, base pain level*, dyschezia*, Partial response status, Complete response status, No response status	-688.192	-646.697
4. BMI*, base pain level*, opiate use*, dyschezia*, Partial response status, Complete response status, No response status	-685.047	-638.365
5. Base pain*, Partial response status, Complete response status, No response status	-678.720	-647.585
Base pain, dyschezia, Partial response, Complete response, baseline EQ-5D-3L	-866	-825
Partial response status, Complete response status, No response status	-680	-656
Based on Table 52 of the CS, ⁴ Table 24.1 and Table 25.5 of the response to the clarification letter ⁴² AIC = Akaike Information Criterion; BIC = Bayesian information criterion; BMI = body mass index; CS = company submission * Variables introduced as binary ones with groups defined by median		

The first model had the lowest AIC and BIC and was therefore selected for the estimation of HRQoL utilities for the response states. That model included the response states, base pain level defined by OPP, and dyschezia as predictors of HRQoL. All coefficients were significant (p-value ≤ 0.05). The impact of the exclusion of baseline data was explored by running this regression model on the second

dataset that included baseline data. The coefficients of regression models for the primary and secondary dataset are shown in Table 4.19.

Table 4.19: Coefficients for the response-based regression models

Coefficient	Primary dataset in CS (excluding baseline data)		Second dataset in CS (including baseline data)		Including baseline EQ-5D-3L as covariate		Only health states as covariates	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	0.64075	0.01305	0.58183	0.01055	0.69521	0.01538	0.71422	0.01057
Base pain < median	0.08010	0.01348	0.10886	0.01317	0.05409	0.01357	-	-
Dyschezia < median	0.06439	0.01361	0.05927	0.01278	0.06830	0.01322	-	-
Partial response	0.05771	0.01389	0.11032	0.01317	0.05436	0.0136	0.06160	0.01395
Complete response	0.14794	0.01592	0.21143	0.01460	0.14800	0.01547	0.15876	0.01509
Baseline EQ-5D-3L < median	-	-	-	-	-0.0822	0.01308	-	-
Based on sheet 'Utility regression' of the electronic model version 09.12.2024 CS = company submission; EQ-5D-3L = European Quality of Life-5 dimensions 5 levels; SE = standard error								

In the initial CS, the HRQoL utility was estimated for each combination of response level, base pain and dyschezia using the regression models presented in Table 4.20. Subsequently, a weighted HRQoL was estimated for each response state using weights based upon the percentage of observations corresponding to each combination of base pain and dyschezia (see Table 4.21). The estimated HRQoL utility score for No response, Partial response and Complete response are also presented in Table 4.21. The inclusion of baseline data led to a substantial decrease in the HRQoL utility for no responders, because the HRQoL at baseline was lower than the HRQoL utility for non-responders at month 3 and month 6. The HRQoL of partial or complete responders slightly increased when baseline data were included in the model.

Table 4.20: HRQoL utilities for response-based states weighted according to the distribution of base pain and dyschezia

	Primary dataset – excluding baseline data (n=862)				Second dataset – including baseline data (n=1325)			
	Base pain < median & dyschezia < median	Base pain ≥ median & dyschezia < median	Base pain < median & dyschezia ≥ median	Base pain ≥ median & dyschezia ≥ median	Base pain < median & dyschezia < median	Base pain ≥ median & dyschezia < median	Base pain < median & dyschezia ≥ median	Base pain ≥ median & dyschezia ≥ median
No response								
N observations	91	25	107	100	182	72	249	283
% observations	28%	8%	33%	31%	23%	9%	32%	36%
Predicted utility*	0.785	0.705	0.721	0.641	0.750	0.641	0.691	0.582
Weighted HRQoL utility	0.713				0.661			
Partial response								
N observations	94	61	31	75	94	61	31	75
% observations	36%	23%	12%	29%	36%	23%	12%	29%
Predicted utility *	0.843	0.763	0.779	0.698	0.860	0.751	0.801	0.692
Weighted HRQoL utility	0.775				0.779			
Complete response								
N observations	104	133	9	32	104	133	9	32
% observations	37%	48%	3%	12%	37%	48%	3%	12%
Predicted utility *	0.933	0.853	0.869	0.789	0.961	0.853	0.902	0.793
Weighted HRQoL utility	0.876				0.888			
Based on Table 53 of the CS ⁴ and electronic model ³⁵ Cs = company submission; HRQoL = health-related quality of life, N = number * Predicted by applying the regression model from Table 4.19 (base pain < median and dyschezia < median are set as 1)								

A summary of all estimated HRQoL utility values using different regression models (as explored in the response to the clarification letter) or data from the relugolix STA²⁷ is shown in Table 4.21.

Table 4.21: HRQoL utilities for different response-based models

Health state	Primary dataset (3 and 6-month data only)	Second dataset (including baseline data)	Including baseline EQ-5D-3L as a covariate (weighted utility)	Excluding any covariates (3 and 6-month data only)	Relugolix STA
Complete response	0.876	0.888	0.877	0.873	0.884
Partial response	0.775	0.779	0.775	0.776	0.801
No response	0.713	0.661	0.711	0.715	0.719
Based on Table B 24.2, Table B 25.6 and Table B 25.8 of the response to the clarification letter ⁴² EQ-5D-3L = European Quality of Life-5 dimensions 3 levels; HRQoL = health-related quality of life					

4.2.8.1.2 Pain-based regression model

Pain intensity was categorised into three distinct levels based on OPP value in the VRS scale:

- No pain/mild: OPP, VRS scale <1
- Moderate pain: $1 \leq \text{OPP}$, VRS scale ≤ 2
- Severe pain: OPP, VRS scale >2

Table 4.22 shows the observed HRQoL utility values in the EDELWEISS 3 study for the three different pain states at different points in time.

Table 4.22: Observed EQ-5D-3L utilities for the different pain-related states

Pain level	Baseline (n)	Month 1 (n)	Month 3 (n)	Month 6 (n)
No pain/mild	0.798 (13)	0.860 (86)	0.872 (194)	0.878 (217)
Moderate	0.695 (247)	0.725 (293)	0.735 (220)	0.747 (173)
Severe	0.547 (216)	0.577 (81)	0.543 (43)	0.489 (33)
EQ-5D-3L = European Quality of Life-5 dimensions 3 levels; n = Number of observations				

Two different datasets were used for the estimation of the pain-based regression models. The primary dataset consisted of the 6-month observations of all patients. Initially, the dataset was restricted to the 6-months observations of the patients with a partial or Complete response, because only these patients will continue linzagolix or the comparative treatment. However, only one of these patients could be classified in the Severe pain category, rendering the estimate highly unreliable. Therefore, the decision was made to develop the regression model on all 6-months observations instead. The second dataset included all available observations (baseline, 3- and 6-months).

Similarly to the response-based models, a series of multiple models with varying covariates were tested to determine the most appropriate fit to the data. However, as only 6-months observations were included in the primary dataset, multivariate linear regression analyses were performed. In the initial company submission, the model was selected according to statistical fit based upon AIC and BIC. The EAG requested to also perform an analysis with baseline European Quality of Life-5 dimensions 3 levels (EQ-5D-3L) as a covariate. The statistical performance of the five best performing pain-based models of the initial submission and the additional requested model are shown in Table 4.23.

Table 4.23: Five best-performing pain-base models that were tested during the regression analysis

Model	AIC	BIC
1. OPP No pain/mild, OPP Moderate, OPP Severe	-795.510	-770.404
2. Dyschezia*, OPP No pain/mild, OPP Moderate, OPP Severe	-794.182	-764.055
3. BMI*, OPP No pain/mild, OPP Moderate, OPP Severe	-791.179	-761.074
4. BMI*, dyschezia*, OPP No pain/mild, OPP Moderate, OPP Severe	-789.521	-754.399
5. Base pain*, OPP No pain/mild, OPP Moderate, OPP Severe	-786.905	-756.779
Base pain*, dyschezia*, OPP No pain/mild, OPP Moderate, OPP Severe, Base EQ-5D-3L level*	-890	-850
Based on Table 55 of the CS ⁴ * Variables introduced as binary ones with groups defined by median AIC = Akaike Information Criterion; BIC = Bayesian information criterion; BMI = body mass index; CS = company submission; OPP = overall pelvic pain		

In the initial CS, the first model, which only includes the pain-based health states, showed to have the best statistical fit according to AIC and BIC. Therefore, this model was used to estimate the HRQoL utilities for the pain-based states. All coefficients were significant (p-value < 0.05). The same regression model was applied to the second dataset to explore the impact on the inclusion of baseline and 3-month data. For this analysis, a multivariate linear-mixed effects regression analysis was performed. The inclusion of baseline and 3-month data had limited impact on the estimation of the No pain/mild or Moderate pain state, but increased the HRQoL utility for patients with Severe pain. In the response to the clarification letter, the inclusion of EQ-5D-3L baseline utility was applied to the primary dataset. Furthermore, a scenario was included in which the utility values from the relugolix STA were used as inputs for the pain-based states as well,²⁷ assuming that No pain/mild had a similar utility value as a Complete response, Moderate pain as Partial response and Severe pain as No response. The coefficients of all regression models are shown in Table 4.24 and the estimated HRQoL utility scores for the pain-based models are shown in Table 4.25.

Table 4.24: Coefficients for the selected pain-based regression model

Coefficient	Primary dataset (6-month data only)		Second dataset (including baseline and 3-month data)		Including baseline EQ-5D-3L as covariate	
	Estimate	SE	Estimate	SE	Estimate	SE
Intercept	0.47701	0.02594	0.5542	0.01271	0.51871	0.02842
No pain/mild	0.33920	0.02801	0.1852	0.01375	0.38126	0.028126
Moderate pain	0.26430	0.02848	0.3203	0.01443	0.24746	-0.05143
Baseline EQ-5D-3L	-	-	-	-	-0.05143	0.01514
Based on sheet 'Utility regression' of the electronic model version 09.12.2024 ED-5D-3L = European Quality of Life-5 dimensions 3 levels; SE = standard error						

Table 4.25: HRQoL utilities for different pain-based models

Health state	Primary dataset (6-month data only)	Second dataset (including baseline and 3-month data)	Including baseline EQ-5D-3L as a covariate (weighted utility)	Relugolix STA
No pain/mild	0.876	0.874	0.876	0.884
Moderate pain	0.741	0.739	0.741	0.801
Severe pain	0.477	0.554	0.477	0.719
Based on Table 25.4 of the response to the clarification letter ⁴² and sheet Utility regression of the electronic model version 09.12.2024 ED-5D-3L = European Quality of Life-5 dimensions 3 levels; HRQoL = health-related quality of life; STA = Single Technology Appraisal				

EAG comment:**Major concerns**

The EAG has two major concerns with respect to the selected models for the response-based and pain-based model.

First, the inclusion of covariates in addition to the health-states complicates the estimation of the utility scores. The covariates are dichotomised on the median and have therefore a limited generalisability to other studies. In other studies, the median could be different. Furthermore, the uncertainty in the distribution among the different categories is difficult to incorporate in a probabilistic sensitivity analysis. For the response-based health states, the simple model (without any covariates in addition to health states) has a higher AIC, but a lower BIC than the model that was selected by the company. There is thus no clear consensus which of these models has the best statistical fit. The EAG acknowledge that the inclusion of baseline EQ-5D leads to a substantial lower AIC and BIC, but the challenges regarding the inclusion of the dichotomized covariates are also applicable to this model. Furthermore, the estimated HRQoL utility only marginally differ between the model selected by the company, the model without any additional covariates, and the model that includes baseline EQ-5D as a covariate (see Table 4.21). Therefore, the EAG prefers to use the model without any covariates in the EAG base-case.

The second major concern of the EAG is the exclusion of baseline data in the estimation of the utilities for the pain-based models. The company excluded the baseline utilities to be consistent with the method used for the estimation of the response-based model. However, the EAG does not consider this a valid argumentation as the nature of the classification of the health states differs between the response-based and the pain-based health states, which makes consistency between the two model types irrelevant. The response classification is based upon the observed change from baseline to 3 or 6 months, while the pain classification is based on the severity of pain at that specific moment. The EAG agrees with the company to exclude baseline utilities for the response-based health states. It is invalid to classify all baseline values in the No response states, because these patients have not yet received treatment and can therefore not be a responder or non-responder. However, as the classification for the pain-based states is derived from the reported severity of pain at certain time points, there is no reason to exclude the baseline data. The inclusion of that data would even improve the validity of the estimated utility for Severe pain as much more patients experience Severe pain at baseline. Therefore, baseline data is included in the models that are used for the estimation of HRQoL utilities for pain-based health states in the EAG base-case.

The changes in the model selection for the response-based and model-based model also have consequences for the utility values for the other health states (see Section 4.2.8.2). Table 4.26 reports all the utility values that are used in the EAG base case.

Additional concerns

The EAG agrees with the company that EDELWEISS 6 might consist of a relatively more favourable patient population as it is likely that mainly patients who experienced benefits from linzagolix choose to continue treatment. Nevertheless, data from month 9 and month 12 in EDELWEISS 6 could have been used in addition to month 6 data in the estimation of the utility scores for the pain-based utility model to increase the sample size and include longer follow-up data. For those health states, the utilities are categorized based on the pain level which might be less influenced by the attrition bias of EDELWEISS 6. The EAG could not explore the impact of the inclusion of that information as this data was not available.

Furthermore, the EAG also identified some aspects which were either not clarified in the response to the clarification letter or were unclear in the company's response. First, it is unclear whether the 1-month HRQoL were also included in the baseline data or not. The EAG assumes that these measurements are included in the baseline data as the company responded that baseline data contains data from day 1. Second, in the response to question 25 of the clarification letter,⁴² the company mention the AIC and BIC of a model that not only includes pain states and baseline EQ-5D-3L, but also base pain level and dyschezia. These two additional variables are not reported in the regression output in the electronic model. Therefore, the EAG considers it possible that a typing error is made in Table 25.1 of the response to the clarification letter with regard to the model structure.

Finally, in Section 4.2.6, the company presented three potential definitions of Partial response, with the base-case definition a response in either dysmenorrhoea or NMPP but not both, and two alternatives based on 1) a clinically relevant response on only dysmenorrhea or 2) a clinically relevant response on only NMPP, with the latter two options explored in scenario analyses. However, in these scenario analyses no re-estimated utilities are used for Partial response and No response, rendering these scenario analyses incomplete. It is not clear how much this would influence the outcomes of these scenario analyses.

4.2.8.2 HRQoL used in CEA

The utilities that have been estimated through the regression analyses for the response-based health states and the pain-based health states (see Section 4.2.8.1) were used as HRQoL input for the health states No response, Partial response, Complete response, No pain/mild, Moderate pain, or Severe pain. In the company base-case, no disutilities for AEs were applied to these health states, as the company assumed that these were already captured within the QoL measurements of EDELWEISS 3. Additionally, no infertility disutilities were assumed during linzagolix treatment (and conservatively, any other medical therapy) because the half-life of linzagolix is approximately 15 hours and ovarian activity may recover within days of treatment cessation.⁴³ The company stated that according to clinical expert opinion, patients wanting to conceive can stop medical therapy at any time, which would justify not applying any disutility for infertility in these health states.

The HRQoL for the other health states were estimated utilising the results of the regression models from EDELWEISS 3. The following algorithm was employed for the estimation of the remaining health states:

- Health states to which patients transition from the No pain/mild health state (i.e. off-treatment, No pain/mild, off-treatment during washing period and conceive, different phases of conception and breastfeeding) were assigned the HRQoL values corresponding to the No pain/mild state as it was assumed that they experience the same (low) level of pain. The assumption regarding the maintenance of treatment effects is derived from EDELWEISS 6.
- Other medical treatments: the mean value of No response, No pain/mild, Moderate and Severe was used. In the response to the clarification letter⁵ this choice was motivated by stating that the use of the average utility from these health states reflects the range of symptom severity and outcomes experienced by patients on subsequent therapy. By applying this approach, patients who are more pretreated have lower QoL as compared to patients responding to initial treatments (because the average also includes lower utility values for No response and Severe). The company state that this algorithm is in line with Wang et al.³
- Waiting period for laparoscopy: the mean value of No response, Moderate and Severe. The company stated that the HRQoL of No pain/mild was not included in this calculation, because these patients typically do not require surgical intervention. The company considered this approach conservative, because these patients were already heavily pretreated (with surgery and a multitude of pharmacological therapies, including GnRH analogues). It is assumed that most patients receive sub-optimal treatment whilst waiting for the next surgical treatment.
- Laparoscopy #1 and #2: The company assumed that during and shortly after surgery, patients had a utility of 0 for 3 days due to the invasive nature of the surgery. This duration of zero utility was taken from Wang et al.³ For the remaining period of the 6-month cycle, the utility was assumed to be the average of No response, No pain/mild, Moderate and Severe. Furthermore, a disutility for surgical complications was added for the proportion of patient experiencing complications. This disutility was taken from literature (see Section 4.2.8.3). A conservative approach was taken to assume similar HRQoL in both laparoscopic health states, although clinical experts indicated that subsequent surgical procedures tend to be more invasive, leading to more complications.³⁰
- Utilities for post-laparoscopy health states #1 and #2 were derived from HRQoL values assigned to other medical treatments and the off-treatment state. It was assumed that 32% of the patients had a utility similar to other medical treatments, because these patients still experience symptoms after surgery and require additional treatment and 68% had a utility score similar to off-treatment state. The company motivated this distribution by stating that this allocation was proportionally to the transitions from these states to the post-laparoscopy state.
- For radical surgery, it was assumed that patients have a zero utility for 7 days. For the remaining days of the 6-months period, it was assumed that the utility value was the average of the utility in the No response, Moderate and Severe pain. Furthermore, disutilities were applied for the proportion of patients experiencing surgical complications (see Section 4.2.8.3).
- The HRQoL for post-radical surgery was assumed to align with the No pain/mild health state, with an additional infertility-related disutility applied to the proportion of patients who wish to preserve fertility. This value is higher than the utility value of the post-laparoscopic states, which is, according to the company, in line with literature.⁴⁴ This could be because most patients are assumed to be cured from endometriosis after radical surgery, whereas some patients would still experience EAP after laparoscopic surgery.

A summary of the HRQoL utility values in the company's CE model can be found in Table 4.26.

Table 4.26: Summary of utility values for the company's and EAG CE analysis

State	Company utility value: mean	Reference in EAG report (Section and table number)	Justification of the company	EAG utility value: mean	Justification EAG
No response	0.713	4.8.1.1.1, Table 4.20	The regression model is based on individual patient-level data.	0.715	Regression model excluding any covariates except response states. Data from 3- and 6-months observations
Partial response	0.775	4.8.1.1.1, Table 4.20	The regression model is based on individual patient-level data.	0.776	
Complete response	0.876	4.8.1.1.1, Table 4.20	The regression model is based on individual patient-level data.	0.873	
No pain/mild	0.876	4.8.1.1.1, Table 4.25	The regression model is based on individual patient-level data.	0.874	Regression model including baseline, 3 month and 6-month data
Moderate	0.741	4.8.1.1.1, Table 4.25	The regression model is based on individual patient-level data.	0.739	
Severe	0.477	4.8.1.1.1, Table 4.25	The regression model is based on individual patient-level data.	0.554	
Off-treatment, No pain/mild	0.876	Assumption	As <i>No pain/mild</i> *	0.874	As <i>No pain/mild</i> *
Off treatment - washing period and conceive (pregnancy 1st step)	0.876	Assumption	As <i>No pain/mild</i> *	0.874	As <i>No pain/mild</i> *
Pregnancy and breastfeeding (2 nd and 3 rd step)	0.876	Assumption	As <i>No pain/mild</i> *	0.874	As <i>No pain/mild</i> *
Other medical treatment	0.702	Calculation	Mean of: <i>No response; No pain/mild; Moderate; Severe</i>	0.722	Mean of**: <i>No pain/mild; Moderate; Severe</i>
Laparoscopy #1 waiting	0.644	Calculation	Mean of: <i>No response; Moderate; Severe</i>	0.647	Mean of: <i>Moderate; Severe</i>
Laparoscopy #1	0.688	Calculation	Mean of: <i>No response; No pain/mild; Moderate; Severe</i> for	0.708	Mean of: <i>No pain/mild; Moderate; Severe</i> for 177 days, 0 utility for 3

			177 days, 0 utility for 3 days and disutilities related to laparoscopic surgeries		days and disutilities related to laparoscopic surgeries
Laparoscopy #2	0.688	Calculation	Mean of: <i>No response; No pain/mild; Moderate; Severe</i> for 177 days, 0 utility for 3 days and disutilities related to laparoscopic surgeries	0.708	Mean of: <i>No pain/mild; Moderate; Severe</i> for 177 days, 0 utility for 3 days and disutilities related to laparoscopic surgeries
Post-laparoscopy #1	0.758	Calculation	Weighted value of health states: <i>other medical treatment</i> and <i>off-treatment</i> . The proportion of patients who require additional treatment (32%) is based upon the proportion of patients who transition from other medical treatment to post-laparoscopy	0.784	Weighted value of health states: <i>No pain/mild, Moderate</i> and <i>other medical treatment</i> . The weights are derived from the transitions to these health states in the surgery comparator, excluding the transition to the laparoscopic surgery. Weights: <i>No pain/mild</i> : $0.32/0.84 = 0.39$, <i>Moderate</i> = $0.18/0.84 = 0.214$, <i>other medical treatment</i> = $0.34/0.84 = 0.405$.
Post-laparoscopy #2	0.758	Calculation	Weighted value of health states: <i>other medical treatment</i> and <i>off-treatment</i> . The proportion of patients who require additional treatment (32%) is based upon the proportion of patients who transition from other medical treatment to post-laparoscopy	0.784	Weighted value of health states: <i>No pain/mild, Moderate</i> and <i>other medical treatment</i> . The weights are derived from the transitions to these health states in the surgery comparator, excluding the transition to the laparoscopic surgery. Weights: <i>No pain/mild</i> : $0.32/0.84 = 0.39$, <i>Moderate</i> = $0.18/0.84 = 0.214$, <i>other medical treatment</i> = $0.34/0.84 = 0.405$.
Radical surgery #1	0.615	Calculation	Mean of: <i>No response; Moderate; Severe</i> for 173 days and 0 utility for 7 days and disutilities related to radical surgeries	0.617	Mean of: <i>Moderate; Severe</i> for 173 days and 0 utility for 7 days and disutilities related to radical surgeries

Radical surgery #2	0.615	Calculation	Mean of: <i>No response; Moderate; Severe</i> for 173 days and 0 utility for 7 days and disutilities related to radical surgeries	0.617	Mean of: <i>Moderate; Severe</i> for 173 days and 0 utility for 7 days and disutilities related to radical surgeries
Post-radical surgery	0.763	Calculation	As <i>No pain/mild</i> and disutilities related to infertility (applied only to the proportion of patients who wish to preserve fertility)	0.761	As <i>No pain/mild</i> and disutilities related to infertility (applied only to the proportion of patients who wish to preserve fertility)
Death	0		Assumption		Assumption
Based on Table 64 of the CS ⁴ CS = company submission; EAH = Evidence Assessment Group					

EAG comment:**Major concerns:**

The estimation of the HRQoL in the other health states rely heavily on assumptions and are mainly based upon estimations from the 6-months HRQoL measurements in the EDELWEISS 3 utility values. It is hard to validate these assumptions as long-term HRQoL information is limited available in the literature (see also Section 4.2.8.3). The EAG has two major concerns with regards to the assumptions of the company.

First, for the ‘other medical treatment’ state the company uses an average utility of the patients in the No pain/mild, Moderate, Severe and No response health state. The EAG agrees with the company that the use of an average HRQoL takes into account that patients respond differently to other medical treatments and have different pain levels. However, the EAG considers it more appropriate to exclude the utility value of non-responders in this estimation of the average utility as these non-responders were already reclassified to the Severe and Moderate pain state. Therefore, in the EAG base-case, the utility values of the ‘other medical treatment’ and surgery states were recalculated by excluding the non-response health state from the estimation (see Table 4.26).

Secondly, the company used the transition probability from ‘other medical treatment’ to laparoscopic surgery (32%) as the probability of patients who experience symptoms after a laparoscopic surgery and need additional medical treatment. The EAG considers this to be incorrect and prefers to use the distribution of patients in No pain/mild (32%), Moderate (18%) and other medical treatments (32%) after laparoscopic surgery (see Sections 4.2.6.2, 4.2.6.4 and 4.2.6.5) to estimate weights for the utility for No pain/mild, Moderate and ‘other medical treatment’ respectively. This results in a utility value of 0.784 for post-laparoscopic surgery #1 and #2.

The EAG doubts whether it is appropriate to only include a disutility for infertility after radical surgery. The company motivates this choice by stating that this disutility was captured by the EQ-5D values collected during the trials as patients were aware of the fact that they could not get pregnant while receiving treatment. The EAG considers that even if this utility decrement would have been captured, it should be emphasised that GnRH agonists are only administered for a maximum of 1.5 year, whereas in the model women can remain on linzagolix treatment until the start of menopause (16 years). Therefore, the impact of the utility decrement due to infertility would be much longer for women on linzagolix compared to those on GnRH agonists. It is unknown whether this longer time of infertility is fully captured by the EQ-5D values in the first 6 months. In the response to the clarification letter, the company provided two additional scenarios in which either infertility was applied to none of the health states or to all health states. According to the EAG, both scenarios are incorrect representations of the reality. However, the evidence is missing to accurately reflect infertility in any of the other health states.

Minor concern:

The company justifies their assumptions by stating that these are in line with Wang et al.³ However, this is not completely true as in Wang et al. the utility for other medical treatment is estimated from a placebo-arm of a clinical trial. Furthermore, the utility for the laparoscopic surgery and radical surgery state in Wang et al. is based upon a reduction in QoL of respectively 12.5% and 15.4% relative to the utility value of No pain/mild off-treatment. The EAG has used this calculation in an EAG scenario analysis. Furthermore, the EAG also run a scenario in which the published values from Wang et al. were used as HRQoL input.³

The EAG is uncertain about the company's expectation that women can conceive right after stopping treatment, without consideration of the time on treatment. In the expert elicitation report (set 2) it is noted that *"Whilst respondents have limited or no experience prescribing linzagolix plus ABT, the majority expect ovulation to resume within 1-3 months, especially if the treatment duration is short (i.e., less than six months). It was noted that it might take up to six months if the treatment duration was longer than six months."*³⁰

However, the EAG considers it likely that adding a 'waiting time' before being able to conceive would only marginally affect the ICER.

4.2.8.3 HRQoL from literature

The SLR for HRQoL identified 11 studies which were potentially relevant to the DP. Out of these studies, two studies were especially relevant as these studies included health states with similar definition as defined by the company.

Aubry et al. 2017⁴⁵ reported EQ-5D scores for a cohort of patients experiencing symptoms which were not captured by the clinical trial data from EDELWEISS, specifically focusing on infertility. A discrepancy was noticed regarding the disutility for infertility in this study, because the utility for patients with infertility (0.66) was higher than the utility for patients without infertility. The authors of the publications were contacted by the company to clarify this discrepancy. However, No response was received at time of submission. The company decided to interchange the utility scores for patients with fertility and without fertility (i.e. higher utility score for patients without infertility) resulting in a disutility of 0.10 for infertility. Although the company aimed to use this estimate in a scenario analysis, this scenario was not run in the electronic model.

Kent et al. 2016⁴⁴ provided QoL (utility) values for patients with Severe endometriosis undergoing various treatments, including GnRH agonists, conservative surgery and pelvic clearance. EQ-5D was measured before the surgery, and 2, 6 and 12 months after surgery. Kent et al. 2016 presented the EQ-5D scores on a scale from 0–100 (see Table 4.27).

Table 4.27: EQ-5D scores reported by Kent et al. 2016

	All patients (n=137)		Conservative surgery (n=109)		Pelvic clearance (n=29)	
	Median	IQ	Median	IQ	Median	IQ
Pre-operative	60	40-73	62.3	43.8-70.8	58	55-75
2 months after surgery	75	71.4-85	70	60-81.5	78	67-88
6 months after surgery	71.3	55-89.3	70	50-85	80	70-90
12 months after surgery	80	60-90	75.3	60-90	86.3	70.8-91.5

The company converted these scores to a 0-1 scale and used these inputs in a scenario analysis. Table 4.28 shows the assumptions made for the estimation of the utility values and the resulting HRQoL utility scores.

Table 4.28: Estimated HRQoL utilities for the scenario analysis.

Health state	Assumption for estimation of utilities	HRQoL utility
Laparoscopy #1 waiting	Pre-operative for conservative surgery	0.623
Laparoscopy #1 and #2	Mean of:	0.674

Health state	Assumption for estimation of utilities	HRQoL utility
	Pre-operative conservative surgery (0.623) 2 months post-operative conservative surgery (0.70) 6 months post-operative conservative surgery (0.70)	
Post-laparoscopy #1 and #2	12 months after conservative surgery	0.753
Radical surgery #1 and #2	After surgery, before pelvic clearance	0.58
Post-radical surgery	Mean of: 6 months post-operative pelvic clearance (0.80) 12 months post-operative pelvic clearance (0.863) Minus disutility for infertility (-0.18) for proportion of patients who wish to conceive (63%)	0.718
HRQoL = health-related quality of life		

The SLR did not yield results specifically focused on HRQoL associated with AEs. Utility data pertaining to AEs and surgical complications were obtained from economic evaluations identified in the CE SLR and supported by clinical expert opinion. Furthermore, relevant inputs were also derived from the NICE STA for relugolix.²⁷ It was assumed that the AEs had a duration of 14 days.

The disutility for patients with infertility in the base-case analysis was assumed to be similar to the disutility used in NICE STA for relugolix and set at a value of 0.18. Disutilities for relevant AEs and surgical complications are shown in Table 4.29.

EAG comment:

Major concern

The disutility for infertility was informed from the World Health Organization (WHO) report on the Global Burden of Disease which was published in 2004 with the original source for this input being the Global Burden of Disease report published in 1990. Therefore, the EAG is uncertain if this value is still representative. In the response to the clarification letter, the company motivated their choice to be consistent with the relugolix STA and the fact that no adequate alternative value was found in the systematic literature search. The EAG explored the impact of using this alternative source (Aubry et al. 2017⁴⁵) in an EAG scenario.

The company did not provide a rationale for not using the utility estimates from Kent et al. 2016 in the base-case analysis. However, the EAG agrees with the company's choice to use these estimates in the scenario analysis because Kent et al. 2016 report median scores on a scale from a 0-100 which is not line with the NICE reference case. As Kent et al. 2016 did not report the use of a tariff, we suspect the use of the VAS score.

There is no rationale given for choosing the value of Roberts et al. for the disutility of surgery complications in the base-case analysis. Furthermore, the alternative disutility values have not been explored in scenario analyses performed by the company. It is expected that these alternative sources will lead to slightly higher ICER, but this will be explored in EAG scenario analyses.

Table 4.29: AE disutility values from the literature

Adverse event	Disutility	Source	Probability						Incorporated in
			Linzagolix		Leuprorelin		Relugolix CT		
			Prob	Source	Prob	Source	Prob	Source	
Depression	-0.12	Wang et al, 2019 ³	0.00%	EDELWEISS 3; month 6	1.71%	NICE STA Relugolix ²⁷	1.67%	NICE STA Relugolix ²⁷	Scenario analysis
Headache	-0.027		0.00%		0.47%		0.24%		Scenario analysis
Hot flushes	-0.011		0.00%		0.40%		0.00%		Scenario analysis
Increased blood pressure	-0.011		0.00%		0.24%		0.24%		Scenario analysis
Radical surgery complications	-0.07	Roberts et al, (2011) ⁴⁶	3.00%						Base-case analysis
	-0.05	Sculpher et al, (2004) ⁴⁷ ; Geale et al, (2017) ⁴⁸	3.00%						Scenario analysis
Laparoscopy complications	-0.07	Roberts et al, (2011) ⁴⁶	5.84%						Base-case analysis
	-0.04	Sculpher et al, (2004) ⁴⁷ ; Geale et al, (2017) ⁴⁸	5.84%						Scenario analysis
Based on Table 60, 61, 62 and 63 of the CS ⁴ AEs = adverse event; CS = company submission; CT = combination therapy (relugolix-oestradiol-norethisterone acetate); STA = Single Technology Appraisal									

4.2.9 Resources and costs

The analysis considered healthcare use and costs related to:

- Drug acquisition and drug administration (for linzagolix and the comparator drug)
- ABT, consisting of Kliovance (for patients on linzagolix and GnRH agonists and for patients who had radical surgery)
- Laparoscopic surgery
- Radical surgeries (i.e., hysterectomy and oophorectomy)
- AEs/adverse reactions associated with linzagolix and the comparator drug
- Complications following laparoscopic surgery
- Complications following radical surgeries
- Other medical therapies (e.g., analgesics and levonorgestrel-releasing intrauterine systems)
- Disease management and regular monitoring

Certain other costs were ignored, including pregnancy costs (assumed to be similar between the intervention and the comparators) and costs of diagnostic tests (as it was assumed that all patients had already been diagnosed). In general, cost prices were taken from UK sources, such as the British National Formulary (BNF) and the ‘National Schedule of NHS costs 2021/2022’, where feasible.⁴⁹

EAG comment: Overall, the approach used to assess resource use and costs seems appropriate. For example, a wide range of costs was included, and cost prices were based on UK sources. Nevertheless, several comments can be made. These are detailed in Sections 4.2.9.1 to 4.2.9.7 below, which explain how resource use and unit cost prices were determined for each cost category.

4.2.9.1 Drug acquisition and drug administration

Linzagolix was assumed to be used continuously, without a predefined treatment duration, until menopause. Based on clinical expert opinion, the treatment duration of the comparator, leuporelin, was set at 18 months to align with clinical practice. The base-case analysis did not consider drug wastage or treatment compliance.

The cost price for the intervention was the price provided by the company. Those of the comparators were derived from the BNF, assuming a 50:50 split between patients treated with the short-acting (1-month) and long-acting (3-month) formulations (Table 4.30). Leuporelin acetate was used as the primary base-case comparator. However, other GnRH agonists (goserelin and triptorelin) were also included as potential comparators in the model, which is why they are included in the table. Based on the cost per pack provided in the table, ‘drug costs per cycle’ were calculated, where a distinction is made between cycle 1 and 2, each 3 months, and the subsequent cycles which are 6 months.

The costs of treatment administration were excluded for the intervention therapy and ABT (as these are administered orally), while for the comparators (administered via subcutaneous or intramuscular injection) these were calculated at the costs of administration by a nurse at a General Practitioners (GP’s) office during a 30-minute visit (£26.50, as mentioned in Table 67 of the CS⁴).

Table 4.30: Drug acquisition costs and dosing

Therapy	Cost per pack	Doses per package	Administrations per cycle		Cost per cycle		Source
			1&2	3+	1&2	3+	
Linzagolix 200 mg	£80.00	28	91	183	£260.00	£522.86	Company*

Therapy		Cost per pack	Doses per package	Administrations per cycle		Cost per cycle		Source
				1&2	3+	1&2	3+	
Leuprorelin acetate	1-month	£75.24	1	3	6	£225.72	£451.44	BNF
	3-month	£225.72	1	1	2			BNF
Other GnRH agonists								
Goserelin	1-month	£70.00	1	3	6	£222.50	£445.00	BNF
	3-month	£235.00	1	1	2			BNF
Triptorelin	1-month	£81.69	1	3	6	£226.04	£452.07	BNF
	3-month	£207.00	1	1	2			BNF
Adapted from Table 65 of the CS ⁴ * Price submitted and accepted for uterine fibroids. BNF = British National Formulary; CS = company submission; GnRH = gonadotropin-releasing hormone								

4.2.9.2 Add-back therapy

Following input from UK gynaecologists, the model assumed that all patients treated with GnRH agonists would receive ABT, initiated at the start of treatment and continued throughout the treatment duration.

The unit cost for ABT (Table 4.31) was also based on the BNF.

Table 4.31: Add-back therapy: drug acquisition costs and dosing

Therapy	Cost per pack	Doses per package	Administrations per cycle		Cost per cycle		Source
			1&2	3+	1&2	3+	
Kliovance tablets	£13.20	84	91	183	£14.30	£28.76	BNF
Adapted from Table 66 of the CS BNF = British National Formulary; CS = company submission							

4.2.9.3 Laparoscopic and radical surgeries

The distributions of specific procedures for patients undergoing laparoscopic surgery (excision or ablation) or radical surgery (hysterectomy or oophorectomy) (Table 4.32) were derived from a 2024 report by the NCEPOD on the quality of care provided to women diagnosed with endometriosis³¹ and from the Endometriosis Market Research Survey.² These weights were combined with unit costs of laparoscopic and radical surgeries, which were primarily derived from NHS data (the 'National Schedule of NHS Costs 2021/2022'), to arrive at costs of surgical procedures per health state (Table 4.32). As there was no unit cost for oophorectomy, the cost of this procedure was estimated as 61% of the cost of a hysterectomy, as was also done in the NICE STA for relugolix.²⁷

Table 4.32: Unit costs of surgical procedures per health state

Health state	Medical procedure	Unit cost	Source	Weight (proportion of patients)	Source	Unit cost
Laparoscopy #1	Laparoscopic surgery	£3,495.94	National Schedule of NHS Costs 2021/2022 ⁴⁹	33%	NCEPOD 2024 ³¹	£2,149.74
	Ablation	£1,261.25		50%		
Laparoscopy #2	Laparoscopic surgery	£3,495.94		100%	Assumption	£3,495.94
Radical surgery #1 & Radical surgery #2	Hysterectomy (laparoscopic or open)	£5,937.28		21%	Endometriosis Market Research Survey for Yselty® (Linzagolix) ²	£4,902.50
	(Bilateral) oophorectomy	£3,647.67	61% of unit cost of hysterectomy (£5,937.28)	17%		
Based on Tables 45, 70, 71, and 72 of the CS ⁴ CS = company submission; NCEPOD = National Confidential Enquiry into Patient Outcome and Death; NHS = National Health Service						

EAG comment: Table 71 of the CS presents the distribution of procedures for patients having laparoscopic or radical surgery, along with the sources used. For laparoscopic procedures (excision and ablation), the NCEPOD report (Figure 6.2) was used as the source. According to Table 71 of the CS, this report was also used as the source for radical surgeries (hysterectomy and oophorectomy). However, from the response to the clarification questions (Question B32)⁵ it appears that the ‘Endometriosis Market Research Survey for Ysely® (Linzagolix),² was used for these procedures. The figures for hysterectomy can indeed be found in Section 8 on Surgical management of this source (a PowerPoint file containing the executive summary). However, the figures for oophorectomy cannot be found in this source, possibly because it only contains a summary of this market research survey.

Additionally, it may be mentioned here that the costs of surgeries in health state ‘radical surgery #2’ were not specified in Table 72 of the CS. However, from the electronic model it appears that these costs were the same as those for the ‘radical surgery #1’ health state.

4.2.9.4 AEs

The frequencies of AEs (i.e., headache, hot flush, depression, and increased blood pressure), which were included only in a scenario analysis, and their costs are highlighted in Table 4.33. They were based on the EDELWEISS 3 study¹⁸ (for linzagolix) and on the NICE STA for relugolix²⁷ (for comparators).

Resource use for the AEs included in the CEA was assumed to consist of one 10-minute consultation with a GP, as shown in Table 77 of the CS.⁴ The cost of this consultation was taken from cost estimates published by the Personal Social Services Research Unit (PSSRU) at the University of Kent.⁵⁰

Table 4.33: AEs: probabilities and costs

Adverse event	Therapy										Unit cost
	Linzagolix 200 mg		Relugolix CT		Leuprorelin acetate		Goserelin		Triptorelin		
	Prob.	Source	Prob.	Source	Prob.	Source	Prob.	Source	Prob.	Source	
Headache	0.00%	EDELWEISS 3 ¹⁸	1.67%	NICE STA Relugolix ²⁷	1.71%	NICE STA Relugolix ²⁷	1.71%	As for leuprorelin	1.71%	As for leuprorelin	£49.00
Hot flush	0.00%		0.24%		0.47%		0.47%		0.47%		£49.00
Depression	0.00%		0.00%		0.40%		0.40%		0.40%		£49.00
Increased blood pressure	0.00%		0.24%		0.24%		0.24%		0.24%		£49.00
Based on Tables 61, 76, and 77 of the CS ⁴ and on Tables 21 and 22 of the response to the clarification questions ⁵ CS = company submission; CT = combined therapy (relugolix-oestradiol-norethisterone acetate); Prob. = probability; STA = Single Technology Appraisal											

EAG comment: The incidence of AEs (depression, headache, hot flushes, and increased blood pressure) was based on the EDELWEISS 3 study (linzagolix) and the NICE STA for relugolix (comparators).²⁷

For linzagolix, the incidence of these AEs was set to 0.0%, based on data from the EDELWEISS 3 trial. However, the clinical effectiveness section of the CS (Section B.2.10) suggests that these adverse reactions do occur in patients treated with linzagolix. In its response to the clarification questions, the company explained that the CE model included only Severe AEs (Grade 3 or higher), that most treatment-emergent adverse events (TEAEs) during the EDELWEISS 3 study were mild or Moderate in intensity, and that the incidence of Severe TEAEs was low and comparable between groups (placebo: 1 Severe TEAE; linzagolix 200 mg plus ABT: 2 Severe TEAE). For this reason, the company opted to use data on AEs in the model exclusively for scenario analysis, and to set the probabilities of such events for linzagolix at 0. The EAG, however, feels that it would have been appropriate to include AEs in the base-case analysis and to exclude them in a scenario analysis (rather than the other way around), despite their low incidence. This is why the EAG included AEs in the EAG base-case (Section 6.1.1). Furthermore, given the uncertainty surrounding AEs associated with linzagolix treatment, the EAG adjusted their incidences in a EAG scenario analysis (Section 6.1.2).

For GnRH agonists, the frequencies of AEs were reported as 0.47%, 1.71%, 0.40%, and 0.24%, for depression, headache, hot flushes, and increased blood pressure, respectively (Table 61 of the CS).⁴ However, the corresponding probabilities included in the electronic model were 0.40%, 0.47%, 1.71%, and 0.24% for the same AEs. In its response to the clarification questions, the company provided the correct values: 0.40%, 1.71%, 0.47%, and 0.24%, for depression, headache, hot flushes, and increased blood pressure, respectively (as shown in Table 4.34). The company also provided a corrected model. Since the costs associated with the AEs which frequencies were erroneously switched in the model were identical, correcting these frequencies had no impact on the results.

The costs of all these AEs, which were included in the scenario analysis, were set at £49.00, based on the assumption that they resulted in one 10-minute consultation with a healthcare professional. According to the EAG, this seems quite a low estimate of the healthcare resource use resulting from (some of) these AEs. In the response to the clarification questions, the company substantiated this assumption, stating that changing the resource use and costs for AEs, occurring at low rates during endometriosis treatment with GnRH analogues, would have a very limited influence on the CE model results. The EAG agrees that setting the costs of the AEs to higher, more realistic, values will likely have a negligible impact on the incremental cost-effectiveness ratio (ICER).

4.2.9.5 Complications following laparoscopic and radical surgeries

Since data on complications following laparoscopic and radical surgeries were unavailable in EDELEWEISS 3 and 6, their frequency was sourced from the NICE STA for relugolix (base-case analysis) and from the literature and expert opinion (scenario analysis) (Tables 63 and 78 of the CS).²⁷ Unit costs for complications following laparoscopic and radical surgeries were taken from the 'National Schedule of NHS costs 2021/2022' (Table 4.35).⁴⁹

Table 4.34: Costs of complications following laparoscopic and radical surgeries

Complication (health state)	Probability (base-case analysis)	Unit cost
Laparoscopy and ablation complications (Laparoscopy #1 and Laparoscopy #2)		
Febrile event	0.00%	£850.09
Wound infection	0.00%	£1,118.39
Urinary tract infection	0.00%	£2,219.67
Impact on other organs	3.00%	£1,159.31
Fistula	0.00%	£3,294.49
Hysterectomy and oophorectomy complications (Radical surgery #1 and Radical surgery #2)		
Febrile event	0.00%	£850.09
Wound infection	0.00%	£2,209.49
Bleeding or haematoma	0.00%	£1,768.59
Ileus	0.00%	£7,842.15
Urinary retention	1.42%	£2,036.71
Urinary tract infection	1.42%	£2,219.67
Fistula	0.04%	£3,294.49
Impact on other organs	3.00%	£1,159.31
Anastomotic leakage	0.00%	£4,973.78
Based on Tables 78 and 79 of the CS ⁴ and on Tables 18, 19, and 20 of the response to the clarification questions ⁵ CS = company submission		

EAG comment: Tables 63 and 78 of the CS define the frequency of surgical complications. The impact on other organs for laparoscopic complications was set at 0% in these tables, while the value was set at 3% in the electronic model. In its response to the clarification questions, the company explained that the correct value is 3% (as included in Table 4.34).

Table 79 of the CS presents the costs for surgery-related complications. Compared to the information in this table, the values for the costs of a wound infection following laparoscopy/ablation and the respective costs following hysterectomy/oophorectomy were reversed in the electronic model. In its response to the clarification questions, the company stated that the costs in the electronic model were correct.

4.2.9.6 Other medical therapies

Other medical therapies, considered the first subsequent treatment following the failure of the intervention or comparator therapy, were modelled as a weighted basket of potential therapeutic options (Table 42 of the CS).⁴ This resulted in the distribution of medical therapies, differentiated by health state, presented in Table 4.35. This distribution was based on the so-called ‘Endometriosis Market Research Survey 2024’ and, for NSAIDs/painkillers, on literature representative of the UK population. Notably, analgesics, included in this basket of therapies, were also included for patients on the initial treatment (the intervention or comparator drug).

Table 4.35 also provides the costs of these therapies calculated per model cycle and categorised into acquisition and administration costs. As mentioned in the electronic model, the cost prices used for

these calculations were mainly based on data from the 'electronic Market Information Tool' (eMIT) database, which provided cost prices for analgesics, NSAIDs, common oral contraceptives, aromatase inhibitors, and intrauterine devices. In addition, the BNF was used to calculate unit costs for common oral progestogens and oral progestin. Finally, unit costs for synthetic steroids were taken from an online pharmacy.

Table 4.35: Other medical therapies used in different health states: distribution of therapies and costs

		Health state							
		Other medical treatment		Laparoscopy #1 waiting		Post-laparoscopy #1		Post-laparoscopy #2	
		Previous treatment		Previous treatment		Previous treatment		Previous treatment	
		GnRH antagonist	GnRH agonist	GnRH antagonist	GnRH agonist	GnRH antagonist	GnRH agonist	GnRH antagonist	GnRH agonist
Distribution of medical therapies									
LNG-IUS		22%	32%	0%	0%	0%	0%	0%	0%
NSAIDs/Painkillers		5%	7%	26%	33%	13%	20%	13%	20%
Common oral contraceptives		7%	10%	20%	26%	21%	32%	21%	32%
Oral progestogen		9%	12%	20%	26%	18%	27%	18%	27%
Synthetic steroids		7%	10%	3%	4%	3%	5%	3%	5%
Aromatase inhibitors		7%	10%	2%	3%	3%	5%	3%	5%
GnRH agonists		43%	0%	28%	0%	33%	0%	33%	0%
GnRH antagonists		0%	20%	0%	7%	7%	11%	7%	11%
Total		100%	100%	100%	100%	100%	100%	100%	100%
Costs									
Drug acquisition costs, per model cycle	1 & 2	£117.54	£74.89	£36.55	£14.60	£58.59	£23.71	£102.97	£41.67
	3+	£235.14	£150.37	£72.97	£29.12	£117.15	£47.38	£205.89	£83.26
Drug administration cost, per model cycle	1 & 2	£26.70	£5.45	£7.38	£0.00	£10.10	£0.00	£17.75	£0.00
	3+	£53.40	£10.91	£14.76	£0.00	£20.19	£0.00	£35.49	£0.00
Based on Tables 81 and 82 of the CS ⁴ CS = company submission; GnRH = gonadotropin-releasing hormone; LNG-IUS = levonorgestrel-releasing intrauterine system; NSAID = non-steroidal anti-inflammatory drug.									

EAG comment: The distribution of different treatments presented in Table 42 of the CS was taken from the ‘Endometriosis Market Research Survey for Ysely® (Linzagolix)’.² This source was not included in the original CS, but it was added to the reference pack during the clarification stage. Table 42 of the CS outlines the recommended second-line treatments upon lack of response or recurrence of symptoms after initial treatment, excluding surgery (which accounts for the remaining 32%). These percentages were derived from Section 6 (‘Second-line treatment of endometriosis’) of the aforementioned market research survey.

Tables 81 of the CS presents the distribution of these treatments, categorised by current health state and previous treatment (with percentages summing to 100%). For all health states, it was assumed that patients with previous GnRH agonist treatment would not be prescribed the same treatment again (so, the percentage was set to 0 in the model), which seems a plausible assumption to the EAG. The same assumption was applied to treatment with GnRH antagonists, except for both post-laparoscopy states (as a result, 7% of the patients in these states with previous GnRH antagonists treatment were assumed to receive GnRH antagonists treatment again, as shown in Table 4.35).

4.2.9.7 Disease management and regular monitoring

The CEA assumed that resource use (e.g., visits to healthcare professionals) was necessary to monitor patients undergoing medical therapy and to follow-up patients during treatment breaks. For example, patients on initial therapy and those on other medical therapies were assumed to require regular monitoring by a nurse at a frequency of four visits per year, while patients on a treatment break with no or mild pain were assumed to require one nurse visit per year. This resource use related to ‘disease management and regular monitoring’, which was based on expert opinion, is summarised in Table 4.36. As the CS did not include a table on this subject, the information presented in Table 4.36 was derived from the Excel file containing the model.

Unit costs for ‘disease management and regular monitoring’ were based on NHS data (the ‘National Schedule of NHS costs 2021/2022’) and on PSSRU cost estimates (Table 73 of the CS).^{49, 50} These unit costs were used to calculate the costs for each health state, as presented in Table 4.36.

Table 4.36: Disease management and regular monitoring: resource use and costs

	Health state													
	No response/response evaluation (one-off)	Initial treatment (per year)	Off-treatment, No pain/mild (per year)	Off treatment, 1 st pregnancy state (one-off)	Entering next line	Other medical treatment (per year)	Laparoscopy #1 waiting (per year)	Laparoscopy #1 (one-off)	Post-laparoscopy #1 (per year)	Laparoscopy #2 (one-off)	Post-laparoscopy #2 (per year)	Radical surgery #1 (one-off)	Radical surgery #2 (one-off)	Post-radical surgery (per year)
Numbers of visits/tests														
Gynaecologist, visit	1,00	-	-	0,67	1,00	-	-	1,00	1,00	1,00	-	1,00	1,00	1,00
Gynaecologist, telephone contact	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GP, visit	-	-	-	-	-	-	-	-	-	-	-	-	-	-
GP, telephone contact	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nurse or midwife, visit	-	4,00	1,00	-	-	4,00	1,99	-	2,28	--	4,00	-	-	-
Nurse or midwife, telephone contact	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fertility specialist, visit	-	-	-	0,33	-	-	-	-	-	-	-	-	-	-
Ultrasound scans	-	-	-	-	-	-	-	1,00	1,00	1,00	1,00	1,00	1,00	1,00
MRI Scan	-	-	-	-	-	-	-	1,00	0,00	1,00	0,00	1,00	1,00	0,00

		Health state													
		No response/response evaluation (one-off)	Initial treatment (per year)	Off-treatment, No pain/mild (per year)	Off treatment, 1 st pregnancy state (one-off)	Entering next line	Other medical treatment (per year)	Laparoscopy #1 waiting (per year)	Laparoscopy #1 (one-off)	Post-laparoscopy #1 (per year)	Laparoscopy #2 (one-off)	Post-laparoscopy #2 (per year)	Radical surgery #1 (one-off)	Radical surgery #2 (one-off)	Post-radical surgery (per year)
Costs															
One-off		£181.26	NA	NA	£142.56	£181.26	NA	NA	£625.04	NA	£625.04	NA	£625.04	£625.04	NA
Per cycle	1&2	NA	£53.00	£13.25	NA	NA	£53.00	£26.39	NA	£134.37	NA	£111.90	NA	NA	£104.22
	3+	NA	£106.00	£26.50	NA	NA	£106.00	£52.79	NA	£268.75	NA	£223.80	NA	NA	£208.43
Based on the Excel file containing the model and on Tables 74 and 75 of the CS⁴ It was assumed that no resources were used in the health states, 'Off treatment - washing period & conceive (2nd pregnancy state)' and 'Off treatment - washing period & conceive (3rd pregnancy state)'. Therefore, these health states were omitted from the table. CS = company submission; GP = general practitioner; MRI = magnetic resonance imaging; NA = not applicable															

4.2.10 Severity

The company stated in their submission that in assessing the proportional and absolute QALY shortfall, it is not anticipated that the treatment of linzagolix 200mg plus ABT for endometriosis will be applicable for any form of severity weighting.

Based on the estimated proportional (0.09) and absolute (1.86) shortfall using the DSU severity shortfall calculator, the EAG concurs with this assessment.⁵¹

5. Cost effectiveness (CE) results

5.1 Company's CE results

5.1.1 Original company's CE results

Table 5.1 shows the company's base-case deterministic CE results for linzagolix 200 mg plus ABT compared to leuprorelin and surgery. Compared with leuprorelin, linzagolix 200 mg plus ABT is associated with incremental costs of £2,252 and incremental QALYs of 0.41, resulting in an ICER of £5,554 per QALY. The comparison of linzagolix 200 mg plus ABT with surgery reports incremental cost of £421 and an incremental QALY of 0.61, resulting in an ICER of £693.

Table 5.1: Company base-case deterministic CE results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER incr (£/QALY)	NMB at £20,000
Linzagolix 200 mg plus ABT	£14,897	11.76	9.33	-	-	-	-	
Leuprorelin	£12,646	11.76	8.93	£2,252	0.00	0.41	£5,554	£5,856
Surgery	£14,476	11.76	8.73	£421	0.00	0.61	£693	£11,732

Based on Table 85 of the CS⁴
 ABT = add-back therapy; CS = company submission; ICER = incremental cost-effectiveness ratio; incr = incremental; LYG = life years gained; NMB = net monetary benefit; QALYs = quality-adjusted life years

5.1.2 Updated company's CE results

The company did not need to change any input parameters during the clarification phase, however, in the response to the clarification letter, the company also provided the incremental results of linzagolix versus relugolix. Furthermore, sensitivity and scenario analyses were provided for all three comparators (leuprorelin, surgery and relugolix). Thus, we provide in the remainder of this Section these updated results.

The base-case deterministic results for all comparisons are shown in Table 5.2, whilst Table 5.3 and 5.4 show the disaggregated results for costs and QALYs. In the comparison of linzagolix with relugolix, linzagolix is associated with slightly higher costs at equal effects.

Table 5.2: Updated company base-case deterministic CE results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER incr (£/QALY)	NMB at £20,000
Linzagolix 200 mg plus ABT	£14,897	11.76	9.33	-	-	-	-	
Leuprorelin	£12,646	11.76	8.93	£2,252	0.00	0.41	£5,554	£5,856
Surgery	£14,476	11.76	8.73	£421	0.00	0.61	£693	£11,732

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER incr (£/QALY)	NMB at £20,000
Relugolix	£14,062	11.76	9.33	£835	0.00	0.00	Dominated	-£835

Based on Table 85 of the CS⁴ and Table 13 of addendum of clarification response²³

ABT = add-back therapy; CE = cost-effectiveness; CS = company submission; ICER = incremental cost-effectiveness ratio; incr = incremental; LYG = life years gained; NMB = net monetary benefit; QALYs = quality-adjusted life years

Table 5.3: Disaggregated QALY results (discounted)

Disaggregated QALYs	Linzagolix	Leuprorelin	Surgery	Relugolix
No response on initial Tx	0.079	0.079	1.171	0.079
Partial response on initial Tx	0.076	0.076	0.000	0.076
Complete response on initial Tx	0.083	0.083	0.000	0.083
No pain/mild on initial Tx	3.565	0.445	1.034	3.565
Moderate on initial Tx	0.570	0.114	0.810	0.570
Severe on initial Tx	0.000	0.000	0.000	0.000
Off-treatment, No pain/mild	0.000	0.899	0.210	0.000
Pregnancy & Breastfeeding	0.581	0.226	0.206	0.581
Other medical Tx	0.625	0.960	0.807	0.625
Laparoscopy #1 waiting	0.195	0.289	0.228	0.195
Laparoscopy #1	0.191	0.291	0.238	0.191
Post-laparoscopy #1	1.156	1.852	1.455	1.156
Laparoscopy #2	0.087	0.141	0.110	0.087
Post-Laparoscopy #2	0.807	1.332	0.970	0.807
Radical surgery #1	0.089	0.145	0.110	0.089
Radical surgery #2	0.002	0.004	0.003	0.002
Post-radical surgery (cumulative)	1.226	1.992	1.373	1.226
Total QALYs	9.333	8.927	8.725	9.333
Based on updated model, following the clarification phase				
QALYs = quality-adjusted life years; Tx = treatment				

Table 5.4: Disaggregated costs results (discounted)

Disaggregated costs	Linzagolix	Leuprorelin	Surgery	Relugolix
Drug acquisition on Initial Tx	5,712	947	2,811	4,877
Drug administration on Initial Tx	0	219	92	0
Resource use on Initial Tx	1,382	497	1,957	1,382
AEs on Initial Tx	0	0	33	0
Resource use on Off-treatment, No pain/mild	0	54	13	0
Resource use on Pregnancy & Breastfeeding	65	25	23	65
AEs and complications on off-treatment	0	0	0	0
Treatment on Other medical Tx	513	441	664	513
Resource use on Other medical Tx	228	345	283	228

Disaggregated costs	Linzagolix	Leuprorelin	Surgery	Relugolix
Treatment on Laparoscopy #1 waiting	53	26	62	53
Resource use on Laparoscopy #1 waiting	68	100	82	68
Treatment on Laparoscopy #1	1,196	1820	1,489	1,196
Resource use on Laparoscopy #1	347	529	432	347
Treatment on Post-laparoscopy #1	419	232	528	419
Resource use on Post-laparoscopy #1	820	1,314	1,033	820
Treatment on Laparoscopy #2	889	1,432	1,120	889
Resource use on Laparoscopy #2	159	256	200	159
Treatment on Post-laparoscopy #2	514	293	618	514
Resource use on Post-laparoscopy #2	65	106	80	65
Treatment on Radical surgery #1	1,423	2,316	1,757	1,423
Resource use on Radical surgery #1	181	295	224	181
Treatment on Radical surgery #2	38	62	47	38
Resource use on Radical surgery #2	5	8	6	5
Treatment on Post-radical surgery	92	150	104	92
Resource use on Post-radical surgery	670	1,088	750	670
AEs and complications on next lines	57	90	71	57
Total Costs	14,897	12,646	14,476	14,062
Based on updated model, following the clarification phase AEs = adverse events; Tx = treatment				

Overall, linzagolix 200 mg plus ABT is modelled to affect QALYs by:

- Increasing the number of QALYs in the No pain/mild on initial treatment because treatment can be continued until menopause (when compared with leuprorelin) or because a larger proportion of patients experiences No pain/mild symptoms (when compared with surgery).
- Decreasing the number of QALYs in the No response state (when compared with surgery) because surgery patients wait 18 months in No response before they receive the surgery.
- Decreasing the number of QALYs in the health states associated with other medical treatment or surgery as fewer patients need these other treatment options.

Overall, linzagolix 200 mg plus ABT is modelled to affect costs by:

- Increasing the drug acquisition costs on initial treatment due to the higher unit costs and the longer treatment duration
- Increasing the resource use costs on initial treatment (in comparison with leuprorelin) due to the longer treatment duration
- Increasing the treatment costs for other medical treatment, laparoscopic waiting and post-laparoscopic treatment (in comparison with leuprorelin), because GnRH agonists, which are more expensive, are part of the treatment baskets for other medical treatment after linzagolix.
- Decreasing the treatment costs for the surgery states as fewer patients need surgery in the linzagolix arm.
- Decreasing the resource use costs for the other medical treatment and surgery states as fewer patients enter these health states.

5.2 Company's sensitivity analyses

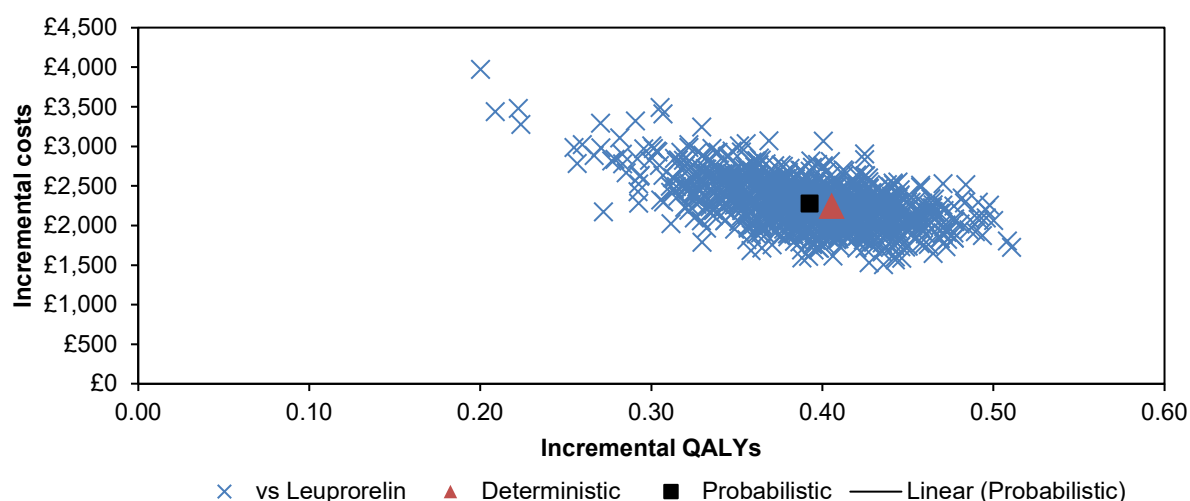
5.2.1 Probabilistic sensitivity analysis (PSA)

In the initial CS, the company only performed a probabilistic sensitivity analysis (PSA) for linzagolix in comparison with leuprorelin. In the response to the clarification letter, a PSA was also performed for linzagolix in comparison with surgery and relugolix. The company performed pair-wise comparisons with each individual comparator. For each PSA, the key model parameters were sampled simultaneously from their corresponding probability distributions over 1,000 iterations. The input parameters and the probability distributions used in the PSA can be found in the "Parameters" sheet of the electronic model. The average PSA results are summarised in Table 5.5 and are overall in line with the deterministic ones shown in Table 5.2.

Table 5.5: Company's base-case probabilistic CE results after clarification

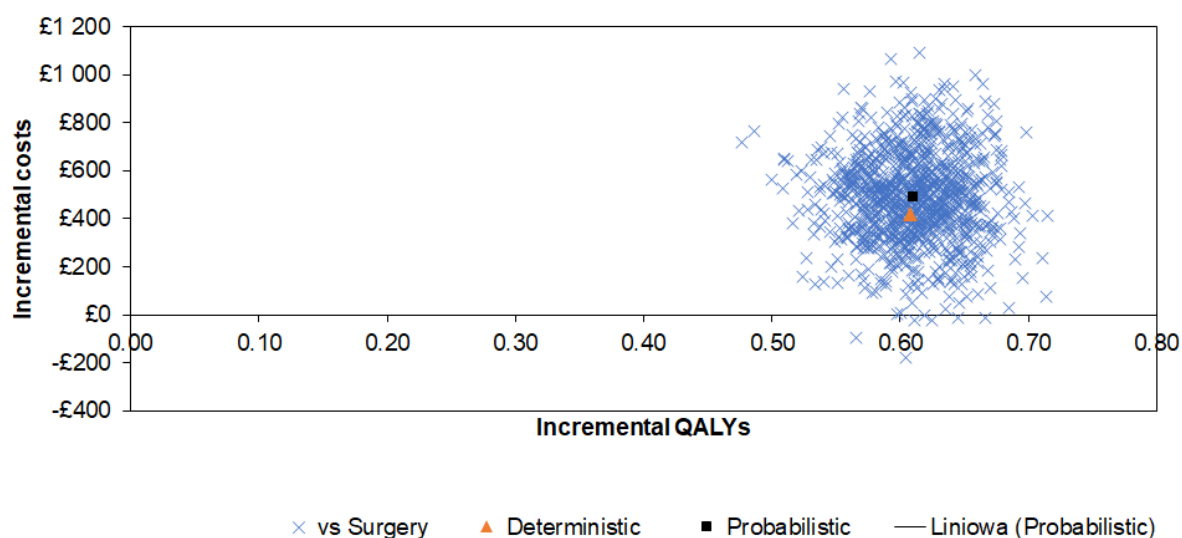
Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER incr (£/QALY)
Linzagolix 200 mg plus ABT	£14,902	11.76	9.32	-	-	-	-
Leuprorelin	£12,621	11.76	8.92	£2,280	0.00	0.39	£5,810
Surgery	£14,411	11.76	8.71	£491	0.00	0.61	£804
Relugolix	£14,081	11.76	9.32	£822	0.00	0.00	Dominated
Based on Table 86 of the CS, ⁴ Table 9 of Clarification response part 1, ⁵ and Table 15 of Addendum of Clarification Response ²³ ABT = add-back therapy; CE – cost-effectiveness; CS = company submission; ICER = incremental cost-effectiveness ratio; Incr = incremental; LYG = life years gained; QALYs = quality-adjusted life years							

The company also plotted the PSA outcomes on the CE plane, as shown in Figures 5.1 to 5.3. In the comparison with leuprorelin, all simulation outcomes were in the northeast quadrant where linzagolix is both more costly and more effective than leuprorelin. In the comparison with laparoscopic surgery, most simulation outcomes were also in the northeast quadrant, whilst a very small proportion of outcomes were in the southwest quadrant indicating lower costs for linzagolix in comparison with laparoscopic surgery. The comparison with relugolix shows an equal distribution of outcomes in the northwest and northeast quadrant indicating, but with very small differences in QALYs between linzagolix and relugolix indicating higher costs for linzagolix and comparable QALYs.

Figure 5.1: PSA CE-plane of linzagolix 200 mg plus ABT versus leuprorelin

Based on Figure 19 of the CS⁴

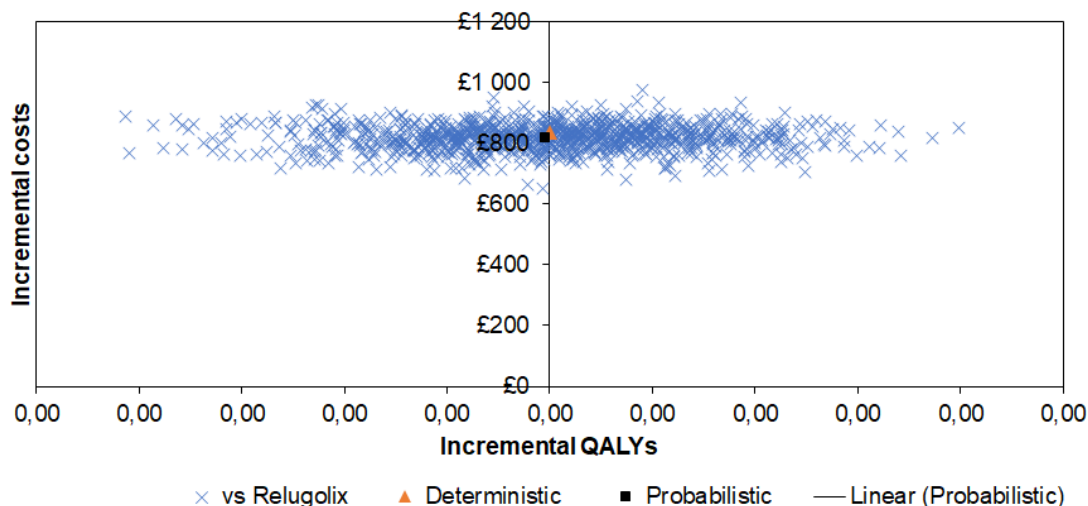
ABT = add-back therapy; CE = cost-effectiveness; CS = company submission; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years

Figure 5.2: PSA CE-plane of linzagolix 200 mg plus ABT versus laparoscopic surgery

Based on Figure 1 of the first part of the response to the clarification letter⁵

ABT = add-back therapy, CE = cost-effectiveness; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years

Figure 5.3: PSA CE-plane of linzagolix 200 mg plus ABT versus relugolix CT

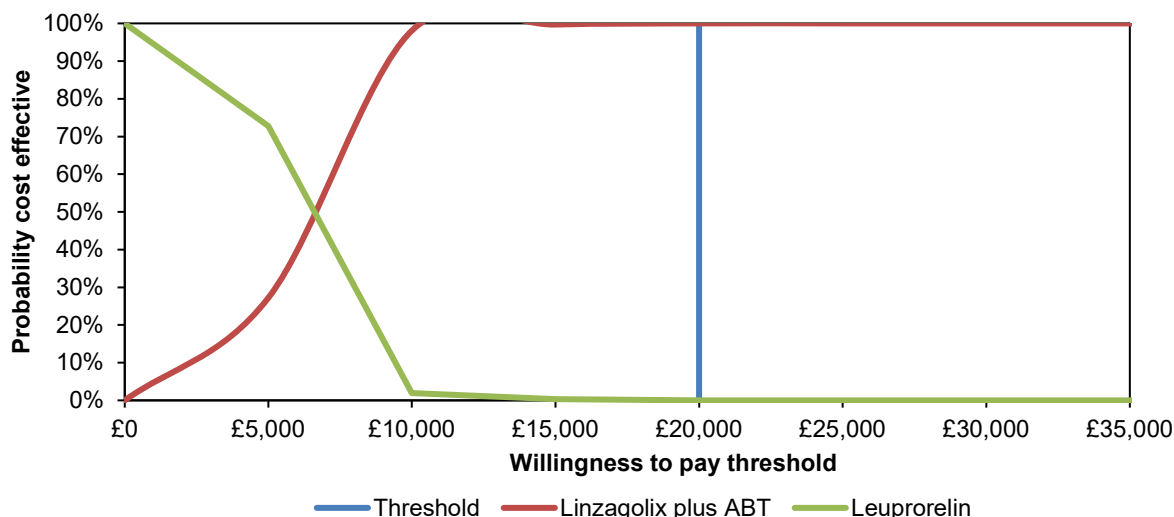


Based on Figure 1 of the addendum to the clarification response²³

ABT = add-back therapy, CE = cost-effectiveness; CT = combination therapy, PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years

From the PSA results, cost-effectiveness acceptability curves (CEAC) were calculated for the comparisons with leuprorelin and surgery and shown in Figures 5.4 and 5.5. The CEAC plots indicate that linzagolix was cost-effective compared to both leuprorelin and surgery in 100% of simulations at a willingness-to-pay (WTP) threshold of £20,000. A CEAC was not constructed for the comparison with relugolix, as the QALY difference between the treatments was zero or close to zero in all iterations.

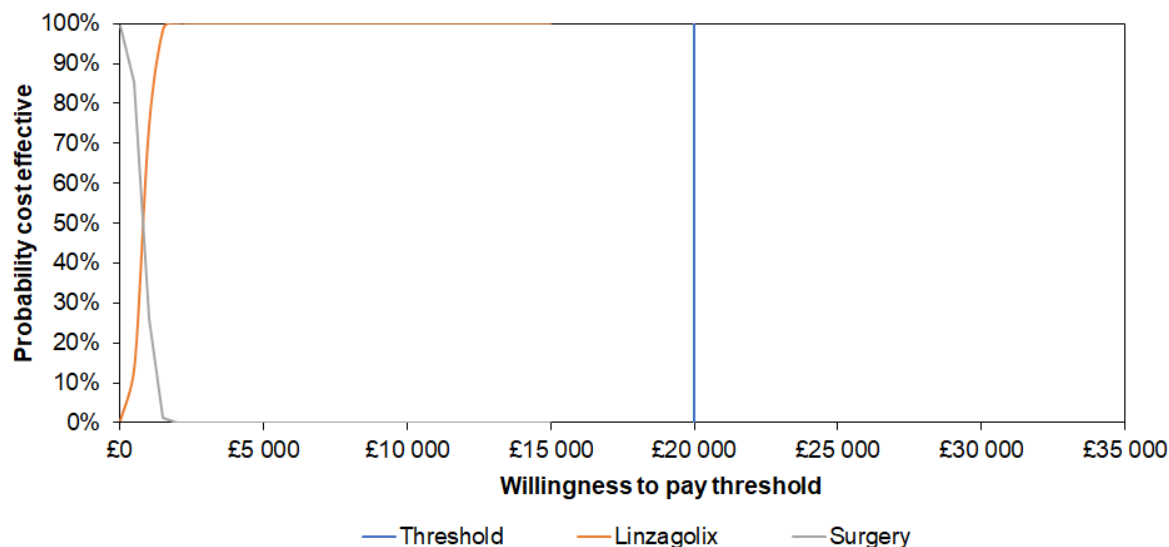
Figure 5.4: CEAC – linzagolix 200 mg plus ABT versus leuprorelin



Based on Figure 20 of the CS⁴

ABT = add-back therapy; CEAC = cost-effectiveness acceptability curve; CS = company submission

Figure 5.5: CEAC – linzagolix 200 mg plus ABT versus laparoscopic surgery



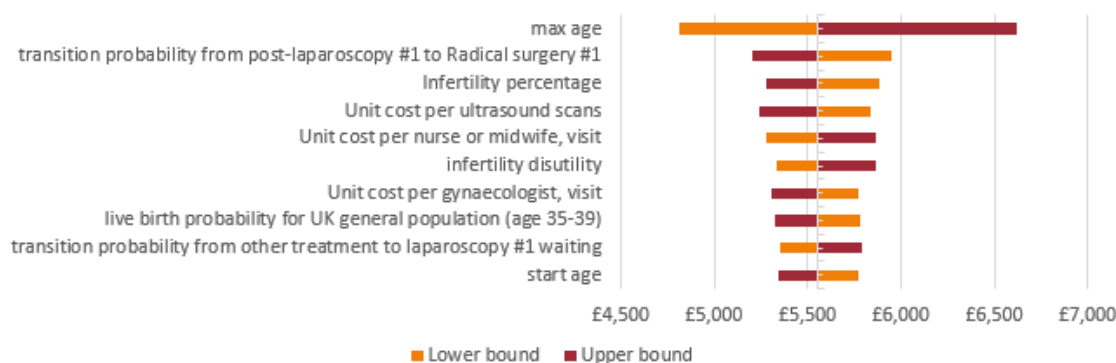
Based on Figure 2 of the first part of the clarification letter⁵

ABT = add-back therapy; CEAC = cost-effectiveness acceptability curve

5.2.2 Deterministic sensitivity analysis (DSA)

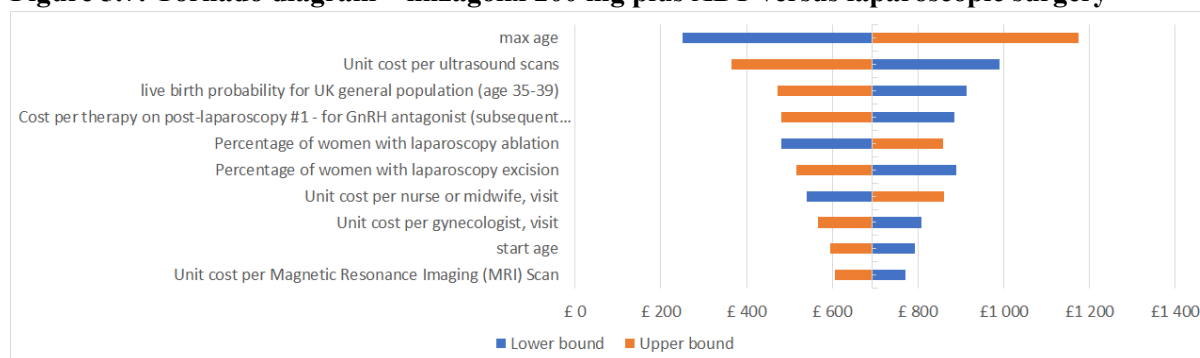
The company also conducted deterministic sensitivity analyses (DSAs) where input parameters were varied using lower and upper estimates of parameter values. These lower and upper values were based on the 95% CI around each base-case value, where the SE was either based on observations (mostly transition probabilities and utility regression equations derived from patient level data) or assumed to be 10% of the mean value. Figures 5.6 to 5.8 present the 10 most influential parameters on the ICER of linzagolix versus leuprorelin, laparoscopic surgery, and relugolix, respectively. The tornado diagrams show that the maximum age of patients with endometriosis has the largest impact on the ICER for all three comparators. The company indicated that none of the input parameters have a considerable impact upon the ICER, as it does not exceed £7,000 per QALY in any of the DSAs.

Figure 5.6: Tornado diagram – linzagolix 200 mg plus ABT versus leuprorelin



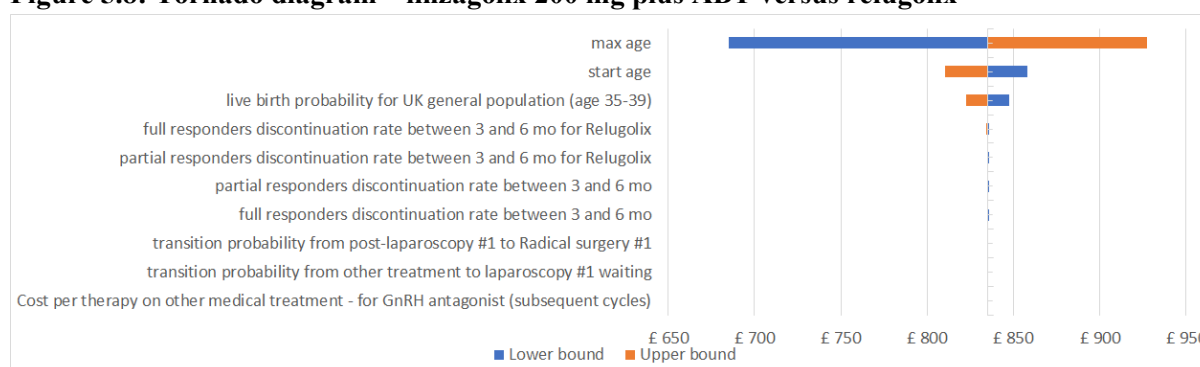
Based on Figure 21 of the CS⁴

ABT = add-back therapy; CS = company submission; max = maximum

Figure 5.7: Tornado diagram – linzagolix 200 mg plus ABT versus laparoscopic surgery

Based on Figure 3 of the first part of the clarification letter⁵

ABT = add-back therapy; max = maximum

Figure 5.8: Tornado diagram – linzagolix 200 mg plus ABT versus relugolix

Based on Figure 2 of the addendum to the clarification response²³

ABT = add-back therapy; max = maximum

5.2.3 Scenario analyses

The company has performed many scenario analyses in which different components of the model were varied. The explored scenarios include changes in the setting (discount rate, time horizon and starting age), changes in the model structure or transition probabilities and changes in the utility and costs/resource use input. An overview of all the scenario's that have been explored by the company at initial submission is shown in Table 5.6.

Table 5.6: Scenario analyses performed by the company in the initial submission

Parameter	Scenario value
Setting	
Discount rate	0%
Discount rate	5%
Discount rate	Costs 3.5%, health effects 0%
Time horizon	10
Time horizon	5
Time horizon	1.5
Starting age	18
Model structure/transition probabilities	
Partial response definition	Only DYS reduction

Parameter	Scenario value
Pregnancy	Pregnancy excluded from the model
Patients continuing treatment after 6 months	Only complete responders
Patients continuing treatment after 6 months	Complete responders and DYS responders
Patients continuing treatment after 6 months	Complete responders and NMPP responders
Comparators discontinuation	Based on clinical studies
GnRH agonists treatment duration	0.5 year
GnRH agonists treatment duration	5 year
Alternative next line transitions scenario 1	see Table 4.13
Alternative next line transitions scenario 2	see Table 4.13
HRQoL input	
Infertility disutility to medical treatment	Infertility disutility applied to medical treatment (other medical treatment, post-laparoscopy #1 and #2)
Infertility and pregnancy assumption	100% of the patients affected by infertility
Infertility and pregnancy assumption	30% of the patients affected by infertility
Infertility and pregnancy assumption	Based on Soliman et al. 2017 ¹
Utility values	The utility values for the response-based and pain-based health states are similar to baseline, other health states are based on literature
Utility values	The utility values for the response-based and pain-based health states include baseline data, the utility values for the other health states are based on literature
Utility values	Adjustment via population norms
Utility values and costs	
AEs	Included
Costs/resource use input	
Complications	Based on literature and KOL opinions
Complications	Not included
Compliance	Included
Pain management	Included
Ablation/laparoscopic weights	50/50%
Percentage of patients treated during waiting for surgery	100%
Percentage of patients treated during waiting for surgery	59%
Percentage of patients treated during post-laparoscopy	57%
Percentage of patients treated during post-laparoscopy	100%
Basked split for post-laparoscopy	Based upon Soliman 2017 ¹

Parameter	Scenario value
Only annual ultrasound after surgery (no annual MRI)	
DYS = dysmenorrhea; GnRH = gonadotropin-releasing hormone; HRQoL = health-related quality of life; KOL = key opinion leaders, MRI = magnetic resonance imaging; NMPP = non-menstrual pelvic pain	

In the CS and response to the clarification letter, the results of the most influential scenarios for each comparator were presented. Table 5.7 shows the results of these scenarios. The overall conclusion differed from the base-case in only one scenario in the comparison of linzagolix with leuprorelin. This was the scenario in which the time horizon was set to 1.5 years. In that scenario, linzagolix generated equal QALYs at lower costs.

In the response to the clarification letter, the company also provided additional scenarios regarding the in- or exclusion of disutilities for infertility and using different utility inputs in the model. The results of these scenarios are shown in Table 5.8.

Table 5.7: Results of scenario analysis for the most influential scenarios

Structural assumption	Base-case scenario	Scenario	Linzagolix versus Leuprorrelin			Linzagolix versus surgery			Linzagolix versus relugolix		
			Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)
Base-case			£2,252	0.41	£5,554	£421	0.61	£693	£835	0	Dominated
Setting											
Discount rates	Discount rates for costs and health effects: 3.5%	Discount rate for costs and health effects: 0%	£2,904	0.53	£5,525	£572	0.72	£799	£1,019	0	Dominated
		Discount rate for health effects: 0%	£2,252	0.53	£4,283	£421	0.72	£588	£835	0	Dominated
Time horizon	15.1 years	1.5 year	-£20	0	Less costly, equal effective	£1 424	0.15	£9 608	£133	0	Dominated
		5 years	£1,011	0.11	£9,573	£7	0.37	£19	£409	0	Dominated
		10 year	£1,403	0.29	£4,838	£110	0.51	£216	£665	0	Dominated
Start age	34.9	18	£4,253	0.52	£8,158	£1 454	0.73	£1 996	£1,034	0	Dominated
Model structure and/or transition probabilities											
Partial response definition	NMPP or DYS reduction	Only DYS reduction	£2,225	0.38	£5,837	£384	0.53	£727	£764	0	Dominated
Pregnancy state included/excluded	Included	Excluded	£2,804	0.4	£6,984	£1 128	0.52	£2 175	£905	0	Dominated

Structural assumption	Base-case scenario	Scenario	Linzagolix versus Leuprorrelin			Linzagolix versus surgery			Linzagolix versus relugolix		
			Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)
Response criteria for continuing treatment after 6 months	Dysmenorrhoea or NMPP responders	Only complete responders	£2,100	0.32	£6,547	£338	0.48	£701	£651	0	Dominated
		Only complete responders and DYS responders	£2,225	0.38	£5,837	£384	0.53	£727	£764	0	Dominated
		Only complete responders and NMPP responders	£2,023	0.26	£7,758	£335	0.31	£1 075	£553	0	Dominated
Comparators discontinuation based on clinical studies	Assumed as linzagolix	Clinical studies	£2,076	0.44	£4,709	£421	0.61	£693	£74	0	Dominated
Alternative transitions between health states post initial treatment	Base case assumption applied in the model (see Section B.3.9) Base case probabilities of patients transitioning to health-states in the model (see Section B.3.3)	Scenario 1 (see Table 4.13)	£2,900	0.4	£7,251	£649	0.60	£1,073	£835	0	Dominated
		Scenario 2 (see Table 4.13)	£3,120	0.4	£7,811	£674	0.6	£1 116	£835	0	Dominated

Structural assumption	Base-case scenario	Scenario	Linzagolix versus Leuprorrelin			Linzagolix versus surgery			Linzagolix versus relugolix		
			Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)
HRQoL input											
Infertility disutility applied to states with medical therapies after initial treatment	No	Yes	£2,252	0.64	£3,505	£421	0.71	£596	£835	0	Dominated
Infertility and pregnancy assumptions	Percentage of patients who wish to perceive = 63%	Soliman et al. 2017 ¹	£2,267	0.3	£7,526	£440	0.59	£749	£836	0	Dominated
Utility values for the CE model health-states based on regression model 1 and literature	Utility values for all health-states based on the regression model only	Utility values for health-states related to surgical procedures based on the literature	£2,252	0.34	£6,561	£421	0.67	£626	£835	0	Dominated
Resource use and costs input											
Ablation/ laparoscopy weights	50.3%/33.2% based on NCEPOD 2024 ³¹	50%/50% (assumption)	£2,185	0.41	£5,390	£173	0.61	£284	£835	0	Dominated
Percentage of women treated during waiting for surgery	49.8% based on EMRS 2024 ²	100% (assumption)	£2,309	0.41	£5,697	£25	0.61	£41	£835	0	Dominated
Basket split for post-laparoscopy health-state	Based on EMRS 2024 ²	Based on Soliman 2017 ¹	£2,025	0.41	£4,995	£1 051	0.61	£1 730	£835	0	Dominated
Based on Table 87 of the CS ⁴ , Table 10 of the first part of the clarification letter ⁵ and Table 16 of the addendum to the clarification response ²³ and the electronic model. ³⁶											

Structural assumption	Base-case scenario	Scenario	Linzagolix versus Leupnorelin			Linzagolix versus surgery			Linzagolix versus relugolix		
			Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)
DYS = dysmenorrhea; Incr = incremental; CE = cost-effectiveness; CS = company submission; EMRS = Endometriosis Market Research Survey; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; NMPP = non-menstrual pelvic pain; NCEPOD = National Confidential Enquiry into Patient Outcome and Death; QALY = quality-adjusted life year											

In the response to the clarification letter, the company performed additional scenarios. Two of these scenarios were related to the in- or exclusion of infertility in the model. The remaining scenarios included different methods to estimate HRQoL utilities. The results of these additional scenarios are shown in Table 5.8. The ICER did not exceed the £20,000 WTP threshold in any of these scenarios.

Table 5.8: Results of additional scenario analysis after the clarification phase

Structural assumption	Scenario	Linzagolix versus Leuporelin			Linzagolix versus surgery			Linzagolix versus relugolix		
		Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)
Base-case		£2,252	0.41	£5,554	£421	0.61	£693	£835	0	Dominated
Infertility	Excluded from all health states	£2,252	0.29	£7,722	£421	0.59	£719	£835	0	Dominated
	Included in all health states	£2,252	0.22	£10,175	£421	0.61	£693	£835	0	Dominated
Utility values	Utility values based on regression model 2 (including baseline data)	£2,252	0.39	£5,767	£421	0.59	£717	£835	0	Dominated
	Utility values based on regression model 3 (excluding any covariates except the different health states)	£2,252	0.40	£5,563	£421	0.61	£694	£835	0	Dominated
	Utility values based on regression model 4	£2,252	0.41	£5,543	£421	0.61	£691	£835	0	Dominated

Structural assumption	Scenario	Linzagolix versus Leuprorelin			Linzagolix versus surgery			Linzagolix versus relugolix		
		Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)	Incr costs (£)	Incr QALYs	ICER (£/QALY)
	(including base EQ-5D as covariate)									
	Utility values based on EDELWEISS 3, 6th month	£2,252	0.40	£5,574	£421	0.60	£699	£835	0	Dominated
	Utility values based on relugolix regression model	£2,252	0.29	£7,635	£421	0.28	£1,522	£835	0	Dominated
Based on Table 15 and 16 of the first part of the response to the clarification letter ⁵ and Tables 28.1, 28.2, 28.3 of Response to the clarification letter Part 2 Response to B24, B25, B28 ⁴² EQ-5D = European Quality of Life-5 dimensions ; ICER = incremental cost-effectiveness analysis, Incr = incremental, QALYs = quality-adjusted life years										

5.3 Model validation and face validity check

Some of the validation efforts conducted on the economic model were briefly discussed in the validation Section of the CS (B.3.14).⁴ These validation efforts refer to an internal validation conducted by the developers. For example, black box testing was done to ensure technical validity. The model structure and clinical assumptions were discussed and ratified through interviews with clinical experts (gynaecologists) in two rounds, the first with six experts and the second with 10 experts.

In the first round the focus was on 1) the treatment pathway(s) in UK clinical practice, 2) where linzagolix would fit in the treatment pathway, if adopted, 3) commonly used outcomes to determine treatment success/failure, and 4) key considerations for treatment-related adverse effects. In the second round of interviews the focus was on 1) validating the model logic and ensure it makes sense from a clinical perspective, 2) validating key data inputs for the CE model, and 3) elicit key model inputs for which values are currently unknown. The company has included full reports of both rounds of interviews with their submission.^{29, 30}

In the remaining of this Section, the validation efforts performed on the model, as presented by the company, are categorised according to the types of validation used in the Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool.⁵²

5.3.1 Validation of the conceptual model

5.3.1.1 Face validity testing (conceptual model)

On page 191 of the CS, the company indicated that the model structure, including e.g. treatment pathway, model health-states, and the most impactful assumptions, was validated with clinical experts.

5.3.1.2 Cross-validity testing (conceptual model)

In response to Question B35 of the clarification letter,⁵ the company explained that their model was largely informed by the NICE STA for relugolix and the publication by Wang et al., 2019, identified during a systematic review of other economic evaluations.^{3, 27} They presented an overview comparing their model to that for relugolix and the model developed by Wang et al., 2019 see Table 5.9.

Table 5.9: Comparison of linzagolix model with other CE studies

Model concept	NICE STA Relugolix ²⁷	Wang et al., 2019 ³	Linzagolix model
Framework	Semi-Markov cohort model simulating progression in women with endometriosis symptoms treated with relugolix-CT and comparator (GnRH agonists).	Markov model with health-state transitions assessing CE of relugolix versus leuprolide acetate in Moderate to Severe endometriosis pain.	Semi-Markov cohort model with initial decision tree simulating progression in women with endometriosis symptoms treated with linzagolix and comparator (GnRH agonists and laparoscopic surgery).
Health-states	Twelve health states representing responses to either medical or surgical interventions.	Twelve health states, including three on-treatment (no/mild, Moderate, Severe symptoms), off-	Seventeen distinct health states that reflect the varied responses to both

Model concept	NICE STA Relugolix ²⁷	Wang et al., 2019 ³	Linzagolix model
		treatment, surgical states, and mortality.	medical therapies and surgical interventions.
Time horizon	16 years, reflecting expected time until menopause in the UK.	1 or 2 years, reflecting the treatment duration and immediate impact of interventions.	15.1 years, reflecting expected time until menopause in the UK.
Cycle length	3 months	3 months	3 months for initial decision tree; 6 months in Markov chain
Patient population	Adult women with Moderate to Severe endometriosis-related pain, as represented in the SPIRIT trials.	Premenopausal women aged 18–49 years with Moderate to Severe endometriosis pain based on Elaris EM-I and EM-II trials.	Premenopausal women with a history of previous medical or surgical treatment for their endometriosis as represented in EDELWEISS 3/6 trials
Discontinuation rates	Uniform rates across treatments, except for GnRH agonists, capped at 1 year.	Treatment-specific premature discontinuation rates derived from Phase III trials, e.g., 11.3% for relugolix 150 mg and 12.3% for relugolix 200 mg.	Uniform rates across treatments, except for GnRH agonists, capped at 1.5 year.
Analgesic use	Assumed similar for all patients, whether on relugolix CT, GnRH agonists, or after surgery. Proportion of patients using analgesics based on SPIRIT trials.	Not explicitly modelled; assumed similar use across treatments.	Assumed similar for all patients, whether on linzagolix, GnRH agonists, or after surgery. Proportion of patients using analgesics based on SPIRIT trials
BMD	Stable BMD across treatments, with add-back therapy mitigating BMD loss for relugolix CT and GnRH agonists.	BMD loss not explicitly modelled but assumed negligible fracture risk over 1–2 years; partial recovery observed post-treatment.	Stable BMD across treatments, with add-back therapy mitigating BMD loss for linzagolix and GnRH agonists.
Treatment duration	Relugolix CT is assumed to continue until menopause or discontinuation, while GnRH agonists are limited to 12 months.	Elagolix: up to 24 months for 150 mg or 6 months for 200 mg; leuprolide acetate: 12 months with add-back therapy for the last 6 months.	Linzagolix is assumed to continue until menopause or discontinuation, while GnRH agonists are limited to 18 months.

Source: Table 17 in Response to the clarification letter⁵

BMD = bone mineral density; GnRH = gonadotropin-releasing hormone; CE = cost-effectiveness; CT = combination therapy (relugolix-oestradiol-norethisterone acetate); NICE = National Institute for Health and Care Excellence; STA = Single Technology Appraisal

5.3.2 Input data validation

5.3.2.1 Face validity testing (input data)

Input parameters were estimated from different sources of data. Some brief discussion about the face validity of some input parameters is presented in an unstructured way throughout the CS, where it is mentioned that experts confirmed certain estimates or assumptions, such as, e.g. the duration of treatment with the comparator GnRH agonists, the distribution of the subsequent strategies to manage endometriosis (following treatment discontinuation), response rate to surgical treatment, recurrence rates following surgery, (dis)utilities for AE, and the use of ABT.

For various parameters, mostly those related to resource use and costs, experts provided estimates for the model, rather than validating input from other sources.

In Section 3.4 the EAGs assessment of the validity of the ITC, comparing leuprorelin and relugolix to linzagolix, is discussed in detail.

5.3.2.2 Model fit testing

In relation to model fit testing, the company reported that for the selection of the parametric curve for recurrence of Moderate to Severe pain following laparoscopic surgery the AIC and the BIC were used to assess goodness of fit and to select the preferred parametric shape.

For the regression models describing utility both for the response health-states and the pain health-states, multiple models were tested for best fit to the data, with the selection based on AIC and BIC.

5.3.3 Validation of the computerised model (technical verification)

1. External review

5.3.3.1 The CS did not mention if external reviewers had done a validation of the Excel model. The EAG did not find technical errors whilst assessing the Excel model.

5.3.3.2 Extreme value testing

In the CS, the Validation section describes that various black-box test were done to ensure technical validity, and several specific examples of black-box tests were provided.

5.3.3.3 Testing of traces

Markov traces can be found on the model sheet “Markov Traces”. The model includes standard checks to test that the distribution of patients across health states always add up to 100%. No discussion about the face validity of the traces was provided by the company.

5.3.3.4 Unit testing

It is unknown whether code verification included checks on specific parts of the model, such as VBA macros, drop-down menus, or model switches/indicators.

5.3.4 Operational validation (validation of model outcomes)

5.3.4.1 Face validity testing (model outcomes)

It is not mentioned in the company submission if any model results were presented to experts to provide some sort of validation, and neither do the reports about the two expert elicitation rounds discuss any of the model outcomes.

The EAG noticed from the Markov traces that the model results show that by the age of 50, almost all women have had at least one surgery, and around 60% a radical surgery. It would have been interesting to see a reflection on the plausibility of this finding.

5.3.4.2 Cross validation testing (model outcomes)

5.3.4.2.1 Comparisons with other TAs

It is not reported if the company compared (some of the) outcomes of the current model to the outcomes of the relugolix model as submitted to NICE.²⁷

5.3.4.2.2 Comparisons with other models (not necessarily TAs)

It is not reported if the company compared (some of the) outcomes of the current linzagolix model to the outcomes of the model by Wang et al., 2019³ or maybe other models identified in Section 4.1.

5.3.4.3 Validation against outcomes using alternative input data

Several scenario analyses were done which used alternative input data for one or more input parameters, to assess their impact on the CE.

5.3.4.4 Validation against empirical data

5.3.4.4.1 Comparison with empirical data used to develop the economic model (dependent validation)

This type of validation was not reported by the company.

5.3.4.4.2 Comparison with empirical data not used to develop the economic model (independent validation)

This type of validation was not reported by the company.

6. Evidence Assessment Group's additional analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

6.1.1 *Explanation of the EAG adjustments for the EAG base-case*

Based on all considerations in the preceding sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the EAG, which together form the 'EAG base-case', were subdivided into three categories (derived from Kaltenthaler et al., 2016):⁵³

- Fixing errors, i.e. correcting the model where the company's submitted model was unequivocally wrong.
- Fixing violations, i.e. correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to.
- Matters of judgement, i.e. amending the model where the EAG considers that reasonable alternative assumptions are preferred.

No unequivocal errors or violations were identified in the company's model, however, at various points the EAG prefers alternative assumptions. This led to the following changes to the company base-case analysis:

1. In Section 4.2.6, it was explained that for the transition probabilities between the various surgery related health states, the company had presented three different sets of, all based on data collected in a market research survey among 47 gynaecologists.² However, the EAG was unable to understand the logic of calculations of the base-case estimates. On the other hand, the alternative approaches defined by the company are more intuitive, but some of the alternative probabilities also appear to be incorrect. Thus, the EAG has calculated alternative transition probabilities, where the simplifying assumption is made that the probability to go from laparoscopy to radical surgery is the same as from post-laparoscopy to radical surgery. This simplification is made as a) it is not clear why 0-3 months was chosen for the immediate transition to radical surgery after a laparoscopy instead of 0-6 months in line with the cycle length, b) if a distinction is made between 0-3 months versus 3-9 or 3-12 months, we should also consider differences between the first year and subsequent years (which is impossible given the Markov property of the model), and c) the distribution of recurrence over time is only based on expert opinion and thus subject to large uncertainty.
2. In Section 4.2.8.1.1 it was discussed that the EAG has some difficulties with the use of covariates dichotomised at the median as the median will differ from population to population. It is also difficult to incorporate uncertainty surrounding these distributions in a probabilistic sensitivity analysis. Furthermore, there was no conclusive evidence that the model with the covariates had the best statistical fit as the model without additional covariates had a higher AIC, but a lower BIC than the model selected by the company. In the end, the estimated HRQoL utilities only marginally deviate from each other. Therefore, the EAG prefers a simpler regression model without any covariates except for the response states.
3. As described in Section 4.2.8.1, the EAG does not agree with the company that because of consistency a similar regression model should be selected for the pain-based model as for the regression-based model. The response-based health states are defined based on the improvement in relation to baseline, while the pain-based health states are defined according to

absolute pain level at a specific moment. Thus, for the regression model for the pain-based health states the EAG believes that there is no reason to exclude baseline data from the regression analysis as pain categories could be adequately identified at baseline. Furthermore, the inclusion of baseline data increases the number of patients with Severe pain and therefore reduces uncertainty about the estimate. Therefore, the EAG prefers to use regression model 2 (including baseline and 3-month data) for the estimation of the utility values for the pain-based health states in the EAG base-case.

4. For the EAG, there is no reason to include the No response health state in the estimation of the average utility for other medical treatment and surgery health states. Therefore, the utility of non-responders is excluded from the estimation of utility values for other medical treatment and surgery health states in the EAG base case.
5. The HRQoL utility for the post-laparoscopic health states is estimated in a different way, as the EAG considered the approach by the company incorrect. The EAG applied weights for No pain/mild, Moderate and other medical treatments. The weights were derived from the proportion of patients who were classified as No pain/mild, Moderate or other medical treatment in the (laparoscopic) surgery comparator arm.
6. In the CS, AEs (i.e., headache, hot flush, depression, and increased blood pressure) were excluded from the base-case analysis and included only in a scenario analysis. In their response to the clarification questions,⁵ the company explained that the reason for this approach was the generally low incidence of Severe AEs during endometriosis treatment with GnRH analogues. Consequently, the company argued that including AEs in the base-case analysis would have a very limited influence on the CE model results. However, the EAG considers that the low incidence of AEs is not a sufficient reason for excluding them from the base-case and feels that it would be more appropriate to include them (as they do entail additional resource use and costs, regardless of their low incidence).

An overview of the EAG changes is presented in Table 6.1.

Table 6.1: Company and EAG base-case preferred assumptions

Base-case preferred assumptions	Company	EAG	
		Type of adjustment	Description
Transition probabilities for the surgery states	Transition probabilities between surgery related health states estimated based on data collected in market research survey. ²	Matter of judgement	Alternative approach to estimating transition probabilities from same data source.
QoL utilities	Regression model including covariates for response-based health states	Matter of judgement	Regression model excluding covariates except the response-based health states
QoL utilities	Regression model for pain-based health states based on only 6-month observations	Matter of judgement	Regression model for pain-based health states based on baseline, 3-month and 6-month observations
QoL utilities	Estimation of utilities for other medical treatment and surgery states includes	Matter of judgement	The utility value of No response is excluded from the estimation of the utility

Base-case preferred assumptions	Company	EAG	
		Type of adjustment	Description
	utilities for No response, No pain/mild, Moderate and Severe pain		values for other medical treatment and surgery states.
QoL utilities	The proportion of patients with a lower HRQoL after laparoscopic surgery is based upon the probability of patients who receive a post-laparoscopy after other medical treatment	Matter of judgement	Weighted value of health states: <i>No pain/mild, Moderate and other medical treatment</i> . The weights are derived from the transitions to these health states in the surgery comparator, excluding the transition to the laparoscopic surgery.
AEs	Exclusion of AEs	Matter of judgement	Inclusion of AEs (i.e., headache, hot flush, depression, and increased blood pressure)
AEs = adverse events; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; QoL = quality of life			

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to assess the impact of alternative assumptions conditional on the EAG base-case.

Scenario 1 and 2: Alternative HRQoL utilities (Section 4.2.8.2)

The company justifies choices in the estimation of HRQoL utilities by referring to Wang et al., 2019.³ However, they did not follow the same approach as Wang et al., 2019. Therefore, the EAG wants to explore the impact on the ICER if a different set of HRQoL utilities is used. In the first scenario, the HRQoL as reported by Wang et al., 2019 are used. In the second scenario, the observed utilities from EDELWEISS 3 are used, but the utility values for the surgery states are based upon the assumptions from Wang et al., 2019. The HRQoL utilities in the two scenarios are shown in Table 6.2.

Table 6.2: Alternative utilities for exploratory scenario analyses

Health state	Utilities from Wang et al., 2019 ³	Adjusted utilities based upon assumptions from Wang et al., 2019 ³	Assumption
No response	0.715	0.715	
Partial response	0.776	0.776	
Complete response	0.873	0.873	
No pain/mild	0.874	0.874	
Moderate	0.777	0.739	
Severe	0.649	0.554	
Off-treatment, No pain/mild	0.842	0.874	

Health state	Utilities from Wang et al., 2019 ³	Adjusted utilities based upon assumptions from Wang et al., 2019 ³	Assumption
Off treatment - washing period and conceive (pregnancy 1st step)	0.842	0.874	
Pregnancy and breastfeeding (2nd and 3rd step)	0.842	0.874	
Other medical treatment	0.741	0.722	
Laparoscopy #1 waiting	0.741	0.6465	
Laparoscopy #1	0.689	0.752	For 177 days a reduction in HRQoL of 12.5% compared to off treatment No pain/mild, for 3 days a utility of 0
Laparoscopy #2	0.689	0.752	For 177 days a reduction in HRQoL of 12.5% compared to off treatment No pain/mild, for 3 days a utility of 0
Post-laparoscopy #1	0.822	0.844	19.6% receive other medical treatment, other patients off-treatment No pain/mild
Post-laparoscopy #2	0.822	0.844	19.6% receive other medical treatment, other patients off-treatment No pain/mild
Radical surgery #1	0.654	0.698	For 170 days a reduction in HRQoL of 15.4% compared to off treatment No pain/mild
Radical surgery #2	0.654	0.698	For 170 days a reduction in HRQoL of 15.4% compared to off treatment No pain/mild
Post-radical surgery	0.84	0.758	1.9% other medical treatment and disutility for infertility
Death	0	0	
HRQoL = health-related quality of life			

Scenario 3: Alternative disutility for infertility (Section 4.2.8.3)

The company described an alternative disutility for infertility and mentioned that this disutility was implemented in a scenario analysis. However, none of the scenario analyses of the company include this disutility. Therefore, the EAG has run this scenario analysis on the EAG base-case.

Scenario 4: Alternative disutility for surgical complication (Section 4.2.8.3)

The company described alternative disutilities for surgical complications and mentioned that these disutilities were applied in scenario analyses. However, none of the scenario analyses of the company included these disutilities.

Scenario 5: AEs following linzagolix (Section 4.2.8.7)

The incidence of AEs (depression, headache, hot flushes, and increased blood pressure) following linzagolix was set to 0.0%, based on data from the EDELWEISS 3 trial. However, the clinical effectiveness section of the CS (Section B.2.10) suggests that AEs do occur in patients treated with linzagolix. Therefore, the EAG ran a scenario in which the incidence of AEs for linzagolix treatment was equated to the incidence of AEs following treatment with the primary base-case comparator (i.e., leuprorelin acetate).

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

6.2.1 Results of the EAG preferred base-case scenario

Table 6.3 shows the results of the deterministic EAG's base-case (discounted). These indicate that linzagolix is more costly but also more effective than leuprorelin and surgery, accruing 0.33 and 0.57 incremental QALYs at £2,810 and £615 additional costs compared to leuprorelin and surgery respectively. These incremental QALYs and costs results in ICERs of £8,638 and £1,082 per QALY gained. Linzagolix is more costly than relugolix with similar effects. Therefore, linzagolix is dominated by relugolix.

When compared to the company base-case (see Table 5.2), we observe that for all treatment strategies the total costs become lower, though the incremental costs of linzagolix versus leuprorelin and versus surgery increase. At the same time, for all treatment strategies the total QALYs increase, whilst the incremental QALYs decrease, which leads to an increase in the ICER compared to leuprorelin from £5,554 to £8,638 and compared to surgery from £693 to £1,082. The incremental costs for linzagolix versus relugolix remains the same as in the company base-case.

Tables 6.4 and 6.5 present the disaggregated results for the EAG preferred base-case.

Table 6.3: EAG base-case CE results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER incr (£/QALY)	NMB at £20,000
Linzagolix 200 mg plus ABT	£14,276	11.7633	9.44	-	-	-	-	
Leuprorelin	£11,466	11.7633	9.12	£2,810	0.00	0.33	£8,638	£3,696
Surgery	£13,661	11.7633	8.88	£615	0.00	0.57	£1,082	£10,756
Relugolix	£13,442	11.7633	9.44	£835	0.00	0.00	Dominated	-£835

ABT = add-back therapy; CE = cost-effectiveness; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; incr = incremental; LYG = life years gained; NMB = net monetary benefit; QALYs = quality-adjusted life years

Table 6.4: Disaggregated QALYs results (discounted)

Disaggregated QALYs	Linzagolix	Leuprorelin	Surgery	Relugolix
No response on initial Tx	0.079	0.079	1.176	0.079

Disaggregated QALYs	Linzagolix	Leuprorelin	Surgery	Relugolix
Partial response on initial Tx	0.076	0.076	0.000	0.076
Complete response on initial Tx	0.083	0.083	0.000	0.083
No pain/mild on initial Tx	3.558	0.444	1.032	3.558
Moderate on initial tx	0.568	0.114	0.807	0.568
Severe on initial tx	0.000	0.000	0.000	0.000
Off-treatment, No pain/mild	0.000	0.897	0.209	0.000
Pregnancy & Breastfeeding	0.580	0.226	0.205	0.580
Other medical tx	0.643	0.988	0.831	0.643
Laparoscopy #1 waiting	0.196	0.290	0.229	0.196
Laparoscopy #1	0.197	0.300	0.245	0.197
Post-laparoscopy #1	1.945	3.153	2.411	1.945
Laparoscopy #2	0.066	0.107	0.082	0.066
Post-Laparoscopy #2	0.691	1.129	0.796	0.691
Radical surgery #1	0.054	0.087	0.066	0.054
Radical surgery #2	0.001	0.001	0.001	0.001
Post-radical surgery (cumulative)	0.708	1.145	0.785	0.708
Total QALYs	9.444	9.119	8.876	9.444
QALYs = quality-adjusted life years; Tx = treatment				

Table 6.5: Disaggregated cost results (discounted)

Disaggregated Costs	Linzagolix	Leuprorelin	Surgery	Relugolix
Drug acquisition on Initial Tx	5712	947	2811	4877
Drug administration on Initial Tx	0	219	92	0
Resource use on Initial Tx	1382	497	1957	1382
AEs on Initial Tx	0	1	34	1
Resource use on Off-treatment, No pain/mild	0	54	13	0
Resource use on Pregnancy & Breastfeeding	65	25	23	65
AEs and complications on off-treatment	0	0	0	0
Treatment on Other medical Tx	513	441	664	513
Resource use on Other medical Tx	228	345	283	228
Treatment on Laparoscopy #1 waiting	53	26	62	53
Resource use on Laparoscopy #1 waiting	68	100	82	68
Treatment on Laparoscopy #1	1196	1820	1489	1196
Resource use on Laparoscopy #1	347	529	432	347
Treatment on Post-laparoscopy #1	682	381	845	682
Resource use on Post-laparoscopy #1	1334	2161	1653	1334
Treatment on Laparoscopy #2	654	1060	811	654
Resource use on Laparoscopy #2	117	189	145	117
Treatment on Post-laparoscopy #2	426	240	490	426

Disaggregated Costs	Linzagolix	Leuprorelin	Surgery	Relugolix
Resource use on Post-laparoscopy #2	39	63	47	39
Treatment on Radical surgery #1	855	1389	1041	855
Resource use on Radical surgery #1	109	177	133	109
Treatment on Radical surgery #2	10	17	12	10
Resource use on Radical surgery #2	1	2	2	1
Treatment on Post-radical surgery	53	87	59	53
Resource use on Post-radical surgery	388	627	430	388
AEs and complications on next lines	43	68	53	43
Total Costs	14,276	11,466	13,661	13,442
AEs = adverse events; Tx = treatment				

6.2.2 Results of the EAG sensitivity and scenario analyses

Table 6.6 shows the probabilistic CE results of the EAG preferred base-case analysis. All results are discounted. The probabilistic results are aligned with the deterministic EAG base-case results. Figures 6.1 and 6.2 show the distribution of all PSA outcomes over the CE plane for each of the comparators. These show clearly that all PSA iterations in the comparison of linzagolix versus leuprorelin and versus surgery show an increase in QALYs at additional costs. Based on the CEACs in Figure 6.3 and 6.4, the results show that the probability of linzagolix being cost-effective at thresholds of £20,000 and £30,000 per QALY gained is 100% compared to leuprorelin and 100% compared to surgery. In the comparison between linzagolix and relugolix, linzagolix is dominated in all iterations.

Table 6.6: EAG base-case PSA results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr costs (£)	Incr LYG	Incr QALYs	ICER incr (£/QALY)
Linzagolix 200 mg plus ABT	£14,267	11.76	9.43				
Leuprorelin	£11,448	11.76	9.11	£2,819	0.00	0.31	£8,957
Surgery	£13,602	11.76	8.86	£664	0.00	0.57	£1,167
Relugolix	£13,448	11.76	9.43	£819	0.00	0.00	-
ABT = add-back therapy; ICER = incremental cost-effectiveness ratio; Incr = incremental; LYG = life years gained; QALYs = quality-adjusted life years							

Figure 6.1: EAG Probabilistic CE-plane of linzagolix 200 mg plus ABT versus leuporelin

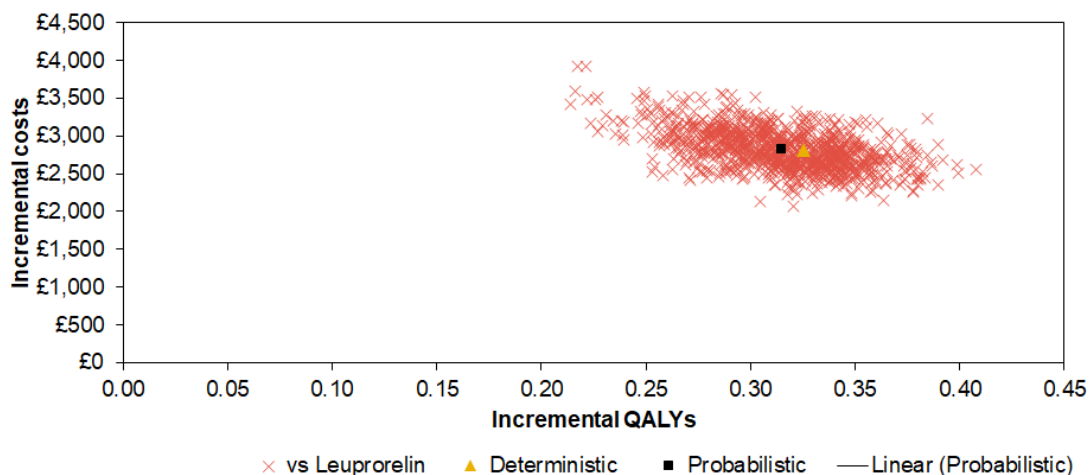


Figure 6.2: EAG Probabilistic CE-plane of linzagolix 200 mg plus ABT versus laparoscopic surgery

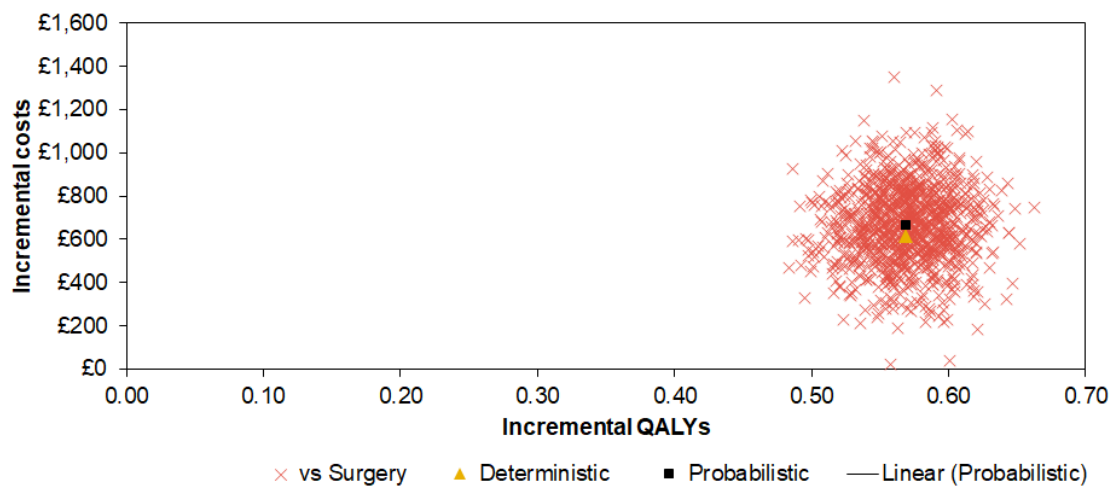


Figure 6.3: EAG CEAC– linzagolix 200 mg plus ABT versus leuporelin

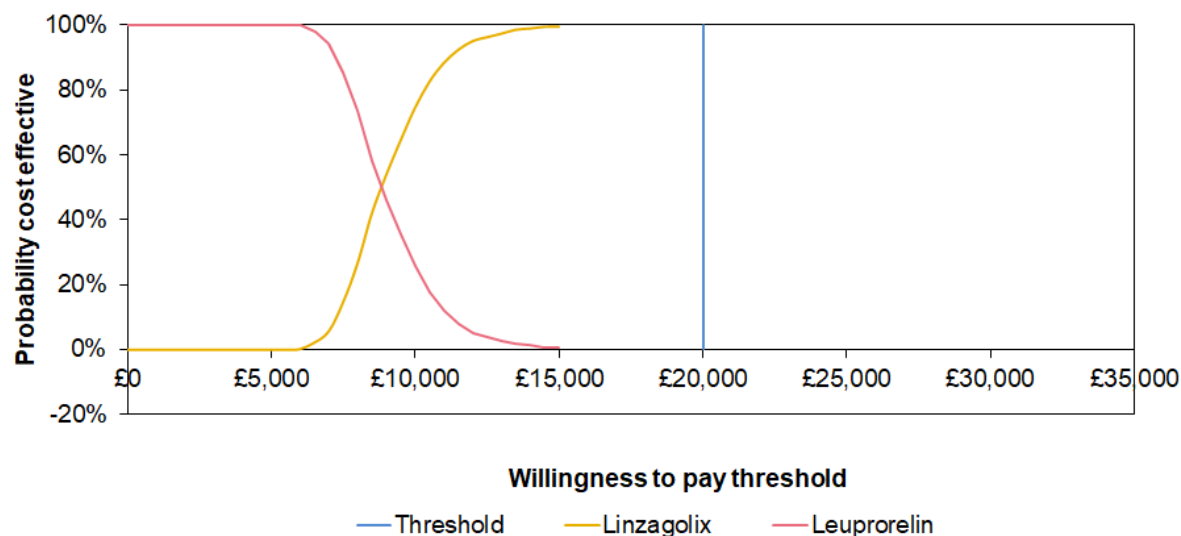
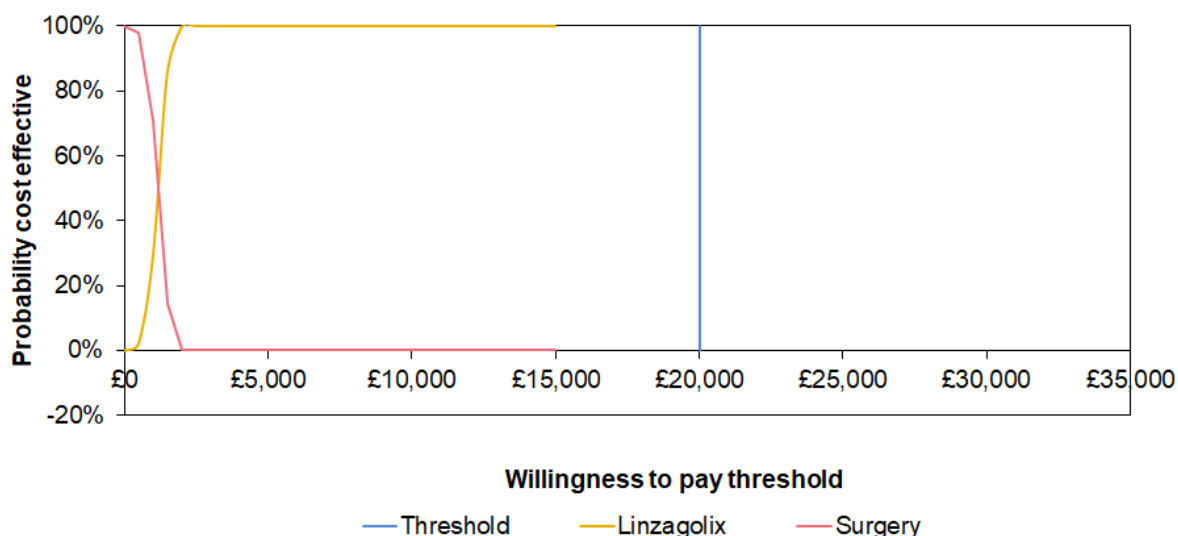


Figure 6.4: EAG CEAC – linzagolix 200 mg plus ABT versus laparoscopic surgery

ABT = add-back therapy; CE = cost-effectiveness; CEAC = cost-effectiveness acceptability curve; EAG = Evidence Assessment Group; QALY = quality-adjusted life year

Tables 6.7 to 6.9 show the results from the one-way sensitivity analyses. It can be observed that the comparison of linzagolix versus surgery is most influenced by changes in the input parameters. But even in this comparison, the ICER never exceeds £1,500 per QALY gained. In the comparison of linzagolix versus leuprorelin all changes result in an ICER that is less than 1,000 larger than the base case ICER. Finally, for the comparison between linzagolix and relugolix, the additional costs are hardly influenced by any changes.

Table 6.7: EAG OWSAS, 10 most influential parameters - linzagolix 200 mg plus ABT versus leuprorelin (base-case £8,638)

Rank	Parameters	Lower bound ICER	Upper bound ICER
1	Max age	£7,968	£9,626
2	Transition probability from post-laparoscopy #1 to Radical surgery #1	£9,039	£8,239
3	Unit cost per ultrasound scans	£9,000	£8,238
4	Cost per therapy on post-laparoscopy #1 - for GnRH antagonist (subsequent cycles)	£8,305	£9,005
5	Infertility percentage	£8,999	£8,326
6	Unit cost per nurse or midwife, visit	£8,330	£8,977
7	Unit cost per gynaecologist, visit	£8,922	£8,325
8	Infertility disutility	£8,391	£8,976
9	Live birth probability for UK general population (age 35-39)	£8,923	£8,351
10	Cost per therapy on other medical treatment - for GnRH antagonist (subsequent cycles)	£8,408	£8,891

ABT = add-back therapy; EAG = Evidence Assessment Group; GnRH = gonadotropin-releasing hormone; ICER = incremental cost effectiveness ratio; OWSAS = one-way sensitivity analysis; UK = United Kingdom

Table 6.8: EAG OWSA, 10 most influential parameters - linzagolix 200 mg plus ABT versus surgery (base-case £1,082)

Rank	Parameters	Lower bound ICER	Upper bound ICER
1	Max age	£579	£1,490
2	Unit cost per ultrasound scans	£1,403	£729
3	Cost per therapy on post-laparoscopy #1 - for GnRH antagonist (subsequent cycles)	£1,302	£839
4	Live birth probability for UK general population (age 35-39)	£1,301	£860
5	Percentage of women with laparoscopy ablation	£857	£1,260
6	Percentage of women with laparoscopy excision	£1,292	£893
7	Unit cost per nurse or midwife, visit	£944	£1,255
8	Unit cost per gynaecologist, visit	£1,207	£944
9	start age	£1,171	£990
10	Unit cost per MRI scan	£1,162	£994
ABT = add-back therapy; EAG = Evidence Assessment Group; GnRH = gonadotropin-releasing hormone; ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; OWSAS = one-way sensitivity analysis; UK = United Kingdom			

Table 6.9: EAG OWSA, 3 most influential parameters - linzagolix 200 mg plus ABT versus relugolix (base-case £835)

Rank	Parameters	Lower bound Incr. costs	Upper bound Incr. costs
1	Max age	£684	£927
2	Start age	£857	£810
3	Live birth probability for UK general population (age 35-39)	£847	£822
ABT = add-back therapy; EAG = Evidence Assessment Group; Incr = incremental; OWSAS = one-way sensitivity analysis; UK = United Kingdom;			

Table 6.10 shows how the model results change when key assumptions or parameters are varied according to various scenarios. Changing the time horizon, or the age at which treatment starts has the largest impact, but the ICER remains well below the common threshold of £20,000 per QALY gained.

Table 6.10: Overview of the most influential company defined scenarios applied to EAG base-case

Most impactful scenarios	Incr costs	Incr QALY	ICER (£/QALY)
Linzagolix versus leuprorelin			
EAG base-case results	£2,810	0.33	£8,638
Time horizon: 1.5 year	-£21	0.00	Less costly, equal effective
Only annual ultrasound after surgery (no annual MRI)	£1,832	0.41	£4,520
Infertility disutility applied to medical treatment (health states: Other medical treatment, Post-laparoscopy #1 and Post-laparoscopy #2)	£2,810	0.62	£4,551
Time horizon: 5 years	£1,093	0.09	£12,492

Most impactful scenarios	Incr costs	Incr QALY	ICER (£/QALY)
Patients continuing treatment after 6 months: only complete responders and NMPP responders	£2,489	0.21	£11,964
Start age: 18	£4,951	0.44	£11,189
Utility values based on regression model 2 and literature	£2,810	0.46	£6,117
Basket split for post-laparoscopy based on Soliman et al., 2017	£2,541	0.40	£6,341
Infertility, pregnancy and fertility treatments based on Soliman et al., 2017	£2,826	0.27	£10,638
Discount costs: 3.5%; Discount health effects: 0%	£2,810	0.42	£6,663
Linzagolix versus surgery			
EAG base-case results	£615	0.57	£1,082
Time horizon: 1.5 year	£1,424	0.15	£9,604
Pregnancy excluded from the model	£1,240	0.49	£2,517
Start age: 18	£1,479	0.69	£2,158
Basket split for post-laparoscopy based on Soliman et al., 2017	£1,258	0.61	£2,079
Percentage of women treated during waiting for surgery: 100%	£220	0.61	£363
Time horizon: 10 years	£252	0.48	£521
Ablation/laparoscopy weights	£368	0.61	£607
Patients continuing treatment after 6 months: only complete responders and NMPP responders	£417	0.31	£1,345
Discount rates 0%	£845	0.66	£1,276
Linzagolix versus relugolix			
EAG base-case results	£835	0.00	Dominated
Time horizon: 1.5 year	£133	0.00	Dominated
Comparators discontinuation based on clinical studies	£387	0.00	Dominated
Time horizon: 5 years	£408	0.00	Dominated
Patients continuing treatment after 6 months: only complete responders and NMPP responders	£552	0.00	Dominated
Start age: 18	£1,033	0.00	Dominated
Patients continuing treatment after 6 months: only complete responders	£650	0.00	Dominated
Discount rates 0%	£1,018	0.00	Dominated
Time horizon: 10 years	£665	0.00	Dominated
Partial response definition: only DYS reduction	£763	0.00	Dominated
Patients continuing treatment after 6 months: complete responders and DYS responders	£763	0.00	Dominated
DYS = dysmenorrhea; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; Incr = incremental; NMPP = non-menstrual pelvic pain; MRI = magnetic resonance imaging; QALY = quality adjusted life year			

6.2.3 Results of the EAG additional exploratory scenario analyses

The EAG performed several exploratory scenario analyses, described in Section 6.1.2, to evaluate the impact of alternative assumptions on the EAG base-case. The results of these analyses are presented in

Table 6.11. Clearly, most scenarios have little impact on the results, only using the health state utilities as reported by Wang et al. leads to a small increase in the ICERs versus leuprorelin and surgery.³ In all scenarios considered, linzagolix remained more expensive and equally effective as relugolix, as was the case in the EAG base-case analysis.

Table 6.11: Deterministic EAG scenario analyses (conditional on EAG base-case, see Section 6.1.2 for description scenarios)

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG base-case					
Linzagolix 200 mg plus ABT	£14,276	9.44			
Leuprorelin	£11,466	9.12	£2,810	0.33	£8,638
Surgery	£13,661	8.88	£615	0.57	£1,082
Relugolix	£13,442	9.44	£835	0.00	Dominated
Scenario 1 Alternative HRQoL utilities					
Linzagolix 200 mg plus ABT	£14,276	9.52			
Leuprorelin	£11,466	9.22	£2,810	0.30	£9,305
Surgery	£13,661	9.08	£615	0.44	£1,394
Relugolix	£13,442	9.52	£835	0.00	Dominated
Scenario 2 Alternative HRQoL utilities					
Linzagolix 200 mg plus ABT	£14,276	9.44			
Leuprorelin	£11,466	9.12	£2,810	0.32	£8,701
Surgery	£13,661	8.87	£615	0.57	£1,076
Relugolix	£13,442	9.44	£835	0.00	Dominated
Scenario 3 Alternative disutility for infertility					
Linzagolix 200 mg plus ABT	£14,276	9.49			
Leuprorelin	£11,466	9.19	£2,810	0.30	£9,483
Surgery	£13,661	8.93	£615	0.56	£1,092
Relugolix	£13,442	9.49	£835	0.00	Dominated
Scenario 4 Alternative disutility for surgical complication					
Linzagolix 200 mg plus ABT	£14,276	9.44			
Leuprorelin	£11,466	9.12	£2,810	0.33	£8,644
Surgery	£13,661	8.88	£615	0.57	£1,082
Relugolix	£13,442	9.44	£835	0.00	Dominated
Scenario 5 AE rates linzagolix equal to leuprorelin					
Linzagolix 200 mg plus ABT	£14,277	9.44			
Leuprorelin	£11,467	9.12	£2,811	0.33	£8,640
Surgery	£13,661	8.88	£616	0.57	£1,083
Relugolix	£13,442	9.44	£835	0.00	Dominated
ABT = add-back therapy; AE = adverse event; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years					

6.3 EAG's preferred assumptions

Table 6.12 shows how individual changes to the company's base-case impact the results plus the combined effect of all EAG changes simultaneously. From this it is clear that using the alternative transition probabilities for the transitions between the various surgery health states has the largest impact, with a smaller impact of changes in the utilities for the health states after the initial treatments.

Table 6.12: Deterministic EAG base-case compared to company base-case, with step-by-step impact

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case					
Linzagolix 200 mg plus ABT	£14,897	9.33	-		
Leuprorelin	£12,646	8.93	£2,252	0.41	£5,554
Surgery	£14,476	8.73	£421	0.61	£693
Relugolix	£14,062	9.33	£835	0.00	Dominated
Alternative transition probabilities for the surgery health states					
Linzagolix 200 mg plus ABT	£14,276	9.34			
Leuprorelin	£11,465	8.94	£2,811	0.40	£7,014
Surgery	£13,660	8.74	£616	0.61	£1,018
Relugolix	£13,441	9.34	£835	0.00	Dominated
Regression model for the response-based states excluding additional covariates					
Linzagolix 200 mg plus ABT	£14,897	9.33			
Leuprorelin	£12,646	8.93	£2,252	0.41	£5,554
Surgery	£14,476	8.73	£421	0.61	£693
Relugolix	£14,062	9.33	£835	0.00	Dominated
Regression model for the pain-based states estimated from baseline, 3-month and 6-month observations					
Linzagolix 200 mg plus ABT	£14,897	9.34			
Leuprorelin	£12,646	8.95	£2,252	0.39	£5,767
Surgery	£14,476	8.75	£421	0.59	£719
Relugolix	£14,062	9.34	£835	0.00	Dominated
Estimation of utilities for other medical treatment and surgery					
Linzagolix 200 mg plus ABT	£14,897	9.31			
Leuprorelin	£12,646	8.90	£2,252	0.42	£5,411
Surgery	£14,476	8.64	£421	0.67	£628
Relugolix	£14,062	9.31	£835	0.00	Dominated
Estimation of utilities for post-laparoscopic surgery					

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Linzagolix 200 mg plus ABT	£14,897	9.38			
Leuprorelin	£12,646	9.00	£2,252	0.38	£5,972
Surgery	£14,476	8.78	£421	0.60	£705
Relugolix	£14,062	9.38	£835	0.00	Dominated
Inclusion of AEs					
Linzagolix 200 mg plus ABT	£14,898	9.33	-		
Leuprorelin	£12,647	8.93	£2,251	0.41	£5,552
Surgery	£14,477	8.73	£420	0.61	£692
Relugolix	£14,063	9.33	£835	0.00	Dominated
EAG base-case					
Linzagolix 200 mg plus ABT	£14,276	9.44			
Leuprorelin	£11,466	9.12	£2,810	0.33	£8,638
Surgery	£13,661	8.88	£615	0.57	£1,082
Relugolix	£13,442	9.44	£835	0.00	Dominated
ABT = Add-back therapy; AEs = adverse events; CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years					

6.4 Conclusions of the CE Section

The company provided a model that was based on previous models for treatment of endometriosis and appeared to reflect the current treatment practice, with highly individualised treatment pathways, appropriately. The company's CEA complied with the NICE reference case. In order to compare the various treatment strategies, indirect comparisons had been done, suggesting that there was no reason to assume a difference in effectiveness between linzagolix, leuprorelin, and relugolix.

The model consists of two parts, first a decision tree, modelling treatment response in 2 cycles of 3 months and then a Markov model where patients are assigned health states based on their pain level with regard to OPP. Treatment response, transitions between health states and treatment discontinuation were estimated based on the EDELWEISS 3 and 6 RCTs.

Transitions between the various surgery health states were estimated based on expert elicitation in a market research survey among 47 gynaecologists.² However, the EAG was unable to understand the rationale for the way the base-case estimates were calculated. The same was, to a lesser extent, true for alternative estimates that the company estimated based on the same information from the market research survey. The EAG finds it unsettling that based on the same underlying data two very distinct estimators are constructed to estimate the transition probabilities, which produce quite different estimations. Using some of the logic of the alternative approach from the company, the EAG calculated alternative transition probabilities, which have been implemented in an EAG preferred base case.

Health state utilities for the three response states and the three pain states were derived from regression models using EQ-5D data from the EDELWEISS 3 study. The utilities for subsequent states were derived using some combination of these six 'core' utilities. The EAG did not agree with the model

selection for the regression models and believes that other models explored by the company should be preferred. For the model for response state utilities, the EAG preferred the model without dichotomised (at the median) covariates. For the model for the pain state utilities, the EAG preferred the model that included baseline data, as it decreases the standard error around the utility estimates, and the EAG does not think there is a compelling reason not to include base line utilities based on the patient's (absolute) pain status at base line.

For the estimation of the average utility for other medical treatment and surgery health states, the EAG does not see a reason to include the No response health state in their estimation. Therefore, the utility of non-responders is excluded from the estimation of utility values for other medical treatment and surgery health states in the EAG base-case. Furthermore, the EAG considered the approach by which the company estimated the HRQoL utility for the post-laparoscopic health states incorrect. The EAG applied weights for No pain/mild, Moderate and other medical treatments. The weights were derived from the proportion of patients who were classified as No pain/mild, Moderate or other medical treatment in the (laparoscopic) surgery comparator arm. This leads to a small increase in this utility.

The EAG had no major comments on the company's methods for estimating resource use and costs, except for a few concerns. First, the methods partly relied on expert opinion (for example, resource use related to disease management and regular monitoring). Second, they also partly relied on assumptions (for example, resource use for the AEs included in the analysis was assumed to consist of one 10-minute consultation with a general practitioner). Finally, some data used in the analysis came from a single, small-scale investigation (e.g., the distribution of procedures for patients having laparoscopic or radical surgery, and the distribution of 'other medical therapies' following the failure of the intervention or comparator therapy). Finally, the EAG decided to include AE in the model as a matter of principle, whilst at the same time acknowledging that this addition is likely to have a negligible impact on the results.

In general, the EAG considered the (reporting on the) model validation efforts rather limited.

The company's base-case deterministic results for linzagolix 200 mg plus ABT compared to leuprorelin and surgery showed ICERs of £5,554 and £693 per QALY gained, respectively. Linzagolix was around £835 more expensive than relugolix, whilst yielding the same number of QALYs.

After implementing the EAG preferred assumptions and estimates, these ICERs increased to £8,638 (linzagolix compared to leuprorelin) and £1,082 per QALY gained (linzagolix compared to surgery,) respectively. The incremental costs for linzagolix versus relugolix remained the same as in the company base-case.

When considering how the individual changes to the company's base-case impact the results using the alternative transition probabilities for the transitions between the various surgery health states has the largest impact, with a smaller impact of changes in the utilities for the health states after the initial treatments. The impact of using different regression models for the utilities of the response states and the pain states was negligible, as was the impact of including adverse effects in the model. However, an accurate estimation of the pain-based health states is in fact important as the HRQoL utilities of the other health states currently depend upon these health states. Furthermore, the HRQoL in these subsequent health states is a driving factor for the difference in QALYs between the treatment alternatives as the proportion of patients who need subsequent treatment differ between linzagolix and leuprorelin or surgery. Unfortunately, empirical evidence is missing with respect to the health-related quality of life in these health states. Therefore, there is a large uncertainty regarding these input parameters.

When accounting for parameter uncertainty, both for the company base-case as for the EAG preferred base case the probability that the ICERs are below the common NICE threshold of £20,000 is 100%.

The company defined a large range of scenarios, which were applied to the EAG preferred base-case. In the comparison between linzagolix versus leuprorelin the ICER did not go above £13,000, with various scenarios yielding an ICER around £10,000. In the comparison between linzagolix and surgery the highest ICER was almost £10,000, when a time horizon of 1.5 years was applied. For all other scenarios the ICER remained below £3,000.

Of the EAG defined exploratory scenario analyses, most had little impact on the results, only using the health state utilities as reported by Wang et al. led to a small increase in the ICERs versus leuprorelin and surgery.³ In all scenarios considered, linzagolix remained more expensive and equally effective as relugolix, as was the case in the EAG base-case analysis.

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Single Technology Appraisal

Linzagolix for treating symptoms of endometriosis [ID6357]

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 the end of **27 January 2025** 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 **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

Issue 1 Exclusion of GnRH agonists other than leuporelin

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 16. The report states that “<i>There continues to be a lack of justification for the exclusion of GnRH agonists other than leuporelin as separate comparators in the CS, and specifically the ITC and the CEA.</i>” This is misleading. All attempts were made to include other agonists in the ITC, but as this was not feasible, leuporelin was used as a proxy, assuming equal efficacy of GnRH agonists. It is not accurate, as other agonists were not excluded but were modelled based on data from leuporelin as a proxy for all agonists. The CS, page 126, provides full justification for using leuporelin data as a proxy for all agonists.	Please change the sentence to “<i>The EAG does not agree with the justification provided for the exclusion of some of the available studies of GnRH agonists from the ITC, and consequently the lack of direct evidence for these agonists in the CEA.</i>”	The statement is potentially misleading	Not a factual inaccuracy.

Issue 2 Population in scope did not rule out post-menopausal women

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report 16 Under key issue 1 the report states: <i>“There are also no restrictions regarding age or menopausal status.”</i> We would like to clarify that the use of linzagolix in this indication would be restricted to women of reproductive age. As stated on page 16 of the CS, the expected UK indication will be for [REDACTED]	Please delete this sentence.	It is important to clarify that the intended population aligns with the expected indication.	The EAG have amended the text in Table 1.2 and Section 1.
EAG report page 17 Under key issue 4 it states: <i>“The population in the scope and the DP does not rule out any age or women who are post-menopausal”</i>	Please delete the first sentence in Table 1.5 or change to <i>“While the population in the scope and the DP does not specifically rule out any age or women who are post-menopausal, the expected indication in the UK limits its use to women of reproductive age, reflective of the population in the EDELWEISS trials.”</i>	As above	The EAG have amended the text in Table 1.2 and Section 1.

As above, although not explicitly stated in the DP, the submission evidence is in line with the expected indication and does not include post-menopausal women.			
EAG report page 28 It is stated that “<i>This therefore increases the uncertainty associated with the population, as well as one regarding the applicability of the trial data if the population is broader than women of reproductive age.</i>” As above, in line with the expected licensed indication, linzagolix will not be used to treat post-menopausal women in clinical practice in the UK.	Please delete the last part of the following sentence as indicated: “<i>This therefore increases the uncertainty associated with the population, ~~as well as one regarding the applicability of the trial data if the population is broader than women of reproductive age.~~</i>”	As above	The EAG have amended the text in Table 1.2 and Section 1.

Issue 3 Logic applied in deriving the transition probabilities between surgery-related health states

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report pages 18	Please remove the last part of this sentence as follows. “ <i>The EAG did not understand the logic applied in</i>	The wording implies there are errors in the way the logic has been applied in the model. The	This is not a factual inaccuracy and no changes have been made. In section 4.2.6.5 the EAG

Under key issue 7, it is stated that <i>“The EAG did not understand the logic applied in deriving the transition probabilities, and appeared wrong at several instances.”</i> The applicant believes that the CS presented both formulas and transparent descriptions of the logic underpinning the transition probabilities. Alternative interpretations are possible as the treatment pathway is complex and not universal (including eight transitions between numerous health states).	<i>deriving the transition probabilities, and appeared wrong at several instances.”</i>	CS presented three scenarios to account for the uncertainty around the transition probabilities.	discusses various instances where the value derived for a transition probability is incorrect, see e.g. <i>“the transition from laparoscopy #1 to Radical surgery #1 is estimated as:</i> <i>(Laparoscopy as first surgical type) x (radical surgery as second surgical type) x (% patients in whom recurrence occurs within 0-3 months after unsuccessful surgery) = 50% * 25% * 16% = 2.04%</i> <i>It is unclear why this calculation starts with the 50% of all first surgeries being a laparoscopy, which is then multiplied by the 25% of all second surgeries being a radical surgery. This calculation estimates the probability that a woman who is referred for surgery will first have a laparoscopy and then a radical surgery. However, in the model we are interested in the probability of needing a radical surgery conditional of just having had a laparoscopy.”</i>

Issue 4 Distributions of specific procedures for patients undergoing laparoscopic surgery or radical surgery

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 137 The report states, “<i>While the use of these two sources may be justified, it is unclear how the percentages in Table 71 of the CS were exactly derived from them.</i>” The applicant believes that this was addressed during clarification (response to question B32). However, further details on the sources and calculations are provided: • The percentage of patients with laparoscopy excision: 33% (NCEPOD¹) • The percentage of patients with laparoscopy ablation: 50% (NCEPOD) • The two values are used only to establish the proportion of excision versus ablative	We believe this has been clarified so the paragraph starting “<i>Table 71 of the CS...</i>” is not required.	This was previously clarified and should be reflected in the report.	Thanks to the clarification provided by the company, it is now clear how the distribution of the procedures for patients having laparoscopic or radical surgery was determined. For the laparoscopic procedures (excision and ablation), the input data were taken from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report on the quality of care provided to women diagnosed with endometriosis (Figure 6.2). We have thus removed ‘probably’ from ‘(probably Figure 6.2)’ Regarding hysterectomy and oophorectomy, the company explained that data from the Endometriosis Market Research Survey were used. The figures for hysterectomy can indeed be found on slide 11 of this source (a PowerPoint file containing the

¹ National Confidential Enquiry into Patient Outcome and Death (NCEPOD). Endometriosis: A Long and Painful Road A review of the quality of care provided to adult patients diagnosed with endometriosis. 2024

procedures. The actual values presented in NCEPOD $165/250 = 0.66$ (i.e. the same as $33\%/50\% = 0.66$) • The percentage of patients with hysterectomy (Endometriosis Market Research Survey [ERMS]² - slide 11): 21% (hysterectomy as first surgical procedure 7% + hysterectomy as second procedure 14%). • The percentage of patients with oophorectomy (ERMS): 17% (oophorectomy as first surgical procedure 6% + hysterectomy as second procedure 11%)			executive summary). However, the figures for oophorectomy cannot be found in this source, possibly because it only contains the executive summary of the market research survey. Thus, we have adjusted the text to reflect this.

Issue 5 Utilities of post-initial treatment health states

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 18	Please change the sentence as follows:	The statement is not accurate.	This is not a factual inaccuracy, and no changes have been made.

² Theramex. Data on File: Endometriosis Market Research Survey for Yselt® (Linzagolix) Final report. 2024 Jul.

Under key issue 8, it is stated that <i>“The model input for these utilities could be validated against literature that reports on the health-related quality of life and utilities in these health states.”</i> Alternate scenarios based on values from the literature were presented in the CS (page 152, Table 59).	<i>“Even though the applicant presented literature on health-related quality of life and utilities for some of the health states and included it in scenario analysis, an additional comparison of values from the literature against values estimated by the applicant could further validate the choice of base case scenario utility values.”</i>		It is true that the company provided scenario analyses regarding alternative values from the literature. However, that comparison does not justify the choice of the base-case utility values. Information is needed regarding the utility value specific to the post-initial treatment health states. The EAG and the company have a different opinion regarding the best way to estimate these utility values using the EDELWISE data. Evidence from the literature and/or expert opinion is needed to justify the choice from the company or the EAG.

Issue 6 The cut-off point for pain-related health states

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 20. Under key issue 10 relating to the classification of patients into pain-based health states, <i>“the EAG noticed an issue that could be a typo and thus a non-issue”</i>.	Key issue 10 should be removed.	We believe that this has been resolved and key issue 10 should be removed from the report.	We have removed this key issue.

The applicant confirms that there was a typographical error. The correct syntax is: No pain/mild VRS ≤ 1; moderate VRS > 1 and ≤ 2; severe VRS > 2. Please note that the patients' scores were the mean of multiple observations, so they were not reported as whole numbers.			
EAG report page 20. The title for table 1.11 states, "<i>Key issue 9...</i>". In the overview of key issues (Table 1.1), this is key issue 10, not key issue 9.	Unless this issue is removed, please amend the title for table 1.11 to "Key issue 10...".	The table caption is incorrect.	The issue was removed, so no longer applicable.
EAG report page 113. As above we can confirm that there was an error in the syntax relating to the classification of patients into pain-based health states.	Please delete the first paragraph under 'Major issues' relating to the classification of patients after six months into pain-based health states.	We believe that this has been resolved, and the first paragraph should be removed from the report.	Removed.

EAG report page 179. As above we can confirm that there was an error in the syntax relating to the classification of patients into pain-based health states.	Please could the following paragraph be deleted <i>“Whilst the estimation of the response probabilities and transition probabilities with the patient level data is relatively straightforward, the EAG noticed an issue that could be a typo and thus a non-issue, or it could imply that transition probabilities need to be re-estimated. In order to classify patients after 6 months into pain-based health states, the VRS score for OPP was used. The CS states that the model health state ‘No pain/mild’ is defined as a VRS score <1, whereas ‘Moderate’ is defined as $1 \leq \text{VRS score} \leq 2$. This would suggest that the health state ‘No pain/mild’ contains only patients scoring ‘No pain’ (VRS=0) and the ‘Moderate’ state contains patients with both mild pain (VRS=1) and Moderate pain (VRS=2). This classification is quite confusing, and the EAG wonders if the cut-off points for the health state classification have been correctly presented in the CS, or if the health state ‘No pain/mild’ was in fact defined as a VRS score ≤ 1. This issue is likely to be resolved by the company.”</i>	We believe that this has been resolved, and the quoted paragraph should be removed from the report.	Removed.

Issue 7 Description of hospital admission data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report pages 25 <i>“The EAG considers that admission to hospital should have been included even if only occurring in 2% of patients.”</i> The statement is incorrect. In the EDELWEISS 3 and 6 studies, fewer than 2% of patients required hospitalisation at any time, or in any treatment arm. In addition, it should be noted that in EDELWEISS 3, only one patient each in the linzagolix 200mg plus ABT arm and the placebo arm were hospitalised over the 6-month study period. In EDELWEISS 6, only one patient each in the linzagolix 200 mg plus ABT arm and the placebo/linzagolix 200 mg plus ABT arm were hospitalised.	Please amend the statement to <i>“The EAG considers that admission to hospital should have been included even if only occurring in fewer than 2% of patients.”</i>	The statement is factually incorrect.	Amended.

Issue 8 Inclusion of opigolix and elagolix as comparators

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 78. The report states “<i>Specifically, the EAG recommended a network meta-analysis (NMA) in order to include non-placebo-controlled trials, as well as including data from graphs and imputing measures of variance, which potentially could have permitted the inclusion of further studies, and more comparators i.e. opigolix and elagolix.</i>” Opigolix and elagolix are not relevant comparators as they are not licensed in this indication in the UK.	Please delete the last part of this sentence, as follows: <i>“Specifically, the EAG recommended a network meta-analysis (NMA) in order to include non-placebo-controlled trials, as well as including data from graphs and imputing measures of variance, which potentially could have permitted the inclusion of further studies, and more comparators i.e. opigolix and elagolix.”</i>	The statement is factually incorrect. Opigolix and elagolix should not be mentioned as comparators as they are not licensed in this indication in the UK.	Not a factual inaccuracy – lack of license does not preclude use in clinical practice. Nevertheless, we have included this new information in Sections 1 and 3.3.

Issue 9 Number of studies in SLR

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 39.	Please revise this text as follows: <i>“Therefore, the SLR ends with four</i>	The statement is factually incorrect.	Corrected.

The report states “<i>Therefore, the SLR ends with four included studies in total.</i>” This is not accurate as the SLR included four reports of two studies.	<i>included reports in total, relating to two studies.”</i>		

Issue 10 Interpretation of adverse event data

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 74 and page 91. The report states, “<i>AE rates appear to have been similar between the placebo and linzagolix 200 mg plus ABT with higher rates for headache, hot flush and mood swings, which were regarded as treatment-related.</i>” This is not accurate since it implies considerably higher rates of headache, hot flush and mood swings for linzagolix 200 mg compared to placebo, however the rates were only slightly numerically higher, and the incidence of mood	Please revise this text as follows: “<i>TEAE rates appear to have been similar between the placebo and linzagolix 200 mg plus ABT. The most common TEAEs related to linzagolix treatment up to month 6 were hot flushes and headache. The most common linzagolix-related TEAEs from month 6 to month 12 included decreased bone density, hot flush and mood swings.</i>”	This is not an accurate representation of the tolerability profile of linzagolix.	Not a factual inaccuracy.

swings was low. The CS also reports treatment-related TEAEs separately from overall TEAEs.			

Issue 11 Imputation of missing CIs for dysmenorrhoea

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 90 The report states that, “<i>The EAG considers that a more valid method would be one that assumes the same SD, as mentioned in the Cochrane Handbook. This means that the SE is calculated as $SD/\sqrt{n}$.</i>” However, using this method would result in the same solution as method 2 provided by the company with MD= -0.35, CI (-0.78; 0.08), and p = 0.11).	Please change the sentence to: <i>“The EAG also questions the validity of method 2 given that the paper cited for the methodology does not seem to describe a method of imputing CIs, but instead how to estimate the precision of indirect comparisons. This method leads, however, to the same solution as mentioned in the Cochrane Handbook that assumes the same SD.”</i>	Since the methods result in the same solution, this is a more accurate statement.	This appears to not be a factual inaccuracy because the SE is a function of n and the SD is not. Therefore, the EAG is unsure as to how the company gets the same results.

Issue 12 Exclusion of studies from the ITC and lack of an NMA

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 77 The report states, <i>“It should be noted that the studies D’Hooghe 2019, Harada 2021, Bergqvist 2000 were not included in the indirect comparison for the following reasons:</i> <i>D’Hooghe 2019 – no comparison of leuprorelin vs placebo, study includes results for comparison of opigolix vs placebo;</i> <i>Harada 2021 [relugolix versus leuprorelin] and Bergqvist 2000 [goserelin versus nafarelin] – no placebo group in the study.”</i> D’Hooghe study was explored in a scenario for the ITC, however, it was erroneously excluded from the CS. The results of this analysis were in line with the main analysis, showing there was no	<i>“It should be noted that the studies D’Hooghe 2019, Harada 2021, Bergqvist 2000 were not included in the indirect comparison for the following reasons:</i> <i>D’Hooghe 2019 – no comparison of leuprorelin vs placebo, study includes results for comparison of opigolix vs placebo (the study was not powered to capture the difference between leuprorelin and placebo);</i> <i>Harada 2021 [relugolix versus leuprorelin] and Bergqvist 2000 [goserelin versus nafarelin] – no placebo group in the study and other limitations such lack of ABT therapy in the relugolix arm and dose of leuprorelin as presented in CS Appendix D.”</i>	Rationale for not including studies in ITC could be more detailed and transparent.	Not a factual inaccuracy. Nevertheless, the EAG has added some text in Sections 1, 3.3 and 3.6 to report these corrections and their implications.

significant difference in efficacy between the two treatments. This can be provided if requested. The study was not included in the base case comparison as it was powered only to capture the difference between opigolix vs placebo. Harada et al. could not be included in the ITC due to lack of ABT therapy in relugolix arm as well as dose of leuprorelin not in line with the SmPC (30% of patients).			

Issue 13 Number of DYS responders reported in Table 4.14

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 115, Table 4.1. The total number of dysmenorrhoea (DYS) responders after 6 months should be 97 (not 107).	Please amend 107 to 97 in the table.	The number presented is incorrect.	This was an error and has been corrected

Issue 14 Incorrect utility value for laparoscopic surgery

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 130, paragraph 3 The report states: <i>“This results in a utility value of 0.784 for laparoscopic surgery #1 and #2.”</i>	Please amend the statement to <i>“This results in a utility value of 0.784 for post-laparoscopic surgery #1 and #2.”</i>	The statement is incorrect.	This was indeed a typo and has been corrected.

Issue 15 Summary of EAGs view – comparison with relugolix

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
EAG report page 21, section 1.6. In paragraph 3, the report states: <i>“In the comparison between linzagolix and relugolix, [REDACTED].”</i> In paragraph 5, the report states: <i>“In all scenarios considered, linzagolix [REDACTED], as [REDACTED].”</i>	Please add a clarification to the statement: <i>“([REDACTED])”</i>	The statement could be interpreted incorrectly.	We have made the proposed amendment.

<i>was the case in the EAG base-case analysis.</i> This could be interpreted as linzagolix being [REDACTED] than relugolix; however, the incremental QALYs are equal.			

Location of incorrect marking	Description of incorrect marking	Amended marking
Pages 21-23, 86, 87, 88,89, 90, 91, 93,105, 106, 138, 148, 149, 150, 152, 154, 157-161, 170-172, 175-181	Results of the ITC versus relugolix, costs, QALYs and ICERs for linzagolix versus relugolix. Since reulgolix is not yet approved by NICE, we request these remain confidential.	The EAG report with updated marking has been sent with this response.