COST-UTILITY ANALYSIS OF LINZAGOLIX 200 MG PLUS ADD-BACK THERAPY (LINZAGOLIX + ABT) FOR SYMPTOMATIC TREATMENT OF ENDOMETRIOSIS

POSTER CODE: **EE304**

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OBJECTIVE

To assess the cost-effectiveness of linzagolix in combination with ABT compared to gonadotropin-releasing hormone (GnRH) agonists, for the treatment of symptomatic endometriosis in women who have not responded to first-line therapy.

BACKGROUND

Endometriosis is a chronic condition that is characterized by pelvic pain and dysmenorrhoea (DYS), significantly impairing health-related quality of life (HRQoL) and causing a substantial humanistic and economic burden [1,2]. First-line therapies typically include combined oral contraceptives or progestins. Current second-line medical treatments comprise injectable GnRH agonists, which are unsuitable for long-term use due to safety concerns, such as osteoporosis, highlighting the unmet need for tolerable and effective medical treatments suitable for long-term use [1,3]. Linzagolix, a novel oral GnRH antagonist, shows promise by effectively reducing endometriosis-associated pain and improving HRQoL while minimizing bone mineral density loss [4].

METHODS

A de novo semi-Markov model was developed from the perspective of the UK National Health Service (NHS). It simulates a cohort of pre-menopausal women diagnosed with symptomatic endometriosis, with moderate to severe endometriosis-associated pain (EAP) and a history of previous medical or surgical treatment for their endometriosis. It encompasses 17 distinct health states that reflect the varied response to both medical therapies and surgical procedures. The model is divided into two main components – an initial decision tree and a Markov chain – to represent the clinical pathway experienced by women with endometriosis in the UK, in which patients transition between defined health states, each associated with specific HRQoL and costs. The simplified model structure and flow of patients among the health states are presented in Figure 1.

Endometriosis treatment is individualized; therefore, patients may follow a multitude of possible treatment pathways, reflected in the subsequent treatment options included in the model. The model structure was informed by current clinical guidelines [1], existing literature on cost-effectiveness models for endometriosis [7,8], a comprehensive market survey representative of multiple European countries [5], and validation by leading clinical experts in gynaecology and surgery [6]. The model concludes with patients reaching menopause, which ultimately resolves endometriosis symptoms in the vast majority of cases [9]. A more detailed model structure and description can be found in the relevant National Institute for Health and Care Excellence (NICE) submission [10].

Table 1. Model characteristics

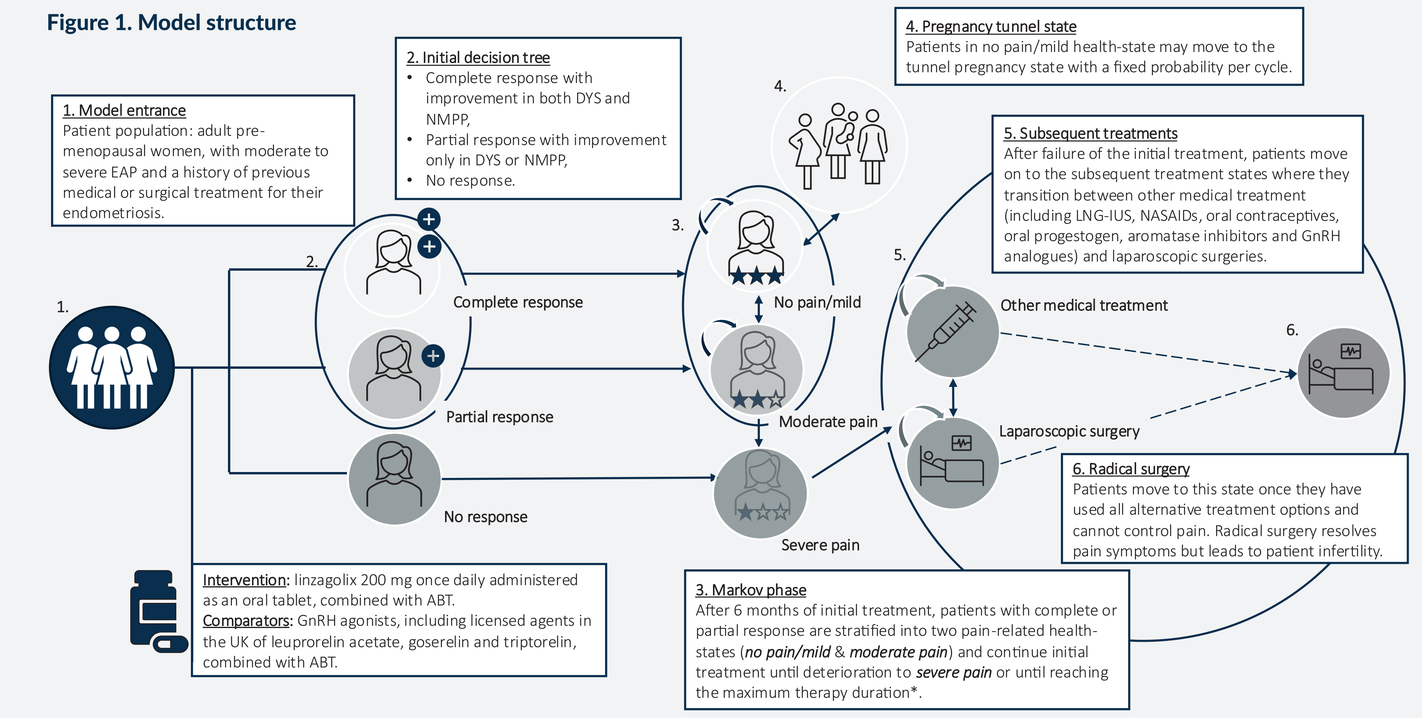
Section	Details
Design & perspective	De novo cost-utility model (hybrid decision-tree → semi-Markov)
Horizon, cycles, discounting	15.1-year horizon (from average baseline age of women in EDELWEISS 3 to average age of menopause in UK); two 3-month decision-tree cycles then 6-month Markov cycles
Discounting	3.5% annual discount for costs, life years (LYs) and quality-adjusted life years (QALYs) (in line with NICE reference case [11])
Population	Adult pre-menopausal women with moderate–severe EAP and prior medical/surgical treatment (mean age 34.9 years; from EDELWEISS 3)
Intervention & comparators	Linzagolix 200 mg + ABT vs composite injectable GnRH agonists (leuprorelin, goserelin, triptorelin)
Efficacy outcomes determining transitions in the model	**Decision tree:** • Complete response: reduction in DYS of ≥1.10 points on the visual rating scale (VRS) and in non-menstrual pelvic pain (NMPP) of ≥0.8 points on the VRS, along with stable or decreased use of analgesics for EAP • Partial response: reduction only in DYS or in NMPP **Markov phase:** patients categorized based on pain severity • No pain/mild: overall pelvic pain (OPP), VRS < 1 • Moderate: 1 ≤ OPP, VRS ≤ 2 • Severe: OPP, VRS > 2
Outcomes	Total and disaggregated costs, LYs, QALYs; incremental cost effectiveness ration (ICER) and £20,000/QALY willingness to pay threshold (WTP)

Abbreviations: ABT, add-back therapy; DYS, dysmenorrhoea; EAP, endometriosis-associated pain; GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYs, life years; NICE, National Institute for Health and Care Excellence; NMPP, non-menstrual pelvic pain; OPP, overall pelvic pain; QALYs, quality-adjusted life years; VRS, visual rating scale; WTP, willingness to pay threshold

MODEL ASSUMPTIONS AND LIMITATIONS

- The model represents a balance between accuracy and transparency and, whilst it is understood that patients could follow a multitude of treatment pathways, it captures the most typical pathways experienced by women according to UK clinical practice. It is assumed that treatment efficacy is evaluated after 6 months and continued only in patients with a response/partial response (as per EDELWEISS 3 VRS thresholds for DYS/NMPP).
- Patients on linzagolix continue treatment whilst in response, or until pregnancy or menopause. GnRH agonist treatment is capped at 1.5 years due to safety, based on the opinion of clinical experts and a market research survey [5, 6].
- The model assumes that women can become pregnant with a fixed probability per model cycle only in the health state representing symptom control (no or mild pain). This reflects a key treatment goal and is in line with clinical guidelines [1, 3].
- It is assumed that linzagolix and GnRH agonists are combined with ABT consisting of low doses of oestrogen and progestin, to prevent menopause-like symptoms. This approach aligns with treatment guidelines [1, 3] and clinical practice [5].

Figure 1. Model structure



Abbreviations: ABT, add-back therapy; DYS, dysmenorrhea; EAP, endometriosis-associated pain; GnRH, gonadotropin-releasing hormone; LNG-IUS levonorgestrel-releasing intrauterine system; NMPP, non-menstrual pelvic pain; NSAIDs, nonsteroidal anti-inflammatory drugs *Until menopause for linzagolix and until 1.5 years for GnRH agonists, in line with clinical practise and market research survey [5,6]

MODEL INPUTS

Table 2. Model inputs

Category	What is used in the model	Source(s)
Clinical efficacy (transition probabilities)	Month-3 and month-6 response splits (None/Partial/Complete) and month-6 continuation	EDELWEISS 3 statistical analysis [12]
	Allocation to pain states after month 6 (None/mild, Moderate, Severe). Cycle-to-cycle transitions among pain states	EDELWEISS 6 statistical analysis [13] ITC results [14-18]
	Transitions across Other medical treatment and Surgical treatment health states	UK market research and validated with clinical experts' opinion [5,6]
Utilities	Response-based utilities (None/Partial/Complete) Pain-based utilities (Severe, Moderate, None/mild)	Mixed effects regression models based on EDELWEISS 3 EQ-5D data [12]
	Utilities for Other medical treatment and Surgical health states. Disutilities related to surgical interventions	As Response-based utilities assuming proportion of patients responding to subsequent treatments. Disutilities based on the literature [19-21]
Resource use and costs	Drug dosing and costs categories	Relugolix STA [8]; SMPCs [22]
	Medical services and procedures costs	NHS tariffs [23]
	Specialist's visits costs and frequencies	Relugolix STA [8], Theramex [5, 6]
	Adverse events and surgery complications frequencies	Relugolix STA [8], EDELWEISS 3 CSR [12], Theramex [5, 6]

Abbreviations: 3L, three level; 5L, five level; CSR, clinical study report; EQ-5D, EuroQol 5-Dimension instrument; ITC, indirect treatment comparison; NHS, National Health Service; NICE DSU, National Institute for Health and Care Excellence Decision Support Unit; SMPCs, summaries of product characteristics; STA, single technology appraisal

RESULTS

Linzagolix was associated with higher QALYs (9.33) than GnRH agonists (8.93), while all treatment options generated the same LYs. Despite GnRH agonists being less expensive, linzagolix is cost-effective as it provides patients with an effective medical treatment until menopause, which reduces the number of surgeries; ICERs ranged between £5,551 and £5,585 (see Table 3). In comparison with GnRH agonists, linzagolix is associated with ICERs well below the UK cost-effectiveness threshold of £20,000 to £30,000 per QALY (see Figure 2). Results are presented for leuprorelin, representative of all GnRH agonists, as it has the greatest market share across major European countries and the UK. ICERs and results of sensitivity analyses are similar for all individual comparators.

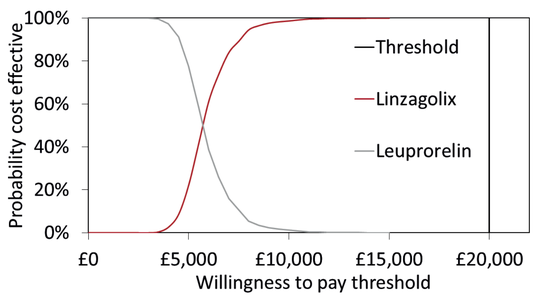
Table 3. Health and cost outcomes with incremental results

	Total			Incremental vs comparators			
Treatment	Costs	LYs	QALYs	ΔCosts	ΔLYs	ΔQALYs	ICER (£/QALY)
Linzagolix 200 mg + ABT	£14,897	11.76	9.33	–	–	–	–
Leuprorelin	£12,646	11.76	8.93	£2,252	0.00	0.41	£5,554
Goserelin	£12,633	11.76	8.93	£2,264	0.00	0.41	£5,585
Triptorelin	£12,647	11.76	8.93	£2,250	0.00	0.41	£5,551

Abbreviations: ABT, add-back therapy; GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years

All ICERs calculated in the deterministic sensitivity analysis remained below the WTP threshold of £20,000. The probability of linzagolix being cost-effective vs leuprorelin reaches 100% at a WTP threshold of around £12,000. Furthermore, the probabilistic mean results are close to the deterministic base case results.

Figure 2. Probabilistic cost-effectiveness acceptability curve



The most influential scenarios for model results are related to the time horizon parameters, the alternative starting age, or the maximum age of patients with the disease. The overall conclusion differed from the base case in only one scenario: setting the time horizon to 1.5 years in linzagolix generating equal QALYs compared to leuprorelin, with slightly reduced incremental costs. In the remaining scenarios, linzagolix continued to be cost-effective compared with leuprorelin, with ICERs between £3,505 and £9,573 per QALY, depending on the assumption tested.

CONCLUSIONS

- The base case results show that **linzagolix 200 mg + ABT is cost-effective** compared to GnRH agonists with an ICER of £5,554/QALY, **well below NICE thresholds**.
- Results indicate that **linzagolix enhances HRQoL** and **reduces the need for radical surgery**, thereby **helping to preserve fertility**.
- **Results are robust**, as the PSA means closely match the base case, and **conclusions are stable across a range of scenarios**.

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