Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

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

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 26 February 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination, and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Theramex Ireland Limited

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 26 February 2024. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Page 5** – "*Moderate to severe symptoms of uterine fibroids include pain, difficulty in conceiving and heavy menstrual bleeding (HMB), which may lead to anaemia.*" **Issue:** There are other important symptoms and issues that can be sequelae of UF that are not included here such as bulk symptoms; these might lead to pelvic

Please return to: **NICE DOCS**

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 26 February 2024. Please submit via NICE Docs.

	pressure, constipation and increased urinary frequency, miscarriage, and pre-term and caesarean delivery. Please see the following references which describe these symptoms; • Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. BMC Womens Health. 2012 Mar 26;12(1):6 • Hunsche E, Rakov V, Scippa K, Witherspoon B, McKain L. The Burden of Uterine Fibroids from the Perspective of US Women Participating in Open-Ended Interviews. Womens Health Rep. 2022 Mar 4;3(1):286–96.
2	**Page 6** – *"The treatments which are offered may depend on the specific treatment aims, patient characteristics (for example comorbidities) and personal preference, which may be not to have hormonal treatments."* **Issue:** We would suggest adding "or specific types of surgery (e.g., to preserve fertility)" at the end of the sentence i.e., that personal preference may also include not wanting to have surgery, or specific types of surgery such as hysterectomy.
3	**Page 9** – *"Secondary outcomes included percentage change from baseline in MBL, fibroid volume and uterine volume, pain, percentage change from baseline in haemoglobin in people with anaemia and change in quality of life (uterine fibroids severity and quality of life [UFS-QoL] and EQ-5D-5L instruments)."* **Issue:** Other endpoints are missing: rates of and time to amenorrhoea (absence of bleeding), number of days of uterine bleeding.
4	**Page 9** – *"The primary outcome for both trials was attainment of response, which was a reduction in HMB defined as menstrual blood loss (MBL) of less than 80 ml and a 50% reduction in MBL from baseline."* **Please correct to** "The primary outcome for both trials was attainment of response, which was a reduction in HMB defined as menstrual blood loss (MBL) of less than or equal to 80 ml and a greater than or equal to 50% reduction in MBL from baseline''.
5	**Page 10** – *"The committee noted that the two trials returned slightly different results with linzagolix appearing slightly more effective for some outcomes in PRIMROSE 2 than PRIMROSE 1. It considered that this represented a source of uncertainty in the analyses."* **Add in wording**; "However US versus European populations are known to have different compliance rates and different rates of adherence to trial protocols.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 26 February 2024. Please submit via NICE Docs.

	This is in part due to more Black women in the US population. This demographic is more likely to have a reduced tolerance for continued heavy menstrual bleeding on treatment, and so might discontinue earlier. This may have an impact on the interpretation on any difference observed." Please see the following reference that describes this effect: • Fraser IS, Parke S, Mellinger U, Machlitt A, Serrani M, Jensen J. Effective treatment of heavy and/or prolonged menstrual bleeding without organic cause: pooled analysis of two multinational, randomised, double-blind, placebo-controlled trials of oestradiol valerate and dienogest. Eur J Contracept Reprod Health Care. 2011 Aug;16(4):258-69. doi: 10.3109/13625187.2011.591456. PMID: 21774563; PMCID: PMC3154543.
6	**Page 11** – *"It noted that people awaiting surgery for uterine fibroids were excluded from the PRIMROSE trials."* **Issue:** This is not wholly factually correct; only patients with severe UFs who required urgent surgery within 6 months regardless of the treatment provided were excluded.
7	**Page 12** - *"At this higher dosage, the BMD reduction was clinically meaningful (a 5% or more reduction)."* **Issue:** This is incorrect. In both PRIMROSE 1 and 2, BMD loss was not clinically meaningful as the percentages were all below 5%. **Please see wording** in the Donnez et al. Lancet 2022 primary publication: ''At 24 weeks, the mean differences were most pronounced in the lumbar spine, with a **3.3% decrease in PRIMROSE 1 and 4.1% decrease in PRIMROSE 2 for participants administered 200 mg linzagolix alone**, a 2.0% decrease in PRIMROSE 1 and 2.1% decrease in PRIMROSE 2 with 100 mg linzagolix, and a 0.8% decrease in PRIMROSE 1 and 1.4% decrease in PRIMROSE 2 with 100 mg with add-back therapy and 200 mg with add-back therapy, compared with 0.4% increases in the PRIMROSE 1 placebo group and 0.5% increases in the PRIMROSE 2 placebo group. (At 52 weeks, the mean percent decreases from baseline in the lumbar spine were 2.2% in PRIMROSE 1 and 2.4% in PRIMROSE 2 with 100 mg linzagolix, 0.0% for PRIMROSE 1 and 1.5% for PRIMROSE 2 with 100 mg with add-back therapy, 0.9% with PRIMROSE 1 and 2.0% with PRIMROSE 2 with 200 mg with add-back therapy, 2.1% in PRIMROSE 1 and 3.1% in PRIMROSE 2 in participants who had received 200 mg linzagolix up to week 24 and then switched to 200 mg with add-back therapy, and a 0.9% decrease in the placebo group in PRIMROSE 1 (placebo treatment was not continued up to week 52 in PRIMROSE 2)." See Figure 3 in Donnez et al. Lancet 2022 publication (mean percentage change values do not drop as low as 5%). Pooled results are similar (all less than 5%).

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 26 February 2024. Please submit via NICE Docs.

8	**Page 13-14** - *"The EAG considered that a lack of statistically significant difference did not support a conclusion of similar clinical effectiveness."* And on **page 14** - *"It noted that the confidence intervals for most doses and outcomes were very wide"* **Issue:** The draft guidance refers to confidence intervals and statistical significance when discussing the NMA analyses, however the NMAs were Bayesian analyses and produced credible intervals which demonstrated the probability that the estimate of effect lies within the range of the interval. Although frequentist and Bayesian analyses are used in a similar manner, the Bayesian NMAs do not relate to hypothesis tests or statistical significance. **Suggested alternative wording:** **Page 13** – "The EAG considered that a lack of there being a high probability of a difference did not support a conclusion of similar clinical effectiveness." Or "The EAG noted that a lack of statistical difference did not infer a conclusion of similar clinical effectiveness." **Page 14** – "It noted that the credible intervals for most doses and outcomes were very wide."
9	**Page 15** – "People in the model moved to the menopause state at 51 years and transitions to the death state were modelled using age-matched general population mortality rates." **Issue:** Mortality was also included for procedural based risks **Suggested alternative wording:** "People in the model moved to the menopause state at 51 years and transitions to the death state were modelled using age-matched general population mortality rates. An additional risk associated with procedural related mortality was also applied to those who had surgery (with the same mortality assumed as that which was incorporated in the previous appraisal for uterine fibroids [TA832])"

Insert extra rows as needed.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Monday 26 February 2024. Please submit via NICE Docs.

- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

New Evidence Submission

April 2024

File name	Version	Contains confidential information	Date
ID1690_Linzagolix_UF_New-Evidence-Submission	1.0	Yes	22-Apr-24

Table of Contents

Abbreviations

ABT	Add Back Therapy
ACM	Appraisal Committee Meeting
BSC	Best Supportive Care
EAG	External Assessment Group
CT	Combination Therapy
GnRH	Gonadotropin-releasing Hormone
ICER	Incremental Cost-effectiveness Ratio
ITC	Indirect Treatment Comparison
LYG	Life Years Gained
NICE	National Institute of Care and Excellence
NMA	Network Meta-analysis
MAIC	Matching Adjusted Indirect Comparison
MBL	Menstrual blood loss
STA	Single Technology Appraisal
UF	Uterine Fibroid
QALY	Quality Adjusted Life Years

1 Overview of the new evidence submission

1.1 Background to the company submission of linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190]

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

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

Following the first ACM and draft guidance issued by NICE, Theramex appreciate the recommendation to reimburse linzagolix for Population #3; specifically, as an option for treating moderate to severe symptoms of uterine fibroids in adults of reproductive age only if:

- they cannot have or do not want hormonal replacement add-back therapy (ABT).
- it is not used as a short-term treatment (usually 6 months or less), for example before uterine fibroid surgery.
- the dosage used is 200 mg once daily up to 6 months, followed by 100 mg once daily.

In the company submission for Populations #1 and #2, a cost-comparison analysis for linzagolix was presented. This approach was based on a blended STA approach explored by NICE at the decision problem stage, population overlap between linzagolix and relugolix CT, the findings of indirect treatment comparisons, clinical expert opinion, and conclusions from the prior NICE appraisal of relugolix CT (see CS Document B, Table 47 for further details).

1.2 Scope of new evidence submission

Theramex would like to thank NICE for the opportunity to submit new evidence for linzagolix, which is indicated for treating moderate to severe symptoms of UF (ID6190). In the NICE draft guidance, the EAG considered that the cost-comparison approach was not appropriate due to the high level of uncertainty associated with the NMA comparing linzagolix with relugolix CT. The committee concluded that it would be necessary to perform a cost-utility analysis that incorporated the various outcomes compared in the NMA, in order to assess cost-effectiveness of linzagolix in Populations #1 and #2. In response to this guidance, a cost-utility analysis has been performed that compares linzagolix to relugolix CT in these two populations.

Theramex has also explored how the new economic analysis could incorporate additional endpoints that are clinically meaningful to patients, beyond response as defined by menstrual blood loss (MBL). In comparison to relugolix CT, linzagolix has shown a greater reduction in fibroid volume in clinical trials, which can be a factor in determining surgical approach for patients with UF.[1–3] There is limited evidence to inform how the relative impact of linzagolix on fibroid volume vs relugolix CT could influence surgery. To address this data gap and key area of uncertainty in the economic model, semi-structured expert elicitation was used to gain both qualitative and quantitative insights, informing surgery distributions used in the model. Theramex engaged with 10 experienced clinicians that are currently treating women with UF across 6/7 NHS England regions.

This new evidence submission also accounts for an ITC error that was previously detected. The updated ITC results are incorporated into the new cost-utility analyses for populations #1 and #2, where they are included as a scenario analysis. The error occurred while extracting data from the LIBERTY 1 and 2 trials (relugolix CT) and impacted the results presented for the network meta-analysis (NMA) and matching adjusted indirect comparison (MAIC). The economic analysis previously presented for population #3 is not affected by this update, as it only relates to the comparison with relugolix CT. A full list of the sections, tables and figures impacted by this ITC update can be found in Appendix 2 (section 5.3).

2 Summary of cost-effectiveness results for populations #1 and #2

This section summarises the results of the additional economic analysis for populations #1 and #2, comparing linzagolix to relugolix CT in a cost-effectiveness framework. A report detailing the full methods, inputs and results can be found in Appendix 3 (section 5.2).

Error! Reference source not found. Table 1 and

Table 2 report the results of the analysis in a deterministic and probabilistic framework for Population #1 and Population #2, respectively. The results of the Population #1 (linzagolix 200 mg for 6 months followed by linzagolix 200 mg + ABT) and Population #2 (linzagolix 200 mg + ABT) analyses in a cost-effectiveness framework indicate that linzagolix is a cost-effective use of NHS resources at a willingness to pay (WTP) threshold of £20,000 to £30,000 per QALY gained.

The cost-effectiveness findings are consistent with expert feedback that both GnRH antagonists could be considered clinically comparable, with linzagolix providing similar costs and outcomes to relugolix CT. The results also reflect the potential added value of linzagolix in achieving fibroid shrinkage by using treatment-specific surgery type distributions. Additionally, the new economic model for population #1 and #2 is consistent with the model submitted for population #3, has considered the committee preferences highlighted in ACM1 and has addressed areas of uncertainty where possible through expert elicitation and scenario analyses.

Table 1 Deterministic and probabilistic results: Population #1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£2,726
Probabilistic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£3,408

Abbreviations: CT, combination therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Table 2 Deterministic and probabilistic results: Population #2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg + ABT	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£5,524
Probabilistic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg + ABT	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£6,001

3 Summary of expert elicitation study

Linzagolix has been shown to have a significant impact on fibroid volume, which can influence the invasiveness of surgery in UF patients.[1,3] The draft guidance issued by NICE indicated that the distribution of surgery types was uncertain and may depend on the location of the clinical practice, as not all practices have access to the same specialist and funding. In order to address this area of uncertainty in the economic model, expert opinion was elicited in a structured way by engaging with 10 independent and experienced practising clinicians treating women with diagnosed UFs. The expert elicitation explored how surgical procedures are used to treat UFs, and specifically:

- the distribution of surgery types performed in current clinical practice.
- the impact of UF size on surgery type distribution for UF patients.
- the potential impact of linzagolix and relugolix CT on surgery type distribution and surgical outcomes for UF patients, after considering the impact of each treatment on fibroid volume.

The results inform surgery distributions for each treatment option in the new cost-effectiveness analysis for population #1 and #2. A report detailing the full methods and results of the expert elicitation can be found in Appendix 1 (section 5.1).

The study demonstrated a large variation in clinical practice for the surgical treatment of UFs in the UK with surgical choice ultimately directed by the individual needs of the woman. However, factors that influence surgery choice such as fibroid size, location and desire to preserve fertility were consistent across the UK. The results indicated a general consensus that linzagolix 200mg without ABT would be expected to lead to less invasive surgeries, better control of symptoms, fewer surgical scars, faster recovery times and a reduction in repeat surgeries, driven by significant reductions in fibroid volume vs relugolix CT.

The aggregated responses for surgery distributions that are used in the economic model are summarised in Table 3, and demonstrate the expected shift from open to laparoscopic surgery with linzagolix 200mg +ABT in particular. It should be noted that whilst it was only possible to elicit surgery type distributions from 8 out of 10 clinicians, the two clinicians not included in the aggregated results qualitatively agreed that a reduction in fibroid volume would result in a shift towards less invasive surgeries, in accordance with the broader consensus.

Table 3 Impact of pharmaceutical treatment on distribution of surgery type

	Distribution of surgery type after treatment with: (n=8)		
Surgery type	**1. Relugolix CT**	**2. Linzagolix 200mg without ABT**	**3. Linzagolix 200mg with ABT**
	10-12% reduction in primary fibroid volume vs placebo, 24 weeks[4]	*+28% extra reduction in primary fibroid volume vs relugolix CT*[4]	*+12% extra reduction in primary fibroid volume vs relugolix CT*[4]
Uterine artery embolisation	[redacted]	[redacted]	[redacted]
Endometrial ablation	[redacted]	[redacted]	[redacted]
Myomectomy (open/abdominal)	[redacted]	[redacted]	[redacted]
Myomectomy (laparoscopic)	[redacted]	[redacted]	[redacted]
Hysterectomy (open/abdominal)	[redacted]	[redacted]	[redacted]
Hysterectomy (laparoscopic)	[redacted]	[redacted]	[redacted]
Transvaginal resection	[redacted]	[redacted]	[redacted]
Sonata	[redacted]	[redacted]	[redacted]

4 Conclusion

Overall, the findings of the new economic analysis presented show that linzagolix provides a cost-effective treatment option in NHS England practice, for women with moderate to severe symptoms of UFs who i) receive short-term treatment of 6

months or less (likely ahead of surgery) and ii) receive longer-term treatment with hormone-based therapy. Furthermore, the expert elicitation suggests that the additional benefit of linzagolix vs relugolix CT associated with fibroid volume reduction could be of real value to UF patients, clinicians and healthcare systems, by alleviating some of the burden associated with more invasive surgeries.

5 Appendices

5.1 Expert elicitation report

5.2 Cost-effectiveness analysis

5.3 ITC update report

6 References

1. Donnez J, Taylor HS, Stewart EA, Bradley L, Marsh E, Archer D, et al. Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. The Lancet. 2022 Sep 17;400(10356):896–907.

2. Al-Hendy A, Lukes AS, Poindexter AN, Venturella R, Villarroel C, Critchley HOD, et al. Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy. N Engl J Med. 2021 Feb 18;384(7):630–42.

3. Dolmans MM, Donnez J, Fellah L. Uterine fibroid management: Today and tomorrow. J Obstet Gynaecol Res. 2019;45(7):1222–9.

4. Theramex. Data on file: ITC report for Linzagolix.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

New evidence submission
Appendix – cost-effectiveness analysis

April 2024

File name	Version	Contains confidential information	Date
ID6190_Linzagolix_UF_Appendices_Economic-Evaluation_[redacted]	1.0	No	22-Apr-24

Contents

List of figures

List of tables

Introduction

To support the case for linzagolix as a treatment for Uterine Fibroids, this document is intended to provide a detailed description of the cost-effectiveness analysis for Populations #1 and #2 and therefore follows a layout consistent to Section B.3 of the NICE submission dossier template, with reference to the original submission dossier (with corresponding section and page or table numbers) where relevant.

The document is therefore split into 8 key sections:

1. Model structure and settings
2. Clinical parameters and variables
3. Health-related quality of life
4. Costs and healthcare resource use
5. Modelling assumptions and uncertainty
6. Base case results
7. Exploration of uncertainty
8. Interpretation and conclusions

Each section details revised base case settings relevant for the cost-effectiveness analysis framework for Populations #1 and #2, as well as detailing where scenario analysis has been provided to address uncertainty.

Throughout the consultation period, following publication of the DGD, Theramex has engaged with 10 independent key opinion leaders who are experienced clinicians in the treatment of uterine fibroids. This expert validation has been detailed where relevant throughout the draft response.

Summary of revised results for Populations #1 and #2

Table 1 and Table 2 report the results of the analysis in a deterministic and probabilistic framework for Population #1 and Population #2, respectively. The results of the Population #1 (linzagolix 200 mg for 6 months followed by linzagolix 200 mg + ABT) and Population #2 (linzagolix 200 mg + ABT) analyses in a cost-effectiveness framework indicate that linzagolix is a cost-effective use of NHS resources at a willingness to pay (WTP) threshold of £20,000 to £30,000 per QALY gained.

Table 1: Deterministic and probabilistic results: Population #1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£2,726
Probabilistic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£3,408

Abbreviations: CT, combination therapy; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Table 2: Deterministic and probabilistic results: Population #2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg + ABT	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£5,524
Probabilistic base case results							
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix 200 mg + ABT	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£6,001

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

Model structure and settings

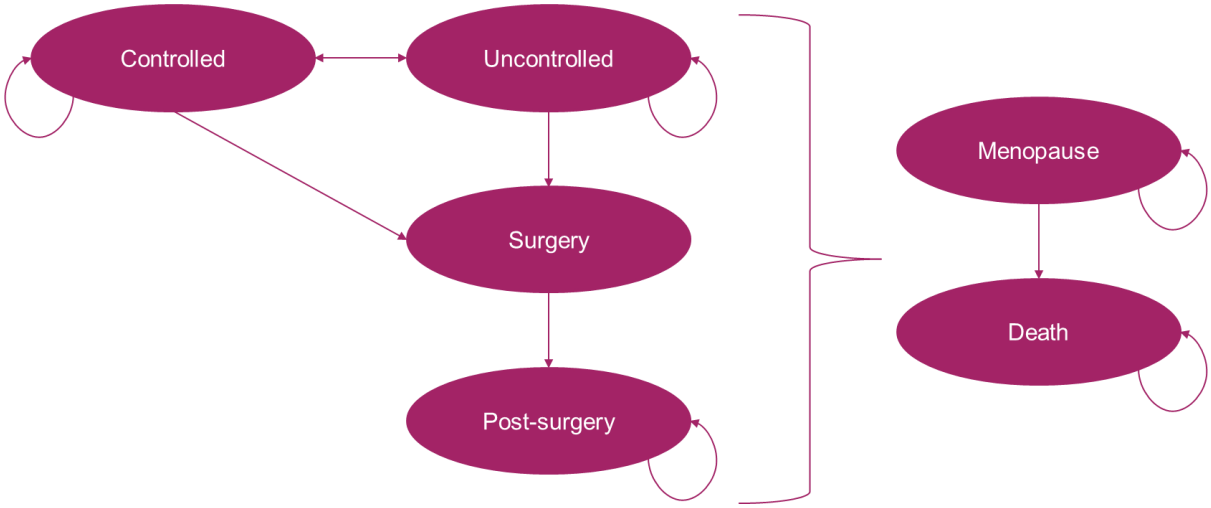
Model structure

The model structure is consistent with that chosen for 'Population #3' and is presented in Figure 1. The model takes a cohort-level Markov structure with four primary health states relating to symptom control and movement to surgery, with further health states considered for menopause and death.

Detailed justification of the model framework and further description of the movements between health states is provided in B.3.2.3.3 of the CS. As reported in the draft guidance, the Committee considered that the model structure was appropriate for decision making (DGD, Section 3.14). As such, the same structure is used for the new cost-effectiveness analyses in Populations #1 and #2.

To ensure EAG and Committee preferences are considered where possible, the EAG-adapted version of the submitted cost-effectiveness model (developed in Microsoft Excel) for Population #3 was adapted for Populations #1 and #2, rather than developing a de novo economic model. The model has been simplified where possible (i.e., by removing settings no longer considered relevant based on the Company base case, the EAG base case settings and the Committee preferences reported in the DGD).

Figure 1: Cost-effectiveness model structure



Intervention and comparator

As described in the CS (Section B.3.2.2), linzagolix received marketing authorisation in June 2022 by the European Commission for the treatment of moderate to severe symptoms of UFs in adult women of reproductive age.

Linzagolix has flexible licensed dosing regimens as follows:

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

Population #1

It is understood that treatment in the short-term setting would be administered with the intention of achieving a reduction in fibroid or uterine volume, ahead of patients receiving procedural/surgical intervention. As such, linzagolix 200 mg is the primary dose of interest for the intervention in Population #1. Of the linzagolix dosing regimens explored in the PRIMROSE studies, 200 mg is associated with the greater reduction in fibroid size volume. Linzagolix 200 mg without ABT resulted in substantial and clinically meaningful mean reductions in fibroid volumes (48% reduction) and uterine volumes (39% reduction) at Week 24 (nominal $p<0.001$ versus placebo).[1,2]

The linzagolix license indicates that the 200 mg dose should be administered as once daily for short-term use (< 6 months) in clinical situations when reduction of uterine and fibroid volume is desired. Due to the risk of bone mineral density (BMD) decrease with prolonged use, the 200 mg dose without concomitant ABT should not be prescribed for longer than 6 months.[3] As such, in the economic analysis, it is assumed that after 6 months of treatment with linzagolix 200 mg, patients will receive linzagolix 200 mg + ABT. This approach is consistent with the PRIMROSE studies.

As outlined in Document B of the original Company Submission, for Population #1 (patients receiving short-term treatment of 6 months or less), the comparator of interest is relugolix CT, based on the recommendations in NICE TA832. Although GnRH agonists are also licensed in the short-term setting, in TA832, it was concluded that relugolix CT is similarly effective to GnRH agonists. Furthermore, the

DGD issued by NICE in this appraisal references clinical input indicating that many patients are likely to receive relugolix CT instead of GnRH agonists, due to the ease associated with oral administration.

In the TA832 final appraisal document, it was noted that although there is a paucity of evidence for the short-term use of relugolix CT in a presurgical setting, it is likely to be used in clinical practice irrespective of whether surgery is planned or not.[4] Theramex therefore consider that relugolix CT is the most appropriate comparator.

Population #2

In Population #2 (people receiving longer-term treatment with hormone-based therapy), linzagolix 200 mg + ABT is the most relevant dosing strategy, and therefore informs the economic model for this population. This is firstly because linzagolix 200 mg + ABT achieved the highest response rate (MBL ≤80 mL and ≥50% reduction from baseline at 24 weeks) of the doses assessed in the PRIMROSE studies (PRIMROSE 1 and 2 pooled data, 84.5%). Secondly, the inclusion of ABT is in line with the longer-term treatment strategy of preserving BMD.

For Population #2, the relevant existing treatment option is relugolix CT. This is aligned with the Committee's draft guidance (DGD, Section 3.4).

In TA832, relugolix CT was recommended as an option for treating moderate to severe symptoms of UFs in adults of reproductive age.[4] Clinical opinion indicates that patients would receive relugolix CT as a long-term treatment option with the aim of symptom resolution/reduced menstrual bleeding, while preventing or delaying surgical intervention.

Population #3

As previously noted, Theramex appreciate the draft guidance issued by NICE recommending linzagolix as an option for treating moderate to severe symptoms of uterine fibroids in Population #3, where the relevant comparator was BSC. Therefore, Population #3 is not explored further in this new economic analysis.

Key model settings

Key model settings for the cost-effectiveness analysis in Populations #1 and #2 are provided in Table 3.

Table 3: Key model features in Population #1 and #2

Model component	Details	Justification
Perspective	NHS and PSS on costs and direct health effects for patients	Consistent with NICE reference case
Time horizon	To menopause (10 years), based on the average age of the cohort at baseline, and the average age of menopause based on NHS data (51 years)[5]	The NICE reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long enough to reflect any differences in costs or outcomes between the technologies being compared. It is understood that fibroids tend to shrink due to low estrogen levels, and as such, after menopause it is assumed that no further surgeries, pharmacological treatments, or healthcare resource usage are required
Cycle length	28-days with half-cycle correction applied	• Considered short enough to adequately capture changes in health status • Aligns with linzagolix pack size, allowing for accurate dosing calculations for costs • Half-cycle correction more accurately reflects the movement of patients in the state transition model
Discount rates	3.5% per annum for costs and QALYs	In line with NICE reference case

Clinical parameters and variables

Baseline characteristics

The baseline age of the cohort was aligned with the population in the pooled PRIMROSE 1 and 2 studies (42.25 years; SD, 5.60) and consistent with the Population #3 analysis from the CS (see B.3.3.1.3). The age at baseline is used to derive age-matched general population mortality rates, which inform transitions to death from alive model health states.[6] Furthermore, baseline age is used to calculate age-matched general population utility values, which in turn are used to age-adjust health-state utility values over time.[7]

The average age of menopause in the model is 51 years, in line with UK-based data, and consistent with NICE TA832 and the Population #3 analysis in the company submission (B.3.3.1.3).[4,5] Also, in line with TA832, it is assumed that all patients transition to the menopause state when the age of the modelled cohort reaches the average age of menopause.[4] After this timepoint, patients are assumed to no longer

experience disease-related symptoms (due to low oestrogen levels shrinking UFs). As such, the model assumes that all further outcomes after menopause are the same on each treatment arm and are assumed equivalent to the age-matched outcomes of the general population; and hence the modelled time horizon of 10 years is considered suitable.

Efficacy (uncontrolled to controlled health state)

Linzagolix

Clinical data informing the linzagolix arms of the cost-effectiveness analysis were primarily based on pooled data from the PRIMROSE 1 and 2 studies, using the primary study endpoint (response, defined as MBL ≤80 mL and ≥50% reduction from baseline at 24 weeks). The model considers patients who achieve response as having 'controlled disease' and patients who do not have a response or those who achieved but subsequently lost their response are categorised as having 'uncontrolled disease'.

Clinical effectiveness results from PRIMROSE 1 and 2 are reported in CS Section B.2.6 and are summarised below (Table 4). The most relevant doses for consideration are linzagolix 200 mg and linzagolix 200 mg + ABT for Populations #1 and #2, respectively. Furthermore, linzagolix 200 mg + ABT outcomes are relevant for patients in Population #1 who have not received surgery after 6 months of treatment.

Consistent with the approach taken to model Population #3 in the Company Submission (B.3.3.2.3), an exponential assumption (Equation 1) was used to estimate the 28-day cycle probability of moving from the uncontrolled to controlled health states, based on the 24-week PRIMROSE response rate.

Equation 1: Exponential formula

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

The model extrapolates the estimated per 28-day cycle response probability for linzagolix beyond the trial period, in the absence of longer-term follow-up data.

Table 4: PRIMROSE 1 and 2, response defined by reduced MBL at 24-weeks and corresponding 28-day probabilities

Treatment arm	24-week response	28-day cycle probability
Linzagolix 100mg	56. 5%	13.0%
Linzagolix 100mg + ABT	71.6%	18.9%
Linzagolix 200 mg	74.5%	20.4%
Linzagolix 200 mg + ABT	84.5%	26.7%

Abbreviations: ABT, add-back therapy; MBL, menstrual blood loss; mg, milligram

Relugolix

As the NICE Committee have requested a cost-effectiveness analysis in Populations #1 and #2, estimates of clinical effectiveness are required to inform the relugolix CT arm of the updated model. As such, relugolix CT data were primarily sourced from the LIBERTY 1 and 2 studies. The studies are summarised below, with further details provided in Section B.2 of the main CS.

LIBERTY 1 and 2 are phase 3, international, randomised, double-blind, placebo-controlled trials, investigating the efficacy and safety of daily oral administration of relugolix in combination with ABT for the management of HMB associated with UFs in premenopausal women.

In general, there was good alignment between the trials (the inclusion and exclusion criteria were identical between LIBERTY 1 and 2, with there also being substantial overlap of criteria between the PRIMROSE and LIBERTY studies). There were also reported outcomes that were defined in the same way in the PRIMROSE and LIBERTY trials, such as response (defined as a volume of MBL <80 ml and a ≥50% reduction in volume from baseline), which is used to inform the cost-effectiveness analysis. Further details on LIBERTY 1 and 2 are provided in CS Section B.2.

Although there were similarities between the PRIMROSE and LIBERTY trials, there were also important differences that limit the reliability to accurately compare the two treatments, which should be noted. Specifically, there were differences in characteristics of patients at baseline, differences in the methods used to collect sanitary products from patients (with product collection being more burdensome on patients in the PRIMROSE trials), as well as differences in how missing data were handled. These factors may mean that outcomes from a network meta-analysis for MBL are a conservative estimate of the relative effectiveness of linzagolix versus relugolix CT.

Firstly, in the LIBERTY trials, patients were required to collect their used sanitary products and return them at each 4-weekly follow-up visit, whereas patients in the PRIMROSE trials were required to return their used sanitary products more frequently (either once their collection box was full or within a maximum of 12-days after using the products). With patients on the placebo arm experiencing more blood loss than patients receiving the active treatment, there is greater burden to return all used products (as set out in the constraints of the PRIMROSE 1 and 2 trial protocol). Hence, there is a risk that some patients, particularly those on placebo, may not have returned all products for logistic reasons. This means that it is possible that patients in PRIMROSE 1 and 2 had higher levels of bleeding than captured (which will be more apparent in those on placebo), thus leading to the relative treatment effect of linzagolix versus placebo being an underestimation. Given the approach is less burdensome for patients in the LIBERTY trials, this risk of underestimation is lower, meaning the overall relative effect of linzagolix versus relugolix CT (with the placebo arm forming the treatment network) may be underestimated.

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

Additionally, there were also differences in the timings used to determine a patients MBL and therefore response status; in the LIBERTY trials, MBL is calculated based on the 35-days prior to follow-up, whereas in the PRIMROSE trials MBL is calculated based on the prior 28-days. This minor difference in endpoint definitions may lead to differences in MBL and response rate between the studies, but the direction and magnitude of this potential bias is unclear.

To inform the cost-effectiveness model, two methods have been considered to apply relugolix outcomes within the cost-effectiveness model, which are listed below and discussed in turn throughout this subsection.

- Naïve comparison, base case
- Network meta-analysis (NMA), scenario analysis
  - Fixed-effects NMA
  - Random-effects NMA

Although an NMA was conducted, outcomes from the naïve comparison of PRIMROSE and LIBERTY response rates are used to inform the cost-effectiveness analysis in the base case, with fixed-effects and random-effects NMA tested in scenario analysis.

Naïve comparison (base case)

Given the factors described above, the placebo effect observed in the PRIMROSE studies that would not be expected in clinical practice, and notable limitations with the NMA (as highlighted by the Company, the EAG and the NICE committee throughout the appraisal process), a naïve comparison of response rates to relugolix CT was considered appropriate for informing the base case analysis. Response outcomes comparing relugolix CT to linzagolix are presented in Table 5. As shown in the table, linzagolix 200 mg and 200 mg + ABT is associated with a higher 24-week response than relugolix CT.

Table 5: Comparing response at 24-weeks LIBERTY 1 & 2 and PRIMROSE 1 & 2

Treatment arm	Trial	24-week response	28-day cycle probability
Linzagolix 100mg	PRIMROSE 1 & 2	56. 5%	13.0%
Linzagolix 100mg + ABT	PRIMROSE 1 & 2	71.6%	18.9%
Linzagolix 200 mg	PRIMROSE 1 & 2	74.5%	20.4%
Linzagolix 200 mg + ABT	PRIMROSE 1 & 2	84.5%	26.7%
Placebo	PRIMROSE 1 & 2	32.2%	6.3%
Relugolix CT	LIBERTY 1 & 2	72.3%	19.3%
Placebo	LIBERTY 1 & 2	16.8%	3.0%

Abbreviations: ABT, add-back therapy; AH, alkaline haematin; CT, combination therapy; PBAC, pictorial blood assessment chart

Network meta-analysis (scenario analysis)

It is acknowledged that naïvely comparing response rates is associated with a degree of uncertainty; therefore, cost-effectiveness results when utilizing the fixed-effects and random-effects NMAs are also presented in scenario analysis.

Full details of the NMA are provided in CS Section B.2.9. However, at the draft guidance stage upon development of the cost-effectiveness analysis for Populations #1 and #2, an error was identified in the data imputed into the NMA, which impacts the results of the relugolix CT comparison for the response (RMBL) endpoint.

Table 6 reports the results of the updated NMAs. However, all other NMAs provided in Section B.2.9 of the CS remain unaffected (including MBL, pain, fibroid volume, haemoglobin percentage change, UFS-QoL).

Table 6: Updated NMA results: OR of relugolix CT versus linzagolix doses

Comparison, relugolix CT versus	OR	CI
Fixed-effects NMA		
Linzagolix 100mg	[redacted]	[redacted]
Linzagolix 100mg + ABT	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]
Linzagolix 200 mg + ABT versus	[redacted]	[redacted]
Random-effects NMA		
Linzagolix 100mg	[redacted]	[redacted]
Linzagolix 100mg + ABT	[redacted]	[redacted]
Linzagolix 200 mg	[redacted]	[redacted]
Linzagolix 200 mg + ABT versus	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CI, confidence interval; CT, combination therapy; OR, odds ratio; SE, standard error

In the updated NMA results for response, the point estimates are similar between the fixed- and random-effects models, but the credible intervals of the random-effects are notably wider. Random-effects models account for heterogeneity in a network, but these estimates are very uncertain, as demonstrated by the wide credible intervals. This suggests that there may not be enough evidence to estimate the between-study heterogeneity, which is unsurprising in such a small network where the estimates of treatment effect for each comparison are produced using only 2 studies (i.e., the pooled PRIMROSE data informs the comparison of linzagolix vs placebo; LIBERTY 1 and LIBERTY 2 inform the comparison of relugolix CT vs placebo).

The results across the range of NMAs, which considered six outcomes (including endpoints presented in Section B.2.9 of the CS and the corrected response endpoint presented above) and compared four linzagolix regimens versus relugolix CT, vary in direction and magnitude, with some results favouring linzagolix and other favouring relugolix CT and the majority of comparisons not showing a high probability of there being a difference in efficacy between linzagolix versus relugolix CT across the fixed- and random-effects NMAs. This may be explained in part by the differences observed between the PRIMROSE and LIBERTY trials (as described above) that are expected to underestimate the relative treatment effect of linzagolix versus placebo which in turn leads to an underestimation of the relative treatment effect of linzagolix versus relugolix CT in the NMAs. For these reasons, the results of the NMAs are highly uncertain, and it may instead be more appropriate to consider a naïve comparison, rather than using complex methods with such limited data available.

Given the Committee requested that linzagolix is compared with relugolix CT using a cost-effectiveness framework for Populations #1 and #2, the corrected NMA outcomes are implemented within the cost-effectiveness model, and any scenario analyses relating to the NMAs reflect this corrected analysis.

Recurrence (controlled to uncontrolled health state)

To inform transitions from the controlled health state to uncontrolled (i.e., loss of response, see Figure 1), a consistent approach was used with the Population #3 model. As presented in CS Section B.3.3.2.3, recurrence rates of UF symptoms are informed by expert opinion elicited from a market research survey with UK gynaecologists (n=50), which reported the rate of recurrence of symptoms for GnRH antagonists.[8] As such, equivalent recurrence rates are applied in the linzagolix and relugolix CT arms of the Population #1 and #2 model.

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

Surgery rates

Proportion of patients receiving surgery

As detailed in the main CS, surgery rates are not available from the PRIMROSE studies, as the requirement for surgery within 6 months regardless of the treatment provided was an exclusion criterion. Therefore, in the base case, the probability of surgery is taken from PEARL II, a study which compared ulipristal acetate with leuprorelin acetate for the pre-operative treatment of symptomatic fibroids. This is the same approach that was incorporated in the Population #3 analysis in the main CS.

In PEARL II, 45.10% of patients went on to have surgery, as reported in NICE TA832.[4] KOL opinion indicated that surgery wait time was up to 18-months. Given movements to the surgery health state are applied on a cyclical basis in the cost-effectiveness model, the corresponding proportion of patients moving per cycle to surgery is 3.02% (using Equation 1).

Although PEARL II is the most relevant study available to inform the proportion of patients receiving surgery, based on clinical understanding of the disease and positioning, it is possible that the PEARL II rate is most applicable to the short-term setting (Population #1), given PEARL II was conducted in a pre-operate setting. Therefore, to capture uncertainty, scenario analyses considering lower surgery proportions are explored in Population #2. Although there is a paucity of information, three exploratory scenarios are considered:

1. Population #2: proportion of patients moving to surgery from the controlled and uncontrolled health states is 1% per 28-day cycle
2. Population #2: proportion of patients moving to surgery from the controlled and uncontrolled health states is 2% per 28-day cycle
3. Population #2: proportion of patients moving to surgery from the controlled health state is 2% per 28-day cycle

Distribution of surgery type received

The draft guidance issued by NICE indicated that the distribution of surgery types was uncertain and may depend on the location of the practice. Whilst it was considered that both the Company base case values (using TA832) and the EAG values used could both be considered in decision making, Theramex has tried to address this uncertainty by seeking further KOL input. Throughout March, Theramex has interviewed 10 UK-based clinicians independently to further understand the types of surgery used in UK clinical practice, and what factors may influence the choice of surgery taken. Of the 10 clinicians interviewed, it was possible to elicit surgery type distributions from 8, and therefore the average of these responses has been used to inform the base case surgery distributions in Populations #1 and #2. Notably, clinicians highlighted that a difference in fibroid volume (as observed with linzagolix treatment, particularly at the 200 mg dose) may influence the choice of surgery (with a general consensus that a reduction in fibroid volume may result in a higher likelihood of a patient receiving laparoscopic surgery). This therefore highlights that those patients receiving linzagolix (in both the 200 mg and 200 mg + ABT) arms may have a different surgery type, when compared with people receiving treatment with relugolix CT. The surgery types elicited from the eight clinicians are presented in Table 7 below, and represent the anticipated surgery distributions when explicitly considering the respective reduction in fibroid size volume for the two relevant doses of linzagolix in Population #1 and Population #2 (based on the NMA as reported in CS Section 2.9, [redacted] reduction of linzagolix 200 mg versus relugolix CT and [redacted] reduction of linzagolix 200 mg + ABT versus relugolix CT, respectively). Throughout the elicitation process, it was highlighted to Theramex that two further surgery types may be considered in practice, which were not previously included in TA832 or the CS in this appraisal (transvaginal resection and Sonata®). For completeness, these surgery types have been included within the updated cost-effectiveness model for Populations #1 and #2, with respective costs, utility values, and procedural related mortality parameters imputed (using a consistent approach with the existing surgery types).

As shown in Table 7, the feedback indicates that a higher proportion of patients receiving linzagolix (at both the 200 mg and 200 mg + ABT doses) would be expected to receive laparoscopic surgery (both hysterectomy and myomectomy)

compared with open/abdominal surgery. There is also an expected increase in the proportion of patients who may be able to receive treatment of the uterine fibroid through transvaginal resection.

Table 7: Surgery type: expert elicitation from eight UK KOLs

Surgery type	General practice	Relugolix CT	Linzagolix 200 mg	Linzagolix 200 mg + ABT
Uterine artery embolisation	[redacted]	[redacted]	[redacted]	[redacted]
Endometrial ablation	[redacted]	[redacted]	[redacted]	[redacted]
MRI guided focused ultrasound surgery	[redacted]	[redacted]	[redacted]	[redacted]
Myomectomy (open/abdominal)	[redacted]	[redacted]	[redacted]	[redacted]
Myomectomy (laparoscopic)	[redacted]	[redacted]	[redacted]	[redacted]
Hysterectomy (open/abdominal)	[redacted]	[redacted]	[redacted]	[redacted]
Hysterectomy (laparoscopic)	[redacted]	[redacted]	[redacted]	[redacted]
Transvaginal resection	[redacted]	[redacted]	[redacted]	[redacted]
Sonata	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CT, combination therapy; KOL, key-opinion leaders; MRI, magnetic resonance imaging

The treatment-specific surgery type distributions have been used to inform the model base case for both populations, and are considered the most appropriate source of for three primary reasons:

1. These distributions reflect the most up-to-date estimates available

2. The distributions account specifically for the relative effect of treatment with relugolix CT versus linzagolix (200 mg and 200 mg + ABT), and therefore allow the model to consider additional endpoints which are clinically meaningful to a patient with UFs, beyond response as defined by RMBL

3. The elicited parameters are obtained from eight independent clinicians who currently treat in UK clinical practice. The values obtained from TA832 were based on an amalgamation of literature with values not specific to the UK (Thus Hospital Episode Statistics and a US study Carls et al 2008 based on a claims database)

It is therefore considered that the feedback obtained from the expert elicitation process are the most reliable information available to inform the surgery distributions within the model.

Following the initial ACM, the committee considered that the surgery types were associated with uncertainty. To address this, several scenarios have been explored, including assuming the same surgery types are received irrespective of treatment arm.

1. Treatment-independent values (elicited from KOL input of eight UK clinicians as 'general practice')
2. TA832 original company submission values (as was the Company base case for Population #3)
3. TA832 EAG values
4. EAG surgery distribution values (as was the EAG base case for Population #3)

Transition probabilities

Table 8 presents the transition probabilities applied within the cost-effectiveness model for Population #1 (linzagolix 200 mg versus relugolix CT) and Population #2 (linzagolix 200 mg + ABT versus relugolix CT).

Given the linzagolix 200 mg dose is only indicated for 6 months, after a 6-month treatment duration within the model, it is assumed that all linzagolix patients who remain on treatment and have not received surgery switch to receive linzagolix 200 mg + ABT. Transition probabilities are updated within the model accordingly beyond 6-months accordingly (as are other model inputs e.g., costs and time-to-treatment discontinuation).

Table 8: Transition probabilities

FROM / TO	Controlled	Uncontrolled	Surgery	Post-surgery	Procedural death
Linzagolix 200 mg					
Controlled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Uncontrolled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Surgery	0.00%	0.00%	0.00%	100.00%	0.00%
Post-surgery	0.00%	0.00%	0.00%	100.00%	0.00%
Procedural death	0.00%	0.00%	0.00%	0.00%	100.00%
Linzagolix 200 mg + ABT					
Controlled	[redacted]	[redacted]	[redacted]	0.00%	0.00%

Uncontrolled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Surgery	0.00%	0.00%	0.00%	100.00%	0.00%
Post-surgery	0.00%	0.00%	0.00%	100.00%	0.00%
Procedural death	0.00%	0.00%	0.00%	0.00%	100.00%
Relugolix CT					
Controlled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Uncontrolled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Surgery	0.00%	0.00%	0.00%	100.00%	0.00%
Post-surgery	0.000%	0.000%	0.000%	100.00%	0.000%
Procedural death	0.000%	0.000%	0.000%	0.000%	100.00%

Note: Transition matrix does not include background mortality which is applied separately within the model calculations
Abbreviations: CT, combination therapy

Mortality

Mortality is incorporated into the cost-effectiveness model in the same framework as the original submission for Population #3, as reported in CS Section B.3.3.4.3. (summarised below).

In the cost-effectiveness model, death is incorporated based on background mortality rates derived from the latest general population ONS data for England (2018-2020)[6], and movements to death do not differ by health state (except surgery) or by treatment arm.

It is possible that surgery-related complications (procedural-related death) may result in a heightened risk of mortality within the surgery health state. Therefore, in addition to background mortality, the model accounts for procedural-related death (which may occur when patients exit the surgery state). Procedure-related death estimates were sourced from TA832 and incorporated a small risk of death associated with some surgeries (summarised in Table 9).[4] Within the modelling framework, procedural death varies based on the type of surgery encountered, and as such a weighted average mortality rate is estimated.

Table 9: Risk of procedural death

Treatment arm	Risk of death	Source
UAE	0.0200%	TA832[4]/Zowall et al., 2008[9]
Endometrial ablation	0.0000%	Assumed same as MRgFUS
MRgFUS	0.0000%	TA832[4]/Gorny et al., 2011[10]
Open/abdominal myomectomy	0.0028%	TA832[4]/Assumption
Laparoscopic myomectomy	0.0000%	TA832[4]/Assumption
Open/abdominal hysterectomy	0.0028%	TA832[4]/Settnes et al 2020[11]
Laparoscopic hysterectomy	0.0020%	TA832[4]/Settnes et al 2020[11]

Transvaginal resection	0.0000%	Assumed same as MRgFUS
Sonata	0.0000%	Assumed same as MRgFUS

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

Adverse events

In the cost-effectiveness analysis for both populations, the costs and HRQoL consequences of AEs are captured. AEs for linzagolix are informed by the pooled PRIMROSE 1 and 2 trials, which reported treatment-emergent AEs by treatment arm. Treatment-emergent AEs occurring in 5% or more of patients across the treatment arms were considered.

To inform the relugolix CT arm, AEs were taken from TA832 (sourced from LIBERTY 1 and 2) defined as AEs reported in >5%. AEs are summarised in Table 10. Details of the impact of AEs on HRQoL and costs are detailed in later sections.

Table 10: Treatment-emergent adverse events included within the cost-effectiveness model

AE	Relugolix CT	Linzagolix 200 mg (population #1)	Linzagolix 200 mg + ABT (population #2)
Anaemia	2.36%	2.86%	6.25%
Headache	9.84%	11.90%	7.69%
Hot flush/flash	8.27%	33.33%	9.62%
Nausea	3.94%	5.24%	1.92%

Abbreviations: ABT, add-back therapy; AE, adverse event, CT, combination therapy

Health-related quality of life

Controlled and uncontrolled health state utility values

Within the original submission, the company base case for Population #3 considered health state utility values derived from the UFS-QoL (collected in PRIMROSE 1 & 2) mapped to the EQ-5D-3L. The Committee considered this methodology appropriate to inform decision making (as noted in the DGD, Section 3.16), and therefore the consistent utility values are considered in the cost-effectiveness analysis for Populations #1 and #2.

For completeness, in line with the original company submission analysis for Population #3, utility values derived from the EQ-5D-5L (collected in PRIMROSE 1 & 2) mapped to the EQ-5D-3L are presented in scenario analysis.

A summary of the resulting health state utility values is provided in Table 11 (base case) and Table 12 (scenario analysis). Full details of the utility analysis are provided in the CS Section B.3.4.

Table 11: Utility values using UFS-QoL mapped to EQ-5D-3L (base case)

Health state	Utility value	Source	Justification
Controlled	[redacted]	PRIMROSE 1 and 2 (UFS-QoL mapped to EQ-5D)	Utilises clinical trial data in a relevant population. Aligns with model health states EQ-5D questionnaire lacks sensitivity in UFs.
Uncontrolled	[redacted]		

Abbreviations: EQ-5D, EuroQol-5 Dimension; UF, uterine fibroid; UFS-QoL, Uterine Fibroid Symptom-Quality of Life

Table 12: Utility values using EQ-5D-5L mapped to EQ-5D-3L (scenario analysis)

Health state	Utility value	Source
Controlled	[redacted]	PRIMROSE 1 and 2 (UFS-QoL mapped to EQ-5D)
Uncontrolled	[redacted]	

Abbreviations: EQ-5D, EuroQol-5 Dimension; UF, uterine fibroid; UFS-QoL, Uterine Fibroid Symptom-Quality of Life

Surgery and post-surgery health state utility values

Health state utility values for the surgery and post-surgery health states were sourced from the literature, consistent with the analysis reported in the original company submission for Population #3. Surgery and post-surgery utility values associated with all surgery types are provided below (Table 13). Utility values for transvaginal resection and sonata (additional surgery types identified during the expert elicitation conducted in March 2024), were assumed equivalent to endometrial ablation and MRgFUS, respectively.

Table 13: Health-state utility values for surgery/post-surgery

Surgery	Health state	Value	Reference
UAE	Surgery	0.620	Manyonda et al. 2020[12]
	Post-surgery	0.800	
Endometrial ablation	Surgery	0.698	Cooper et al. 2019[13]
	Post-surgery	0.801	
MRgFUS	Surgery	0.783	Zowall et al. 2008[9]
	Post-surgery	0.802	
Open/abdominal myomectomy	Surgery	0.628	Assumption based on the reported disutility difference between abdominal and laparoscopic myomectomy in TA832
	Post-surgery	0.878	
Laparoscopic Myomectomy	Surgery	0.630	Manyonda et al. 2020[12]
	Post-surgery	0.880	
Open/abdominal Hysterectomy	Surgery	0.705	Assumption based on the reported disutility difference between abdominal and laparoscopic hysterectomy in TA832
	Post-surgery	0.834	
Laparoscopic hysterectomy	Surgery	0.707	Cooper et al. 2019[13]
	Post-surgery	0.836	
Transvaginal resection	Surgery	0.698	Assumed same as endometrial ablation (Cooper et al 2019)[13]
	Post-surgery	0.801	

Sonata	Surgery	0.783	Assumed same as MRgFUS (Zowall et al. 2008)[9]
	Post-surgery	0.802	

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

Based on the distribution of surgery types for each treatment arm (Section 'Distribution of surgery type received'), weighted average utility values are obtained for the surgery and post-surgery health states (summarised in Table 14).

Table 14: Base case surgery-related utility values

Treatment arm	Surgery	Post-surgery
Linzagolix 200 mg	0.682	0.833
Linzagolix 200 mg + ABT	0.682	0.833
Relugolix CT	0.681	0.833

Abbreviations: ABT, add-back therapy; CT, combination therapy.

Adverse events

The impact of adverse events (AEs) on HRQoL was explored in the cost-effectiveness model in the same format as Population #3 (reported in Company Submission B.3.4.4).

The disutility values of AEs applied for linzagolix and relugolix CT were identified from published sources and are presented in Table 15. The frequency of AEs for both linzagolix arms was obtained from the pooled PRIMROSE 1 and 2 studies (as outlined in Section B.3.4 of the original Company Submission), and relugolix CT AEs were obtained from the LIBERTY 1 and 2 trials (applied in TA832).[4] As a simplifying approach, the duration of AEs was assumed to be one model cycle (28-days) and resulting QALY decrements were applied as a one-off in the first model cycle.

Table 15: Adverse event disutility values

AE	Disutility	Source
Anaemia	-0.0209	Sullivan et al. 2006[14] ICD-9 185
Headache	-0.0297	Sullivan et al. 2006[14] ICD-9 346
Hot flush/flash	-0.0600	Hux et al. 2015[15]
Nausea	-0.0480	Nafees et al. 2008[16]

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

Using the AE frequencies from the PRIMROSE and LIBERTY trials (Table 10) and the disutility values (Table 15), a one-off QALY decrement per treatment arm was calculated and applied in the first cycle of the cost-effectiveness model (reported in Table 16).

Table 16: AE QALY decrement

Treatment arm	AE disutility
Linzagolix (200 mg, base case Population #1)	-0.002
Linzagolix (200 mg + ABT, base case Population #2)	-0.001
Relugolix CT	-0.001

Abbreviations: ABT, add-back therapy; AE, adverse event; BSC, best supportive care; CT, combination therapy; mg, milligram

Age-adjusted utilities

In line with the approach used for Population #3, an age-related utility decrement was included within the model to account for the natural decline in quality of life associated with age. This was applied as a utility multiplier (calculated using the algorithm by Ara and Brazier, 2010).[7] The utility multiplier was the calculated per increase in age and applied in each cycle throughout the model time horizon.

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

Scenario analysis to capture fibroid shrinkage

As discussed in the context of surgery type distributions, fibroid shrinkage is associated predominantly with linzagolix 200 mg, but is also observed with linzagolix 200 mg + ABT.

Hux et al. (2015)[15], a paper identified in the literature and introduced in the main CS, was a study aiming to elicit utility values associated with pre-menopausal women suffering from symptomatic uterine fibroids. The study considered that larger fibroid size may be associated with increased pressure on the pelvis and discomfort associated with an enlarged abdomen, as well as an increased difficulty with urinary urges. The reported utility improvement associated with smaller fibroid size of 0.03 (95% CI: 0.02, 0.04) has been incorporated within the model in scenario analyses, to account for the potential improvement in HRQoL associated with a reduction in fibroid size.[15] In addition to impacting the HRQoL of patients with UFs ahead of surgery, it is also considered plausible that a reduction in fibroid size may simplify surgery (beyond the type received, but also the procedure itself), it is possible that there are post-surgery benefits associated with a reduction in fibroid size ahead of surgery. As such, two exploratory scenario analyses are presented (for both populations) which test the impact of a health state utility increment in the linzagolix arm of the model due to fibroid shrinkage. To estimate the linzagolix specific utility increment, the value identified by Hux et al. is multiplied by the additional proportion

of patients experiencing fibroid shrinkage based on the NMA ([redacted] for linzagolix 200 mg versus relugolix CT and [redacted] for linzagolix 200 mg + ABT versus relugolix CT, as reported in Section B.2.9 of the CS). The scenarios considered are as follows:

1. Applying the Hux et al. increment to the controlled and uncontrolled health states ahead of surgery (acknowledging that patients who have uncontrolled symptoms due to HMB may still experience fibroid reduction)

2. Applying the Hux et al. increment to the post-surgery health states

Costs and healthcare resource use

Drug and administration costs

Drug and administration costs for linzagolix are the same as those reported in the Company Submission (Section B.3.5.1). As both linzagolix and relugolix CT are oral treatments, no administration costs are applied within the cost-effectiveness model for either population. This is aligned with the Company and EAG preferred settings from the original analysis.

Table 17: Drug unit costs

Treatment	Units and pack size	Dose	Pack cost	Source	Description
Linzagolix	100 mg x 28 tablets	100 mg daily	List price: [redacted] PAS price: [redacted]	Theramex	Yselty 100 mg
Linzagolix	200 mg x 28 tablets	200 mg daily	List price: [redacted] PAS price: [redacted]	Theramex	Yselty 200 mg
Relugolix CT	40 mg x 28 tablets	40 mg daily	£72.00	BNF 2023[17]	Ryeqo 40 mg/1 mg/0.5 mg
Relugolix CT	40 mg x 84 tablets	40 mg daily	£216.00	BNF 2023[17]	

Abbreviations: CT, combination therapy; PAS, patient access scheme

For relugolix CT, in line with the original cost-comparison analysis, it is assumed that the cost of ABT is included in the combined formulation, therefore no additional ABT costs are applied in the relugolix CT arm. For linzagolix 200 mg + ABT, the cost of estradiol 1 mg and norethisterone 0.5 mg is applied in line with the license (Table 18).

In line with both the Company and EAG base case from the original submission, it is assumed that concomitant medication is administered to 100% of patients. Treatment specific concomitant medication proportions sourced from PRIMROSE (linzagolix) and TA832 (relugolix CT) are explored in scenario analysis. Furthermore, in line with the EAG base case, vitamin D and calcium (at a cost of £1.38 per 28-day cycle) are included as concomitant medications (in addition to ibuprofen and iron supplements). The exclusion of vitamin D and calcium as concomitant medications (per the original company submission) is tested in scenario analysis, as the draft guidance reports that the committee concluded that both the company and EAG definitions were appropriate for decision making (DGD, Section 3.18).

Table 18: Hormonal ABT and concomitant medication unit costs

Treatment	Units and pack size	Pack cost	Source	Description
Oestradiol/ norethisterone	1 mg / 0.5 mg x 84 tablets	£13.20	BNF 2023[17]	Kliovance tablets
Ibuprofen	200 mg x 24 tablets	£0.36	eMIT 2023[18]	Quantity: 78,257 SD: £0.21
Ferrous sulfate	200 mg x 28 tablets	£0.54	eMIT 2023[18]	Quantity: 584,493 SD: £0.28

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

Treatment discontinuation

To estimate drug acquisition costs, in line with the Population #3 analysis per the main CS (Section B.3.5.1.1), discontinuation of linzagolix is considered using withdrawal data from the pooled PRIMROSE 1 and 2 studies. To inform discontinuation in the relugolix CT arm, withdrawal data were sourced from TA832 (22% in LIBERTY 1 and 18% in LIBERTY 2).[4]

The discontinuation data from the observed period of the trials (24-weeks) is converted in to a 28-day probability (consistent with the approach used for efficacy), which is then applied throughout the time horizon for all patients in the ‘Controlled’ and ‘Uncontrolled’ health states on both treatment arms. It is assumed that upon entry to the ‘Surgery’ or ‘Menopause’ states, pharmacological therapy is no longer required.

Table 19 presents discontinuation rates used for linzagolix 200 mg (Population #1 up to 6 months), linzagolix 200 mg + ABT, (Population #1 beyond 6 months, and Population #2) and relugolix CT (Populations #1 and #2).

Table 19: Discontinuation rates from PRIMROSE 1 and 2 & LIBERTY 1 and 2, 24-week follow-up

Treatment arm	Discontinuation rates	Converted 28-day discontinuation rate
Linzagolix 200 mg	[redacted]	[redacted]
Linzagolix 200 mg + ABT	[redacted]	[redacted]
Relugolix CT	20.08%	3.67%

Abbreviations: BSC, best supportive care; mg, milligram

Resource use costs

Resource use estimates are aligned with those included in the EAG base case (EAG report, Section 4.2.7, Table 23 and Table 25), with estimates for GnRH antagonists applied to both the linzagolix and relugolix CT arms. Similarly, resource use unit costs are aligned with the EAG base case (EAG report, Section 4.2.7, Table 23 and Table 26). For brevity these have not been included as part of the response to draft guidance.

Adverse event costs

In line with the Population #3 analysis, adverse event management costs are captured within the cost-effectiveness model for Population #1 and #2 as a one-off cost in the first model cycle, as a simplifying assumption.

Adverse event unit costs (presented in Table 20 below) are combined with the AE probabilities (reported in Table 10) to estimate adverse event management costs in the linzagolix and relugolix CT arms. The total AE management costs by treatment arm are provided in Table 21.

Table 20: Individual treatment-related adverse event costs applied in the cost-effectiveness model

AE	Cost	Reference
Anaemia	£42.00	PSSRU 2022.[19] Assumed to be the cost of a GP appointment (surgery consultation lasting 9.22 minutes). In line with TA832
Headache	£0.00	Assumed no cost incurred (self-managed/no treatment sought). In line with TA832[4]
Hot flush/flash	£0.00	Assumed no cost incurred (self-managed/no treatment sought). In line with TA832[4]

Nausea	£0.96	Treatment with metclopramadine (cost from BNF assuming 10 mg pack size 28) in line with TA832[4,17]

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

Table 21: One-off AE costs applied in first model cycle

Treatment	AE cost
Linzagolix (200 mg, Population #1)	£1.25
Linzagolix (200 mg + ABT, Population #2)	£2.64
Relugolix CT	£1.03

Abbreviations: ABT, add-back therapy; AE, adverse event; CT, combination therapy.

Surgery costs

In line with the approach taken to model applicable costs in Population #3 (see Company Submission Section B.3.5.4), the cost of surgery is included within the cost-effectiveness analysis and is calculated based on a weighted average of surgery types. Surgery costs are applied to the proportion of patients moving to surgery in each model cycle (see Section 'Surgery rates').

As KOL elicitation indicated that additional surgery types beyond those reported in the CS may be used in the treatment of UFs, unit costs have been provided below for transparency (Table 22).

Weighted surgery costs, based on the distribution of surgery types received by treatment arm elicited from clinical expert opinion (see Section 'Surgery rates'), are presented in Table 23.

Table 22: Costs by surgery type (applied to cost-comparison model and cost-effectiveness model)

Surgery type	Cost	Reference
UAE	£2,786	NHS schedule of NHS costs 2021/2022.[20] Uterine Artery Embolisation (YR55Z). Total HRGs.
Endometrial ablation	£1,261	NHS schedule of NHS costs 2021/2022.[20] Resection or Ablation Procedures for Intrauterine Lesions (MA12Z)
MRgFUS	£1,131	NHS schedule of NHS costs 2021/2022.[20] Radiofrequency Ablation or Cryoablation, for Pain Management (AB15Z). Total HRGs.
Open/abdominal myomectomy	£4,670	NHS schedule of NHS costs 2021/2022.[20] Intermediate Open Upper Genital Tract Procedures (MA11Z). Total HRGs.
Laparoscopic myomectomy	£3,496	NHS schedule of NHS costs 2021/2022.[20] Intermediate, Laparoscopic or Endoscopic, Upper Genital Tract Procedures, with CC Score 2+ (MA09A) and 0-1 (MA09B). Total HRGs.
Open/abdominal hysterectomy	£6,336	NHS schedule of NHS costs 2021/2022.[20] Major Open Upper Genital Tract Procedures with CC score 5+ (MA07E), 3-4 (MA07F), and 0-2 (MA07G). Total HRGs.
Laparoscopic hysterectomy	£5,273	NHS schedule of NHS costs 2021/2022.[20] Major, Laparoscopic or Endoscopic, Upper Genital Tract Procedures with CC score 2+ (MA08A) and 0-1 (MA08B). Total HRGs.

Transvaginal resection	£1,261	NHS schedule of NHS costs 2021/2022.[20] Resection or Ablation Procedures for Intrauterine Lesions (MA12Z)
Sonata	£1,131	NHS schedule of NHS costs 2021/2022.[20] Radiofrequency Ablation or Cryoablation, for Pain Management (AB15Z)

Abbreviations: MRgFUS, Magnetic resonance-guided focused ultrasound; UAE, uterine artery embolization

Table 23: Weighted average surgery costs

Treatment	Surgery cost
Linzagolix (200 mg, Population #1)	£3,612.74
Linzagolix (200 mg + ABT, Population #2)	£3,667.92
Relugolix CT	£3,723.93

Abbreviations: ABT, add-back therapy; CT, combination therapy.

Model assumptions and uncertainty

Key assumptions

Table 24 lists the key assumptions associated with the new cost-effectiveness analysis for Populations #1 and #2.

Table 24: Model assumptions

Category	Population #1 assumption	Population #2 assumption
Linzagolix dose	200 mg for 6 months followed by 200 mg + ABT. In line with the license, patients cannot receive linzagolix 200 mg (without ABT) for more than 6 months. As such, it is assumed that those who are on treatment and have not received surgery by 6 months would go on to receive linzagolix 200 mg + ABT, in line with the PRIMROSE studies.	200 mg + ABT. Linzagolix 200 mg + ABT achieved the highest response rate in the pooled PRIMROSE studies, and the inclusion of ABT is in line with the longer-term treatment strategy of preserving BMD.
Time horizon	10 years is sufficient for capturing differences in costs between treatment arms, based on the average age at baseline (42 years) and the average age of menopause based on NHS data (51 years). After menopause, no further treatment costs are applied due to fibroid shrinkage because of estrogen levels.	
Cycle length	It is assumed that a 28-day cycle length is appropriate and adequate for capturing meaningful changes in health status (in line with Population #3 in the original CS).	
Relugolix CT efficacy	Relugolix CT efficacy is informed by the LIBERTY 1 and 2 studies. The direct evidence is used in a naïve comparison with PRIMROSE (given limitations in the NMA, as highlighted in the DGD and in this response document). Use of the fixed- and random-effects NMAs to inform the efficacy of relugolix CT versus linzagolix is considered in scenario analysis.	
Transition probabilities (uncontrolled to controlled health state)	An exponential assumption is used to derive per 28-day cycle transition probabilities across all populations to reflect patients moving from 'uncontrolled' symptoms to 'controlled'. In all treatment arms and populations, the rates observed in the trials for the respective arms are converted into a per-cycle rate (28-days) and applied.	
Recurrence (controlled to uncontrolled health state)	In line with the Population #3 analysis presented in the main CS, recurrence rates of UF symptoms (used to derive the probability of losing response and moving from 'controlled' to 'uncontrolled') are informed by expert opinion elicited from a market research survey with UK gynaecologists. As the elicitation reported recurrence rates for GnRH antagonists, the rates are assumed equal between linzagolix and relugolix CT in the Population #1 and #2 model.	

Surgery rates (transitions to surgery) are informed by the PEARL II study	Surgery rates are not available from the PRIMROSE studies, as the requirement for surgery within 6 months regardless of the treatment provided was an exclusion criterion. In TA832, surgery rates were also sourced from PEARL II.	
	As PEARL II was a pre-operative study in the treatment of symptomatic fibroids, no alternative scenarios are explored	As PEARL II surgery rates may be more applicable to Population #1, exploratory scenarios which explore lower proportions are tested for the longer-term population
Surgery type distributions are treatment-specific and based on clinical expert opinion	The indirect treatment comparison indicates that linzagolix can achieve greater fibroid shrinkage (particularly the 200 mg dose). Clinical expert opinion indicated that fibroid/uterine shrinkage can impact the type of surgery a patient would receive. Treatment-specific surgery type distributions, elicited by clinical experts, are therefore used in the base case. Treatment independent surgery type distributions are explored in scenario analyses.	
Surgery type costs and outcomes	In the absence of alternative data, surgery costs and outcomes for transvaginal resection are assumed equal to endometrial ablation, and Sonata assumed equal to MRgFUS.	
Number of surgeries	As a simplifying assumption to avoid excessive model complexity and tracking of patients after an initial surgery distribution, it is assumed only 1 round of surgery is required. As commented in the DGD, whilst recurrence may happen in practice, this is unlikely to be a key driver of model results.	
Mortality	UFs are not associated with a heightened risk of mortality compared with general population. Death is incorporated based on background mortality rates derived ONS data for England. A heightened risk of mortality within the surgery health state is incorporated within the model, based on surgery type.	
Treatment discontinuation	Treatment discontinuation rates are informed by those observed within respective arms of the trials. PRIMROSE 1 and 2 are used to inform the linzagolix arm, while discontinuation rates from LIBERTY 1 and LIBERTY 2 inform the relugolix treatment discontinuation rates. In line with efficacy, an exponential assumption is used to calculate per-model cycle discontinuation.	

Abbreviations: ABT, add-back therapy; BMD, bone mineral density; CT combination therapy; DGD, draft guidance document; GnRH, gonadotropin-releasing hormone; ITC, indirect treatment comparison; MRgFUS, magnetic resonance-guided focused ultrasound; TA, technology appraisal; UF, uterine fibroids

Uncertainty

Throughout this response document, Theramex has strived to address uncertainties raised as part of the NICE process. The document details methodology taken to construct a robust cost-effectiveness analysis to compare outcomes of linzagolix (200 mg and 200 mg + ABT) to relugolix CT for patients with uterine fibroids. In addition to this, Theramex has implemented findings from the expert elicitation exercise (conducted in March 2024), which consisted of 10 independent expert elicitation interviews. Revised surgery distribution types are therefore included within the model based on findings from the interviews. Treatment-specific values inform the base case, with treatment-independent distributions considered in scenario analysis.

The base case results sections below are reflective of the analysis that Theramex considers to be most appropriate base case settings to explore the cost-

effectiveness of linzagolix versus relugolix CT. Key structural uncertainties are explored in scenario analyses. These scenarios relate to:

- Indirect treatment comparison approach: fixed- and random-effects NMA
- Discount rates: relevant to the NICE manual and reference case
- Surgery distributions: relevant to the uncertainty surrounding the potential differences in the appropriate route of surgery given that linzagolix has the ability to reduce the fibroid size/volume
- Concomitant medication costs: relevant to the DGD which indicated that both scenarios (with and without additional Vitamin D and Calcium) were appropriate
- Utility values: relevant given the potential improvement in HRQoL, pre- and post-surgery for patients experiencing a reduction in fibroid size
- Proportion of patients transitioning to surgery in Population #2: relevant given the reduction in fibroid size and long-term treatment with linzagolix may offer patients the opportunity to refrain from having surgery (the base case values, which were sourced from PEARL II reflect a population intending of receiving surgery, and are therefore more closely aligned with Population #1)

In addition to scenario analyses, in line with the Population #3 cost-effectiveness analysis presented in the original CS, parameter uncertainty is explored in the Population #1 and #2 cost-effectiveness model through probabilistic sensitivity analysis (PSA) and one-way sensitivity analysis (OWSA).

Base case results

The following section details base-case deterministic results of the cost-effectiveness analysis comparing linzagolix with relugolix CT, in Populations #1 and #2 respectively.

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

Base-case deterministic cost-effectiveness results for Population #1 are presented in Table 25, using the linzagolix PAS price. In the short-term treatment setting, as previously described, linzagolix will be administered without hormone-based therapy in clinical practice (200 mg for 6 months, followed 200 mg + ABT in line with the license).

The results demonstrate that, when compared with relugolix CT over the 10-year time horizon, linzagolix is associated with a QALY gain of [redacted] at an incremental cost of [redacted], resulting in an ICER of £2,726. The base case results indicate that linzagolix is cost-effective at a WTP threshold of £20,000 to £30,000; however, it is acknowledged that differences between the two treatments are marginal, and total costs and QALYs are broadly similar across arms.

Incremental net-monetary benefit is considered a useful outcome measure for assisting with the interpretation of results in cases where incremental QALY gains are broadly comparable between treatments. An INMB greater than £0 is indicative of cost-effectiveness at a pre-specified WTP threshold. The resulting INMB for linzagolix versus relugolix CT is [redacted] to [redacted] at a WTP threshold of £20,000 to £30,000 per QALY gained.

The Population #1 results suggest that linzagolix is a cost-effective use of resources in NHS England practice.

Table 25: Base-case results (Population #1), with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INMB at £20,000	INMB at £30,000
Relugolix CT	[redacted]	9.971	[redacted]						
Linzagolix 200 mg	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£2,726	[redacted]	[redacted]

Abbreviations: CT, combination therapy; ICER, incremental cost-effectiveness ratio; INMB, incremental net-monetary benefit; LYG, life-years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

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

Base-case deterministic cost-effectiveness results for Population #2 are presented in Table 26, using the linzagolix PAS price. In the longer-term treatment setting with hormone-based therapy, linzagolix will be administered at the 200 mg + ABT dose in clinical practice.

The results demonstrate that compared with relugolix CT over the 10-year time horizon, linzagolix is associated with a QALY gain of [redacted] at an incremental cost of [redacted], resulting in an ICER of £5,524. As with Population #1, the findings of the cost-effectiveness analysis for Population #2 are that costs and QALYs are broadly similar between linzagolix and relugolix CT, with a marginal QALY gain for linzagolix (a result of the increased response rate associated with linzagolix 200 mg + ABT). The resulting INMB is [redacted] to [redacted] at a WTP threshold of £20,000 to £30,000 per QALY gained.

The ICER in the Population #2 analysis falls below the WTP threshold specified by NICE of £20,000 to £30,000 per QALY gained; as such, the Population #2 results suggest that linzagolix is a cost-effective use of resources in NHS England practice.

Table 26: Base-case results (Population #2), with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INMB £20,000	INMB £30,000
Relugolix CT	[redacted]	9.971	[redacted]						
Linzagolix	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£5,524	[redacted]	[redacted]

Abbreviations: CT, combination therapy; ICER, incremental cost-effectiveness ratio; INMB, incremental net-monetary benefit; LYG, life-years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Exploration of uncertainty

Probabilistic sensitivity analysis

PSA was used to assess joint parameter uncertainty in the cost-effectiveness model for Populations #1 and #2. All parameters associated with uncertainty were varied jointly within their assigned probability distributions, and the PSA was run for 1,000 iterations (by which point results had stabilised).

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

The mean PSA results for Population #1 are presented in Table 27 and the cost-effectiveness plane showing incremental costs and QALYs for the 1,000 iterations is presented in Figure 2. The probabilistic results show consistency with the deterministic analysis, with similar total costs and QALYs across treatment arms. The resulting probabilistic ICER of £3,408, and INMB of [redacted] to [redacted], support the deterministic findings that linzagolix is a cost-effective use of NHS resources at the £20,000-£30,000/QALY WTP threshold.

Figure 3 presents the cost-effectiveness acceptability curve (CEAC) for linzagolix versus relugolix CT. Based on the 1,000 PSA iterations, the probability of linzagolix being the cost-effective option at the £20,000-30,000/QALY WTP threshold is 53%-54%.

Table 27: PSA results (Population #1), with PAS

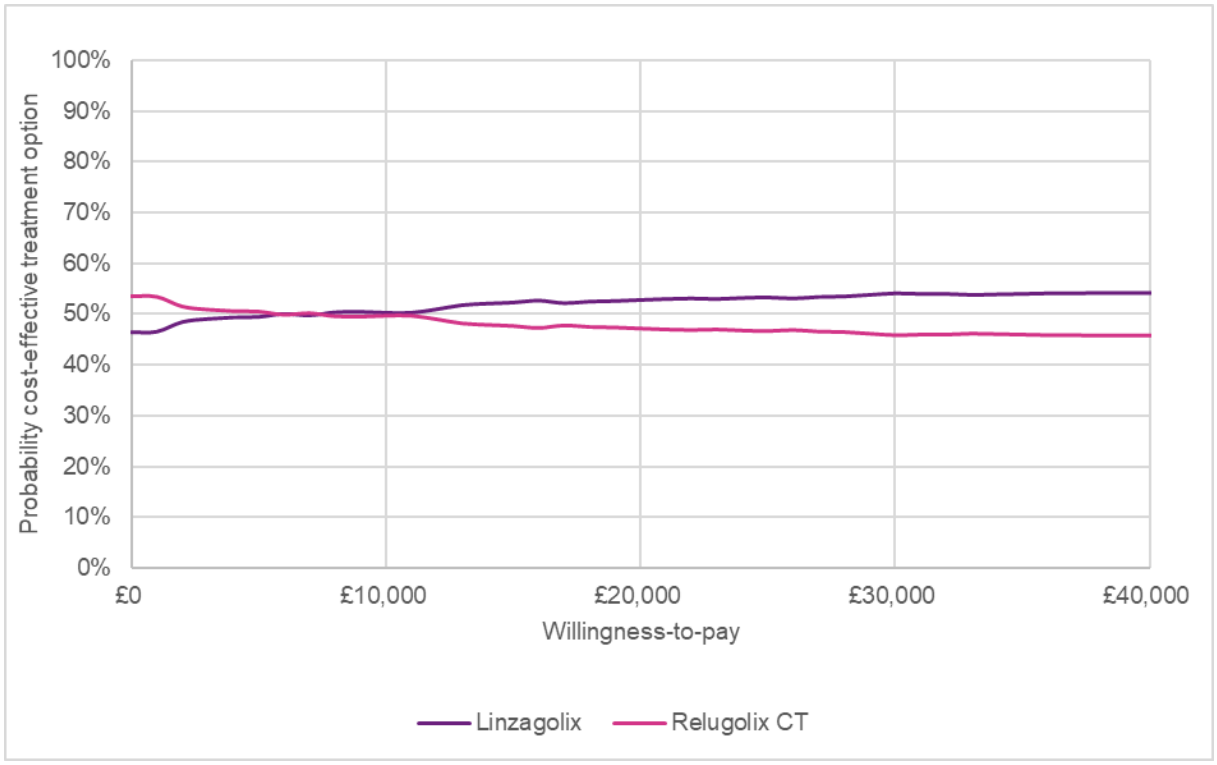
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INMB at £20,000	INMB at £30,000
Relugolix CT	[redacted]	9.971	[redacted]						
Linzagolix 200 mg	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£3,408	[redacted]	[redacted]

Abbreviations: CT, combination therapy; ICER, incremental cost-effectiveness ratio; INMB, incremental net-monetary benefit; LYG, life-years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 2: Cost-effectiveness plane (Population #1)

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness to pay
Note: Figure uses a WTP threshold of £20,000 per QALY gained

Figure 3: Cost-effectiveness acceptability curve (Population #1)



Abbreviations: CT, combination therapy

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

The mean PSA results for Population #2 are presented in Table 28 and the cost-effectiveness plane showing the 1,000 iterations is presented in Figure 4. The probabilistic results show consistency with the deterministic analysis. The probabilistic ICER of £6,001 supports the finding that linzagolix is a cost-effective use of NHS resources at the £20,000-£30,000/QALY WTP threshold.

Figure 5 presents the CEAC for linzagolix versus relugolix CT. Based on the 1,000 PSA iterations, the probability of linzagolix being the cost-effective treatment option is projected to be 58% to 59% at the £20,000 to £30,000/QALY WTP threshold.

Table 28: PSA results (Population #2), with PAS

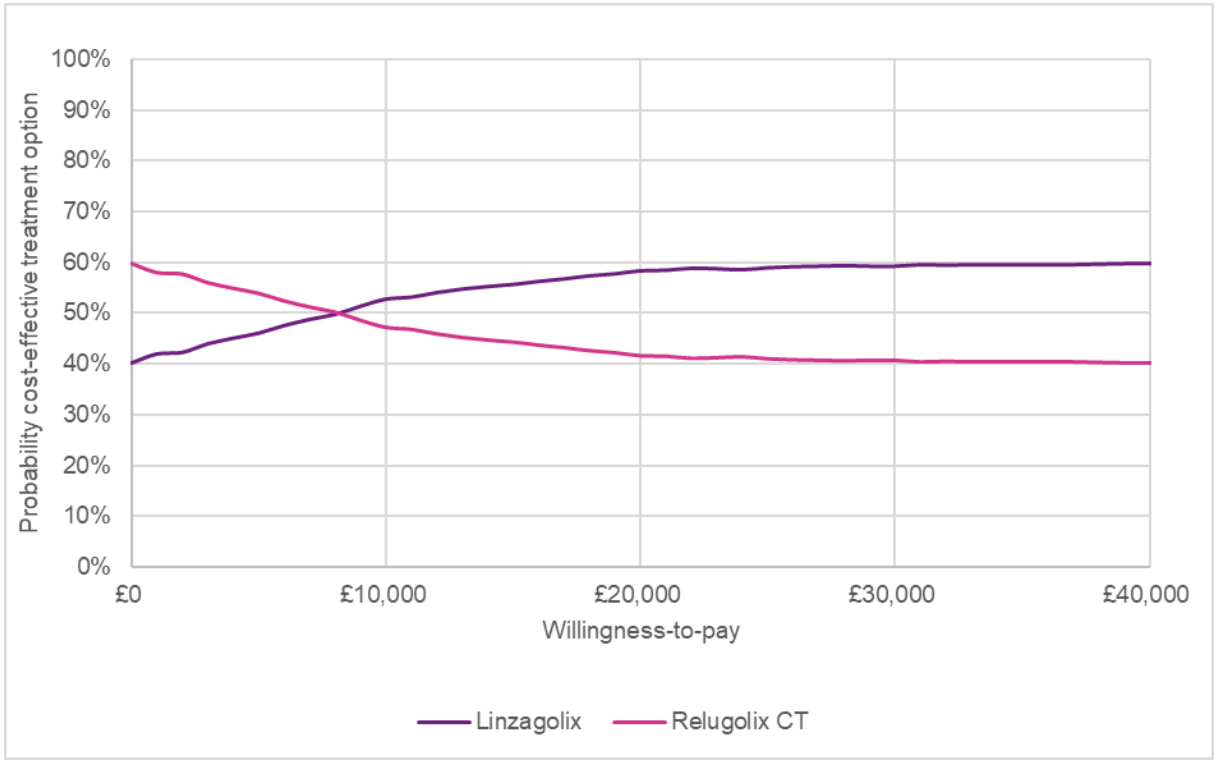
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INMB at £20,000	INMB at £30,000
Relugolix CT	[redacted]	9.971	[redacted]						
Linzagolix 200 mg	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£6,001	[redacted]	[redacted]

Abbreviations: CT, combination therapy; ICER, incremental cost-effectiveness ratio; INMB, incremental net-monetary benefit; LYG, life-years gained; PAS, patient access scheme; QALYs, quality-adjusted life years

Figure 4: Cost-effectiveness plane (Population #2)

Abbreviations: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness to pay
Note: Figure uses a WTP threshold of £20,000 per QALY gained

Figure 5: Cost-effectiveness acceptability curve (Population #2)



Abbreviations: CT, combination therapy

One-way sensitivity analysis

OWSA was conducted to test the impact of individual parameters at their lower and upper limits of the confidence intervals. If the variance of any input was not published or available, a simplified assumption was made assuming the standard error was 10% of the mean value. Due to the occurrence of negative ICERs, which can be difficult to interpret, OWSA results are presented using INMB.

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

Table 29 and Figure 6 present the tabulated OWSA results (INMB) and the tornado plot of the top 10 parameters which had the largest impact on the INMB, in Population #1.

The post-surgery health state utility values, TTD rates, and response rates were the inputs with the largest individual impact on cost-effectiveness results. This is expected given that treatment-specific surgery distributions based on KOL opinion are used to inform the model, TTD rates are a driver of drug acquisition costs, and response rates are used to determine the proportion of patients entering the controlled health state. Cost-effectiveness results were generally robust to individual parameter uncertainty.

Table 29: OWSA results (Population #1), with PAS

Parameter	INMB (WTP of £20,000/QALY)	
	Lower bound	Upper bound
Utility value, Abdominal hysterectomy, post-surgery	[redacted]	[redacted]
Utility value, Abdominal myomectomy, post-surgery	[redacted]	[redacted]
Utility value, Transvaginal resection, post-surgery	[redacted]	[redacted]
TTD, relugolix CT: % risk of discontinuation per cycle	[redacted]	[redacted]
Utility value, Laparoscopic hysterectomy, post-surgery	[redacted]	[redacted]
Relugolix response % (24-week RHMB) - LIBERTY 1 & 2	[redacted]	[redacted]
TTD, Linzagolix 200mg + ABT: % risk of discontinuation per cycle	[redacted]	[redacted]
Utility value, Laparoscopic myomectomy, post-surgery	[redacted]	[redacted]
Linzagolix 200mg, response % (24-week RHMB)	[redacted]	[redacted]
TTD, Linzagolix 200mg: % risk of discontinuation per cycle	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CT, combination therapy; INMB, incremental net-monetary benefit; OWSA, one-way sensitivity analysis; mg, milligram; PAS, patient access scheme; QALY; quality-adjusted life year; RHMB, reduced heavy menstrual bleeding; TTD, time to treatment discontinuation; WTP, willingness to pay

Figure 6: Tornado plot (Population #1), INMB (WTP of £20,000/QALY), with PAS

Abbreviations: ABT, add-back therapy; CT, combination therapy; INMB, incremental net-monetary benefit; mg, milligram; PAS, patient access scheme; QALY; quality-adjusted life year; RHMB, reduced heavy menstrual bleeding; TTD, time to treatment discontinuation; WTP, willingness to pay

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

Table 30 and Figure 7 present the tabulated OWSA results (INMB) and the tornado plot of the top 10 parameters which had the largest impact on the INMB, in Population #2.

Across the majority of parameters included in the OWSA, when inputs were varied at their 95% confidence interval, linzagolix remained cost-effective at the £20,000/QALY threshold (with corresponding INMBs above £0). The OWSA demonstrates the robustness of results to individual parameter uncertainty. Key drivers were consistent with the Population #1 analysis.

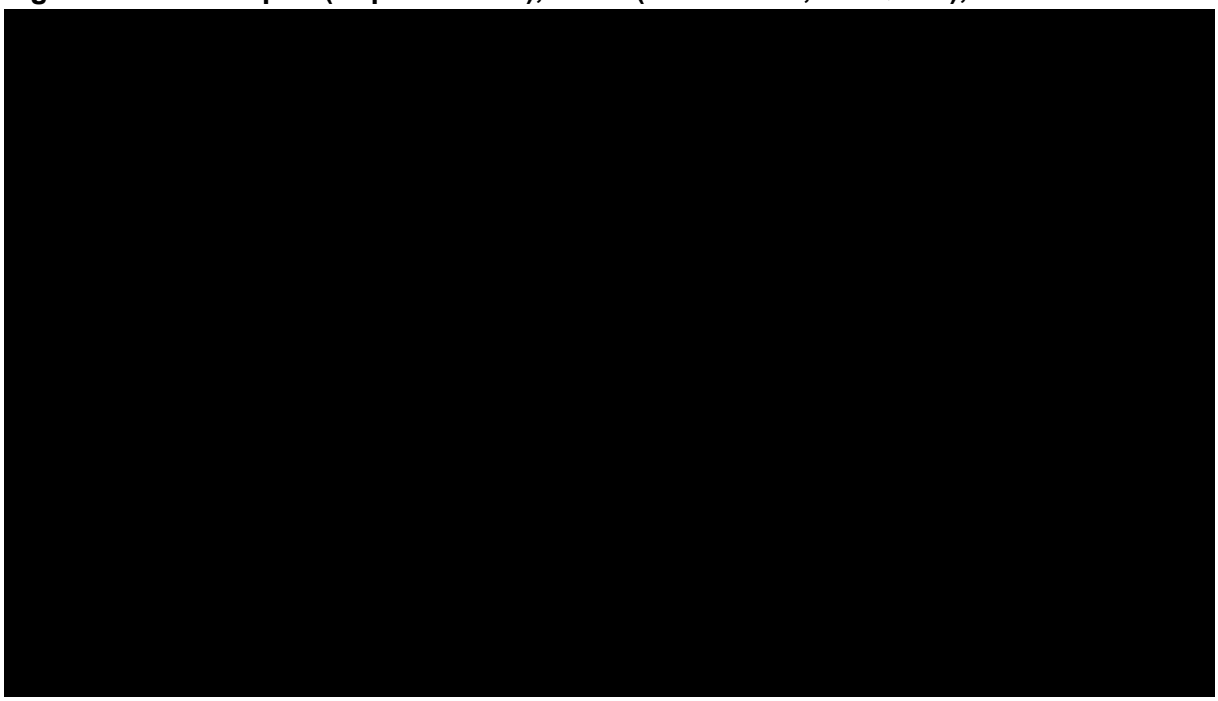
Table 30: OWSA results (Population #2), with PAS

Parameter	INMB (WTP of £20,000/QALY)	
	Lower bound	Upper bound
Utility value, Abdominal hysterectomy, post-surgery	[redacted]	[redacted]
Utility value, Abdominal myomectomy, post-surgery	[redacted]	[redacted]
TTD, Linzagolix 200mg + ABT: % risk of discontinuation per cycle	[redacted]	[redacted]
TTD, relugolix CT: % risk of discontinuation per cycle	[redacted]	[redacted]
Relugolix response % (24-week RHMB) - LIBERTY 1 & 2	[redacted]	[redacted]
Linzagolix 200mg + ABT, response % (24-week RHMB)	[redacted]	[redacted]
Utility value, Laparoscopic hysterectomy, post-surgery	[redacted]	[redacted]

Utility value, Transvaginal resection, post-surgery	[redacted]	[redacted]
Utility value, UAE, post-surgery	[redacted]	[redacted]
Utility value, Sonata, post-surgery	[redacted]	[redacted]

Abbreviations: ABT, add-back therapy; CT, combination therapy; INMB, incremental net-monetary benefit; mg, milligram; PAS, patient access scheme; QALY, quality-adjusted life year; RHMB, reduced heavy menstrual bleeding; TTD, time to treatment discontinuation; UAE, uterine artery embolization; WTP, willingness to pay

Figure 7: Tornado plot (Population #2), INMB (WTP of £20,000/QALY), with PAS



Abbreviations: ABT, add-back therapy; CT, combination therapy; INMB, incremental net-monetary benefit; mg, milligram; PAS, patient access scheme; QALY, quality-adjusted life year; RHMB, reduced heavy menstrual bleeding; TTD, time to treatment discontinuation; UAE, uterine artery embolization; WTP, willingness to pay

Scenario analysis

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

For Population #1, Table 31 presents cost-effectiveness results when using the fixed- and random-effects NMAs to inform clinical effectiveness in the relugolix CT arm of the model. As outlined in the 'Uncertainty' Section, additional automated scenarios are presented in Table 32.

When using the NMAs, costs and QALYs remain similar between linzagolix and relugolix CT (incremental costs [redacted], incremental QALYs [redacted]). In all other scenarios, linzagolix remains a cost-effective treatment option at a WTP of £20,000 QALY gained, in line with the base case analysis.

Table 31: Scenario, NMA (Population #1), with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INMB at £20,000	INMB at £30,000
Fixed-effects NMA									
Relugolix CT	[redacted]	9.971	[redacted]						
Linzagolix	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	Strictly dominated	[redacted]	[redacted]
Random-effects NMA									
Relugolix CT	[redacted]	9.971	[redacted]						
Linzagolix	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	Strictly dominated	[redacted]	[redacted]

Abbreviations: CT, combination therapy; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NMB, net-monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 32: Additional scenario analysis (Population #1), with PAS

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	INMB at £20,000	INMB at £30,000
Discount rates, 1.50%	[redacted]	[redacted]	£2,140	[redacted]	[redacted]
Discount rates, 6.00%	[redacted]	[redacted]	£3,424	[redacted]	[redacted]
Surgery distribution, TA832 CS	[redacted]	[redacted]	£18,017	[redacted]	[redacted]
Surgery distribution, TA832 EAG	[redacted]	[redacted]	£18,017	[redacted]	[redacted]
Surgery distribution, EAG	[redacted]	[redacted]	£18,017	[redacted]	[redacted]
Surgery distribution, KOL feedback treatment independent	[redacted]	[redacted]	£18,017	[redacted]	[redacted]
Concomitant medication cost - exclude Vitamin D and calcium	[redacted]	[redacted]	£2,726	[redacted]	[redacted]
Concomitant medication distribution - treatment specific	[redacted]	[redacted]	£2,035	[redacted]	[redacted]
Utility model, PRIMROSE, EQ-5D-5L to 3L	[redacted]	[redacted]	£8,318	[redacted]	[redacted]
Include Hux et al. utility increment for fibroid reduction – post-surgery	[redacted]	[redacted]	£613	[redacted]	[redacted]
Include Hux et al. utility increment for fibroid reduction - prior to surgery (controlled/uncontrolled)	[redacted]	[redacted]	£306	[redacted]	[redacted]

Abbreviations: CS, company submission; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; INMB, net-monetary benefit; KOL, key opinion leader; PAS, patient access scheme; QALYs, quality-adjusted life years; TA, technology appraisal

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

For Population #2, Table 33 presents cost-effectiveness results when using the fixed- and random-effects NMAs to inform clinical effectiveness in the relugolix CT arm of the model. As outlined in Section: Uncertainty, additional automated scenarios are presented in Table 34.

When using the NMAs, costs and QALYs remain similar between linzagolix and relugolix CT (with incremental costs of [redacted], and incremental QALYs [redacted] [fixed effects] to [redacted] [random effects]). In all other scenarios, linzagolix remains a cost-effective treatment option at a WTP of £20,000 QALY gained, in line with the base case.

Table 33: Scenario, NMA (Population #2), with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	NMB at £20,000	NMB at £30,000
Fixed-effects NMA									
Relugolix CT	[redacted]	9.971	[redacted]						
Linzagolix	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	Strictly dominated	[redacted]	[redacted]
Random-effects NMA									
Relugolix CT	[redacted]	9.971	[redacted]						
Linzagolix	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	Strictly dominated	[redacted]	[redacted]

Abbreviations: CT, combination therapy; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NMB, net-monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years

Table 34: Additional scenario analysis (Population #2), with PAS

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NMB at £20,000	NMB at £30,000
Discount rates, 1.50%	[redacted]	[redacted]	£5,337	[redacted]	[redacted]
Discount rates, 6.00%	[redacted]	[redacted]	£5,741	[redacted]	[redacted]
Surgery distribution, TA832 CS	[redacted]	[redacted]	£8,818	[redacted]	[redacted]
Surgery distribution, TA832 EAG	[redacted]	[redacted]	£8,818	[redacted]	[redacted]
Surgery distribution, EAG	[redacted]	[redacted]	£8,818	[redacted]	[redacted]
Surgery distribution, KOL feedback treatment independent	[redacted]	[redacted]	£8,818	[redacted]	[redacted]
Concomitant medication cost – exclude Vitamin D and calcium	[redacted]	[redacted]	£5,524	[redacted]	[redacted]
Concomitant medication distribution – treatment specific	[redacted]	[redacted]	£5,184	[redacted]	[redacted]
Utility model, PRIMROSE, EQ-5D-5L to 3L	[redacted]	[redacted]	£11,682	[redacted]	[redacted]
Include Hux et al. utility increment for fibroid reduction – post-surgery	[redacted]	[redacted]	£3,391	[redacted]	[redacted]
Include Hux et al. utility increment for fibroid reduction - prior to surgery (controlled/uncontrolled)	[redacted]	[redacted]	£2,260	[redacted]	[redacted]
28-day surgery probability - 1%	[redacted]	[redacted]	£4,616	[redacted]	[redacted]
28-day surgery probability - 2%	[redacted]	[redacted]	£5,113	[redacted]	[redacted]
28-day surgery probability (from controlled health state) - 1%	[redacted]	[redacted]	£3,251	[redacted]	[redacted]

Abbreviations: CS, company submission; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; KOL, key opinion leader; NMB, net-monetary benefit; PAS, patient access scheme; QALYs, quality-adjusted life years; TA, technology appraisal

Interpretation and conclusions

As outlined in the original company submission, there remains an unmet need for effective, well tolerated pharmacological treatments that meet the individualised treatment needs of people with UFs. The new analysis presented aims to directly address concerns and key areas of uncertainty raised by the committee during ACM1 by:

- Comparing linzagolix with relugolix CT for Population #1 and Population #2 in a cost-effectiveness framework, rather than a cost-comparison framework.
- Using inputs elicited from KOL interviews to inform the model, to reduce uncertainty around surgery type distributions relevant to NHS England practice and to indirectly consider endpoints beyond reduced menstrual blood loss (namely, fibroid shrinkage).

For transparency and consistency, the EAG-adapted Population #3 model that was used for decision making in ACM1 was further adapted to develop the Population #1 and #2 model reported in this new evidence submission, meaning the analysis conforms to the principles of the NICE reference case (e.g., discount rates), and aligns with committee preferences from ACM1 that are population agnostic (e.g., use of the UFS-QoL utility model).

For Population #1 (people receiving short-term treatment of 6 months or less), the results of the base case cost-effectiveness analyses suggest linzagolix is associated with an ICER of £2,726 versus relugolix CT. In the Population #2 analysis (people receiving longer-term treatment with hormone-based therapy), the ICER for linzagolix versus relugolix CT is £5,524. In both populations, the ICER falls well below the decision-making threshold used by NICE. Although this is the case, it is also acknowledged that incremental outcomes between linzagolix and relugolix CT are close to zero, suggesting that the treatment options may be considered at least comparable.

The findings of the cost-effectiveness analysis are therefore broadly consistent with the findings of the ITC and supporting clinical opinion that was presented in the original CS and throughout the committee meeting. Clinical expert opinion to the

company supported that both GnRH antagonists (linzagolix and relugolix CT) could be considered clinically comparable in NHS practice with regards to MBL, and ITC results did not generally indicate differences in treatment efficacy (with the majority of comparative results having shown no substantial differences between the treatment arms). However, notably in the ITC, those treated with linzagolix 200 mg (without ABT) achieved a larger decrease in fibroid volume than those treated with relugolix (and the credible interval did not contain zero). Findings from the expert elicitation indicated that this difference in the reduction in fibroid volume may change the type of surgery patients with UFs receive (with a reduced fibroid size indicative of a movement towards laparoscopic surgery or less invasive surgery types such as transvaginal resection). This sentiment has been reflected in the revised cost-effectiveness analysis which includes treatment specific surgery distributions elicited from 8 UK clinicians with scenario analysis exploring more conservative alternative (treatment independent) assumptions.

With the above in mind, Theramex considers the cost-effectiveness findings externally valid; with linzagolix providing similar costs and outcomes to relugolix CT, and the potential additional value of linzagolix in achieving fibroid shrinkage reflected in the cost-effectiveness results though treatment-specific surgery type distributions. Key drivers of cost-effectiveness are the linzagolix and relugolix CT response rates as observed in PRIMROSE and LIBERTY, the treatment-specific surgery type distributions elicited from clinical experts, and treatment discontinuation rates which are used to estimate treatment acquisition costs over the modelled time horizon.

The key strengths of the cost-effectiveness model for Population #1 and #2 are i) its consistency with the Population #3 model, ii) that the analysis considers committee preferences from ACM1, iii) committee concerns and areas of uncertainty have been acknowledged and directly addressed within the revised model, iv) the model uses a combination of clinical trial data and KOL input directly, and v) the model includes the flexibility to test parameter and methodological uncertainties through a broad range of sensitivity and scenario analysis.

The key limitations of the analysis primarily relate to the ITC (as highlighted by the EAG and committee). Whilst Theramex acknowledges that naively comparing response rates is associated with limitations, outcomes from any comparison

between the PRIMROSE and LIBERTY studies have some level of uncertainty due to the inherent differences between trials that cannot be accounted for (such as the methods used to collect sanitary products from patients with product collection being more burdensome on patients in the PRIMROSE trials, as well as differences in how missing data were handled). Theramex has endeavoured to explore uncertainty where possible by considering use of the naïve comparison in the model base case (given limitations in the NMA), and exploring NMA outcomes in scenario analysis, which, when tested, total costs and QALYs between linzagolix and relugolix CT remained comparable. Generally, the results of the cost-effectiveness analysis were robust to parameter and methodological uncertainties.

Overall, the findings of the revised economic analysis support the expectation that linzagolix provides a cost-effective treatment option in NHS England practice, for people with moderate to severe symptoms of UFs who i) receive short-term treatment of 6 months or less (likely ahead of surgery) and ii) receive longer-term treatment with hormone-based therapy.

References

1. Data on File: PRIMROSE 1 and 2 Pooled Analysis, 16-OBE2109-008_and_16-OBE2109-009_Combined. 21-09-08. 2021.

2. Linzagolix EPAR [Internet]. 2022 Jan [cited 2022 Dec 28]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/yselty

3. Linzagolix SPC [Internet]. EMA; 2023 [cited 2023 May 23]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/yselty

4. Gedeon Richter Limited. NICE Single technology appraisal. Relugolix with oestradiol and norethisterone acetate for treating uterine fibroids [ID3842; GID-TA10734]. Available at: https://www.nice.org.uk/guidance/ta832 (Last accessed: 3 April 2022). 2021.

5. NHS Inform. Menopause [Internet]. [cited 2022 Nov 25]. Available from: https://www.nhsinform.scot/healthy-living/womens-health/later-years-around-50-years-and-over/menopause-and-post-menopause-health/menopause

6. Office for National Statistics (ONS). National life tables: England [Internet]. [cited 2022 Nov 25]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables

7. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010 Aug;13(5):509–18.

8. Data on File: Uterine Fibroids Market Research Survey for Yselty (Linzagolix) Full Report. 2022.

9. Zowall H, Cairns JA, Brewer C, Lamping DL, Gedroyc WMW, Regan L. Cost-effectiveness of magnetic resonance-guided focused ultrasound surgery for treatment of uterine fibroids. BJOG. 2008 Apr;115(5):653–62.

10. Gorny KR, Woodrum DA, Brown DL, Henrichsen TL, Weaver AL, Amrami KK, et al. Magnetic resonance-guided focused ultrasound of uterine leiomyomas: review of a 12-month outcome of 130 clinical patients. J Vasc Interv Radiol. 2011 Jun;22(6):857–64.

11. Settnes A, Topsoee MF, Moeller C, Dueholm M, Kopp TI, Norrbom C, et al. Reduced Complications Following Implementation of Laparoscopic Hysterectomy: A Danish Population-based Cohort Study of Minimally Invasive Benign Gynecologic Surgery between 2004 and 2018. J Minim Invasive Gynecol. 2020;27(6):1344-1353.e3.

12. Manyonda I, Belli AM, Lumsden MA, Moss J, McKinnon W, Middleton LJ, et al. Uterine-Artery Embolization or Myomectomy for Uterine Fibroids. N Engl J Med. 2020 Jul 30;383(5):440–51.

13. Cooper K, Breeman S, Scott NW, Scotland G, Hernández R, Clark TJ, et al. Laparoscopic supracervical hysterectomy compared with second-generation endometrial ablation for heavy menstrual bleeding: the HEALTH RCT. Health Technol Assess. 2019 Sep;23(53):1–108.

14. Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. Med Decis Making. 2006;26(4):410–20.

15. Hux M, Ng C, Ortega GL, Ferrazzi S, Goeree R. Utility values for pre-menopausal women suffering from symptomatic uterine fibroids. Expert Rev Pharmacoecon Outcomes Res. 2015 Feb;15(1):181–9.

16. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008 Oct 21;6:84.

17. BNF content published by NICE [Internet]. 2023 [cited 2023 Jul 25]. Available from: https://bnf.nice.org.uk/

18. Drugs and pharmaceutical electronic market information tool (eMIT) [Internet]. GOV.UK. 2023 [cited 2023 Jul 25]. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit

19. Jones KC, Weatherly H, Birch S, Castelli A, Chalkley M, Dargan A, et al. Unit Costs of Health and Social Care 2022 Manual [Internet]. Personal Social Services Research Unit; 2022 [cited 2023 Jul 25]. Available from: https://kar.kent.ac.uk/id/eprint/100519

20. NHS England. National Cost Collection for the NHS [Internet]. [cited 2022 Nov 25]. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Company response to draft guidance

Appendix – Expert Elicitation

April 2024

File name	Version	Contains confidential information	Date
ID6190_Linzagolix_UF_Appendices_Expert-Elicitation	1.0	Yes	22-Apr-24

Contents

List of Tables:

Abbreviations

ABT – Add-back Therapy
CT – Combination Therapy
GnRH – Gonadotropin-releasing hormone
HMB – Heavy Menstrual Bleeding
ITC – Indirect Treatment Comparison
NICE – National Institute for Care and Excellence
NMA – Network Meta-Analysis
TCRE – Transvaginal Resection
UAE – Uterine artery Embolisation
UF – Uterine Fibroid

1 Introduction

Women with uterine fibroids (UFs) often require surgical intervention to treat the symptoms of their fibroids and maintain their fertility.[1] A wide variety of surgical procedures are available in the UK and the choice of surgical treatment is dependent on many factors including the size and location of the fibroid as well as patient choice and surgeon specialty.[2] The presurgical reduction of a UF using pharmaceutical treatment is often required to increase the chances of a successful surgery and improve outcomes.[3] In current clinical practice, gonadotrophin-releasing hormone (GnRH) agonists are typically given for the presurgical reduction of fibroids.[3] However, GnRH agonists are administered by subcutaneous injections and usually require healthcare professionals either in a secondary outpatient setting or community setting and use is limited to less than 6 months due to safety concerns associated with full estradiol suppression.[4–6] More recently, the oral GnRH antagonist relugolix estradiol-norethisterone acetate combination therapy (CT) has been approved for use in the UK.[7] Relugolix CT can be used for longer than 6 months however, needs to be administered in a fixed combination with hormonal add-back therapy (ABT) which reduces the ability to shrink the size of the fibroid.[7,8] As such, there remains an unmet need for oral therapies that can be used for the pre-surgical reduction of UFs and can be tolerated in the long term.

Linzagolix is a novel oral GnRH antagonist available with or without ABT (linzagolix 100mg or 200mg +/- ABT) and is licensed for the treatment of moderate to severe symptoms of UFs in adult women of reproductive age.[9] Treatment with linzagolix 200mg without ABT resulted in full estradiol suppression and a 45% ($p<0.001$) and 49% ($p<0.001$) reduction in fibroid volume from baseline at 24 weeks in the PRIMROSE 1 and PRIMROSE 2 trials respectively.[10] Linzagolix 200mg with ABT resulted in partial estradiol suppression and a 25% ($p=0.012$) and 22% (0.028) reduction in fibroid volume at 24 weeks respectively between PRIMROSE 1 and 2.[11,12] These doses could provide a good option for the presurgical reduction of UFs as well as long-term treatment. Indeed, linzagolix is currently undergoing a reimbursement application to the National Institute of Care and Excellence (NICE) [ID6190][13] and three patient sub-populations that could benefit from treatment with linzagolix have been identified:

- Population 1 - Short-term treatment of 6 months or less, for example before surgery
- Population 2 - Long-term treatment with ABT
- Population 3 - Long-term treatment without ABT

Following feedback from the NICE technology appraisal committee, it was advised that a cost-utility analysis would be beneficial to demonstrate whether linzagolix is cost-effective in populations 1 and 2 compared to relugolix CT, which has already received reimbursement in the UK for the treatment of moderate to severe symptoms of UFs (TA832).[7] However, there is a paucity of data on current clinical practice of UFs in the UK, particularly in the surgical treatment of UFs relevant to the cost-utility analyses for population 1.

An indirect treatment comparison (ITC) has already been conducted to compare the reduction in fibroid size of linzagolix and relugolix CT using data gathered from four pivotal trials; PRIMROSE 1 and 2 (linzagolix) and LIBERTY 1 and 2 (relugolix

CT).[10,14,15]. However, additional data on the current clinical practice for surgical treatment of UFs as well as the impact of a reduction in fibroid size would help to inform the analyses requested by NICE.

2 Aim and Objectives

The aim of this study was to understand the use of surgical procedures to treat UFs to inform a cost-utility analysis for linzagolix in comparison with relugolix CT. The cost-utility analysis will determine whether linzagolix is cost-effective in two of the eligible patient populations identified in the NICE submission:

- Population 1: Short-term treatment of 6 months or less, for example before surgery
- Population 2: Long-term treatment with ABT

2.1 Objective

The objectives of the study were:

- To estimate the distribution of surgery types performed in current clinical practice.
- To understand the impact of UF size on surgery type distribution for UF patients.
- To estimate the potential impact of linzagolix vs relugolix CT on surgery type distribution and surgical outcomes for UF patients, after considering the impact of each treatment on fibroid volume

3 Research Methods

3.1 Study Design

The study was a qualitative expert elicitation with a cross-sectional timeframe. Primary data was collected from clinicians with experience treating UFs in the UK. This approach was considered the most appropriate for this type of research as it is commonly used for exploratory studies and allows both quantitative and qualitative data to be collected.[16] Semi-structured interviews were conducted by consultant gynaecologists and a semi-structured interview guide was developed to aid in addressing the aim of the study (see Section 3.1.2). The interviews were conducted in line with market research guidelines and took place in February 2024.[17]

3.1.1 Clinician sample

Participants were practicing clinicians treating women with diagnosed UFs in either public or private clinical practice. The inclusion criteria for this study were as follows:

- Participant is a consultant gynaecologist in a UK clinic or hospital
- Participant has at least 5 years experience managing women with UFs

There were no exclusion criteria for the study. There was no pre-determined number of interviews planned however, efforts were made to ensure that clinicians from a range of geographical regions were represented in the sample.

3.1.2 Interview Process

Before conducting the interview, the clinicians were provided with pre-read materials which consisted of two published literature sources; Al Hendy, et al. (2021) and Donnez, et al (2022).[10,18] At the start of the interview, interviewees were provided with the aim of the study and asked to consent to the interview based on this aim. The interviews were conducted virtually and were approximately 60 minutes long.

An interview guide was prepared to ensure that pre-determined questions that addressed the aim of the study were discussed. A moderator deck was also developed including the aim of the study, the questions from the interview guide and the results of the ITC between linzagolix and relugolix CT. This deck was presented to clinicians during the interview.

The interview guide included two main sections: current clinical practice of surgery for the treatment of UFs in the UK and the impact of a reduction in UF size on the surgical treatment. The interview guide included questions on the distribution of surgical procedures and techniques in current clinical practice and the impact of a reduction of fibroid size on this distribution, as well as clinical outcomes, requirements for follow on surgeries and waiting times. The results of the ITC were presented to clinicians before asking questions on the impact of a reduction in fibroid size in order to ground responses in data. Linzagolix is not commercially available and relugolix CT is not routinely used in clinical practice and as such, clinicians reported on the expected impact on surgery after treatment with these medications.

The questions were primarily qualitative in nature allowing clinicians to add rationale and justification to capture the context of their insights.

3.2 Data Management and analyses

Following the completion of the interviews, quantitative data was reported as descriptive statistics. Data from each interview was aggregated into one database for analyses. For the quantitative data, responses were quality checked in situ; with any anomalous or missing results confirmed in real-time during the interview. For the surgery distributions, clinicians were asked to provide the proportion of patients who received a certain surgery type, the average of these proportions were reported and adjusted to ensure the final distribution equalled 100%.

To ensure results could be aggregated, where clinicians provided a range of responses, the midpoint of the range was used. Where clinicians reported <X, X was used in the calculation. Where clinicians provided the relative change instead of the absolute percentage, numbers were adjusted to ensure the final distribution equalled 100%.

Qualitative data was analysed using informal thematic content analyses. All responses were reviewed to identify any themes repeated in the data and were captured in the analyses.

4 Results

4.1 Clinician characteristics

Clinicians were either a consultant gynaecologist or a gynaecologist and obstetrician. Clinicians represented a large geographic spread across the UK with 6/7 NHS England regions represented including London (2), Midlands (1), Northeast and Yorkshire (1), Northwest (2), Southeast (1) and the Southwest (1). Two clinicians from Scotland were also represented.

4.2 Surgery for the treatment of UFs

Clinicians reported on the distribution of surgery currently performed in their clinical practice including the proportion of patients by surgery type (Table 1), the proportion of patients requiring a second surgery (

Table 2) and the proportion of patients by surgery type for this second surgery (Table 3). Two clinicians were excluded from these analyses as they were unable to provide estimates for these specific inputs. As such, the following results are reported for n=8 clinicians. Qualitative insights were included for all clinicians.

4.2.1 Distribution of surgery type for first surgery

Table 1 shows there was a large variation in clinical practice for choice of first surgery. Hysterectomies were the most common surgery with [redacted] of patients receiving either an open [redacted] or laparoscopic [redacted] procedure. Myomectomies (25.4%) and transvaginal resections [redacted] were also common procedures. MRI-guided ultrasound surgery and radiofrequency ablation were not used by clinicians and other minimally invasive procedures such as uterine artery embolisation [redacted], and the Sonata procedure[redacted] were also less frequently used.

Table 1: Distribution of surgery type for first surgery in current clinical practice

	Distribution of surgery type used for the treatment of UFs in current clinical practice (n=8)
Surgery Type	**Mean**
Uterine artery embolisation	[redacted]
Endometrial ablation	[redacted]
MRI guided focused ultrasound surgery	[redacted]
Myomectomy (open/abdominal)	[redacted]
Myomectomy (laparoscopic)	[redacted]
Hysterectomy (open/abdominal)	[redacted]
Hysterectomy (laparoscopic)	[redacted]
Transvaginal resection	[redacted]
Radiofrequency fibroid ablation	[redacted]
Sonata	[redacted]

4.2.1.1 Qualitative Insights

Clinicians reported that the choice of surgery to treat UFs was patient-specific influenced by the individual needs of the woman e.g. wanting to preserve fertility. However, several other factors also impact the choice of surgery including surgeon specialty and availability of surgical equipment. These variations are reflected in the results with a range of distributions reflecting clinicians' individual clinical practice.

The largest factor impacting choice of surgery was the individual needs of the woman. All clinicians commented that the size of the fibroid was the determining factor; laparoscopic procedures (myomectomies or hysterectomies) or procedures requiring removing the fibroid through the vagina (such as resections) cannot be performed if the fibroid is too big. Another determining factor was the need to preserve fertility. Although there is still a risk of infertility post-surgery, myomectomies, transvaginal resections, and other less invasive procedures are performed in women who wish to preserve their fertility/uterus whilst hysterectomies, although could be considered curative, are performed only for women where fertility is no longer important. For example, one clinician reported that 90% of women received a hysterectomy as their first surgery in their practice but clarified that he primarily saw patients who had completed their families. Multiple other patient-specific factors were mentioned including menopause or risk of sarcomas in women aged 45 and over (laparoscopic procedures not recommended due to morcellation of the fibroid) as well as a patient history of childbirth that included vaginal delivery (laparoscopic procedures can be performed on larger fibroids as vaginal tissue is more elastic to enable delivery of the fibroid).

Some clinicians reported more logistical factors in determining surgery choice. One clinician reported that uterine artery embolisation (UAE) is restricted in some hospital trusts due to funding or lack of equipment, the Sonata procedure was only reported by one centre and MRI focused ultrasound surgery was rarely used as it wasn't available. Similarly, one clinician noted that their practice has access to surgical robots that assist in laparoscopic surgeries (this allows for slightly larger fibroids to be removed laparoscopically), however, this technology is not available in all practices. In addition, surgeon choice and specialty were factors. For example, surgeons that specialise in minimally invasive surgical techniques have the expected tendency to perform more surgeries laparoscopically whilst one clinician stated that they specialised in transvaginal resection and so women desiring this type of procedure would specifically approach this clinician's practice.

4.2.2 Distribution of surgery type for second or follow on surgeries

Table 2 shows the proportion of patients requiring a second surgery of any kind by the surgery type they received for their first surgery. The number of clinicians reporting results for this question was dependent on their clinical practice for first surgery and varies as a result. Approximately 1/3 of patients required a follow-up surgery after a uterine artery embolisation [redacted] endometrial ablation [redacted] or a MRI guided ultrasound [redacted]. Around 20% of patients required a second surgery after either an open [redacted] or laparoscopic [redacted] myomectomy as well as a transvaginal

resection [redacted]. Other results should be interpreted with caution due to the low sample size reported for these surgeries.

Table 2: Proportion of patients requiring a second surgery of any kind by surgery type in current clinical practice

	Proportion of patients requiring a second surgery by surgery type (n=8)	
Surgery type	**N**	**Mean**
Uterine artery embolisation	6	[redacted]
Endometrial ablation	5	[redacted]
MRI guided focused ultrasound surgery	2	[redacted]
Myomectomy (open/abdominal)	8	[redacted]
Myomectomy (laparoscopic)	7	[redacted]
Transvaginal resection	8	[redacted]
Radiofrequency fibroid ablation	1	[redacted]
Sonata	1	[redacted]

Table 3 shows the distribution of these second or follow-on surgery, by surgery type in clinical practice. The majority of second surgeries were hysterectomies [redacted] with the majority of women receiving a laparoscopic [redacted] procedure, although a significant number received an open/abdominal procedure [redacted]. All other procedures represented <10% of the total proportion of women receiving a second or follow-up surgery with the most common being open myomectomies [redacted] and transvaginal resections [redacted]

Table 3: Distribution of surgery type for second surgery in current clinical practice

	Distribution of surgery type used for the treatment of UFs in current clinical practice (n=8)
Surgery type	**Mean**
Uterine artery embolisation	[redacted]
Endometrial ablation	[redacted]
MRI guided focused ultrasound surgery	[redacted]
Myomectomy (open/abdominal)	[redacted]
Myomectomy (laparoscopic)	[redacted]
Hysterectomy (open/abdominal)	[redacted]
Hysterectomy (laparoscopic)	[redacted]
Transvaginal resection	[redacted]
Radiofrequency fibroid ablation	[redacted]
Sonata	[redacted]

4.2.2.1 Qualitative insights

The need for a second or follow-up surgery is driven by the individual patient's circumstance. Second surgeries are evidently dependent on the fibroid returning after the first surgery which is dependent on the individual patient. Patients who have undergone a first surgery at a younger age are more likely to undergo a second surgery in the following years.[19] Additionally, in some women undergoing transvaginal resection, multiple staged surgeries may be required if the fibroid is particularly large, smaller fibroids can be excised in a single surgery.

However, clinicians reported that the choice of first surgery would also impact the need for a second or follow-up surgery. For example, procedures such as UAE ([redacted] requiring second surgery) and endometrial ablation ([redacted] requiring second surgery) have a higher proportion of patients requiring a second surgery, however, would still be a good choice for patients with smaller fibroids as they are less invasive. Follow-up surgeries required after myomectomies or transvaginal resection could be dependent on whether the surgeon was able to excise the entire fibroid during the first surgery. For example, one clinician stated that in cases where the fibroid extends into the uterine cavity, it is not possible to excise the entire fibroid with transvaginal resection.

However, most patients receive a hysterectomy [redacted] for their second surgery. Clinicians commented that this is due to women being older and with complete families by the time they require a second surgery. Some women will tolerate the symptoms of their UFs until their family is complete before they return for a second surgery. One clinician also reported that they would advise women against less invasive procedures as there is a higher chance of them requiring a third surgery before menopause.

4.3 Impact of reduction of UF size

Clinicians were presented with the results of the ITC which suggests that at 24 weeks linzagolix 200mg without ABT had an additional 28% reduction in primary fibroid volume vs relugolix CT, and linzagolix 200mg with ABT had an additional [redacted] reduction in primary fibroid volume vs relugolix CT. As discussed, due to the availability of these treatments in clinical practice (see Section 3.1.2), clinicians reported on the expected impact on surgery after 24 weeks of treatment.

Clinicians reported on the expected impact of a reduction in UF size on surgical distributions (
Table 4) and additional qualitative insights into the expected impact on surgery type, surgical approach and surgical outcomes were also reported. As before, two clinicians were excluded from the distribution analyses (
Table 4) however, qualitative insights were included for all clinicians.

4.3.1 Distribution of surgery type after reduction of UFs

Treatment with linzagolix 200mg without ABT was expected to have the largest impact on surgery distributions compared to treatment with relugolix CT. There was a decrease in open hysterectomies [redacted] and open myomectomies [redacted],

with these being replaced by laparoscopic procedures or less invasive procedures such as transvaginal resection [redacted]. No clear pattern was seen for endometrial ablation with the proportion staying relatively consistent with different treatments. Treatment with linzagolix 200mg with ABT was expected to have a similar although lesser impact than linzagolix 200mg without ABT when compared to relugolix CT treatment. Similarly, there was an expected shift from open [redacted] to laparoscopic [redacted] hysterectomies and open [redacted] to laparoscopic [redacted] myomectomies. There was also an expected increase in less invasive procedures such as transvaginal resection, radiofrequency ablation and uterine artery embolisation as before.

Table 4: Impact of pharmaceutical treatment on distribution of surgery type

	Distribution of surgery type after treatment with: (n=8)		
Surgery type	**1. Relugolix CT**	**2. Linzagolix 200mg without ABT**	**3. Linzagolix 200mg with ABT**
	10-12% reduction in primary fibroid volume vs placebo, 24 weeks[18]	*+28% extra reduction in primary fibroid volume vs relugolix CT*[2]	*+12% extra reduction in primary fibroid volume vs relugolix CT*[2]
Uterine artery embolisation	[redacted]	[redacted]	[redacted]
Endometrial ablation	[redacted]	[redacted]	[redacted]
MRI guided focused ultrasound surgery	[redacted]	[redacted]	[redacted]
Myomectomy (open/abdominal)	[redacted]	[redacted]	[redacted]
Myomectomy (laparoscopic)	[redacted]	[redacted]	[redacted]
Hysterectomy (open/abdominal)	[redacted]	[redacted]	[redacted]
Hysterectomy (laparoscopic)	[redacted]	[redacted]	[redacted]
Transvaginal resection	[redacted]	[redacted]	[redacted]
Radiofrequency fibroid ablation	[redacted]	[redacted]	[redacted]
Sonata	[redacted]	[redacted]	[redacted]

4.3.1.1 Qualitative Insights

Clinicians reported distributions based on the ITC data presented during the interview but clarified that there were many factors outside of fibroid size that influenced the choice of surgery (see Section 4.2.1.1). However, since fibroid size is a determining factor; the reduction of fibroid size after treatment with linzagolix vs relugolix CT was universally expected to impact the choice of surgery. The main impact discussed was the ability to move from open/abdominal to laparoscopic procedures. The shift to less invasive procedures has an added benefit to the healthcare system as patients can be treated in outpatient clinics over inpatient stays.

Clinicians also highlighted the benefits of an oral treatment over existing subcutaneous administration of current GnRH agonists for shrinking fibroid size. Oral

medications are more convenient for patients as they can be taken at home, are associated with less side effects and pose less of a burden on health systems as they do not need to be given by a health care practitioner.

Use of relugolix CT was limited in clinical practice with [redacted] clinicians mentioned having had some experience with the treatment. It should also be noted that two clinicians clarified that relugolix CT was typically used to control symptoms of UFs. Indeed, the majority of clinicians stated that the [redacted] reduction after treatment with relugolix CT would not impact the choice of surgery. All (10/10) clinicians' commented that the additional 28% reduction in fibroid size seen with linzagolix 200mg without ABT vs relugolix CT (as determined in ITC) would impact the choice of surgery whilst 4/10 clinicians thought that the additional 12% reduction in fibroid size achieved with Linzagolix 200mg with ABT vs relugolix CT (as determined in the ITC) would have an impact.[20]

Most clinicians also added context that the impact of a reduction would depend on the size and location of the fibroid in the first place. However, several clinicians stated that although linzagolix 200mg with ABT may have less impact on the choice of surgery type, it would have an important impact on the proportion of patients' requiring surgery. Clinicians suggested that a reduction in fibroid volume with longer-term treatment (beyond 24 weeks) with linzagolix 200mg + ABT could decrease the need for surgery by controlling symptoms enough to delay surgery until menopause and therefore negate the need for surgery altogether. It could also be used to prevent further fibroid growth in women who require surgery but face long waiting times before their procedure.

4.3.2 Impact of reduction of UF size on surgical outcomes

Clinicians indicated that the benefit of symptom control is important in parallel to improvement of surgical outcomes. Linzagolix 200mg with and without ABT significantly reduced menstrual blood loss at 24 weeks in PRIMROSE 1 and 2. Linzagolix 200mg without ABT reduced HMB by 71.4% and 77.7% and linzagolix 200mg with ABT reduced HMB by 75.5% and 93.9% across PRIMROSE 1 and PRIMROSE 2 respectively ($p<0.001$ for all values). Linzagolix 200mg with and without ABT also showed increased haemaglobin levels in anaemic subjects.[10]

Another key benefit is that reduction in fibroid volume means that smaller incisions can be made to access the fibroid. In the case of abdominal surgeries, midline incisions can be replaced by a Pfannenstiel incision (bikini line incision) and when open surgeries have been replaced by laparoscopic, only small incisions are required to access the ports. The improved aesthetic and reduction in scar tissue was stated to improve a woman's quality of life and anxiety around receiving surgery. Some clinicians commented that in cases where the fibroid size impacts the chance of success (e.g transvaginal resection and myomectomies), the additional 28% reduction would also lead to an increased rate of successful surgeries, reducing the proportion of women who will go on to require additional surgeries.

The impact of the move from open/abdominal to laparoscopic or less invasive procedures has a parallel effect on surgical outcomes for women. Laparoscopic and less invasive procedures are associated with less inpatient stays, quicker recovery

times (meaning less time off work), fewer surgical complications (less intraoperative bleeding and lower risk of blood transfusion), and less anaesthetic load.[21,22,23]

5 Discussion

To our knowledge, this is one of the first insights into the expected impact of linzagolix and relugolix CT on the surgical treatment of UFs in the UK. Given the timeframe of the study, 10 clinicians were recruited (and two were excluded from the distributions) and as such, results from the study should be considered descriptive and interpreted with caution. However, the results on distribution of surgeries are considered robust; consistent data management and quality checking was completed (see Section 3.2) and 8 clinicians provided responses that were suitable for modelling purposes. As such, this data is considered appropriate to inform inputs on the current distribution of surgeries as well as the impact of linzagolix or relugolix CT for the cost utility analyses.

Distribution of surgical treatment in current clinical practice did show large variation however, qualitative insights confirmed that the rationale for this variation was consistent across practices. The choice of surgery is patient specific and depends on the individual needs of the women with fibroid size and desire to preserve fertility being the determining factors. Other factors such as surgeon specialty and availability of surgical equipment does impact the choice of surgery however, since the determining factors are consistent across practices, the average proportion of patients by surgery type can be considered relatively reflective of UK clinical practice.

Opnions on the expected impact on surgery after treatment with linzagolix or relugolix CT were gathered across 6/7 of regions in England as well as Scotland in an attempt to gain insights that may be generally considered representative of the UK. All clinicians were presented with the results of the ITC and provided with published literature (see Section 3.1.2). In addition, since linzagolix is not commercially available and clinician experience of relugolix CT was limited; it can be assumed that all clinicians made their judgement on the expected impact of these treatments from a similar set of assumptions. This is reflected in the results as there was a general consensus that the additional 28% reduction after treatment with linzagolix 200mg without ABT vs relugolix CT would lead to a shift from open/abdominal to laparoscopic or less invasive procedures. Although not all clinicians believed that the choice of surgery would be impacted by the additional 12% reduction after treatment with linzagolix 200mg with ABT, they highlighted that the ability to give longer term treatment would impact the overall rates of surgery, particularly in women who are approaching menopause. It is also worth noting that this study recruited clinicians with at least 5 years' experience who were more likely to perform complex surgeries; a reduction in fibroid size may have a larger impact on less experienced surgeons who are more likely to perform open surgeries.

In addition, there was a general consensus that a reduction in fibroid size would lead to an improvement in surgical outcomes. This is in line with the consensus that women would receive laparoscopic or less invasive procedures that are associated with less complications and better outcomes. Clinicians also highlighted the

importance of being able to conduct Pfannenstiel incision (bikini line incision) over a midline incision for women who do require open or abdominal surgeries.

5.1 Limitations

There are limitations related to the study design. Cross-sectional studies are difficult to interpret as they do not estimate a cause-and-effect relationship. The interview format used to collect data also has limitations, as expert elicitation is susceptible to bias. In addition, the sample size is small, and the results are not generalisable. However, given that the study aim was to provide expert opinion on specific inputs to inform a cost utility analyses, these limitations were not considered to have impacted addressing the objectives of this study. In addition, it was highlighted by clinicians that quantifying the distribution of surgery types is complex and the distributions provided would only be an estimate of the true distribution as the choice of surgery is specific to the individual needs of the patient. However, similarly, since the aim of this study is to understand the average distribution to inform economic modelling, this was not considered a large limitation for the study.

6 Conclusion

The study demonstrated a large variation in clinical practice for the surgical treatment of UFs in the UK with surgical choice ultimately directed by the individual needs of the woman. However, factors that ultimately direct surgery choice such as fibroid size and desire to preserve fertility were consistent across the UK.

There was general consensus that a reduction in fibroid size after treatment with linzagolix 200mg without ABT will allow for less invasive surgeries, better control of symptoms, less surgical scars, faster recovery times and a reduction in repeat surgeries. Reduction in fibroid size after treatment with linzagolix with ABT will have less of an impact on surgical choice but will still impact the treatment landscape by allowing patients to avoid surgery by controlling symptoms until menopause.

Data from this study can be considered robust and appropriate to inform the cost utility analyses as requested by NICE, and supports the value messages for linzagolix highlighted in the application.

7 References

1. Dolmans MM, Cacciottola L, Donnez J. Conservative Management of Uterine Fibroid-Related Heavy Menstrual Bleeding and Infertility: Time for a Deeper Mechanistic Understanding and an Individualized Approach. *J Clin Med*. 2021;10(19):4389. doi:10.3390/jcm10194389

2. Cianci S, Gulino FA, Palmara V, et al. Exploring Surgical Strategies for Uterine Fibroid Treatment: A Comprehensive Review of Literature on Open and Minimally Invasive Approaches. *Medicina (Kaunas)*. 2023;60(1):64. doi:10.3390/medicina60010064

3. Barra F, Evangelisti G, Ferrero S. Preoperative Hormonal Treatment Before Laparoscopic Approach for Uterine Fibroids: Do We Need It? *J Invest Surg*. 2021;34(4):451-453. doi:10.1080/08941939.2019.1655118

4. Hodgson R, Bhave Chittawar P, Farquhar C. GnRH agonists for uterine fibroids. *Cochrane Database Syst Rev*. 2017;2017(10):CD012846. doi:10.1002/14651858.CD012846

5. EMA. SPC Lucrin. Accessed December 22, 2023. https://www.geneesmiddeleninformatiebank.nl/smpc/h30198_smpc.pdf

6. SmPC Esmya.

7. Gedeon Richter Limited. *NICE Single Technology Appraisal. Relugolix with Oestradiol and Norethisterone Acetate for Treating Uterine Fibroids [ID3842; GID-TA10734]. Available at: Https://Www.Nice.Org.Uk/Guidance/Ta832 (Last Accessed: 3 April 2022)*.; 2021.

8. Moroni RM, Martins WP, Ferriani RA, et al. Add-back therapy with GnRH analogues for uterine fibroids. *Cochrane Database Syst Rev*. 2015;2015(3):CD010854. doi:10.1002/14651858.CD010854.pub2

9. Linzagolix SPC. Published online May 2, 2023. Accessed May 23, 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/yselty

10. Donnez J, Taylor HS, Stewart EA, et al. Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. *The Lancet*. 2022;400(10356):896-907. doi:10.1016/S0140-6736(22)01475-1

11. *Data on File: PRIMROSE 1 CSR Week 24, v2.0*.; 2021.

12. *Data on File: PRIMROSE 2 CSR Week 52, v2.0*.; 2021.

13. NICE. Project documents | Linzagolix for treating moderate to severe symptoms of uterine fibroids [ID6190] | Guidance | NICE. Published April 24, 2024. Accessed September 20, 2023. https://www.nice.org.uk/guidance/indevelopment/gid-ta11131/documents

14. Myovant Sciences GmbH. *LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered With and Without Low-Dose Estradiol and Norethindrone Acetate in Women With Heavy Menstrual Bleeding Associated With Uterine Fibroids*.; 2022. Accessed February 13, 2023. https://clinicaltrials.gov/ct2/show/study/NCT03049735

15. Myovant Sciences GmbH. *LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered With and Without Low-Dose Estradiol and Norethindrone Acetate in Women With Heavy Menstrual Bleeding Associated With Uterine Fibroids*.; 2022. Accessed February 13, 2023. https://clinicaltrials.gov/ct2/show/NCT03103087

16. Bryman A, Bell E. *Business Research Methods 3e*. OUP Oxford; 2011.

17. Guidelines & Legislation | BHBIA. Accessed March 28, 2024. https://www.bhbia.org.uk/guidelines-and-legislation

18. Al-Hendy A, Lukes AS, Poindexter AN, et al. Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy. *N Engl J Med*. 2021;384(7):630-642. doi:10.1056/NEJMoa2008283

19. Kramer KJ, Ottum S, Gonullu D, et al. Reoperation rates for recurrence of fibroids after abdominal myomectomy in women with large uterus. *PLoS One*. 2021;16(12):e0261085. doi:10.1371/journal.pone.0261085

20. Theramex. *Data on File: ITC Report for Linzagolix*.

21. Uccella S, Morosi C, Marconi N, et al. Laparoscopic Versus Open Hysterectomy for Benign Disease in Uteri Weighing >1 kg: A Retrospective Analysis on 258 Patients. *Journal of Minimally Invasive Gynecology*. 2018;25(1):62-69. doi:10.1016/j.jmig.2017.07.005

22. Kotani Y, Murakami K, Fujishima R, et al. Quality of life after laparoscopic hysterectomy versus abdominal hysterectomy. *BMC Women's Health*. 2021;21(1):219. doi:10.1186/s12905-021-01364-8

23. Kim T, Purdy MP, Kendall-Rauchfuss L, et al. Myomectomy associated blood transfusion risk and morbidity after surgery. *Fertility and Sterility*. 2020;114(1):175-184. doi:10.1016/j.fertnstert.2020.02.110

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

New Evidence Submission

Appendix – Indirect Treatment Comparison update

April 2024

File name	Version	CIC	Date
ID_6190_Linzagolix_UF_Appendices_ITC-Update	1.0	Yes	22-Apr-24

Table of Contents

Abbreviations

ABT	Add-back therapy
BMI	Body mass index
BSC	Best supportive care
CI	Confidence interval
CrI	Credible interval
DIC	Deviance information criteria
ITC	Indirect treatment comparison
MAIC	Matching-adjusted indirect treatment comparison
NMA	Network meta-analyses
OR	Odds ratio
Relugolix CT	Relugolix combination therapy (Ryeqo®; relugolix with estradiol and norethisterone acetate
UFS-QoL	Uterine Fibroid Symptom-quality of life

1 Summary of ITC update

An error occurred while extracting data from the LIBERTY 1 and 2 trials and has impacted the results presented for the NMA and MAIC in the original company submission, specifically section B.2.9.6 of Document B and the appendices. The updated results and their implications are fully detailed in this section.

The ITC was conducted to compare linzagolix and relugolix CT. Data was extracted from the PRIMROSE 1 and 2 trials (linzagolix) and the LIBERTY 1 and 2 trials (relugolix CT). This data was used to conduct a NMA and MAIC. An error occurred while extracting data from the LIBERTY 1 and 2 trials and has impacted the results presented for the NMA and MAIC in section B.2.9.6 of Document B, and the appendices in the original company submission.

Although the updated NMA results now present lower ORs in terms of response for linzagolix vs relugolix CT, the results for the most clinically comparable dose (i.e., full suppression of serum estradiol), linzagolix 200 mg + ABT, demonstrate no clear difference in response between the two treatments. The remaining treatment comparisons and other outcomes considered in the NMA are unaffected by this update and, on balance, suggest there is limited evidence of a difference in treatment efficacy. Whilst patients on linzagolix 200 mg achieved a lower rate of amenorrhea and a lower reduction in menstrual blood loss, there is strong evidence that linzagolix 200 mg achieved a larger reduction in log-transformed fibroid volume.

The economic analysis presented in the original company submission for population #3 (long-term treatment without hormone-based therapy comparing linzagolix to BSC) is not affected by this update, as it only relates to the comparison with relugolix CT. The updated ITC results are incorporated into the new cost-utility analyses for populations #1 and #2 presented as part of the new evidence submission. A full list of the sections, tables and figures impacted by this ITC update is described in the following sections.

1.1 Updates to the ITC results in Document B:

Table 1: sections in Document B impacted by this update

#	Section in CS	Output affected	Details
1.1.1	B.2.9.6.1	NMA results for response (descriptive summary) Table 26: Fixed-effects network meta-analysis for response Figure 12: Forest plot for median log ORs and 95% CrI from the fixed-effects network meta-analysis for response Figure 13: Residual deviance from the fixed-effects network meta-analysis for response	Description of results relating to response. ORs for 100 mg, 100 mg + ABT and 200 mg shifted more in favour of relugolix CT. OR for 200 mg + ABT now favours relugolix CT, whereas previously it had favoured linzagolix. Relevant tables and figures have also been updated accordingly
1.1.2	B.2.9.8	Conclusions of the NMA	Overall conclusion is the same, however, patients treated with 200 mg + ABT did not achieve a larger response rate than relugolix CT in the updated results (as was previously stated)

1.1.1 NMA results for response.

The results of the NMA for response are summarized in section B.2.9.6 of Document B. The original results indicated that there was limited difference in treatment response between linzagolix and relugolix CT, with credible intervals crossing 1 for all doses except linzagolix 100 mg. The updated results estimate that linzagolix 100 mg, 100 mg + ABT and 200 mg are less likely to achieve a response than relugolix CT (ORs: [redacted], respectively). Given that the credible intervals do not include 1, there is a high probability (≥95%) that the treatments differ in efficacy. Linzagolix 200 mg + ABT is now 0.88 times as likely to achieve response as relugolix CT, where the original result favoured linzagolix. However, as the credible interval does contain 1 it still does not provide clear evidence of a difference in efficacy between the two treatments at this dose.

Tables and figures related to this result in section B.2.9.6 of Document B have also been updated accordingly. Please see updated results below.

Table 2: Fixed-effects network meta-analysis for response using individual linzagolix arms – LIBERTY only comparisons [table 26 in Document B]

Median odds ratio (95% CrI)	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00

Linzagolix 100 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Linzagolix 200 mg + ABT	[redacted] R-hat = 1.00	[redacted] R-hat = 1.00
Model fit statistics: Residual deviance = 8.19; pD = 8.01; DIC = 16.20		

Green – OR favours linzagolix

Underlined – 1 is not within the 95% CrI (i.e., there's a high probability that there is a difference in efficacy)

[redacted]

[redacted]

Figure 2: Residual deviance from the fixed-effects network meta-analysis for response using individual linzagolix arms – LIBERTY only comparisons [Figure 13 in Document B]

1.2 Updates to the ITC results in the appendices document:

The random-effects network meta-analysis for response (table 3, item 1) has been updated and, similar to the fixed-effects results presented above (table 2), the odd ratios for 100 mg, 100 mg + ABT and 200 mg have shifted more in favor of relugolix CT. Linzagolix 200 mg + ABT is now favoring relugolix CT (median OR = [redacted]) whereas previously it had favored linzagolix, though the credible interval does still cross 1. The updated MAIC of response (table 3, item 4) is similar to the results observed in the NMA, with comparative results now favoring relugolix CT at all doses of linzagolix. However, this difference in efficacy is only statistically significant for those treated with linzagolix 100 mg and 100 mg + ABT after weighting. The remaining updates listed in table 3 are very minor or rounding errors that have no impact on how results would be interpreted.

Table 3: sections in the appendices document impacted by this update

#	Section in CS	Output affected	Details
1.2.1	D.3.5.3	Table 12: Random-effects network meta-analysis for response.	ORs for 100 mg, 100 mg + ABT and 200 mg shifted more in favour of relugolix CT. OR for 200 mg + ABT now favours relugolix CT, whereas previously it had favoured linzagolix.
1.2.2	D.3.8.4	Table 19: Summary of baseline characteristics, matched on the proportion of black patients,	Very minor updates to figures presented in table for 'PRIMROSE 1

		menstrual blood loss, haemoglobin, total fibroid volume, and uterine volume.	& 2 – after weighting', and 'LIBERTY 1 & 2' columns.
1.2.3	D.3.8.4	Figure 6: Distribution of weights when matching on the proportion of black patients, menstrual blood loss, haemoglobin, total fibroid volume, and uterine volume.	Very minor update to the figure, with no impact on overall shape or interpretation of results.
1.2.4	D.3.8.5	Table 20: Matching adjusted indirect comparison of response, anchored via placebo. Figure 7: Forest plot for Log ORs and 95% CIs before weighting for response, anchored via placebo. Figure 8: Forest plot for Log ORs and 95% CIs after weighting for response, anchored via placebo.	ORs for 100 mg, 100 mg + ABT and 200 mg shifted more in favour of relugolix CT. OR for 200 mg + ABT now favours relugolix CT, whereas previously it had favoured linzagolix. This difference in efficacy is only statistically significant for those treated with linzagolix 100 mg and 100 mg + ABT after weighting. Relevant figures have also been updated accordingly.
1.2.5	D.3.8.5	Table 21: Matching adjusted indirect comparison of the percentage change in menstrual blood loss, anchored via placebo. Figure 9: Forest plot for mean differences and 95% CIs before weighting for the percentage change in menstrual blood loss, anchored via placebo. Figure 10: Forest plot for mean differences and 95% CIs after weighting from the matching adjusted indirect comparison of the percentage change in menstrual blood loss, anchored via placebo.	Original results indicated that the comparisons favoured relugolix CT with a statistically significant difference across all doses after weighting. Updated results demonstrate that there is no significant difference in efficacy between linzagolix 200 mg + ABT and relugolix CT (confidence interval crosses 0). Relevant figures have also been updated accordingly.
1.2.6	D.3.8.5	Table 23: Matching adjusted indirect comparison of the percentage change in primary fibroid volume, anchored via placebo. Figure 13: Forest plot for mean differences and 95% CIs before weighting for the percentage change in primary fibroid volume, anchored via placebo. Figure 14: Forest plot for mean differences and 95% CIs after weighting from the matching adjusted indirect comparison of the percentage change in primary fibroid volume, anchored via placebo.	Very minor updates due to rounding, with no impact on interpretation of results. Relevant figures have also been updated accordingly.

1.2.7	D.3.8.5	Table 24: Matching adjusted indirect comparison of the percentage change in haemoglobin, anchored via placebo. Figure 15: Forest plot for mean differences and 95% CIs before weighting for the percentage change in haemoglobin, anchored via placebo. Figure 16: Forest plot for mean differences and 95% CIs after weighting from the matching adjusted indirect comparison of the percentage change in haemoglobin, anchored via placebo.	Very minor updates due to rounding, with no impact on interpretation of results. Relevant figures have also been updated accordingly.
1.2.8	D.3.8.5	Table 25: Matching adjusted indirect comparison of the change in uterine fibroid symptom and quality of life (UFS QoL) total score, anchored via placebo. Figure 17: Forest plot for mean differences and 95% CIs before weighting for the change in uterine fibroid symptom and quality of life (UFS QoL) total score, anchored via placebo. Figure 18: Forest plot for mean differences and 95% CIs after weighting from the matching adjusted indirect comparison of the change in uterine fibroid symptom and quality of life (UFS QoL) total score, anchored via placebo.	Very minor updates due to rounding, with no impact on interpretation of results. Relevant figures have also been updated accordingly.

1.2.1 Random-effects network meta-analysis for response

Table 4: Random-effects network meta-analysis for response [table 12 in appendices]

Median odds ratio (95% CrI)	Placebo	Relugolix CT
Linzagolix 100 mg	[redacted] R-hat = 1.01	[redacted] R-hat = 1.00
Linzagolix 100 mg + ABT	[redacted] R-hat = 1.01	[redacted] R-hat = 1.01
Linzagolix 200 mg	[redacted] R-hat = 1.01	[redacted] R-hat = 1.00
Linzagolix 200 mg + ABT	[redacted] R-hat = 1.01	[redacted] R-hat = 1.00
Model fit statistics: Residual deviance = 8.78; pD = 8.76; DIC = 17.54		

Green – OR favours linzagolix
Underlined – 1 is not within the 95% CrI (i.e., there's a high probability that there is a difference in efficacy)

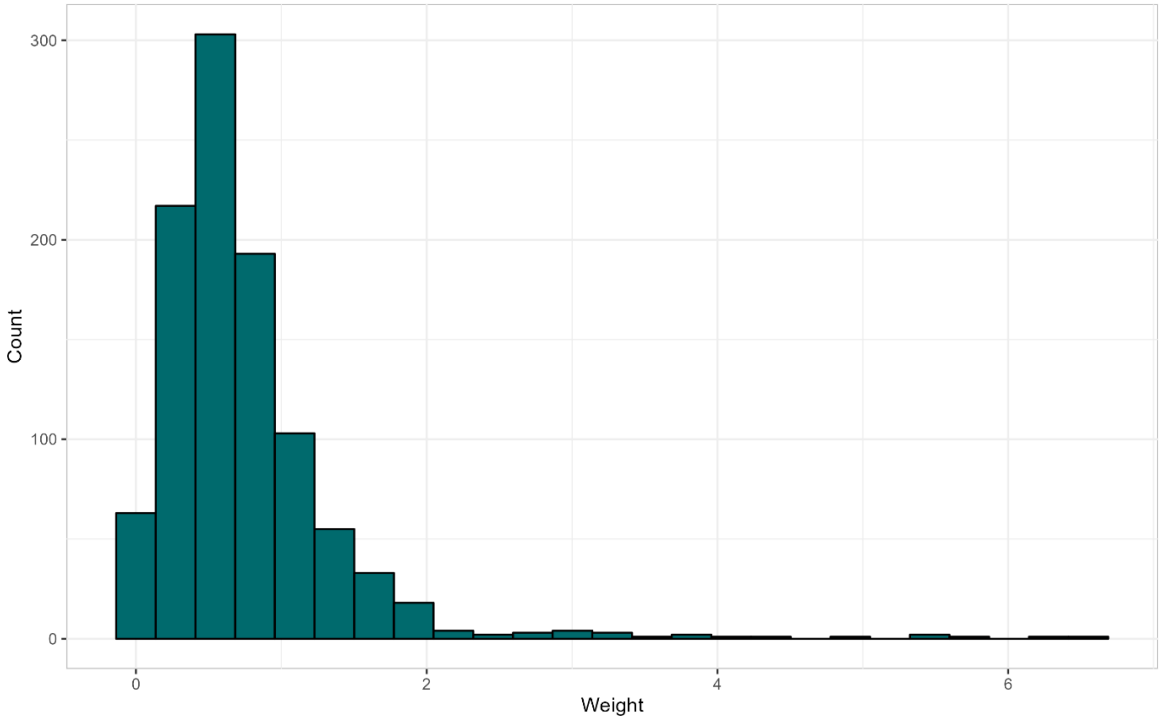
1.2.2 Summary of baseline characteristics for MAIC

Table 5: Summary of baseline characteristics, matched on the proportion of black patients, menstrual blood loss, haemoglobin, total fibroid volume, and uterine volume [table 19 in appendices]

Characteristic (matched on - ✓)			PRIMROSE 1 & 2 - before weighting					PRIMROSE 1 & 2 - after weighting					LIBERTY 1 & 2	
			Placebo	Linzagolix 100mg	Linzagolix 100mg + ABT	Linzagolix 200mg	Linzagolix 200mg + ABT	Placebo	Linzagolix 100mg	Linzagolix 100mg + ABT	Linzagolix 200mg	Linzagolix 200mg + ABT	Placebo	Relugolix CT
N/WSS; ESS			205	191	208	208	200	WSS = 162.5; ESS = 123.0	WSS = 133.8; ESS = 114.2	WSS = 147.8; ESS = 108.2	WSS = 175.8; ESS = 114.6	WSS = 141.9; ESS = 115.7	256	253
Age (years)			42.5	42.3	42.1	42.0	42.4	42.0	42.3	42.4	42.2	42.2	42.0	42.5
BMI (kg/m^2)			29.5 ***	30.3	30.1	29.7 *	29.9	30.7 *	31.3	31.0	30.5	30.9	32.2	31.3
Race	White		65.4% ***	63.4% **	61.1% **	63.0% **	65.0% ***	46.9%	47.1%	47.3%	48.0%	47.7%	41.0%	48.2%
	Black	✓	34.1% ***	33.5% **	36.1% *	35.6% *	33.0% **	52.7%	49.8%	51.1%	51.0%	50.5%	54.3%	47.8%
Ethnicity (Hispanic or Latino)			12.7% *	10.5% **	11.5% *	13.0% *	11.0% *	9.3% **	8.8% **	7.3% ***	10.4% **	13.6%	21.5%	20.6%
Menstrual blood loss (ml)		✓	205.9	221.1	197.6 ***	210.6 *	203.5 **	218.7	246.9	224.7	239.0	216.7	215.6	242.9
Menstrual blood loss <225ml			71.7%	66.5%	71.6%	69.7%	74.0% *	68.4%	58.5%	61.2%	60.5%	72.0%	66.8%	64.8%
Haemoglobin (g/dl)		✓	11.3	10.9 *	10.9	11.1	11.1	11.4	11.0	11.2	11.5	11.1	11.2	11.2
Total fibroid volume (cm^3)		✓	95.8 (N=200) *	110.2 (N=182) **	103.9 (N=202) *	88.2 (N=204)	97.8 (N=196) *	74.0 (WSS = 162.5; ESS = 123.0)	83.7 (WSS = 133.8; ESS = 114.2)	68.4 (WSS = 147.8; ESS = 108.2)	73.0 (WSS = 175.8; ESS = 114.6)	66.0 (WSS = 141.9; ESS = 115.7)	73.0	72.8
Uterine volume (cm^3)		✓	338.3 (N=203) *	351.4 (N=185)	320.6 (N=207) *	321.4 (N=208) *	311.2 (N=198) **	397.2 (WSS = 162.5; ESS = 123.0)	417.3 (WSS = 133.8; ESS = 114.2)	371.9 (WSS = 147.8; ESS = 108.2)	418.3 (WSS = 175.8; ESS = 114.6)	356.9 (WSS = 141.9; ESS = 115.7)	402.8	383.4
Pain score ≥4			74.4% (N=203)	80.4% (N=184) *	79.4% (N=204) *	79.0% (N=200) *	72.4% (N=196)	72.4% (WSS = 161.3; ESS = 121.6)	80.1% (WSS = 129.0; ESS = 109.5) *	78.8% (WSS = 145.6; ESS = 105.7)	80.3% (WSS = 165.6; ESS = 116.3) *	77.9% (WSS = 139.7; ESS = 113.1)	74.2%	70.0%
Bone mineral density (g/cm^3)	Lumbar spine		1.19 (N=189) **	1.19 (N=179)	1.19 (N=191)	1.19 (N=194)	1.18 (N=179)	1.22 (WSS = 144.4; ESS = 119.5)	1.21 (WSS = 126.6; ESS = 107.6)	1.19 (WSS = 133.0; ESS = 96.4)	1.20 (WSS = 166.4; ESS = 105.9)	1.19 (WSS = 128.1; ESS = 101.1)	1.24	1.19
	Total hip		1.06 (N=192)	1.07 (N=184)	1.07 (N=194)	1.06 (N=194)	1.07 (N=184)	1.08 (WSS = 147.8; ESS = 121.9)	1.08 (WSS = 129.7; ESS = 110.1) *	1.08 (WSS = 133.8; ESS = 97.2) *	1.07 (WSS = 166.5; ESS = 106.0)	1.07 (WSS = 130.8; ESS = 103.4)	1.07	1.04

1.2.3 Distribution of weights in MAIC

Figure 3: Distribution of weights when matching on the proportion of black patients, menstrual blood loss, haemoglobin, total fibroid volume, and uterine volume [figure 6 in appendices]



1.2.4 MAIC of response

Table 6: Matching adjusted indirect comparison of response, anchored via placebo [table 20 in appendices]

Odds ratios (95% CI)	Relugolix CT	
	Before weighting	After weighting
Linzagolix 100mg	[redacted]	[redacted]
Linzagolix 100mg + ABT	[redacted]	[redacted]
Linzagolix 200mg	[redacted]	[redacted]
Linzagolix 200mg + ABT	[redacted]	[redacted]

Green – odds ratio favours linzagolix
Underlined – one is not within the 95% CI (i.e., there's a statistically significant difference)

Figure 4: Forest plot for Log ORs and 95% CIs before weighting for response for linzagolix (PRIMROSE 1 & 2) versus relugolix CT (LIBERTY 1 & 2), anchored via placebo – using individual linzagolix arms [figure 7 in appendices]

1.2.5 MAIC of percentage change in menstrual blood loss

Table 7: Matching adjusted indirect comparison of the percentage change in menstrual blood loss for linzagolix (PRIMROSE 1 & 2) versus relugolix CT (LIBERTY 1 & 2), anchored via placebo - using individual linzagolix arms [table 21 in appendices]

Mean difference (95% CI)	Relugolix CT	
	Before weighting	After weighting
Linzagolix 100mg	[redacted]	[redacted]
Linzagolix 100mg + ABT	[redacted]	[redacted]
Linzagolix 200mg	[redacted]	[redacted]
Linzagolix 200mg + ABT	[redacted]	[redacted]

Green – mean difference favours linzagolix
Underlined – zero is not within the 95% CI (i.e., there's a statistically significant difference)

[redacted]

[redacted]

[redacted]

[redacted]

1.2.6 MAIC of percentage change in log-transformed primary fibroid volume

Table 8: Matching adjusted indirect comparison of the percentage change in log-transformed primary fibroid volume for linzagolix (PRIMROSE 1 & 2) versus relugolix CT (LIBERTY 1 & 2), anchored via placebo - using individual linzagolix arms [table 23 in appendices]

Mean difference (95% CI)	Relugolix CT	
	Before weighting	After weighting
Linzagolix 100mg	[redacted]	[redacted]
Linzagolix 100mg + ABT	[redacted]	[redacted]
Linzagolix 200mg	[redacted]	[redacted]
Linzagolix 200mg + ABT	[redacted]	[redacted]

Green – mean difference favours linzagolix
Underlined – zero is not within the 95% CI (i.e., there's a statistically significant difference)

[redacted]

[redacted]

1.2.7 MAIC of percentage change in haemoglobin

Table 9: Matching adjusted indirect comparison of the percentage change in haemoglobin for linzagolix (PRIMROSE 1 & 2) versus relugolix CT (LIBERTY 1 & 2), anchored via placebo - using individual linzagolix arms [table 24 in appendices]

Mean difference (95% CI)	Relugolix CT	
	Before weighting	After weighting
Linzagolix 100mg	[redacted]	[redacted]
Linzagolix 100mg + ABT	[redacted]	[redacted]
Linzagolix 200mg	[redacted]	[redacted]
Linzagolix 200mg + ABT	[redacted]	[redacted]

Green – mean difference favours linzagolix
Underlined – zero is not within the 95% CI (i.e., there's a statistically significant difference)

[redacted]

[redacted]

[redacted]

[redacted]

1.2.8 MAIC of change in UF QoL

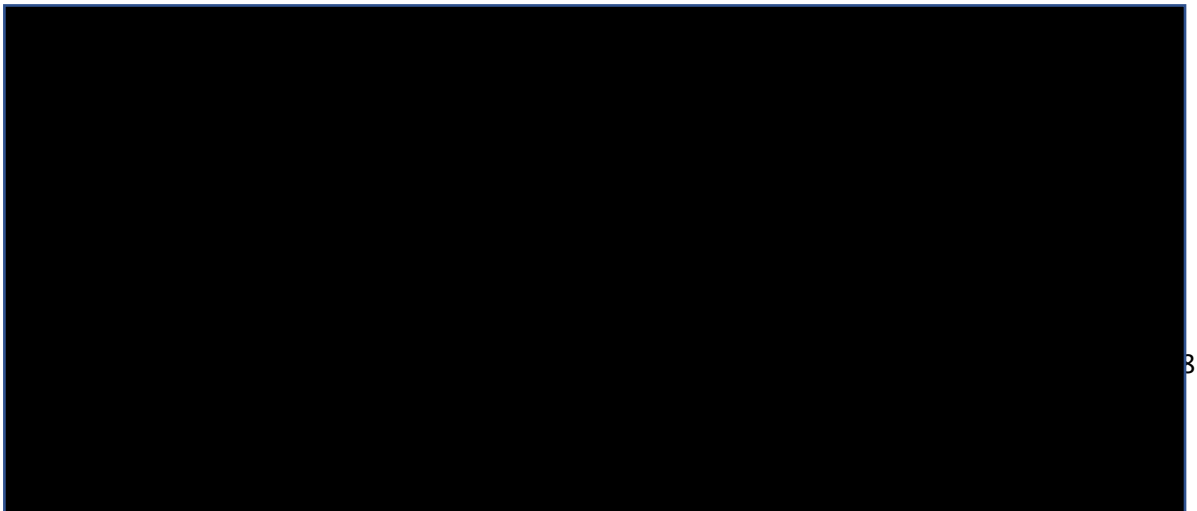
Table 10: Matching adjusted indirect comparison of the change in uterine fibroid symptom and quality of life (UFS QoL) total score for linzagolix (PRIMROSE 1 & 2) versus relugolix CT (LIBERTY 1 & 2), anchored via placebo - using individual linzagolix arms [table 25 in appendices]

Mean difference (95% CI)	Relugolix CT	
	Before weighting	After weighting
Linzagolix 100mg	[redacted]	[redacted]
Linzagolix 100mg + ABT	[redacted]	[redacted]
Linzagolix 200mg	[redacted]	[redacted]
Linzagolix 200mg + ABT	[redacted]	[redacted]

Green – mean difference favours linzagolix
Underlined – zero is not within the 95% CI (i.e., there's a statistically significant difference)

[redacted]

[redacted]



CONFIDENTIAL UNTIL PUBLISHED

Linzagolix for treating moderate to severe symptoms of uterine fibroids (ID6190)

External Assessment Group's critique of the company's Response to the Draft NICE Guidance

CONFIDENTIAL

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Geoff Frampton, Principal Research Fellow, Evidence Synthesis Lois Woods, Senior Research Assistant, Evidence Synthesis and Information Specialist
Correspondence to	Dr Geoff Frampton Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation Faculty of Medicine University of Southampton G.K.Frampton@southampton.ac.uk
Date completed	5th March 2024

1 Introduction

NICE issued Draft Guidance (DG) on 30th January 2024 for consultation on the appraisal of linzagolix for treating moderate to severe symptoms of uterine fibroids. The company, Theramex, submitted a response to the DG which the External Assessment Group (EAG) received on 27th February 2024.

The company's response to the DG consists of a factual accuracy and completeness check of the DG. No new evidence or analyses were provided by the company at this stage. The EAG note that, on request from NICE following the Advisory Committee Meeting on 9th January 2024, the company are intending to submit a cost-utility analysis (CUA) for Populations #1 and #2 of their Decision Problem. This is expected later, in April 2024, and therefore is not discussed within this document.

2 EAG critique of the company's comments on the Draft Guidance

The company's comments on the DG are summarised in Table 1 below, together with the EAG's responses.

Table 1 Company comments on the Draft NICE Guidance and the EAG's responses

Issue # and DG section	Company comments	EAG response
(1) Page 5	"*Moderate to severe symptoms of uterine fibroids include pain, difficulty in conceiving and heavy menstrual bleeding (HMB), which may lead to anaemia."* **Issue:** There are other important symptoms and issues that can be sequelae of UF that are not included here such as bulk symptoms; these might lead to pelvic pressure, constipation and increased urinary frequency, miscarriage, and pre-term and caesarean delivery. Please see the following references which describe these symptoms; • Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K. Prevalence, symptoms and management of uterine fibroids: an international internet-based survey	The DG statement is correct since the DG does not claim to list all symptoms and the DG does clearly state (twice) that the moderate to severe symptoms have a substantial effect on quality of life. But symptoms related to fibroid bulk can be important for patients (and in Population #1 may relate to patients' rationale for wanting surgery). We also note that, at least compared to placebo, linzagolix had a positive effect on fibroid and uterine volume. We therefore agree with the company that it may be helpful to include these symptoms in the list in the DG, if feasible.

	of 21,746 women. BMC Womens Health. 2012 Mar 26;12(1):6 • Hunsche E, Rakov V, Scippa K, Witherspoon B, McKain L. The Burden of Uterine Fibroids from the Perspective of US Women Participating in Open-Ended Interviews. Womens Health Rep. 2022 Mar 4;3(1):286–96.	
(2) Page 6	*"The treatments which are offered may depend on the specific treatment aims, patient characteristics (for example comorbidities) and personal preference, which may be not to have hormonal treatments."* **Issue:** We would suggest adding "or specific types of surgery (e.g., to preserve fertility)" at the end of the sentence i.e., that personal preference may also include not wanting to have surgery, or specific types of surgery such as hysterectomy.	The DG statement is correct. However, the company's suggestion appears reasonable to optimise clarity, and would entail only a minor addition to the DG wording.
(3) Page 9	*"Secondary outcomes included percentage change from baseline in MBL, fibroid volume and uterine volume, pain, percentage change from baseline in haemoglobin in people with anaemia and change in quality of life (uterine fibroids severity and quality of life [UFS-QoL] and EQ-5D-5L instruments)."* **Issue:** Other endpoints are missing: rates of and time to amenorrhoea (absence of bleeding), number of days of uterine bleeding.	The DG statement is correct; it does not claim to list all outcomes. However, to give a more complete picture of the outcomes reported, the company's suggested minor amendment to mention outcomes related to amenorrhoea (absence of bleeding) and uterine bleeding would be reasonable.
(4) Page 9	*"The primary outcome for both trials was attainment of response, which was a reduction in HMB defined as menstrual blood loss (MBL) of less than 80 ml and a 50% reduction in MBL from baseline."* **Please correct to** "The primary outcome for both trials was attainment of response, which was a reduction in HMB defined as menstrual blood loss (MBL) of less than or equal to 80 ml and a greater than or equal to 50% reduction in MBL from baseline''.	The EAG agree that the DG is inaccurate, and that the company's suggested amendment would be appropriate.

(5) Page 10	**Page 10** – *"The committee noted that the two trials returned slightly different results with linzagolix appearing slightly more effective for some outcomes in PRIMROSE 2 than PRIMROSE 1. It considered that this represented a source of uncertainty in the analyses."* **Add in wording**; "However US versus European populations are known to have different compliance rates and different rates of adherence to trial protocols. This is in part due to more Black women in the US population. This demographic is more likely to have a reduced tolerance for continued heavy menstrual bleeding on treatment, and so might discontinue earlier. This may have an impact on the interpretation on any difference observed." Please see the following reference that describes this effect: Fraser IS, Parke S, Mellinger U, Machlitt A, Serrani M, Jensen J. Effective treatment of heavy and/or prolonged menstrual bleeding without organic cause: pooled analysis of two multinational, randomised, double-blind, placebo-controlled trials of oestradiol valerate and dienogest. Eur J Contracept Reprod Health Care. 2011 Aug;16(4):258-69. doi: 10.3109/13625187.2011.591456. PMID: 21774563; PMCID: PMC3154543.	We agree with the company's comment that the differences in outcomes between the trials could reflect differences in the geographical and ethnic composition of the trial populations. We note that healthcare systems differ between the USA and Europe and so it is not easy to determine whether the observed differences in outcomes between the trials reflect differences in the location, ethnic composition, care received and/or other trial aspects. Addition of a concise statement to the DG such as "the differences in outcomes between the trials could reflect differences in the geographical and ethnic composition of the trial populations" may help to clarify the nature of the uncertainty referred to.
(6) Page 11	*"It noted that people awaiting surgery for uterine fibroids were excluded from the PRIMROSE trials."* **Issue:** This is not wholly factually correct; only patients with severe UFs who required urgent surgery within 6 months regardless of the treatment provided were excluded.	We agree with the company. The PRIMROSE trial exclusion criteria specify "*The subject's condition was so severe that she would require surgery within 6 months regardless of the treatment provided*". This is consistent with information in the Table for Key Issue 3 in the EAG Report.
(7) Page 12	*"At this higher dosage, the BMD reduction was clinically meaningful (a 5% or more reduction)."* **Issue:** This is incorrect. In both PRIMROSE 1 and 2, BMD loss was not clinically meaningful as the percentages were all	We agree with the company. EAG report section 3.2.5.5.3 states that the changes in BMD were generally small. We suggest that the DG wording "*the BMD reduction was clinically meaningful (a 5% or more reduction)*" could be changed to "*the BMD*

	below 5%. **Please see wording** in the Donnez et al. Lancet 2022 primary publication: ''At 24 weeks, the mean differences were most pronounced in the lumbar spine, with a **3.3% decrease in PRIMROSE 1 and 4.1% decrease in PRIMROSE 2 for participants administered 200 mg linzagolix alone**, a 2.0% decrease in PRIMROSE 1 and 2.1% decrease in PRIMROSE 2 with 100 mg linzagolix, and a 0.8% decrease in PRIMROSE 1 and 1.4% decrease in PRIMROSE 2 with 100 mg with add-back therapy and 200 mg with add-back therapy, compared with 0.4% increases in the PRIMROSE 1 placebo group and 0.5% increases in the PRIMROSE 2 placebo group. (At 52 weeks, the mean percent decreases from baseline in the lumbar spine were 2.2% in PRIMROSE 1 and 2.4% in PRIMROSE 2 with 100 mg linzagolix, 0.0% for PRIMROSE 1 and 1.5% for PRIMROSE 2 with 100 mg with add-back therapy, 0.9% with PRIMROSE 1 and 2.0% with PRIMROSE 2 with 200 mg with add-back therapy, 2.1% in PRIMROSE 1 and 3.1% in PRIMROSE 2 in participants who had received 200 mg linzagolix up to week 24 and then switched to 200 mg with add-back therapy, and a 0.9% decrease in the placebo group in PRIMROSE 1 (placebo treatment was not continued up to week 52 in PRIMROSE 2).'' See Figure 3 in Donnez et al. Lancet 2022 publication (mean percentage change values do not drop as low as 5%). Pooled results are similar (all less than 5%).	*reduction was not clinically meaningful (i.e. not 5% or more)*"
(8) Pages 13-14	**Page 13:** *"The EAG considered that a lack of statistically significant difference did not support a conclusion of similar clinical effectiveness."* And on **page 14** - *"It noted that the confidence intervals for most doses and outcomes were very wide"* **Issue:** The draft guidance refers to confidence intervals and statistical significance when discussing the NMA analyses, however the NMAs were Bayesian	We agree with the company. EAG Report section 3.7 refers to credible intervals and not statistical significance. We note that the Table for EAG Report Key Issue 1 does mention statistical significance, but that statement refers more broadly to lack of information provided by the company on how to interpret clinical similarity from the NMA results. We suggest rewording the

	analyses and produced credible intervals which demonstrated the probability that the estimate of effect lies within the range of the interval. Although frequentist and Bayesian analyses are used in a similar manner, the Bayesian NMAs do not relate to hypothesis tests or statistical significance. **Suggested alternative wording:** **Page 13** – "The EAG considered that a lack of there being a high probability of a difference did not support a conclusion of similar clinical effectiveness." Or "The EAG noted that a lack of statistical difference did not infer a conclusion of similar clinical effectiveness." **Page 14** – "It noted that the credible intervals for most doses and outcomes were very wide."	text on DG page 13 to "*The EAG noted that wide credible intervals did not permit an inference of similar clinical effectiveness*." We agree that in the second sentence in DG page 14 "confidence intervals" should be changed to "credible intervals".
(9) Page 15	"People in the model moved to the menopause state at 51 years and transitions to the death state were modelled using age-matched general population mortality rates." **Issue:** Mortality was also included for procedural based risks **Suggested alternative wording:** "People in the model moved to the menopause state at 51 years and transitions to the death state were modelled using age-matched general population mortality rates. An additional risk associated with procedural related mortality was also applied to those who had surgery (with the same mortality assumed as that which was incorporated in the previous appraisal for uterine fibroids [TA832])"	We agree with the company. EAG Report section 4.2.5.2.7 states that additional mortality risks associated with the complications from different surgery types were applied to the economic model for Population #3. These risks were obtained from TA832, as highlighted in the company's suggested wording.

External Assessment Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Linzagolix for treating moderate to severe symptoms of uterine fibroids (ID 6190)

Appendix: EAG critique of the company's updated economic analyses following the first Appraisal Committee Meeting

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Asyl Hawa, Research Fellow, Health Economics Neelam Kalita, Senior Research Fellow, Health Economics Geoff Frampton, Principal Research Fellow, Evidence Synthesis
Correspondence to	Dr Geoff Frampton Southampton Health Technology Assessments Centre (SHTAC) School of Healthcare Enterprise and Innovation Faculty of Medicine University of Southampton G.K.Frampton@southampton.ac.uk
Date completed	13th May 2024 (Updated 24th May 2024 after Factual Accuracy Check)

[redacted]

Table of Contents

LIST OF TABLES

LIST of FIGURES

LIST OF ABBREVIATIONS

ABT	Add-back therapy
ACM	Advisory Committee Meeting
CI	Confidence interval
CrI	Credible interval
CS	Company submission
DGD	Draft Guidance Document
EAG	External Assessment Group
EQ-5D-3L	European Quality of Life Working Group Health Status Measure 3 Dimensions, 3 Levels
EQ-5D-5L	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
INMB	Incremental net monetary benefit
ITC	Indirect treatment comparison
KOL	Key opinion leader
MAIC	Matching-adjusted indirect comparison
MBL	Menstrual blood loss
MRgFUS	Magnetic resonance guided focused ultrasound surgery
NMA	Network meta-analysis
ONS	Office for National Statistics
OWSA	One-way sensitivity analysis
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life year
UAE	Uterine artery embolisation
UFS-QoL	Uterine Fibroid Symptom Quality of Life scale

1 INTRODUCTION

The original company submission (CS) for this topic was received by the External Assessment Group (EAG) on 7th September 2023, and included the following economic analyses:

- Cost-comparison analysis of linzagolix versus relugolix CT and GnRH agonists for patients having short-term treatment of 6 months or less whilst awaiting a surgical intervention (Population #1)
- Cost-comparison analysis of linzagolix versus relugolix CT for patients having longer-term treatment with hormone-based therapy (Population #2)
- Cost-utility analysis of linzagolix versus best supportive care for patients having longer-term treatment without hormone-based therapy (Population #3)

In the EAG's Report, submitted to NICE on 9th November 2023, the EAG raised concerns about uncertainty of the company's cost comparison analysis for Population #1 and Population #2, due to limitations of the network meta-analyses (NMAs) and matching-adjusted indirect comparisons (MAICs) that provided the efficacy outcome estimates. The CS and EAG Report were discussed by NICE at the first Appraisal Committee Meeting (ACM) for this topic on 9th January 2024 and NICE issued their Draft Guidance Document (DGD) on 30th January 2024.

As stated in the DGD, the NICE evaluation committee considered that the NMAs and MAICs did not show that linzagolix provides similar health benefits to relugolix CT, so it is not possible to conclude that linzagolix provides a cost-effective treatment option based on the cost-comparison analyses for Population #1 and #2. The committee concluded that it would be necessary to see results of a cost-utility analysis, incorporating the various outcomes compared in the NMAs, to determine whether linzagolix would be cost effective for the treatment of moderate to severe symptoms of uterine fibroids in Populations #1 and #2 (DGD section 3.13).

The company provided a response to the DGD in two parts:

- The first part, received by the EAG on 27th February 2024, provided a narrative commentary on the DGD but did not include any updates to the company's economic analysis. The EAG's critique of the company's narrative response is provided in a separate Appendix (submitted to NICE on 5th March 2024).

- The company requested additional time to provide the cost-utility analysis for Population #1 and Population #2 recommended by NICE in the DGD. This analysis was received by the EAG on 22nd April 2024.

This EAG Report Appendix provides the EAG's critique of the company's cost-utility analysis for Populations #1 and #2. It includes a critique of the NMAs and MAICs that provide the clinical efficacy evidence (section below) and a critique of the economic analysis approach (section 2.2 below).

The company's updated submission contains several appendices. For brevity we refer to the company documents as described in Table 1.

Table 1 Summary names of company documents referenced by the EAG

Company document name	Summary name used in this EAG Report Appendix
New Evidence Submission	CS update
New evidence Appendix ITC update	ITC Appendix
New evidence Appendix Cost-effectiveness analysis	Economic Analysis Appendix
New evidence Appendix Expert Elicitation	Expert Elicitation Appendix

1.1 Key issues

The EAG note the following key issues relating to the company's updated CS. These are described in more detail in relation to the clinical efficacy analyses in section 2 and in relation to the cost-effectiveness analyses in section 3:

- GnRH agonists are relevant comparators for the cost-utility analysis for Population #1 as specified in the NICE scope and DGD but the company have not included these comparators (see section 2.2.1).

- There is uncertainty in the clinical efficacy evidence used for the response parameter within the cost-effectiveness model. In their base case model, for both Population #1 and Population #2, the company used the response rate from a naïve comparison based on the linzagolix and relugolix CT arms of the PRIMROSE and LIBERTY trials respectively. However, this approach has serious limitations (see section 2.2.2.3). EAG scenario analyses show that using response rate odds ratios from the NMAs and MAICs instead influences the overall cost-effectiveness results, with the ICER for linzagolix vs Relugolix CT ranging from £37,485 per QALY to linzagolix being

dominated (more expensive and less effective) compared to relugolix CT, and incremental QALYs ranging from [redacted] to [redacted].

2 EAG CRITIQUE OF THE CLINICAL EFFICACY EVIDENCE

2.1 Corrections made to the original company submission

The company state in their CS update that an error occurred in the extraction of data from the LIBERTY 1 and LIBERTY 2 trials in their original CS. The company have provided corrected analyses in the ITC Appendix. The company do not specify the nature of the error and have not provided any analysis input data or statistical code for the EAG to verify the corrections. According to ITC Appendix Tables 1 and 3 it appears that the error affects the MBL response and MBL change from baseline outcomes. Minor corrections were applied to three other outcomes to address rounding errors (see section 2.2.3 below).

2.2 Clinical efficacy evidence

2.2.1 Comparators

In their original CS the company included relugolix CT (Population #1 and #2) and GnRH agonists (Population #3) as the comparators for the cost comparison analyses. The company's cost-utility analysis in their CS update has been limited to relugolix CT as the sole comparator for both populations. NICE's draft recommendation acknowledges that relugolix CT is the relevant comparator for Population #2 (longer-term use, DGD section 3.4), but states that GnRH agonists as well as relugolix CT are relevant comparators for Population #1 (short-term use, DGD section 3.3). The company did not investigate the feasibility of including GnRH analogue comparators in the Population #1 analysis, although they mention that the relugolix CT market share is expected to increase; and they refer to the DGD issued by NICE where clinical input indicated that many patients would be likely to receive relugolix CT instead of GnRH agonists, due to the ease associated with oral administration. We note that Population #1 would be expected to receive linzagolix 200mg without ABT if the goal is to reduce fibroid size prior to surgery, and as relugolix CT contains add-back therapy it might not necessarily be the most suitable comparator for achieving that goal (in the company's MAIC analysis the 200mg but not the 200mg + ABT regimen of linzagolix significantly reduced fibroid volume).

In their clarification response for the original CS the company were only able to construct limited NMA networks for GnRH agonists. However, the methods of those analyses were poorly described and unclear, and the company did not explore alternative approaches for including a wider range of comparators (e.g. whether unanchored MAIC would be feasible).

The EAG disagree with the company's exclusion of GnRH agonists for Population #1. We consider that a more thorough feasibility assessment for including/excluding GnRH agonists should have been conducted, including consideration of whether relevant non-randomised studies could facilitate comparisons of linzagolix against GnRH agonists for this population.

2.2.2 Indirect treatment comparison (ITC) methods

In the absence of trials directly comparing linzagolix to relugolix CT and other GnRH analogues the company employed three ITC approaches: network meta-analysis (NMA), anchored matching-adjusted indirect comparison (MAIC), and a naïve comparison. The NMA and MAIC results in the original CS were interpreted from the perspective of a cost comparison, which required inferences on the clinical similarity (i.e. non-inferiority) of linzagolix relative to relugolix CT. For the cost-utility analyses the same NMAs and MAICs are used as in the original CS (after applying the corrections noted in section 2.1 above), but the results are interpreted from a superiority perspective (i.e. focusing on whether results for linzagolix and relugolix CT differ).

2.2.2.1 NMA

The company's NMAs have several limitations which have been discussed in the original CS and EAG Report. In summary:

- There was a marked placebo effect for the MBL response outcome. This was 32.2% in the pooled linzagolix (PRIMROSE) trials and 16.8% in the pooled relugolix CT (LIBERTY) trials. The NMAs in the company's original CS and the CS update do not adjust for this.

- The NMAs do not adjust for observed differences in the baseline characteristics of the included trials (there are insufficient data to conduct meta-regression) (EAG Report section 3.3.3.1).

- There are differences in the way menstrual blood loss was assessed in the PRIMROSE and LIBERTY trials, as well as differences in the time periods over which MBL was assessed and in how missing MBL data were handled between the PRIMROSE and LIBERTY trials. The company claim that these differences may explain the placebo effect and would lead to underestimation of the effectiveness of linzagolix relative to relugolix CT (CS section B.2.9.7 and Clarification Response A8). However, the EAG and our clinical expert considered that the reason for the

observed placebo effect is uncertain. Regression to the mean might explain at least some of the placebo effect (EAG Report section 3.2.5.1).

- The EAG were unable to validate the company's NMAs provided in their original CS as no input data for the NMAs were provided with the statistical code, and the NMA code did not contain sufficient detail of the data sets analysed (e.g. sample size for the input data used) (EAG Report section 3.4.1). These limitations also apply to the company's updated NMAs.

For their NMAs the company report results of fixed-effects and random-effects analyses. These analyses provide broadly similar point estimates for the response outcome but the random-effects model results have wider credible intervals (as shown in Table 13 below). The revised cost-effectiveness analyses used only the point estimates for the odds ratios, ignoring their credible intervals, so did not capture the uncertainty in the odds ratios. We conducted scenario analyses to illustrate the potential impact of this uncertainty on the cost-effectiveness results (see section 3.5 below).

2.2.2.2 MAIC

The main advantage of the MAIC analyses is that they can adjust for heterogeneity in the baseline characteristics of the included trials that NMAs do not adjust for, subject to the MAIC adequately matching the reference and comparator trial characteristics.

The company's anchored MAICs do, however, have several limitations:

- They do not specifically adjust for the difference in placebo effect between the trials. MAIC analysis can in theory adjust for the placebo effect if the treatment effect modifiers responsible for the placebo effect are among the characteristics adjusted for. However, it is unclear which if any of the included treatment effect modifiers explain the placebo effect).

- They cannot account for the differences in the assessment of MBL between the PRIMROSE and LIBERTY trials mentioned above.

- The EAG do not have access to the individual patient data from the PRIMROSE trials that are used in the company's MAIC analyses. And the company did not provide the input data or statistical code for their analyses meaning that the EAG are unable to verify that the statistical methods were implemented appropriately.

2.2.2.3 Naïve comparison

The company chose a naïve comparison that used the linzagolix response rate from the pooled PRIMROSE trials and the relugolix CT response rate from the pooled LIBERTY trials for their economic analysis base case. The company's rationale for this (as stated on page 13 of the Economic Analysis Appendix) is that the NMAs had limitations including the differences mentioned above in how MBL outcomes were assessed and handled between the PRIMROSE and LIBERTY trials and the presence of placebo effect heterogeneity across the trials. The EAG do not agree with this rationale since a naïve comparison cannot account for the heterogeneity of the MBL assessment methods. The naïve comparison approach merely ignores the placebo arms and implicitly assumes that there is no placebo effect. Furthermore, the naïve comparison approach does not account for differences in baseline characteristics of the trials being compared. An unanchored MAIC would have been preferable over a naïve comparison to ensure that the differences in baseline characteristics are accounted for. As noted above for the anchored MAIC, an unanchored MAIC could in theory account for at least part of the placebo effect if treatment effect modifiers responsible for the placebo effect are included in the matching, but it is unclear which trial characteristics these are.

2.2.2.4 EAG conclusion on the ITC approaches

- Naïve comparison is not an appropriate ITC method as it fails to account for differences between trials in baseline characteristics and placebo effects.

- For the comparisons conducted by the company anchored MAICs would be preferable over NMAs, subject to adequate matching of baseline characteristics being achieved. Information provided in Table 5 and Figure 3 of the company's ITC Appendix suggests that the MAIC achieved reasonably successful matching of the trial baseline characteristics, with no very high weights required, albeit some imbalances remained for the single ethnicity characteristic reported. However, the MAIC results are not used in the company's economic analyses.

- Odds ratios with credible intervals are reported for the company's NMAs but the credible intervals are not used in the economic analysis NMA scenarios. Uncertainty in the response outcome is therefore not considered in their scenario analyses.

As shown in section 3.5 below, the EAG conducted scenario analyses that included the credible intervals for both the NMA and MAIC analyses to investigate the impact of the uncertainty in response odds ratios on the cost-effectiveness results.

2.2.3 Outcomes

Results for the outcomes reported in the company's CS update are summarised in Table 2 below. In addition to the corrected MBL outcomes, the company also provided corrections to three other outcomes which ITC Appendix Table 3 states were to correct rounding errors and have no impact on interpretation of the results.

Two of the outcomes analysed in ITCs provide comparative efficacy parameter inputs for the cost-utility analysis: the MBL response rate is the key clinical efficacy outcome used in the economic model base case (see section 3.1.4.1) whilst the relative percentage change in primary fibroid volume informs utility calculations in scenario analyses (see section 3.1.5).

Overall, the ITC results suggest that the linzagolix 200mg and 200mg + ABT dose regimens are [redacted] efficacious than relugolix CT, except for improvements in fibroid volume and haemoglobin, for which the linzagolix 200mg and 200mg + ABT regimens respectively were [redacted] over relugolix CT (Table 2). However, there is ambiguity in the way that fibroids were selected and measured in the PRIMROSE trials, and we are uncertain whether this could have introduced bias or heterogeneity in the change in fibroid volume outcome (see EAG Report section 3.2.3.1.3). We assume that the haemoglobin results reported are for a select group of patients who had moderate anaemia at baseline (EAG Report section 3.2.5.2.3), although this is not explicit in the CS update.

Table 2 Summary of corrected results for the clinical efficacy outcomes reported in the CS update

Outcome	Indirect treatment comparison (ITC) approach		
	Fixed effects NMA	**Random effects NMA**	**MAIC**
MBL Response	[redacted] odds of relugolix CT than linzagolix 200mg achieving response but [redacted] between relugolix CT and linzagolix 200mg + ABT (ITC Appendix Table 2 and Figure 1).	Odds of achieving a response [redacted] between linzagolix 200mg or 200mg + ABT and relugolix CT. But CrIs wide (ITC Appendix Table 4).	Odds of achieving a response [redacted] between linzagolix 200mg or 200mg + ABT and relugolix CT (ITC Appendix Table 6 and Figure 5).
Change in primary fibroid volume	Not reported in the CS update (the company confirmed that the result is correct in the original CS).	Not reported in the CS update (the company confirmed that the result is correct in the original CS).	Primary fibroid volume statistically [redacted] linzagolix 200mg compared to relugolix CT but [redacted] between

			linzagolix 200mg + ABT and relugolix CT (ITC Appendix Table 8 and Figure 9).
Change in menstrual blood loss (MBL)	Not reported in the CS update (the company confirmed that the result is correct in the original CS).	Not reported in the CS update (the company confirmed that the result is correct in the original CS).	Change in MBL statistically [redacted] for linzagolix 200mg than relugolix CT but [redacted] between linzagolix 200mg + ABT and relugolix CT (ITC Appendix Table 7 and Figure 7).
% change in haemoglobin among patients anaemic at baseline	Not reported in the CS update (the company confirmed that the result is correct in the original CS).	Not reported in the CS update (the company confirmed that the result is correct in the original CS).	% change in Hb statistically [redacted] linzagolix 200mg + ABT compared to relugolix CT but [redacted] between linzagolix 200mg and relugolix CT (ITC Appendix Table 9 and Figure 11).
Change in UFS-QoL score	Not reported in the CS update (the company confirmed that the result is correct in the original CS).	Not reported in the CS update (the company confirmed that the result is correct in the original CS).	Change in score [redacted] between linzagolix 200mg or 200mg + ABT and relugolix CT (ITC Appendix Table 10 and Figure 13).

3 EAG CRITIQUE OF THE COST-UTILITY ANALYSES

3.1 Summary and critique of the company's submitted economic evaluation by the EAG

3.1.1 Model structure

The original company submission for Population #1 and Population #2 was a cost-comparison model. This has been updated to a cost-utility analysis. The model structure is consistent with the model used for Population #3 in the original CS (CS section B.3.2.3.3) and is reproduced in Figure 1 below. For the current analyses, the company further adapted the EAG's adaptation of the original cost-effectiveness model for Population #3. Briefly, the key features of the model are as follows:

- The model is a cohort-level Markov model with six health states:
  - Controlled (defined as achieving MBL ≤ 80mL and ≥50% reduction from baseline)
  - Uncontrolled (define by MBL >80mL per cycle)
  - Surgery
  - Post surgery
  - Menopause
  - Death
- Time horizon: 10 years
- Discounting: 3.5%
- Perspective: NHS/PSS
- Cycle length: 28 days
- Half cycle correction

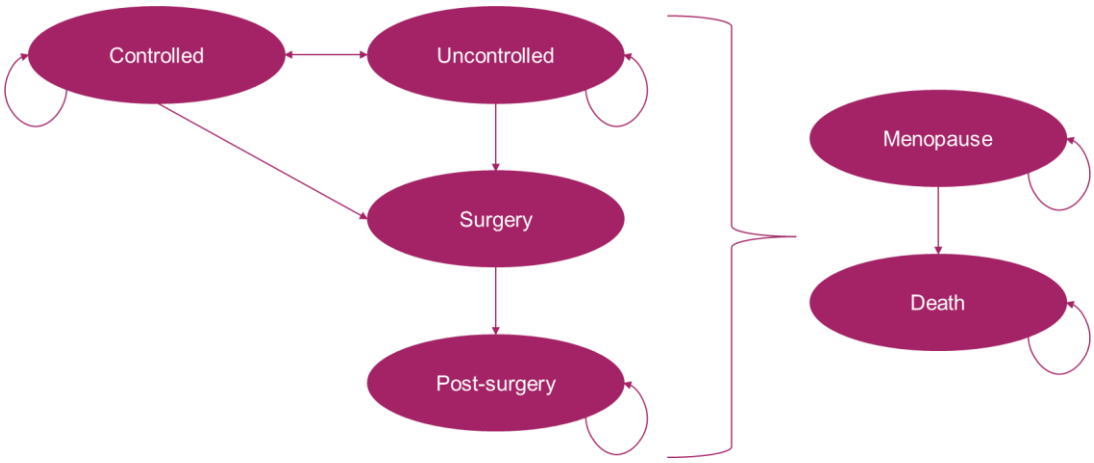


Figure 1 Cost-effectiveness model structure

EAG conclusion on the model structure and key features

We agree with the company's approach to adapting the EAG's cost-effectiveness model for Population #3 and applying this to Population #1 and Population #2. We did not identify any inconsistencies in the model structure or features.

3.1.2 Population

For the current analyses, the two population subgroups are:

- Population #1: People with short-term treatment (< 6 months) with an intention of achieving a reduction in fibroid or uterine volume, ahead of receiving a procedural or surgical intervention.
- Population #2: People receiving longer-term treatment with hormone-based therapy.

The baseline characteristics used in the economic analyses were mean age (42.25 years) and average age of menopause (51 years). The CS assumes that all patients transitioned to the menopause state on reaching the age of 51 years, after which they did not experience any disease-related symptoms.

EAG conclusion on the modelled population

The patient subgroups included in the company analyses align with the final NICE scope for this appraisal. Patient characteristics in the company's analyses, based on the pooled PRIMROSE trial populations and TA832, are reflective of UK clinical practice.

3.1.3 Interventions and comparators

The interventions and comparators included in the Economic Analysis Appendix are summarised in Table 3.

Table 3 Intervention and comparators included in the updated analyses

Subgroup	Intervention	Comparator
Population #1	Linzagolix 200mg for 6 months, followed by Linzagolix 200mg +ABT	Relugolix CT
Population #2	LInzagolix 200mg +ABT	Relugolix CT

As discussed in section 2.2.1.above, For Population #1, the company excluded GnRH agonists as comparators. This is inconsistent with their original submission which included relugolix CT and GnRH agonists as comparators for this subgroup. Furthermore, the

exclusion of the GnRH agonists also deviates from section 3.3. of the NICE Draft Guidance Document which states that GnRH agonists and relugolix CT are appropriate comparators for this subgroup.

EAG conclusion on intervention and comparators

We disagree with the exclusion of GnRH agonists as comparators for Population #1 but we agree with the comparator for Population #2.

3.1.4 Treatment effectiveness and extrapolation

The company discuss the clinical parameters in their Economic Analysis Appendix. We present a summary of the sources of these parameters in Table 4 and critique them in the following subsections.

Table 4: Summary of the clinical parameters informing the updated model for Population #1 and Population #2

Clinical parameters	Linzagolix	Relugolix CT
Response rate (defined as MBL ≤80ml and ≥50% reduction from baseline at 24 weeks).	• Pooled PRIMROSE trials (base case) • NMA (scenario analysis)	• Pooped LIBERTY trials (base case) • NMA (scenario analysis)
Recurrence rate	Market research survey with UK gynaecologist (n=50)	
Surgery	PEARL II; UK clinical opinion (10 experts)	
Adverse events	Pooled PRIMROSE trials	TA832 (sourced from pooled LIBERTY trials)
Mortality	ONS; surgery related death from TA832	

The company applied the following transition probabilities (shown in Table 5, reproduced from Table 8 of the Economic Analysis Appendix) in their updated economic model for Population #1 and Population #2.

Table 5: Transition probabilities used in the economic model

FROM / TO	Controlled	Uncontrolled	Surgery	Post-surgery	Procedural death
Linzagolix 200 mg					
Controlled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Uncontrolled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Surgery	0.00%	0.00%	0.00%	100.00%	0.00%
Post-surgery	0.00%	0.00%	0.00%	100.00%	0.00%
Procedural death	0.00%	0.00%	0.00%	0.00%	100.00%

Linzagolix 200 mg + ABT					
Controlled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Uncontrolled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Surgery	0.00%	0.00%	0.00%	100.00%	0.00%
Post-surgery	0.00%	0.00%	0.00%	100.00%	0.00%
Procedural death	0.00%	0.00%	0.00%	0.00%	100.00%
Relugolix CT					
Controlled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Uncontrolled	[redacted]	[redacted]	[redacted]	0.00%	0.00%
Surgery	0.00%	0.00%	0.00%	100.00%	0.00%
Post-surgery	0.000%	0.000%	0.000%	100.00%	0.000%
Procedural death	0.000%	0.000%	0.000%	0.000%	100.00%
Source: Table 8 of the Economic Analysis Appendix Note: The transition matrix does not include background mortality which is applied separately within the model calculations					

3.1.4.1 Response

As discussed earlier in section 2.2.2, the company employed NMA and anchored MAIC analyses for the comparison for a comparative clinical efficacy evidence. However, in the economic model, the company used the following sources of clinical efficacy evidence:

- A naïve comparison for their base case.
- An NMA (including both fixed effects and random effects) for their scenario analysis.

For their base case, the clinical data for linzagolix were informed by the pooled data from the PRIMROSE 1 and 2 trials, and relugolix CT data was sourced from the pooled LIBERTY 1 and 2 trials. The 24-week PRIMROSE response rates for the linzagolix arm were converted to per 28-cycle probabilities by applying the same approach used for Population #3 in the original CS.

In Table 6, we have reproduced the 24-week response rates obtained from the clinical trials for the two treatment arms and estimated per cycle probability. These estimates informed the base case model.

Table 6 Response rates at 24 weeks in LIBERTY 1 & 2 and PRIMROSE 1 & 2 (Naïve comparison)

Treatment arm	Trial	24-week response	28-day cycle probability
Linzagolix 100mg	PRIMROSE 1 & 2	56. 5%	13.0%

Linzagolix 100mg + ABT	PRIMROSE 1 & 2	71.6%	18.9%
Linzagolix 200 mg	PRIMROSE 1 & 2	74.5%	20.4%
Linzagolix 200 mg + ABT	PRIMROSE 1 & 2	84.5%	26.7%
Placebo	PRIMROSE 1 & 2	32.2%	6.3%
Relugolix CT	LIBERTY 1 & 2	72.3%	19.3%
Placebo	LIBERTY 1 & 2	16.8%	3.0%
Source: Table 5 of the Economic Analysis Appendix			

As discussed above (section 2.2.2) there are uncertainties associated with each of the three ITC approaches. While the naïve comparison ignores the placebo effect, the NMA also does not consider this. For response, the placebo effect was larger for linzagolix than relugolix CT so the naïve analysis could potentially be biased in favour of linzagolix.

The company did not conduct any scenario analyses using the odds ratios obtained from the MAICs. Therefore, we conducted a range of scenarios to assess the impact of using a range of estimates obtained from these approaches on the overall ICERs. For further details, see section 3.5.

EAG conclusion on the response rates

As noted in section 2.2.2 the ITC methods that provide odds ratios for the response rates suffer from several key limitations and the uncertainty around the odds ratios has not been considered in the economic analysis. We have conducted scenario analyses to address some of this uncertainty where possible. For further details, see section 3.5.

3.1.4.2 Recurrence

Recurrence rates of uterine fibroid symptoms are informed by expert opinion elicited from a market research survey with UK gynaecologists which reported the rate of recurrence of symptoms for GnRH antagonists. Equivalent rates are applied in the linzagolix and relugolix CT arms of the model: recurrence rates ([redacted]) were converted into 28-day cycle probabilities ([redacted]) using the same exponential formula as for response rates. The company used the same approach for recurrence rates as with the Population #3 analysis.

EAG conclusion on the recurrence rates

We agree with the company's estimate and approach as it aligns with the NICE committee's conclusion in the draft guidance document (outlined in DGD section 3.15).

3.1.4.3 Treatment discontinuation

Treatment discontinuation rates for the linzagolix arm were informed by PRIMROSE 1 and 2 while discontinuation rates from LIBERTY 1 and LIBERTY 2 informed the relugolix treatment discontinuation rates. Like the response rates, these rates were converted to per-cycle probabilities. We agree with the company's approach.

3.1.4.4 Surgery rates

The probability of surgery in the base case is taken from PEARL II, as surgery rates are not available from the PRIMROSE trials. The same approach was used as for the Population #3 analysis. The proportion of patients moving to the surgery health state per cycle is 3.02%, using an exponential distribution. The company performed scenario analyses considering lower surgery proportions for Population #2.

The NICE draft guidance document indicates uncertainty in the distribution of surgery types. Therefore, the company interviewed 10 UK-based clinicians (referred to as key opinion leaders, KOL), and of the 10 responses, eight responses could be interpreted in a quantitative framework to include the modelling of surgery types. Averages of these responses were used to inform the base case surgery distributions (reproduced below in Table 7). The clinicians highlighted the following key points:

- A difference in fibroid volume may influence the choice of surgery – reduction in fibroid volume results in a higher likelihood of laparoscopic surgery.
- Therefore, patients receiving linzagolix may have a different surgery type in comparison with people receiving treatment with relugolix CT.
- Two additional surgery types may be considered in practice: transvaginal resection and Sonata, which they included in the economic model for completeness. These were excluded in the model for Population #3.
- The company performed scenario analyses using the KOL-derived treatment independent values, the original values from TA832, and EAG's surgery distribution values (those used in the EAG base case for the Population #3 analysis).

Table 7 Surgery type distributions

Surgery type	General practice	Relugolix CT	Linzagolix 200 mg	Linzagolix 200 mg + ABT
Uterine artery embolisation	[redacted]	[redacted]	[redacted]	[redacted]
Endometrial ablation	[redacted]	[redacted]	[redacted]	[redacted]
MRI guided focused ultrasound surgery	[redacted]	[redacted]	[redacted]	[redacted]
Myomectomy (open/abdominal)	[redacted]	[redacted]	[redacted]	[redacted]

Myomectomy (laparoscopic)	[redacted]	[redacted]	[redacted]	[redacted]
Hysterectomy (open/abdominal)	[redacted]	[redacted]	[redacted]	[redacted]
Hysterectomy (laparoscopic)	[redacted]	[redacted]	[redacted]	[redacted]
Transvaginal resection	[redacted]	[redacted]	[redacted]	[redacted]
Sonata	[redacted]	[redacted]	[redacted]	[redacted]

EAG conclusion on surgery

The EAG were unable to verify the company's revised distribution of surgery type across the treatment arms with clinical experts. Therefore, further discussion on the estimates is warranted.

3.1.4.5 Mortality

Age-adjusted background mortality rates obtained from the ONS data for England were incorporated in the economic model. Mortality associated with surgery related complications were also incorporated. The company incorporated mortality into the economic model in the same way as with Population #3. The same risks of procedural death were implemented, with the risks for the two additional surgery types, transvaginal resection, and Sonata, set at 0% (assumed to be equivalent to magnetic resonance guided focused ultrasound surgery (MRgFUS)).

EAG conclusions on mortality

The company's approach to modelling background mortality is appropriate. We also agree with the assumption of excess mortality associated with surgical procedures. As indicated in the case for Population #3, based on clinical advice, we view that there is likely to be a higher risk of mortality associated with hysterectomies and myomectomies as these are major surgeries, whereas uterine artery embolization (UAE) is less risky than open surgery, although using a decreased mortality rate for UAE is unlikely to have any significant impact on the cost-effectiveness results.

3.1.4.6 Adverse events

Adverse events for linzagolix are acquired from the pooled PRIMROSE 1 and 2 trials, whilst TA832 was used to inform the relugolix CT arm. Table 3 below reports the adverse events implemented in the economic model.

Table 8 Adverse events

AE	Relugolix CT	Linzagolix 200 mg (population #1)	Linzagolix 200 mg + ABT (population #2)
Anaemia	2.36%	2.86%	6.25%
Headache	9.84%	11.90%	7.69%
Hot flush/flash	8.27%	33.33%	9.62%
Nausea	3.94%	5.24%	1.92%

EAG conclusion on adverse events

Overall, we agree with the company's approach to modelling adverse events. Clinical advice to the EAG (obtained as part of the original submission for Population #3) suggested that anaemia should be expected to improve on treatment in patients with uterine fibroids. Furthermore, allergies and intolerances to medications are common adverse events witnessed among these patients, which are not included. However, inclusion of these events is unlikely to make any significant impact on the overall cost-effectiveness results.

3.1.5 Health related quality of life

An overview of the utility values used in the economic model is presented in Table 9. For the controlled and uncontrolled health states for Populations #1 and #2, the company implemented the same health state utility values they had used for Population #3, derived from the UFS-QoL mapped to the EQ-5D-3L. The surgery and post-surgery health state utility values are consistent with those from Population #3, with transvaginal resection and Sonata (additional surgery types identified during the KOL expert elicitation) assumed equivalent to endometrial ablation and MRgFUS respectively.

Table 9 Utility values used in the economic model

Health state	Treatment arm	Utility value	Source
Controlled	These estimates are non-treatment specific in the economic model	[redacted]	PRIMROSE 1 and 2 (UFS-QoL mapped to EQ-5D-3L)
Uncontrolled		[redacted]	
Surgery	Linzagolix 200mg	0.682	Weighted average utility values were obtained based on the distribution of surgery types for each treatment arm
	Linzagolix 200mg + ABT	0.682	
	Relugolix CT	0.681	
Post-surgery	Linzagolix 200mg	0.833	
	Linzagolix 200mg + ABT	0.833	
	Relugolix CT	0.833	
Source: Tables 11 and 14 in the Economic Analysis Appendix			

Adverse event disutilities and QALY decrements used for Populations #1 and #2 are also in line with those used for Population #3 (see Tables 15 and 16 of the Economic Analysis Appendix). An age-adjusted utility decrement was also included in the model to account for the decline in quality of life with respect to aging.

The company discussed the impact of fibroid size on the patient's quality of life, reporting information from Hux et al. (2015). They stated that larger fibroids may be associated with discomfort from an increase in pelvic pressure and difficulties with urinary urges. They accounted for this by performing two scenario analyses for each population, implementing a utility improvement of 0.03 associated with smaller fibroid size in the linzagolix arm of the model. The utility increment is multiplied by the proportion of patients experiencing fibroid shrinkage based on results from the NMAs: [redacted] for linzagolix 200mg vs relugolix CT, and [redacted] for linzagolix 200mg + ABT vs relugolix CT. The utility increment is applied to the controlled and uncontrolled health states prior to surgery, and in the post-surgery health state. In Population #1, the ICER decreases from £2,726 per QALY to £613 per QALY and £306 per QALY in the prior to surgery and post-surgery scenarios, respectively. For Population #2, the ICER decreases from £5,524 per QALY to £3,391 per QALY and £2,260 per QALY in the prior to surgery and post-surgery scenarios, respectively.

EAG conclusions on health-related quality of life

The company adopted an identical approach as used for Population #3 to estimate utilities for the health states, using UFS-QoL mapped to EQ-5D-3L. This is consistent with the DGD for linzagolix, with the committee noting that the EQ-5D may not capture the full effects on quality of life of symptoms of uterine fibroids. The EAG also performed exploratory scenarios with equivalent weighted surgery utility for both linzagolix and relugolix CT arms, see section 3.5.

3.1.6 Resources and costs

The drug and administration costs for linzagolix and relugolix CT are equivalent to those used in the original cost-comparison analysis (see CS section B.3.5.1). The company opted to include the cost of vitamin D and calcium in the base case, as had been suggested by the EAG for Population #3. Linzagolix treatment discontinuation is evaluated using withdrawal data from the pooled PRIMROSE trials, and for relugolix CT the withdrawal data were sourced from TA832. The 24-week observed discontinuation data were converted into 28-day probabilities applied to all patients in the controlled and uncontrolled health states in

both the linzagolix and relugolix CT arms. Table 19 of the Economic Analysis Appendix reports the discontinuation rates used in the economic model.

The same resource use estimates and unit costs from the EAG base case (EAG report section 4.2.7) are used in the economic model for Populations #1 and #2. Adverse event costs are in line with Population #3 and are applied as a one-off cost in the first model cycle (see Tables 20 and 21 of the Economic Analysis Appendix).

As discussed in section 3.1.4.3, two further surgery types (transvaginal resection and Sonata) were included in the economic model. The original surgery costs remain the same as with Population #3, but the additional surgery types and costs results in a change in the weighted average surgery costs. **Table *10*** below reports the average surgery costs for the linzagolix and relugolix CT arms used in the model.

Table 10 Weighted average surgery costs

Treatment	Surgery cost
Linzagolix (200 mg, Population #1)	£3,612.74
Linzagolix (200 mg + ABT, Population #2)	£3,667.92
Relugolix CT	£3,723.93
Source: Table 23 of the Economic Analysis Appendix	

EAG conclusion on resources and costs

The company have opted for the EAG preferred base case resource use and unit costs used in the Population #3 analysis, which mitigates the concerns raised in the main EAG report (for further details, see EAG report section 4.2.7.2.2) and aligns with the NICE draft guidance (DGD section 3.17). We agree with the implementation of the resource use and unit costs used in the economic model for Population #1 and Population #2.

3.2 Company's cost effectiveness results

The company reported the deterministic base case results for Population #1 and Population #2 in Table 25 and Table 26 of the Economic Analysis Appendix update which are reproduced in Table 11 and Table 12 below. Note that all the results use the PAS price for linzagolix.

Table 11 Company base case results for Population #1 (using PAS price for linzagolix)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Relugolix CT	[redacted]	9.971	[redacted]				

Linzagolix	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£2,726

Table 12 Company base case results for Population #2 (using PAS price for linzagolix)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Relugolix CT	[redacted]	9.971	[redacted]				
Linzagolix	[redacted]	9.971	[redacted]	[redacted]	0.000	[redacted]	£5,524

3.3 Company sensitivity analyses

3.3.1 Deterministic sensitivity analysis

A one-way sensitivity analysis (OWSA) was conducted for both Population #1 and Population #2, where the ranges of variation for the input parameters were based on 95% confidence intervals. In the absence of confidence intervals, the company assumed the standard error was 10% of the mean value. The company presented OWSA results using incremental net monetary benefit (INMB) as some ICERs were negative when inputs were sampled at their lower and upper bounds. Table 29 and Table 30 of the Economic Analysis Appendix report the top 10 most influential parameters for Population #1 and Population #2, respectively. The results indicate that the utility values for abdominal hysterectomy and abdominal myomectomy (post-surgery) are the main drivers of the model for both populations.

3.3.2 Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) with input parameter distributions as presented in CS Appendix N. The PSA was run for 1,000 iterations, and mean results are reported in Table 27 and Table 28 of the Economic Analysis Appendix for Population #1 and Population #2, respectively. The cost-effectiveness planes and cost-effectiveness acceptability curves are presented in Figures 2 and 3 and Figures 4 and 5 of the Economic Analysis Appendix for Population #1 and Population #2, respectively. The probabilistic results were in line with the deterministic results when run by the EAG.

3.3.3 Scenario analyses

The company performed scenario analyses using fixed- and random-effects NMAs to inform clinical effectiveness in the relugolix CT arm of the model for both Population #1 and Population #2, as presented in Table 31 and Table 33 of the Economic Analysis Appendix. In both populations the incremental costs remained the same between linzagolix and relugolix CT, whilst the incremental QALY changed from [redacted] to [redacted] in Population #1

and changed from [redacted] to [redacted] for fixed-effects NMAs and [redacted] for random-effects NMAs in Population #2. Note that these analyses utilised the point estimates for the response odds ratios but not their credible intervals, and so do not consider uncertainty in the odds ratios. We explored this uncertainty in EAG scenario analyses (section 3.5 below). The company also provided additional scenario analyses for both populations in Table 32 and Table 34 of the Economic Analysis Appendix, with scenarios exploring discount rates, sources of surgery distribution, concomitant medications, and choice of utility model. For Population #2, the company also conducted scenario analyses on 28-day surgery probabilities. The ICERs in both populations [redacted], with a high of [redacted] per QALY for changes in surgery distributions for Population #1, and a high of [redacted] per QALY using the EQ-5D-5L to EQ-5D-3L utility model for Population #2.

EAG conclusion on sensitivity analyses

The EAG did not find any errors in any of the company's analyses, except for a reporting error of the results for the scenario regarding lowering surgery proportions for Population #2 (the results for "post-surgery" were reported for the "prior to surgery" scenario in the model, and vice-versa). The company included all necessary parameters in the PSA, with appropriate corresponding distributions. However, uncertainty in the response odds ratios, reflected in their credible intervals, was not considered.

3.4 Model validation and face validity checks

We conducted a range of checks on the update economic model as outlined below:

- Input checks: comparison of all parameter values in the model against the values stated in the company submission and cited sources.
- Output checks: replication of results reported in the company submission using the company model.
- 'White box' checks: manual checking of formulae working from the cohort-level Markov model, which includes reviewing the calculations across each cycle and working backwards to trace links to input parameters and forwards to the results.
- 'Black box' checks: working through a list of tests to assess whether changes to key model inputs or assumptions have the expected effects on the model results.

The EAG consider the model to be well-implemented, and no coding errors were identified, except for one reporting error in the results for a scenario analysis regarding lowering surgery proportions for Population #2 (discussed above).

3.5 EAG's additional analyses

We conducted a range of exploratory scenario analyses on the company's base case model for Population #1 and Population #2, covering baseline characteristics, treatment discontinuation, surgery utilities and NMA and MAIC odds ratios (shown in Table 13). These scenarios, except those for the response rates, are consistent with those conducted by the EAG on the company's base case model for Population #3. Results are reported below in **Table *14* Scenarios conducted by the EAG on the company's model for Population #1Table *14*** and **Table *15*** for Population #1 and Population #2 respectively.

Table 13 NMA and MAIC odds ratios and credible intervals

OR (CI)	Fixed-effects NMA	Random-effects NMA	MAIC [a]
Relugolix CT vs linzagolix 200mg	[redacted]	[redacted]	[redacted]
Relugolix CT vs linzagolix 200mg + ABT	[redacted]	[redacted]	[redacted]

Sources: Table 6 of the Economic Analysis Appendix, Table 6 of the ITC Appendix

[a] Estimates from the weighted anchored MAICs, note these values are from the reciprocal of the linzagolix vs relugolix CT odds ratios from Table 6 of the ITC Appendix.

Table 14 Scenarios conducted by the EAG on the company's model for Population #1 (using the linzagolix PAS price)

	Treatment	Total costs	Total QALY	ICER (£/QALY)
Company base case	Relugolix CT	[redacted]	[redacted]	£2,726
	Linzagolix	[redacted]	[redacted]	
Baseline characteristics				
Patient mean age -10%	Relugolix CT	[redacted]	[redacted]	£2,564
	Linzagolix	[redacted]	[redacted]	
Patient mean age +10%	Relugolix CT	[redacted]	[redacted]	£5,476
	Linzagolix	[redacted]	[redacted]	
Average menopause age -10%	Relugolix CT	[redacted]	[redacted]	£7,432
	Linzagolix	[redacted]	[redacted]	
Average menopause age +10%	Relugolix CT	[redacted]	[redacted]	£2,579
	Linzagolix	[redacted]	[redacted]	
Recurrence rate				
10% for both treatment arms	Relugolix CT	[redacted]	[redacted]	£4,734
	Linzagolix	[redacted]	[redacted]	
25% for both treatment arms	Relugolix CT	[redacted]	[redacted]	£2,631
	Linzagolix	[redacted]	[redacted]	
Treatment discontinuation				
[redacted]% for linzagolix 200mg, linzagolix 200mg+ABT, and relugolix CT	Relugolix CT	[redacted]	[redacted]	£10,529
	Linzagolix	[redacted]	[redacted]	
[redacted]% for linzagolix 200mg, linzagolix 200mg+ABT, and relugolix CT	Relugolix CT	[redacted]	[redacted]	£8,958
	Linzagolix	[redacted]	[redacted]	
	Relugolix CT	[redacted]	[redacted]	£10,632

20.08% for linzagolix 200mg, linzagolix 200mg+ABT, and relugolix CT	Linzagolix	[redacted]	[redacted]	
Utility				
Weighted surgery utility for relugolix CT equal to linzagolix 200mg (0.682)	Relugolix CT	[redacted]	[redacted]	£2,768
	Linzagolix	[redacted]	[redacted]	
Response rates (using ORs from NMAs and MAICs)				
Fixed-effects NMA: lower credible interval (CrI)	Relugolix CT	[redacted]	[redacted]	£37,485
	Linzagolix	[redacted]	[redacted]	
Fixed-effects NMA: upper CrI	Relugolix CT	[redacted]	[redacted]	-£905 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Random-effects NMA: lower CrI	Relugolix CT	[redacted]	[redacted]	£86
	Linzagolix	[redacted]	[redacted]	
Random-effects NMA: upper CrI	Relugolix CT	[redacted]	[redacted]	-£481 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
MAIC	Relugolix CT	[redacted]	[redacted]	-£1,723 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
MAIC: lower CrI	Relugolix CT	[redacted]	[redacted]	£5,814
	Linzagolix	[redacted]	[redacted]	
MAIC: upper CrI	Relugolix CT	[redacted]	[redacted]	-£928 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; OR, odds ratio; NMA, network meta-analysis; CrI, credible interval.

[a] Linzagolix is more expensive and less effective compared to Relugolix CT

Table 15 Scenarios conducted by the EAG on the company's model for Population #2 (using the linzagolix PAS price)

	Treatment	Total costs	Total QALY	ICER (£/QALY)
Company base case	Relugolix CT	[redacted]	[redacted]	£5,524
	Linzagolix	[redacted]	[redacted]	
Baseline characteristics				
Patient mean age -10%	Relugolix CT	[redacted]	[redacted]	£5,522
	Linzagolix	[redacted]	[redacted]	
Patient mean age +10%	Relugolix CT	[redacted]	[redacted]	£6,255
	Linzagolix	[redacted]	[redacted]	
Average menopause age -10%	Relugolix CT	[redacted]	[redacted]	£6,809
	Linzagolix	[redacted]	[redacted]	
Average menopause age +10%	Relugolix CT	[redacted]	[redacted]	£5,528
	Linzagolix	[redacted]	[redacted]	
Recurrence rate				
10% for both treatment arms	Relugolix CT	[redacted]	[redacted]	£6,664
	Linzagolix	[redacted]	[redacted]	
25% for both treatment arms	Relugolix CT	[redacted]	[redacted]	£5,446
	Linzagolix	[redacted]	[redacted]	

Treatment discontinuation				
[redacted]% for linzagolix 200mg+ABT and relugolix CT	Relugolix CT	[redacted]	[redacted]	£9,920
	Linzagolix	[redacted]	[redacted]	
20.08% for linzagolix 200mg+ABT and relugolix CT	Relugolix CT	[redacted]	[redacted]	£10,677
	Linzagolix	[redacted]	[redacted]	
Utility				
Weighted surgery utility for relugolix CT equal to linzagolix 200mg (0.682)	Relugolix CT	[redacted]	[redacted]	£5,562
	Linzagolix	[redacted]	[redacted]	
Response rates (using ORs from NMAs and MAICs)				
Fixed-effects NMA: lower CrI	Relugolix CT	[redacted]	[redacted]	£8,781
	Linzagolix	[redacted]	[redacted]	
Fixed-effects NMA: upper CrI	Relugolix CT	[redacted]	[redacted]	-£7,140 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Random-effects NMA: lower CrI	Relugolix CT	[redacted]	[redacted]	£385
	Linzagolix	[redacted]	[redacted]	
Random-effects NMA: upper CrI	Relugolix CT	[redacted]	[redacted]	-£2,904 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
MAIC	Relugolix CT	[redacted]	[redacted]	-£19,298 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
MAIC: lower CrI	Relugolix CT	[redacted]	[redacted]	£9,353
	Linzagolix	[redacted]	[redacted]	
MAIC: upper CrI	Relugolix CT	[redacted]	[redacted]	-£6,505 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; OR, odds ratio; NMA, network meta-analysis; CrI, credible interval

[a] Linzagolix is more expensive and less effective compared to Relugolix CT

The above results indicated that, across both the subgroups (i.e., Population #1 and Population #2), using alternative response rates obtained from the NMA and the MAICs had the most significant impact on the overall cost-effectiveness results, with the ICER for linzagolix vs relugolix CT ranging from £37,485 per QALY to linzagolix being dominated (more expensive and less effective) compared to relugolix CT. For the remaining scenarios, the ICER for linzagolix compared to relugolix CT remained below £20,000 per QALY.

The company conducted scenario analyses on their base case as reported in the Economic Analysis Appendix. We have repeated these scenario analyses on the company's model using a base case where the efficacy for relugolix CT versus linzagolix is informed by fixed- and random-effects NMAs. These results are provided in Table 16 to Table 19 below.

Table 16 Scenarios conducted on company's model using fixed-effects NMA results for Population #1 (using the linzagolix PAS price)

	Treatment	Total Costs	Total QALYs	ICER (£/QALY)
Company fixed-effects NMA Population #1	Relugolix CT	[redacted]	[redacted]	-£1,534 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
	Linzagolix	[redacted]	[redacted]	
The below scenarios are conducted on the above model, i.e., company's model using fixed effects NMA				
Surgery distribution: TA832 CS	Relugolix CT	[redacted]	[redacted]	-£12,587 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: TA832 EAG	Relugolix CT	[redacted]	[redacted]	-£12,587 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: EAG	Relugolix CT	[redacted]	[redacted]	-£12,587 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: KOL feedback treatment independent	Relugolix CT	[redacted]	[redacted]	-£12,587 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
	Linzagolix	[redacted]	[redacted]	
Include Hux et al. utility increment for fibroid reduction: post-surgery	Relugolix CT	[redacted]	[redacted]	£444
	Linzagolix	[redacted]	[redacted]	
Include Hux et al. utility increment for fibroid reduction: prior to surgery	Relugolix CT	[redacted]	[redacted]	£1,633
	Linzagolix	[redacted]	[redacted]	

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; KOL, key opinion leaders; NMA, network meta-analysis.

[a] Linzagolix is more expensive and less effective compared to Relugolix CT

Table 17 Scenarios conducted on company's model using random-effects NMA for Population #1 (using the linzagolix PAS price)

	Treatment	Total Costs	Total QALYs	ICER (£/QALY)
Company random-effects NMA Population #1	Relugolix CT	[redacted]	[redacted]	-£1,567 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
The below scenarios are conducted on the above model, i.e., company's model using random effects NMA				
Surgery distribution: TA832 CS	Relugolix CT	[redacted]	[redacted]	-£12,876 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: TA832 EAG	Relugolix CT	[redacted]	[redacted]	-£12,876 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: EAG	Relugolix CT	[redacted]	[redacted]	-£12,876 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: KOL feedback treatment independent	Relugolix CT	[redacted]	[redacted]	-£12,876 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Include Hux et al. utility increment for fibroid reduction: post-surgery	Relugolix CT	[redacted]	[redacted]	£442
	Linzagolix	[redacted]	[redacted]	
Include Hux et al. utility increment for fibroid reduction: prior to surgery	Relugolix CT	[redacted]	[redacted]	£1,598
	Linzagolix	[redacted]	[redacted]	

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; KOL, key opinion leaders; NMA, network meta-analysis.

[a] Linzagolix is more expensive and less effective compared to Relugolix CT

Table 18 Scenarios conducted on the company's model using fixed-effects NMA results for Population #2 (using the linzagolix PAS price)

Scenario	Treatment	Total Costs	Total QALYs	ICER (£/QALY)
Company fixed effects NMA Population #2	Relugolix CT	[redacted]	[redacted]	-£25,683 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
The below scenarios are conducted on the above model, i.e., company's model using fixed effects NMA				
Surgery distribution: TA832 CS	Relugolix CT	[redacted]	[redacted]	-£67,208 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: TA832 EAG	Relugolix CT	[redacted]	[redacted]	-£67,208 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: EAG	Relugolix CT	[redacted]	[redacted]	-£67,208 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: KOL feedback treatment independent	Relugolix CT	[redacted]	[redacted]	-£67,208 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Include Hux et al. utility increment for fibroid reduction: post-surgery	Relugolix CT	[redacted]	[redacted]	£4,494
	Linzagolix	[redacted]	[redacted]	
Include Hux et al. utility increment for fibroid reduction: prior to surgery	Relugolix CT	[redacted]	[redacted]	£13,338
	Linzagolix	[redacted]	[redacted]	

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; KOL, key opinion leaders; NMA, network meta-analysis.

[a] Linzagolix is more expensive and less effective compared to Relugolix CT

Table 19 Scenarios conducted on the company's model using random-effects NMA results for Population #2 (using the linzagolix PAS price)

Scenario	Treatment	Total Costs	Total QALYs	ICER (£/QALY)
Company random-effects NMA Population #2	Relugolix CT	[redacted]	[redacted]	-£29,103 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
The below scenarios are conducted on the above model, i.e., company's model using random effects NMA				
Surgery distribution: TA832 CS	Relugolix CT	[redacted]	[redacted]	-£81,898 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: TA832 EAG	Relugolix CT	[redacted]	[redacted]	-£81,898 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: EAG	Relugolix CT	[redacted]	[redacted]	-£81,898 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
Surgery distribution: KOL feedback treatment independent	Relugolix CT	[redacted]	[redacted]	-£81,898 (Linzagolix is dominated) [a]
	Linzagolix	[redacted]	[redacted]	
	Linzagolix	[redacted]	[redacted]	
	Relugolix CT	[redacted]	[redacted]	£4,403

Include Hux et al. utility increment for fibroid reduction: post-surgery	Linzagolix	[redacted]	[redacted]	
Include Hux et al. utility increment for fibroid reduction: prior to surgery	Relugolix CT	[redacted]	[redacted]	£12,571
	Linzagolix	[redacted]	[redacted]	
Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; KOL, key opinion leaders; NMA, network meta-analysis. [a] Linzagolix is more expensive and less effective compared to Relugolix CT				

In both the fixed- and random-effects NMA scenarios for Populations #1 and #2, all scenarios except those concerning the utility increment for fibroid reduction resulted in linzagolix being strictly dominated (more expensive and less effective) in comparison with relugolix CT. For the fibroid shrinkage scenarios, the ICER remained under £20,000 per QALY in both populations; for Population #1, the ICERs dropped to below £2,000 per QALY.

3.6 Conclusions on the cost-effectiveness evidence

The company adapted the EAG's cost-utility model for Population #3 to develop the cost-effectiveness model for Population #1 and Population #2. The EAG did not identify any technical errors on checking the model, except for one inconsistency in reporting which did not have any impact on the overall results. Overall, we note the following key issues relating to the company's CS update:

- The company excluded GnRH agonists are relevant comparators for the cost-utility analysis for Population #1 as specified in the NICE scope).
- For both Population #1 and Population #2, the model results are very sensitive to the clinical efficacy evidence used for the response parameter. The company used estimates from the naïve comparison for the base case, which has serious limitations as discussed earlier in section 2.2.2.3. Using the response rate odds ratios from the NMAs and MAICs influenced the overall cost-effectiveness results significantly, with the ICER for linzagolix vs relugolix CT ranging from £37,485 per QALY to linzagolix being dominated (more expensive and less effective) compared to relugolix CT.

3.7 Additional uncertainties

Note that the differences between trials in how MBL was measured cannot be addressed by any of the ITC methods, potentially leaving residual uncertainty that is not accounted for. Uncertainty due to heterogeneity in the placebo effect is also not accounted for in the current analyses. Furthermore, due to the limited timescale available for the EAG's critique we did

not explore the impact of the corrected MAIC estimates or their credible intervals for the comparative percentage reduction in fibroid volume versus relugolix CT ([redacted] and [redacted] for the linzagolix 200mg and 200mg + ABT regimens respectively) (ITC Appendix Table 8) as compared to the NMA estimates ([redacted] and [redacted]).