Linzagolix for treating moderate to severe symptoms of uterine fibroids

Technology appraisal committee C [09 January 2024]

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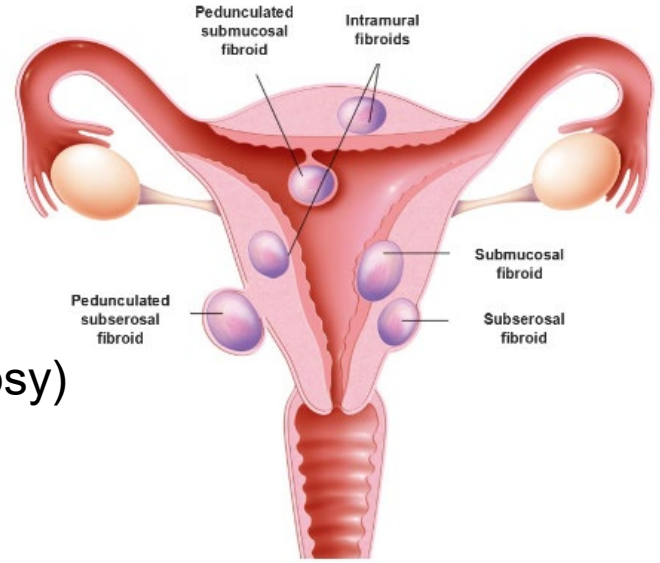
Company: Theramex

Background on uterine fibroids



Diagnosis and classification

- Uterine fibroids common but often too small to cause symptoms
- In symptomatic people diagnosis confirmed by ultrasound scan (possibly with biopsy)

Epidemiology

- ~66% of women develop at least one uterine fibroid during their lifetime
- UK incidence estimated at 5.8 per 1,000 woman-years and prevalence estimated at 4.5% of those aged 15 to 49
- Risk factors include age up to menopause, vitamin D deficiency, family history, nulliparity and having Black African ethnicity

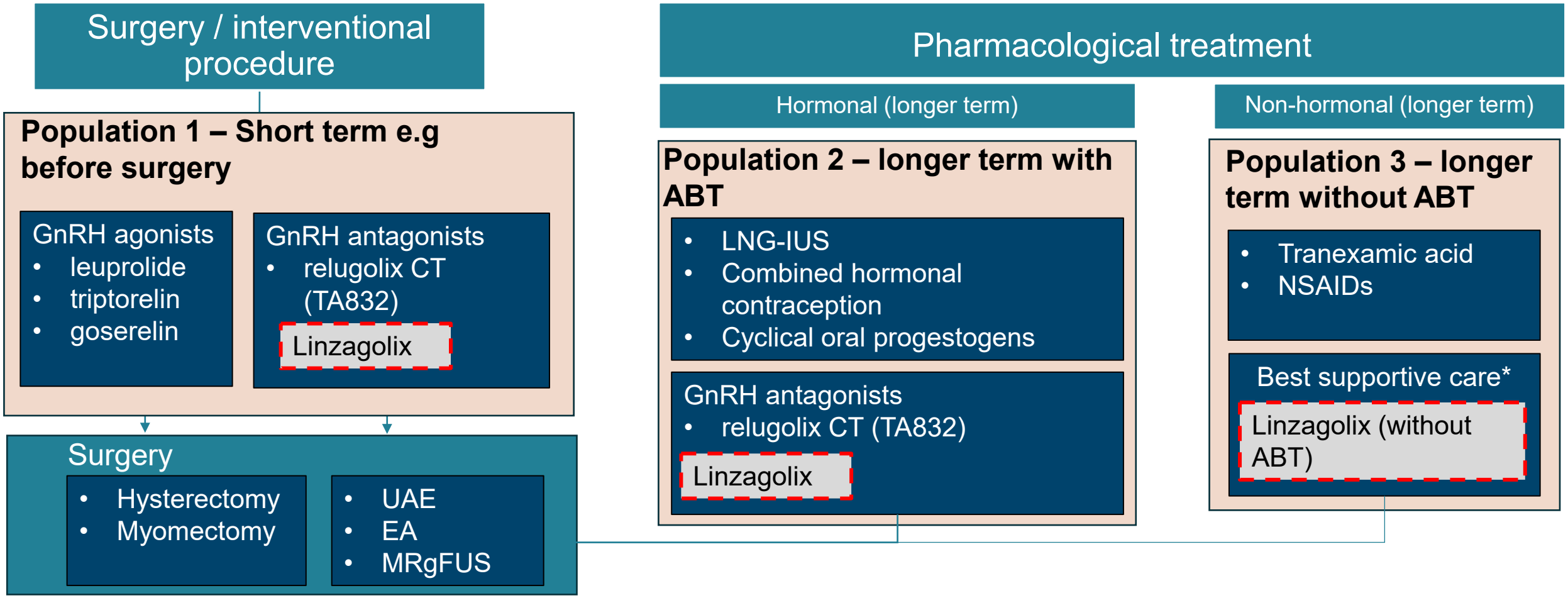
Symptoms, prognosis and treatment types

- 25-30% of people with uterine fibroids experience moderate to severe symptoms
- Moderate to severe symptoms include pain, heavy menstrual bleeding (HMB) potentially leading to anaemia and reproductive dysfunction
- Pharmacological treatments include GnRH analogues, comprising GnRH agonists (overstimulate GnRH receptors resulting in later desensitisation) and GnRH antagonists (which bind and block those receptors)
- GnRH antagonists may use hormonal add back therapy to reduce adverse effects (e.g bone mineral density loss)

Abbreviations: GnRH, gonadotropin releasing hormones

Treatment pathway

Moderate to severe symptoms of uterine fibroids



Abbreviations: GnRH, gonadotropin releasing hormone; UAE, uterine artery embolization; EA, endometrial ablation; MRgFUS, magnetic resonance guided focused ultrasound; LNG-IUS, levonorgestrel intrauterine system; NSAID, non-steroidal anti-inflammatory drug; ABT, add back therapy; CT, combination therapy

*Diagram reproduced from company submission Figure 5 which is based upon NG88 and TA832

Patient perspectives

No submissions were received from patient organisations for this appraisal. Key points from the patient organisation submission for TA832 (relugolix CT) are presented below.

Fibroid Embolisation: Information, Support, Advice (FEmISA)

Current treatment limitations:

- Treatment of symptomatic fibroids used for short-term before hospital treatment
- Ulipristal acetate withdrawn due to unacceptable side effects and liver failure association
- Hysterectomy and endometrial ablation not options for women wishing to preserve fertility

Unmet need

- A non-invasive, safe and effective treatment associated with low morbidity and mortality and that preserves fertility, sexual function, with minimal side effects and ability to return to work and normal life quickly

Long term effectiveness and safety (TA832 Appeal) – The recommendation from TA832 was appealed by FEmISA

- FEmISA raised concerns that the clinical effectiveness and safety evidence was only available for 1 year but the FAD stated that it could be used long term in line with the marketing authorisation

- A second appeal point was that the FAD stated that relugolix CT preserved the uterus and fertility however there was no evidence of any preservation of fertility by relugolix CT.

Abbreviations: GnRH, gonadotropin releasing hormone; FAD, final appraisal document; CT, combination therapy

Clinical perspectives

Clinically meaningful response

- Amelioration of patients symptoms and improvement of quality of life
- In some cases this would include decrease in fibroid size and prevention of regrowth

Unmet need, innovation and benefits

- Therapies that reduce symptoms with minimal adverse effects and that are amenable to individualised medicine needed
- Different linzagolix regimens beneficial for individualised care and allow titration in response to adverse events or desired effect
- Linzagolix would be more beneficial for those who do not want or cannot have ABT

Longer term efficacy and safety

- 2 year data published for relugolix CT (another GnRH antagonist) showed that 52 week response and safety profile were maintained at 104 weeks.
- Expects that people who would have linzagolix for over 52 weeks would respond in line with the PRIMROSE trials

"As more women become aware that they can have GnRH antagonists without addback with bone preservation with lower doses they may opt for this method of treatment"

Linzagolix offers choice to administer medication on an individualised basis depending on the clinical scenario, response and adverse event profile or a patient. It is thus an innovation above existing therapies

NICE Abbreviations: ABT, add back therapy; GnRH, gonadotropin releasing hormone; CT, combination therapy

Equality considerations

- Black women have an increased risk of developing uterine fibroids, are more likely to have large and multiple fibroids and on average these develop 5-6 years earlier than White women
- Black women also experience higher rates of hospitalisation and surgical intervention compared to White women
- The risk of uterine fibroids increases with age up to menopause
- Linzagolix would be available to everyone with moderate to severe symptoms of uterine fibroids; this may include people who are trans or non-binary
- Clinic visits for treatment with GnRH agonists can result in significant financial and time costs – this could be a particular problem for people from lower socioeconomic groups
- **Clinical expert**: “Black women suffer from lack of equity of access and outcomes when it comes to certain managements for uterine fibroids”

Key issues

Type of issue	Issue	Resolved?	Impact	Analysis
Decision problem and analysis used	Definition of populations in decision problem and appropriateness of type of economic evaluation chosen	No	Large	Both
	Uncertainty around market share of relugolix CT and its use as a comparator in cost-comparison analyses	No	Large	CCA
Evidence on clinical effectiveness	Similar health benefits between linzagolix and GnRH agonists and relugolix CT	No	Large	Both
	Uncertainty around generalisability of PRIMROSE trials	No	Moderate	Both
Cost effectiveness	Uncertainty around post-surgery recurrence of symptoms	Not currently resolvable	Unknown	Both
	Source of data and analysis used to calculate utility values	No	Large	CUA
	Inclusion of vitamin D and calcium in BSC	No	Small	CUA
	Distribution of surgery types	No	Small	Both
	Health resource usage and unit costs	No	Small	CUA
	How discontinuation is modelled (AE only versus all reasons)	Yes	Small	CUA

Abbreviations: CT, combination therapy; GnRH, gonadotropin releasing hormone; BSC, best supportive care; CCA, cost-comparison analysis; CUA, cost-utility analysis; CT, combination therapy

Linzagolix (Yselty, Theramex)

Technology details

Marketing authorisation	• "Treatment of moderate to severe symptoms of Uterine Fibroids in adult women of reproductive age" – Granted 14/06/2022
Mechanism of action	• GnRH antagonist which mediates a dose dependent reduction in serum estradiol and progesterone. This may reduce symptoms and size of uterine fibroids.
Administration	• Oral tablet taken once daily. • Four dosing regimens available, 100mg and 200mg with or without add back therapy. Selected based on individual's needs* • ABT is estradiol 1mg and norethisterone acetate 0.5mg (once daily additional tablet)
Price	• [redacted] per 28-pack of 100mg or 200mg tablets, £13.20 per 84 pack of ABT tablets • List price for 12 months of treatment is [redacted] (no ABT) or [redacted] (with ABT) • A confidential patient access scheme applies to Linzagolix.

***EAG note: It is unclear what proportions of the indicated population correspond to each dose regimen**

 Abbreviations: LH, luteinising hormone; ABT, hormone add back therapy

Population subgroups summary

Population 1	Population 2	Population 3
• Linzagolix for 6 months or less (e.g waiting for surgery) • Company estimates [redacted] of UK patients have surgery and [redacted] of patients treated with the aim of reducing fibroid volume short term had a GnRH antagonist	• Linzagolix with ABT longer term (may or may not have surgery) • Company estimates [redacted] of UK patients have long-term pharmacological treatment	• Add back therapy not suitable. Linzagolix alone longer term (may or may not have surgery) • Company market research estimates [redacted] and [redacted] of UK patients contraindicated to or would prefer not to have ABT
• Intervention: 200mg linzagolix without ABT	• Intervention: Linzagolix 200mg with ABT	• Intervention: Linzagolix only, 200mg for 6 months followed by 100mg
• Comparators: relugolix CT (GnRH antagonist), GnRH agonists	• Comparators: relugolix CT	• Comparators: BSC

EAG:

- Uncertainty around size of population 3 in practice. Clinical expert had not encountered anyone from this group
- Note that neither company submission nor SMPC give criteria for selecting a dose
- Company's market research methodology and relevance to moderate to severe patients is unclear

Is linzagolix positioned in the appropriate populations?
What are the most appropriate comparators for linzagolix in each of the three populations?

Abbreviations: GnRH, gonadotropin releasing hormone; ABT, add back therapy; CCA, cost-comparison analysis; CUA, cost-utility analysis; BSC, best supportive care

Key issue: Comparator market share

Background

- Cost-comparison requires intervention to have similar clinical efficacy to at least one NICE approved comparator

EAG comments [mention tech team considerations if relevant]

- EAG expert estimated 90% of people have GnRH agonists in their practice and relugolix CT uptake is low
- Uncertain if their experts' estimates reflect wider NHS practice
- Company have not provided market share data for the specific population subgroups

Company

- Market research estimates that [redacted] of people using pharmacological treatments for purposes of longer term reduction in uterine fibroid volume in the UK use GnRH antagonists and [redacted] use GnRH agonists.

NICE technical team comments

- NICE cost comparison methods "The chosen comparator must be established in practice and have substantial use in the NHS"

Clinical expert

- All patients who present with anaemia and HMB and awaiting surgery would have relugolix CT (~10-20% of those waiting for hysterectomy or myomectomy) – *Corresponds roughly to Population 1*
- ~20% of people requiring longer term use after no response to first line treatment would have relugolix CT

Are relugolix CT and GnRH agonists appropriate comparators for the cost-comparison analyses for populations 1 and 2?

NICE

Abbreviations: EAG, external assessment group; GnRH, gonadotropin releasing hormone; CT, combination therapy

Clinical effectiveness

- PRIMROSE 1 and 2 trials (double blind RCTs) and their pooled analysis

- PRIMROSE 3, open label off treatment extension trial

NICE National Institute for Health and Care Excellence

Key clinical effectiveness evidence

Clinical trials for linzagolix

- PRIMROSE 1 and 2 trials compare the 4 linzagolix regimens with placebo. Primary outcome is response (reduction in HMB*), various other outcomes measured include change in uterine and fibroid volume.
- Duration 52 wks, key outcomes reported at 24 wks. OLE (PRIMROSE 3) reported some outcomes past 52 weeks.

Other relevant trials – for indirect comparisons

- LIBERTY 1 and 2 trials compare relugolix CT with placebo with a primary outcome of response (reduction in HMB)
- PEARL trials compare leuprolide acetate to placebo. Outcome of reduction in HMB defined differently (PBAC score of less than 75) to PRIMROSE and LIBERTY trials (< 80ml MBL and 50% reduction from baseline, assessed using biochemical AH method)

Indirect treatment comparisons (NMAs and MAICs)

- NMAs were used to compare linzagolix regimens to relugolix CT for: response, % change in MBL, pain improvement, % change in primary fibroid volume, % change in haemoglobin, HRQoL change
- NMAs were provided for the pooled PRIMROSE analysis and for PRIMROSE 1 and 2 separately

- MAICs also used to explore impact of differences in baseline characteristics in PRIMROSE and LIBERTY trials.

- NMAs alone were used to compare linzagolix regimens to leuprolide acetate (GnRH agonist proxy) only possible for three outcomes (response, change in primary fibroid volume and change in haemoglobin from baseline).
  - EAG considered this comparison to be unreliable

Abbreviations: MBL, menstrual blood loss; HMB, heavy menstrual bleeding; OLE, open label extension; AH, alkaline haematin; CT, combination therapy; HRQoL, health related quality of life; CT; combination therapy; NMA, network meta-analysis
*Response defined as ≤80ml reduction in MBL and ≥50% from baseline, assessed using biochemical AH method).

Key issue: Generalisability of clinical trial evidence

Background – Populations in the model were excluded from the PRIMROSE trials

- Population 1: People who would use linzagolix for 6 months or less (e.g whilst waiting for surgery)
- Population 2: People who would use linzagolix longer term (with ABT)
- Population 3: People who would use linzagolix longer term but who can or will not have ABT
- Within trial baseline characteristics similar between arms however differences in ethnicity and BMI between trials

EAG comments

- People in the trials not eligible to have surgery within 6 months (Population 1)
- Maximum trial duration 52 of weeks (some outcomes at 64 weeks) does not fully reflect Population 2
- People contraindicated to ABT excluded from PRIMROSE trials. Company assume patients randomised to the "no ABT" regimens are suitable proxies for contraindicated people. Uncertain if this is valid. (Population 3)
- EAG Clinical expert considered that Population 3 was very small and its relevance to practice uncertain.
- Each trial represents one aspect of NHS clinical practice. PRIMROSE 1 akin to practice in London, PRIMROSE 2 more reflective of EAG expert's own practice in Southampton

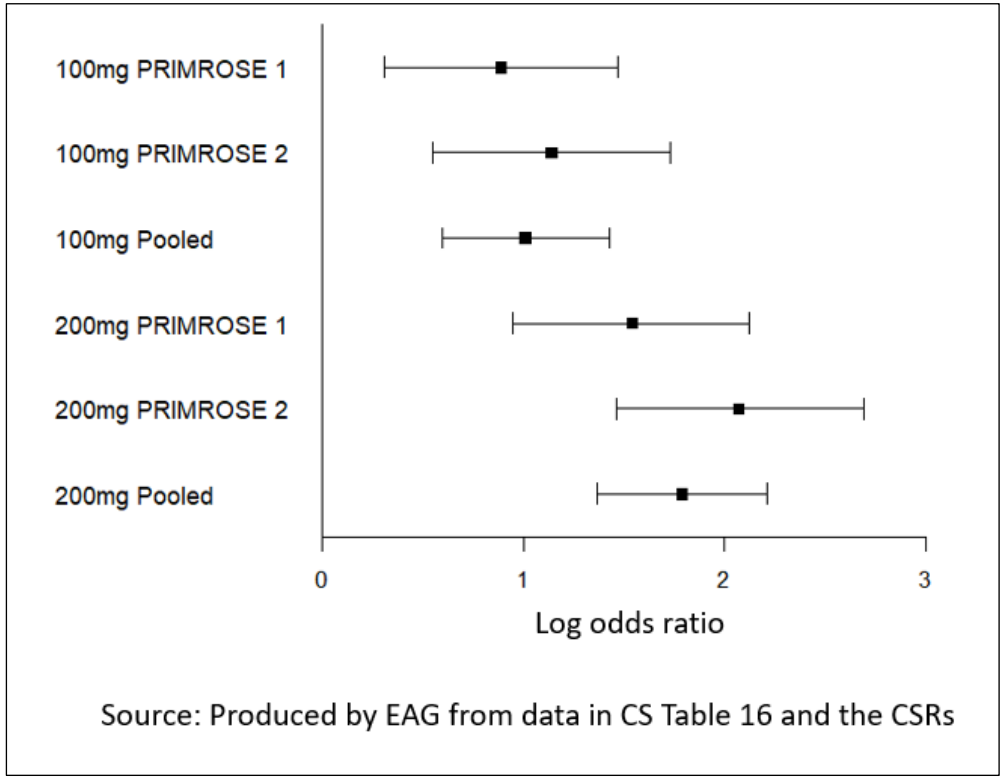
Clinical expert

- Does not expect responses to differ between the PRIMROSE trial populations and the three modelled populations but notes that future studies should investigate this issue
- Combination of PRIMROSE 1 and 2 is reflective of people who have severe uterine fibroid symptoms in the UK

Is the evidence from the PRIMROSE trials generalisable to the clinical practice populations that were modelled and to the population in NHS practice?

Abbreviations: ABT, hormone add back therapy; HMB, heavy menstrual bleeding; EAG, external assessment group

PRIMROSE trials – primary outcome week 24 (reduced HMB)



Source: Produced by EAG from data in CS Table 16 and the CSRs

	Placebo n=205 (%)	100mg n=191 (%)	100mg + ABT n=208 (%)	200mg n=208 (%)	200mg + ABT n=200 (%)
Yes	66 (32.2)	108 (56.5)	149 (71.6)	155 (74.5)	169 (84.5)
No	139 (67.8)	83 (43.5)	59 (28.4)	53 (25.5)	31 (15.5)
OR		2.75	5.54	5.99	10.77
95%CI		1.82; 4.16	3.61; 8.50	3.92; 9.15	6.66; 17.42

- People on linzagolix more likely to respond than placebo (dose response effect)
- Difference between all linzagolix doses and placebo statistically significant at 24 weeks (separate and pooled analysis) which was maintained at week 52 for all groups

- Results suggest a placebo effect which company suggest may be caused by non-compliance with sanitary product collection in trial (which would affect placebo group more as they have higher bleeding)
- EAG acknowledge as speculative and there could be other reasons for effect (e.g. regression to the mean). Notes that placebo effect increases slightly from 24 to 52 weeks
- Linzagolix regimens associated with statistically significant improvements versus placebo in secondary outcomes with exception to EQ-5D-5L (all regimens) and primary and uterine volume (100mg no ABT only) – See backup slide

NICE Abbreviations: EAG, external assessment group; OR, odds ratio; 95%CI, 95% confidence intervals;

Adverse events

- Incidence of TEAEs was slightly higher across the linzagolix regimens compared with placebo
- Most TEAEs were mild or moderate in severity. Serious and severe TEAEs were rare and broadly similar across all groups
- TEAEs leading to permanent discontinuation was low and similar across all groups
- At week 52 fewer TEAEs were reported than at week 24 and most that were reported were mild to moderate in severity.
- Incidence of serious and severe TEAEs was low and incidence lower than at week 24.
- Appears to be a dose-dependent reduction in BMD during the first months of treatment. This was only clinically meaningful for the 200mg (no ABT) dose at 24 weeks. (assuming a ≥5% change would be clinically meaningful)
- **EAG note:** during continued treatment BMD loss was less rapid although it is uncertain whether this pattern would be sustained in the longer term.
- **Clinical expert note**: Publication of longer term (2 year) safety data shows no new adverse events through 104 weeks for relugolix CT.

Is the adverse events evidence from the PRIMROSE trials generalisable to the clinical practice populations that were modelled and to the population in NHS practice?

Abbreviations: TEAE, treatment emergent adverse event; ABT, hormonal add back therapy; BMD, bone mineral density; CT, combination therapy

NMA results – Linzagolix vs relugolix CT – Response (fixed effects)

Fixed effects NMAs for response

Random effects NMA for response (pooled only)

[Please note different X axis scale]

- EAG were unable to verify the NMA code used
- Credible intervals in the fixed and random effects analysis are so wide it is not possible to estimate where the true effect may lie
- Linzagolix 200mg + ABT likely [redacted] to relugolix CT (See clarification response table 13)
- This appears to be driven by large effect in PRIMROSE 2
- relugolix CT is likely [redacted] to all other linzagolix regimens whose credible intervals lie [redacted]
- Similarity of linzagolix and relugolix CT at eliciting response [redacted]
- EAG prefer random effects NMA due to between trial heterogeneity.
- Ideally, non-inferiority analyses would have been pre-specified to inform NMAs and allow conclusion on treatment similarity
- To make a conclusion on clinical similarity with trials powered for superiority analysis would require sufficiently narrow credible intervals

Abbreviations: NMA, network meta-analysis; MAIC, matching adjusted indirect comparison; ABT, hormone add back therapy, ESS effective sample size;

NMA results – Other outcomes summary (linzagolix vs relugolix)

Outcome	Model	Linzagolix 100 mg	Linzagolix 100 mg plus add back therapy	Linzagolix 200 mg	Linzagolix 200 mg plus add back therapy
Response	Fixed effects				
Response	Random effects				
% change in menstrual blood loss	Fixed effects				
% change in in menstrual blood loss	Random effects				
Pain	Fixed effects				
Pain	Random effects				
% change in primary fibroid volume	Fixed effects				
% change in primary fibroid volume	Random effects				
% change in haemoglobin	Fixed effects				
% change in haemoglobin	Random effects				
Change in uterine fibroid symptom quality of life score	Fixed effects				
Change in uterine fibroid symptom quality of life score	Random effects				

Please see backup slides 36 to 40 for details

Key issue: Similar health benefits (Pop. 1 and 2)

Unclear if the analyses show that linzagolix is clinically similar to comparators

Background

- Cost-comparison methodology (populations 1 and 2), requires similar clinical efficacy between linzagolix and comparators, which is uncertain

Company

- Prefer fixed effects NMAs with have credible intervals that do not indicate a difference in efficacy between most linzagolix regimens and relugolix CT for most outcomes.

EAG comments

- EAG prefers random effects NMAs (greater accounting of heterogeneity, which appears to be present)
- 200mg without ABT (population 1) statistically [redacted] only for reduction in primary fibroid volume
- 200mg + ABT appears to have [redacted] efficacy against relugolix CT (response and reduction in fibroid volume)
- Company appears to assume that statistical non-significance equals similarity in clinical efficacy
- Conclusions on clinical similarity are difficult to make due to the wide credible intervals for many NMAs
- Clinical similarity between linzagolix regimens and relugolix CT does not appear to be supported for key outcomes
- NMAs for linzagolix versus leuprolide acetate hard to interpret due to lack of reporting and are of limited use

Does the committee consider that linzagolix is clinically similar to relugolix CT and GnRH agonists?

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

Cost effectiveness

Cost-comparison model for populations 1 and 2

Cost utility model for population 3

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Company's model overview

Populations 1 & 2 cost-comparison

- Four states, on/off treatment, menopause, death
- 28-day cycle
- Costs included: drug, administration, healthcare resource use and surgery
- 45.1% of people assumed to have surgery, applied as a one of cost in cycle 0.

Population 1 (200mg, no ABT)

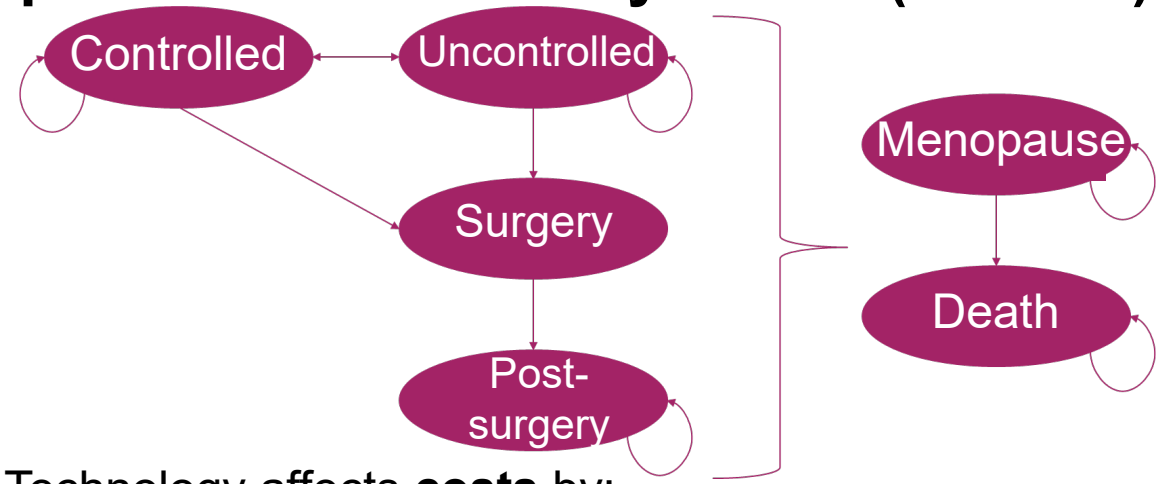
- Time horizon: 6 months
- No clinical efficacy parameters included, everyone is on treatment for 6 months

Population 2 (200mg, with ABT)

- Treatment discontinuation rate of [redacted] discontinuation from PRIMROSE trials was converted to [redacted] per cycle in the model
- Menopause and general mortality modelled from literature estimates
- No treatment or surgery after menopause

Abbreviations: QALY, quality adjusted life year; UFS-QoL, uterine fibroids symptoms and quality of life score; PSS, prescribed specialist services

Population 3 cost-utility model (no ABT)



- Technology affects **costs** by:
  - Accruing drug and health state resource costs
  - Rates of surgery and distribution of types
- Technology affects **QALYs** by:
  - Affecting transition through health states and associated utility (and adverse event incidence)
    - Transition probabilities derived from 24 week clinical trial results
  - Reducing overall probability of surgery
  - Changing distribution of surgery
- Assumptions with greatest ICER effect:
  - Recurrence rate and treatment withdrawal rates
  - Choice of HRQoL data (EQ-5D-5L vs UFS-QoL)

Key issue: Utilities (Population 3 only)

Background

- PRIMROSE 1 & 2 trials collected QoL data using UFS-QoL and EQ-5D-5L instruments, (mapped to EQ-5D-3L and using a linear mixed model to estimate utility for controlled and uncontrolled bleeding health states)
- Key driver of cost-effectiveness estimates

Company

- Base case uses UFS-QoL mapped to EQ-5D-3L utility values (controlled [redacted], uncontrolled [redacted],) as the disease-specific UFS-QoL is a more reliable measure to capture QoL in people with uterine fibroids
- Scenarios provided using EQ-5D-5L mapped to EQ-5D-3L (controlled [redacted], uncontrolled [redacted],) and utility estimates from the Hux et al (2015) study (controlled 0.73, uncontrolled 0.55)

EAG comments

- Company's mapping is consistent with TA832 (relugolix CT) where UFS-QoL was mapped to EQ-5D-3L (in the absence of complete EQ-5D-5L data)
- Unable to verify the linear mixed model used to estimate utility. Provide scenarios to explore LMM utility function.
- Using the EQ-5D-5L mapped to EQ-5D-3L scenario increases the total QALYs more for the BSC arm, which decreases the incremental QALYs and raises the linzagolix ICER substantially. (EAG base case)
- Acknowledge company preference for disease specific measures (confirmed by their expert) but also note that NICE reference case prefers EQ-5D data where available.

Do the committee consider the utility estimates mapped from the UFS-QoL or the EQ-5D-5L to be more appropriate?

Abbreviations: QoL, quality of life; UFS-QoL, uterine fibroid severity quality of life score; ICER, incremental cost-effectiveness ratio

Key issue: Post surgery recurrence of symptoms

Background

- The model assumes that once people enter the “post-surgery” state they stay there until moving to the menopause state. This implies that there is no recurrence of symptoms after any surgery type.

EAG comments

- Uncertainty about how the prognosis of different surgery types will vary and whether patients who have surgeries other than hysterectomies might experience recurrence of UF symptoms
- Would have preferred an option in the model to allow modelling of recurrence from the post-surgery state for both arms.

Clinical expert

- Not possible to have zero recurrence after all surgery types. As long as the womb is retained there is a chance of recurrence as fibroids develop from single muscle fibres within the uterus.
- The recurrence of fibroids and symptoms is complex, depending on: type of surgery, number and size of fibroids and the expertise of the surgeon
- As a general rule recurrence is more common after laparoscopic surgery than after open surgery and is least common for hysteroscopic surgery. (People having hysterectomy have no chance of recurrence of symptoms)
- 5-10% of women having surgical interventions for fibroids will need another intervention within 5-10 years (this proportion will fall with increasing age)

NICE

Is it appropriate to assume no recurrence of symptoms of uterine fibroids after surgery?

Costs breakdown (Population 3)

Linzagolix drug costs

- Treatment discontinuation modelled at [redacted], and [redacted] per cycle for 100mg and 200mg of linzagolix respectively and [redacted] per cycle for BSC in both base cases
- At 6 months everyone on linzagolix 200mg moves to the 100mg regimen (see line X on graph)
- Total costs largely driven by high cost of surgery. Incremental costs driven by drug costs of linzagolix.

Analysis	Intervention	Surgery costs	Drug costs	Administration costs	Resource use costs	AE costs	Total
Company	Linzagolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base	Linzagolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
case	BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Month	% on treatment
0	[redacted]
6	[redacted]
12	[redacted]
18	[redacted]
24	[redacted]

NICE Abbreviations: BSC, best supportive care; TTD, time to discontinuation

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Source of utilities	PRIMROSE UFS-QoL mapped to EQ-5D-3L	PRIMROSE EQ-5D-5L mapped to EQ-5D-3L
Unit costs	Gynaecologist £185.51, MRI £197.37	Gynaecologist £181.26, MRI £255.41
Medications used for BSC	NSAIDs and iron supplements	Addition of Vitamin D and Calcium
Surgery and HRU	See backup slide	

Clinical expert

- The company surgery numbers are reflective of general clinical practice. However there is published literature that differs from both estimates
- Both scenarios would be appropriate depending on how linzagolix is introduced (hospital only vs shared care with GP). However there are no one year follow ups at present for GnRH antagonists

What are the committee preferred assumptions for each of these parameters?

Abbreviations: NSAID, non-steroidal anti inflammatory drug; BSC, best supportive care; HRU, healthcare resource use
*Company base case as per TA832. EAG base case after consultation with EAG clinical expert.

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Company base case results – Cost comparison

Treatment	Population #1		Population #2	
	Total costs	Incremental costs	Total costs	Incremental costs
Linzagolix	[redacted]	-	[redacted]	-
relugolix CT	£3,411	[redacted]	£4,752	[redacted]
Leuprorelin	£3,441	[redacted]	-	-
Goserelin	£3,407	[redacted]	-	-
Triptorelin	£3,482	[redacted]	-	-

EAG base case results – Cost comparison

Treatment	Population #1		Population #2	
	Total costs	Incremental costs	Total costs	Incremental costs
Linzagolix	[redacted]		[redacted]	-
relugolix CT	£3,417	[redacted]	£4,757	[redacted]
Leuprorelin	£3,446	[redacted]	-	-
Goserelin	£3,413	[redacted]	-	-
Triptorelin	£3,488	[redacted]	-	-

Base case results – Population 3 (200mg no ABT)

Company deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
BSC	[redacted]	[redacted]	-	-	-	-	
Linzagolix 200mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,392	0.02	0.04

EAG deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB (£20k /QALY)	NHB (£30k /QALY)
BSC	[redacted]	[redacted]					
Linzagolix 200mg	[redacted]	[redacted]	[redacted]	[redacted]	£28,973	-0.017	0.001

EAG notes that company probabilistic results were in line with deterministic ones.

No.	Scenario (applied to company base case)	Δcosts (£)	Δ QALYs	ICER (£/QALY)
1	Include vitamin D and calcium in BSC and EAG surgery distribution	[redacted]	[redacted]	£15,705
2	EAG healthcare resource use and unit costs	[redacted]	[redacted]	£14,478
3	Utilities mapped from EQ-5D-5L	[redacted]	[redacted]	£28,973

Abbreviations: ICER, incremental cost effectiveness ratio; NHB, net health benefit

NICE National Institute for Health and Care Excellence

Thank you.

Backup slides follow

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

PRIMROSE trials baseline characteristics

Within trial baseline characteristics similar between arms. However, there are differences between trials.

Characteristic	PRIMROSE 1 (N=511)	PRIMROSE 2 (N=501)
Age (years)	42	43
Weight (Kg)	88	74
BMI	32.7	27
Black ethnicity	324 (63%)	25 (5%)
White ethnicity	167 (33%)	476 (95%)

EAG comments

- Each trial reflects an aspect of NHS practice. PRIMROSE 1 more reflective of a London practice, PRIMROSE 2 more reflective of Southampton for example
- Note that Black women are at higher risk for the development of uterine fibroids and often have more and larger fibroids, more severe symptoms earlier in life and higher rates of hospitalisation

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Source of utilities	PRIMROSE UFS-QoL mapped to EQ-5D-3L	PRIMROSE EQ-5D-5L mapped to EQ-5D-3L
Unit costs	Gynaecologist £185.51, MRI £197.37	Gynaecologist £181.26, MRI £255.41
Medications used for BSC	NSAIDs and iron supplements	Addition of Vitamin D and Calcium
Surgery and HRU	As per table below	

Type of surgery	Company*	EAG*
UAE	4.8%	20%
Endometrial ablation	0.0%	0.0%
MRgFUS	3.0%	0%
Abdominal myomectomy	25.7%	0%
Laparoscopic myomectomy	8.2%	0%
Hysteroscopic myomectomy	-	20%
Abdominal hysterectomy	51.8%	6%
Laparoscopic hysterectomy	6.4%	54%

Event	Company base case*		EAG base case*	
	Linzagolix	BSC	Linzagolix	BSC
GP Visit	0	0	2	2
DEXA scan	1	0	0	0
Full blood count	1	1	2	2
MRI	1	1	0	0

Clinical expert The company surgery numbers are reflective of general clinical practice. However there is published literature that differs from both estimates

Clinical expert - Both scenarios would be appropriate depending on how linzagolix is introduced (hospital only vs shared care with GP)
- However there are no one year follow ups at present for GnRH antagonists

Abbreviations: NSAID, non-steroidal anti inflammatory drug; BSC, best supportive care; HRU, healthcare resource use
*Company base case as per TA832. EAG base case after consultation with EAG clinical expert.

PRIMROSE pooled trial results – Secondary outcomes (24 weeks)

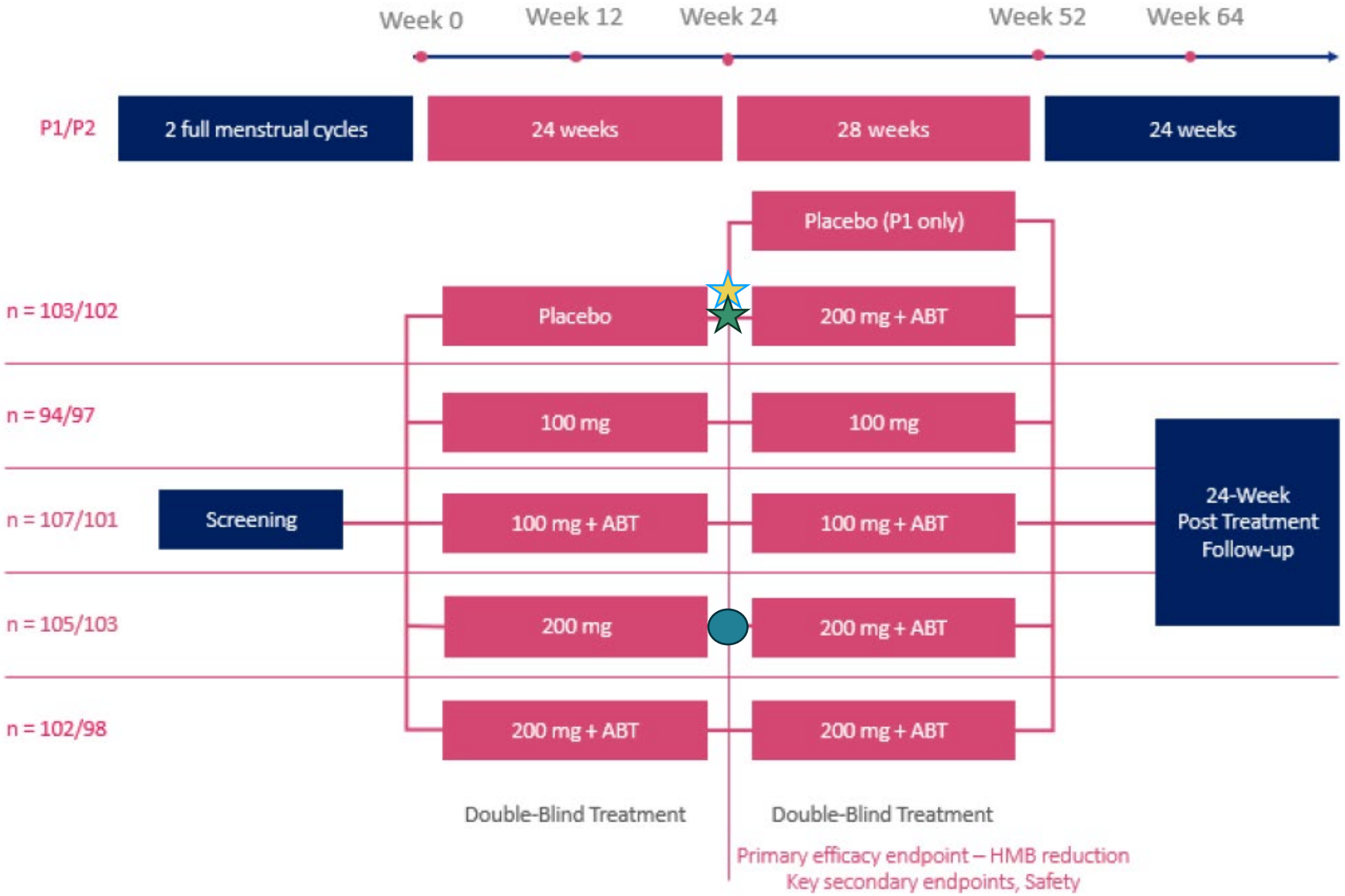
	Linzagolix regimen vs Placebo			
Outcome	100mg	100mg + ABT	200mg	200mg + ABT
1º fibroid volume CFB LS means of ratio to placebo (95%CI)	0.774 (0.633 to 0.945)	0.874 (0.716 to 1.067)	0.536 (0.441 to 0.650)	0.802 (0.659 to 0.977)
Uterine volume CFB LS means of ratio to placebo (95%CI)	0.834 (0.753 to 0.923)	0.925 (0.836 to 1.024)	0.609 (0.551 to 0.672)	0.841 (0.761 to 0.930)
Time to reduced HMB. HR (95%CI)	2.10 (1.54 to 2.85)	4.33 (3.22 to 5.81)	4.29 (3.20 to 5.74)	5.73 (4.28 to 7.67)
Amenorrhea OR (95% CI)	2.84 (1.77 to 4.56)	5.40 (3.43 to 8.49)	8.99 (5.68 to 14.24)	10.25 (6.42 to 16.35)
Pain – LS means difference from placebo (95%CI)	-1.29 (-1.88 to -0.69)	-1.64 (-2.23 to -1.05)	-2.38 (-2.97 to -1.80)	-2.12 (-2.71 to -1.53)
UFS-QoL LS means difference from placebo (95%CI)	9.18 (4.11 to 14.24)	15.49 (10.49 to 20.50)	19.40 (14.45 to 24.36)	18.85 (13.85 to 23.86)
EQ-5D-5L LS means difference from placebo (95%CI)	0.021 (-0.013 to 0.054)	-0.009 (-0.0042 to -0.024)	-0.003 (-0.035 to 0.030)	0.020 (-0.013 to 0.053)

- EAG note discrepancy around QoL results with the UFS-QoL showing a statistical improvement for all doses but the EQ-5D-5L not showing any significant differences.
- Note: Not all secondary outcomes presented. See Section B.2.6.2 of CS for details

NICE

Abbreviations: CBF, change from baseline; HR, hazard ratio; OR, odds ratio; CI, confidence intervals; ABT, hormone add back therapy; UFS-QoL, uterine fibroids symptom and quality of life score;
Green, linzagolix regimen statistically superior to placebo; yellow, linzagolix regimen not found to be statistically different to placebo

PRIMROSE trials study design



★ PRIMROSE 1 (P1)
- 50% of patients from placebo group switch to 200mg + ABT at week 52

★ PRIMROSE 2
- All people from placebo group switch to 200mg + ABT at week 52.

● Both trials
- ABT added to 200mg group to reduce risk of oestrogen deficiency

NICE

Abbreviations: ABT, hormone add back therapy

How company incorporated evidence into CUA model (Pop 3)

Input	Assumption and evidence source
Baseline characteristics	Aligned with PRIMROSE trial populations
Surgery	Rate and distribution of surgery types: As per TA832 and equal across arms Mortality risk from surgeries: TA832 and literature estimates. Recurrence not modelled.
Intervention efficacy	Uncontrolled > controlled: 24-week response rate from PRIMROSE pooled analysis used to estimate per 28-day cycle transition probability Controlled > uncontrolled: Expert opinion from market research (n=50)
Treatment discontinuation	Obtained from the PRIMROSE trials for linzagolix. relugolix CT assumed to be the same as Linzagolix 200mg + ABT
Other health states	Mortality: Age-matched general population mortality rates used Menopause (move to general population outcomes): Set to 51 years in line with UK based data and TA832
Comparator efficacy	24 week response rate for placebo from PRIMROSE trials.
Adverse events	Anaemia, headache, hot flush and nausea modelled based on PRIMROSE 1 and 2
Utilities	PRIMROSE UFS-QoL mapped to EQ-5D-3L. (Surgery related values from literature)
Costs	BNF, eMIT, NHS reference costs 2021/2022, PSSRU, literature sources
Resource use	Assumed the same as TA832

Abbreviations: ABT, hormone add back therapy; UFS-QoL, uterine fibroids symptoms and quality of life score; PSSRU, prescribed specialist services research unit; BNF, British national formulary

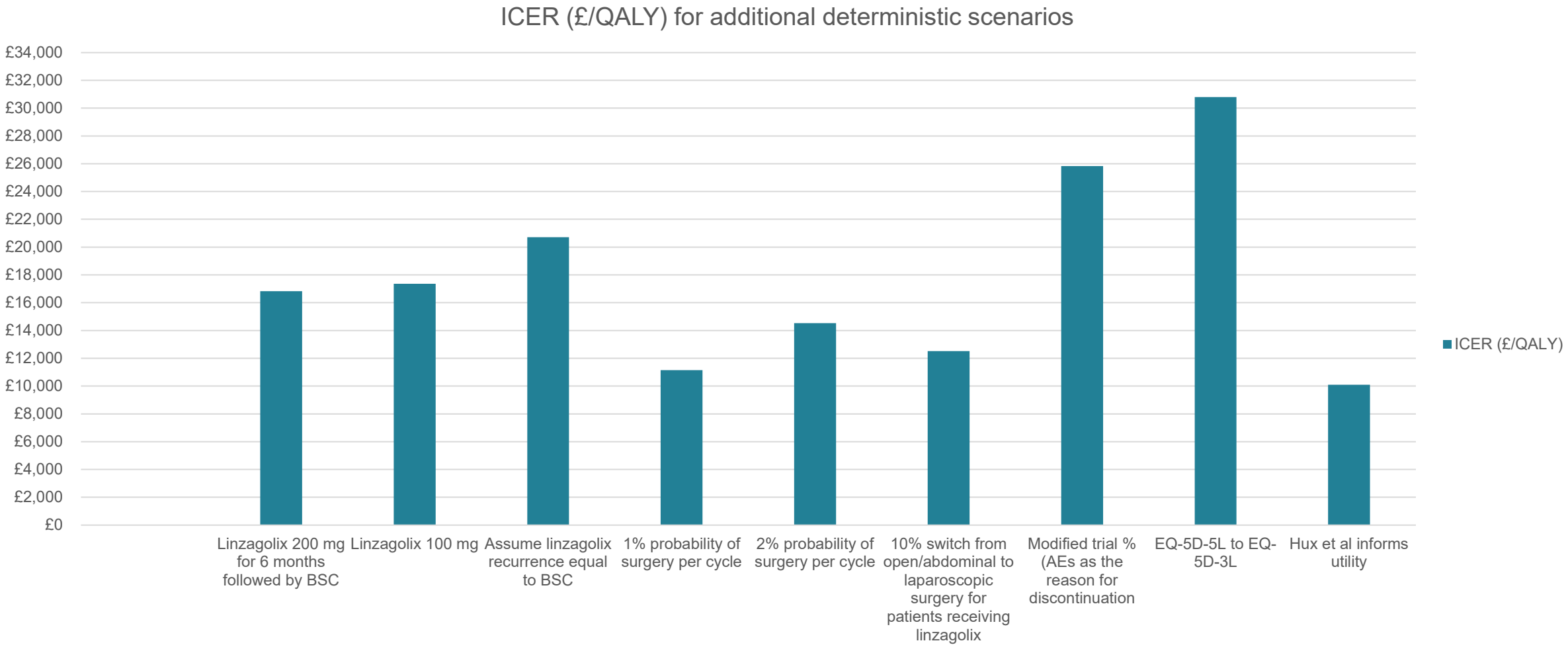
Key deterministic scenario analysis (CUA)

No.	Scenario (applied to company base case)	Incremental costs (£) versus relugolix CT	Incremental QALYs versus relugolix CT	ICER (£/QALY) versus relugolix CT
1	**Company base case**	[redacted]	[redacted]	£15,392
2	Use EQ-5D-5L mapped to EQ-5D-3L for utility	[redacted]	[redacted]	£30,803

No.	Scenario (applied to EAG base case)	Incremental costs (£) versus relugolix CT	Incremental QALYs versus relugolix CT	ICER (£/QALY) versus relugolix CT
1	**EAG base case**	[redacted]	[redacted]	£28,973
2	Use UFS-QoL mapped to EQ-5D-3L for utility	[redacted]	[redacted]	£14,478

NICE Abbreviations: CUA, cost-utility analysis

Company further deterministic scenario analysis (CUA)



Additional ICERs for scenarios which change ICER by 5% or more

Abbreviations:

NMA results – Linzagolix vs relugolix CT – MBL

[redacted]

Fixed versus random effects NMA for MBL

- Pooled analysis is EAG preferred for making inferences
- Using posterior rank probability (fixed effects NMA), relugolix CT is most likely to be the clinically [redacted] regimen
- Good agreement between fixed and random effects NMAs for this outcome

Abbreviations: NMA, network meta analysis; CT, combination therapy; MBL, menstrual blood loss; MAIC, matching adjusted indirect comparison

NMA results – Linzagolix vs relugolix CT – fibroid related pain

[redacted]

Fixed versus random effects NMA for fibroid related pain

- Pooled analysis has highest ESS but lower than for other outcomes suggesting poor matching
- Posterior rank probability (fixed effects) suggests Linzagolix 200mg regimens are most likely to be clinically [redacted].
- CI for random effects NMA are so wide no clear conclusion can be made on clinical similarity for either NMA model

NICE

Abbreviations: NMA, network meta analysis; CT, combination therapy; ESS, effective sample size; MAIC, matching adjusted indirect comparison

NMA results – Linzagolix vs relugolix CT – primary fibroid volume

[redacted]

Fixed versus random effects NMA for change in fibroid volume

- Pooled analysis has highest ESS but some missing data
- Uncertainties around approach used for measuring fibroid volume (how “primary fibroid” is defined)
- Posterior rank probabilities (fixed effects NMA) suggest 200mg regimen statistically [redacted]
- Random effects generally confirm results of fixed effects.

NICE

Abbreviations: NMA, network meta analysis; CT, combination therapy; ESS, effective sample size; MAIC, matching adjusted indirect comparison

NMA results – Linzagolix vs relugolix CT – haemoglobin % change*

[redacted]

[redacted]

Fixed versus random effects NMA for change in fibroid volume

- All ESS were below [redacted] suggesting poor matching
- Very wide credible intervals for both fixed and random effects NMAs. Not possible to determine clinical [redacted]

NICE

Abbreviations: NMA, network meta analysis; CT, combination therapy; ESS, effective sample size; MAIC, matching adjusted indirect comparison

*% change from baseline in patients with anaemia at baseline

NMA results – Linzagolix vs relugolix CT – UFS-QoL score

[redacted]

Fixed versus random effects NMA for UFS-QoL total score

- Pooled analysis highest ESS range but some missing data
- Posterior rank probabilities (fixed effects NMA) suggest relugolix CT is most likely to be the [redacted] regimen
- EAG consider that none of the linzagolix regimens are [redacted] to relugolix CT
- Random effects model shows greater uncertainty but does not change EAG consideration

Abbreviations: NMA, network meta analysis; CT, combination therapy; MBL, ESS, effective sample size; MAIC, matching adjusted indirect comparison

Other issue: Modelling of treatment discontinuation

Background

- Drug discontinuation for both arms in the model is informed from the PRIMROSE trials 24-week data.
- Two options for informing discontinuation. Trial based (all discontinuation from trial) or modified (only discontinuation due to AEs)
- Trial based includes: *participant request, loss to follow-up, adverse event, lack of efficacy, pregnancy, other.*
- Using the modified approach to discontinuation resulted in a much lower per cycle probability stopping treatment.

Treatment	Base case (Trial based)		Scenario analysis (modified)	
	Any reason withdrawal	Per cycle probability	AE only withdrawal	Per cycle prob. of TTD
Linzagolix 100mg	[redacted]	[redacted]	[redacted]	[redacted]
Linzagolix 200mg	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments

- Company's approach to modelling discontinuation is reasonable as in practice people may discontinue due to many reasons other than just AEs
- Considers it more appropriate though to use longer term 52-week data to inform discontinuation.

NICE Abbreviations: AE, adverse event

NMA/ITC Linzagolix versus relugolix CT– Populations 1 & 2

- NMAs used to compare PRIMROSE 1 & 2 trials (pooled) with LIBERTY 1 and 2 trials for: Response, % change in MBL, pain improvement, % change in primary fibroid volume, % change in haemoglobin, improvement in HRQoL
- EAG: good alignment between trials and similarly defined outcomes but differences in baseline characteristics

Characteristic	PRIMROSE 1	PRIMROSE 2	LIBERTY 1	LIBERTY 2
Black ethnicity	63%	5%	47%	42%
Hispanic/latino ethnicity**	11%		20.7%	
Uterine volume**	328.2		393.2	
Uterine fibroid volume**	98.9		72.0	
Baseline MBL (ml)*	207.6		229.2	
% Pain score ≥4*	77.1%		71.8	

- Company included scenario analysis using a MAIC to explore impact of differences in baseline characteristics
- EAG requested NMAs that included PRIMROSE trials separately which company provided
- Fixed and random effect models provided. EAG prefer random effects due to heterogeneity and possible treatment effect modifiers. Company prefer fixed.

Abbreviations: NMA, network meta-analysis; MBL, menstrual blood lost; MAIC, matching adjusted indirect comparison;

NICE * Significant to P<0.05, ** Significant to P<0.001, Highlighted orange = used as covariate for matching in MAICs (with change in haemoglobin). Ethnicity presented for individual trials to demonstrate differences between trials for each intervention.

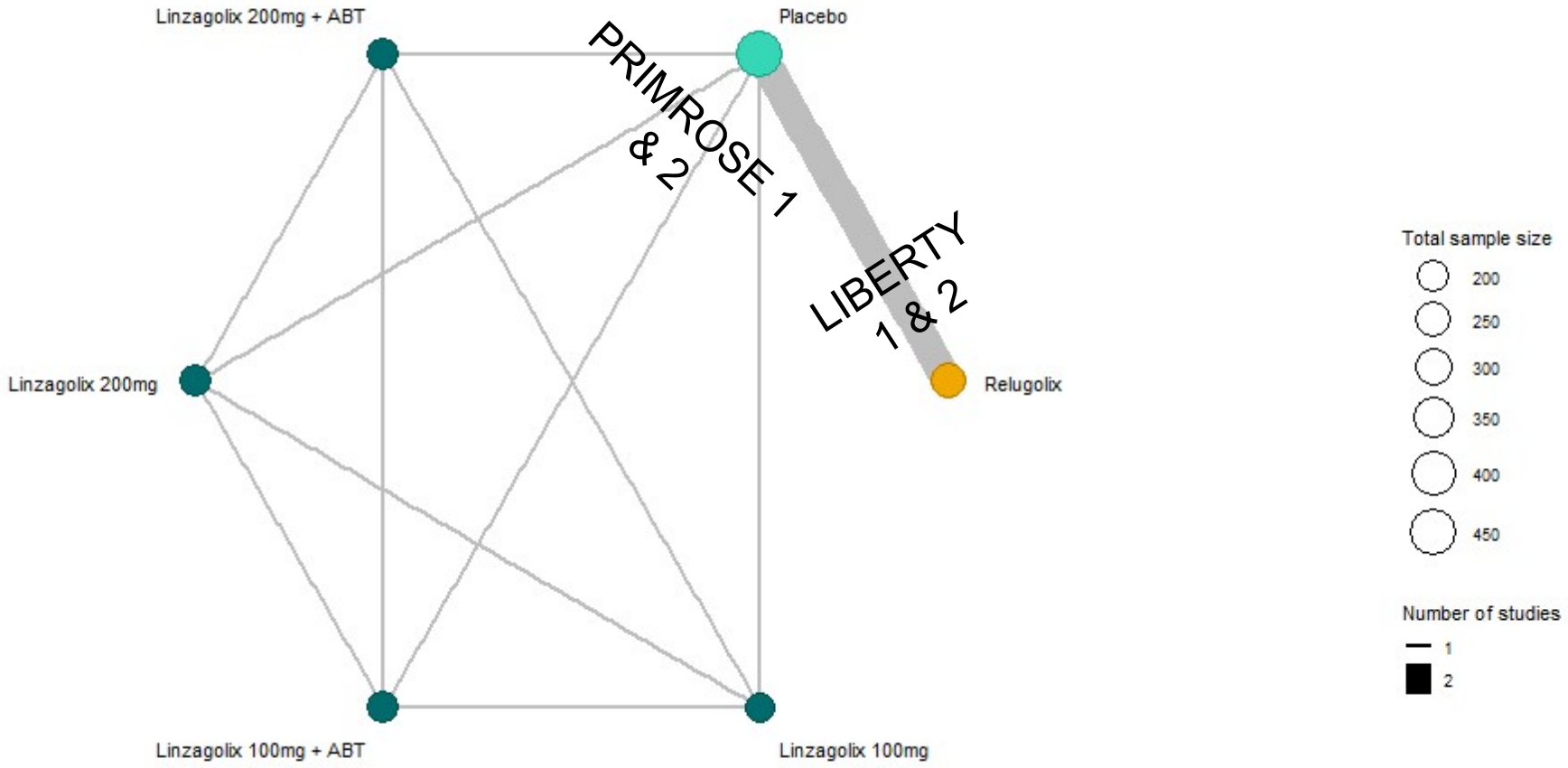
NMA/ITC methodology – Populations 1 & 2

Linzagolix versus GnRH agonists

- Company extended NMA to leuprolide acetate (as a proxy for GnRH agonists) for three outcomes: response (PRIMROSE, LIBERTY and PEARL trials) change in fibroid volume and change in haemoglobin from baseline (PRIMROSE and PEARL trials only). It was not possible to compare other outcomes.
    - PRIMROSE uses AH to measure MBL whereas PEARL uses PBAC, TA832 notes these are incompatible without adjustment. Unclear if adjustment has been done here
    - PEARL outcomes reported at 13 weeks compared to 12 or 24 weeks in PRIMROSE, unclear which were used in NMA
    - Heterogeneity in baseline characteristics of the PEARL trials compared to PRIMROSE and LIBERTY
- Company did not provide a MAIC to explore impact of heterogeneity in trial characteristics on the linzagolix versus leuprolide acetate NMAs.
- Fixed effect models only provided. EAG would prefer random effects due to heterogeneity and possible treatment effect modifiers.
- There are extensive limitations of the NMAs which compare linzagolix to leuprolide acetate and EAG consider the usefulness of the results limited.

Abbreviations: GnRH, gonadotropin releasing hormone; AH, alkaline haematin; PBAC, pictorial bleeding assessment chart; NMA, network meta-analysis

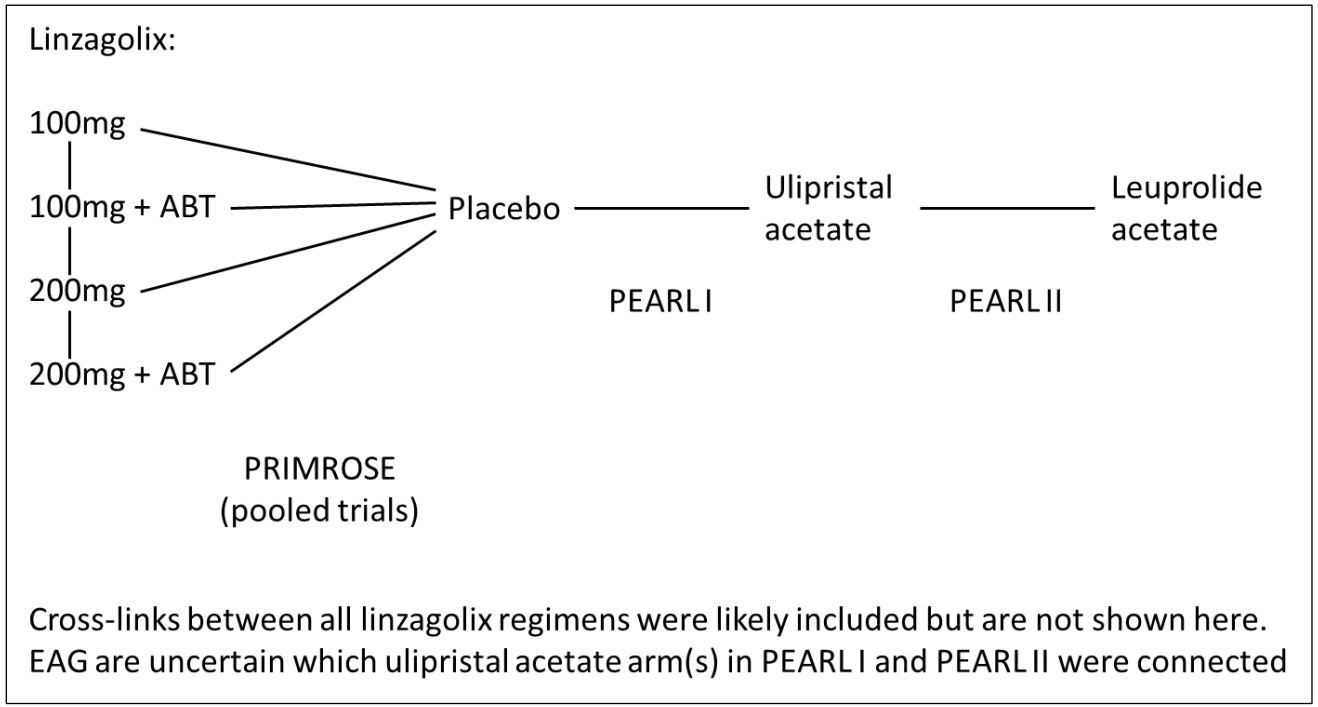
NMA/ITC network diagram(s)



Evidence network for NMAs comparing Linzagolix to relugolix CT (*Trial names added by NICE tech team)*

 Abbreviations: NMA, network meta-analysis

NMA/ITC network diagram(s)



EAG:

- Evidence network not provided in company clarification response. The above diagram shows EAG's assumed network for NMA with GnRH agonists
- Lack of methodological details about how the NMAs were conducted precludes any interpretation of whether linzagolix might have clinical similarity to leuprolide acetate.

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

How company incorporated evidence into cost-comparison model (Pop 1 & 2)

Input	Assumptions and evidence source	
	Population 1	Population 2
Surgery	Taken from TA832 (originally from PEARL II trial), 45.1% of patient assumed to have surgery. Average costs applied once in first cycle. Distribution from TA832 used.	
Treatment discontinuation	Not modelled (all people assumed to be on treatment for 6 months)	From pooled PRIMROSE trials. Assumed the same for linzagolix 200mg + ABT and relugolix CT [redacted]
Intervention efficacy	Not modelled. Assumed to be the same between all technologies. **(Key Issue)**	
Comparator efficacy		
Utilities	N/A	
Costs	BNF, eMIT, NHS reference costs 2021/2022, PSSRU, literature sources	

NMA/ITC results – Linzagolix versus leuprolide acetate

- Insufficient evidence has been provided by the company to determine whether linzagolix 200mg would have comparable effectiveness to other GnRH analogues

- EAG: “Given the extensive limitations of the NMAs comparing linzagolix against leuprolide acetate noted above, results of these analyses are provided in Appendix 3 for reference only”

NICE Abbreviations: GnRH, gonadotropin releasing hormones; EAG, external assessment group; NMA, network meta-analysis

Probabilistic base case

Company probabilistic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]			
Linzagolix 200mg	[redacted]	[redacted]	[redacted]	[redacted]	£15,357

Abbreviations: GnRH, gonadotropin releasing hormones; EAG, external assessment group; NMA, network meta-analysis