Relugolix-estradiol-norethisterone acetate for treating symptoms of endometriosis

For public - redacted

This is a single technology appraisal topic.

Highly specialised technologies evaluation committee [7 March 2024], assessing ID3982 as a single technology appraisal

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Company: Gedeon Richter

Relugolix-estradiol-norethisterone acetate for treating symptoms of endometriosis

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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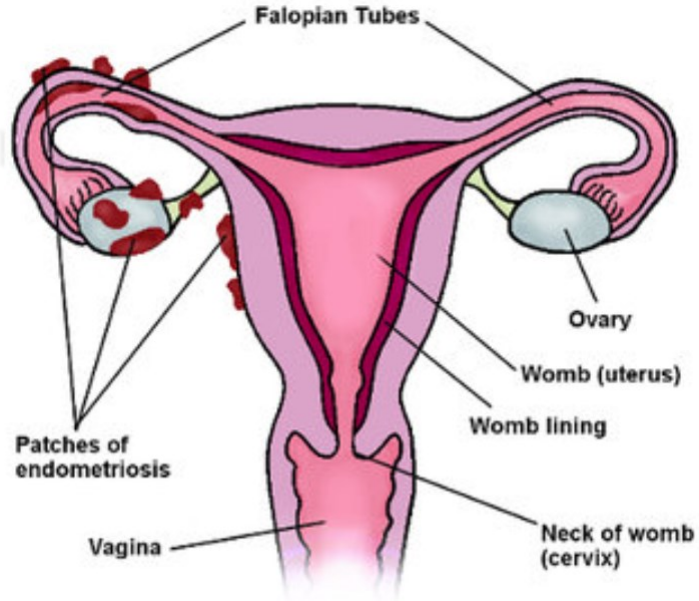
Background on endometriosis

Common, long-term disease in reproductive years causing chronic pain, subfertility and severe impact on quality of life



Source: Endometriosis UK

Condition and cause

- Endometriosis: chronic, long-term disorder where tissue normally lining womb (endometrium) grows elsewhere; when this tissue breaks down in a normal menstrual cycle it becomes trapped in the pelvis.
- Cause unknown but hormone mediated (associated with menstruation)

Epidemiology

- "Approximately 1 in 10 women and those assigned female at birth in the UK"

Diagnosis

- Laparoscopy (thin tube with a camera on the end) but may be less invasive i.e. ultrasound
- Average time from onset of symptoms to diagnosis 8 years

Symptoms and prognosis

- Symptoms vary depending on extent and location but include chronic pelvic pain and painful periods, subfertility, fatigue, significant physical, sexual, psychological and social impact
- Exists throughout reproductive life but sometimes beyond

Patient perspectives

Endometriosis is debilitating with daily pain and overall low quality of life

Submission from Endometriosis UK

- Symptoms vary depending on location and extent of disease; chronic pain most common
- Extremely challenging to live with; detrimental symptoms impact day-to-day lives (physical, mental well-being and quality of life)
- Current NHS care inadequate: process of diagnosis, treatment and aftercare (i.e. follow-up appointments) a struggle; patients need to self-advocate and "fight" in appointments so not dismissed
- All current hormonal treatments (including relugolix CT) can have considerable side effects and not suitable if wishing to conceive
- Relugolix-CT: all-in-one daily tablet (with ABT) desirable as do not have to remember to take ABT and taking ABT can mitigate negative longer-term effects of menopause (i.e. bone density), but the HRT used as ABT included may not suit all; use longer than other available drugs, and can stop quickly if side effects (unlike 3-month injections)

For 95%, symptoms have negative or very negative impact on wellbeing (Endometriosis All Party Parliamentary Group report, 2020)

Respondents…positive at the prospect of…this treatment for a longer period of time than current available treatments

Abbreviations: ABT, add-back therapy; HRT, hormone-replacement therapy; relugolix CT, relugolix combination therapy

Clinical perspectives

Relugolix CT, as an oral treatment, is step change in treatment of endometriosis

Submissions from clinical experts

- No cure; treatments aim to improve quality of life and maximise fertility
- Issues with delayed diagnosis and accessing services
- Relugolix CT considered if symptoms unmanageable or to avoid surgery
- Relugolix CT reduces treatment burden, is more convenient (oral administration) as can be taken at home, improves autonomy and adherence, reduces healthcare utilisation (clinic visits), transportation expenses and missed workdays compared with GnRH agonists
- Relugolix CT less likely effective after menopause; not appropriate if wishing to conceive (but can be given prior), in people with liver failure, or with history of low trauma fracture or risk factors for osteoporosis or bone loss
- Evidence of non-clinically relevant decrease in bone mineral density lower risk than GnRH agonists; regular bone density scan needed after 1 year and then as appropriate
- Relugolix CT could decrease reliance on opioids and enhance QOL for people with the condition

"huge unmet need…can negatively affect a patient's physical health, …quality of life and productivity or ability to work"

"Relugolix CT …an extra choice to tackle significant gap in medical care for endometriosis' standard of care"

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Abbreviations: GnRH, gonadotropin-releasing hormone; relugolix CT, relugolix combination therapy; QOL, quality of life

Technology (Ryeqo®, Gedeon Richter)

Marketing authorisation*	• Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis • European Medicines Agency reliance route – GBMA expected [redacted]
Mechanism of action	• **Relugolix** is a non-peptide GnRH antagonist that blocks the pituitary gland from releasing LH and FSH which decreases progesterone and oestrogen • **Oestradiol** is a natural sex hormone that helps to reduce symptoms from decreased oestrogen caused by relugolix but can cause growth of the womb • **Norethisterone** is a synthetic progestogen that reduces the effects of oestradiol on the womb, reducing the risk of endometrial growth
Administration	• Daily oral tablet, with or without food • Each tablet of relugolix CT contains relugolix (40mg), oestradiol (1 mg) and norethisterone acetate (0.5 mg)
Price	• £72 per pack (28 tablets) to be taken once daily • ~£938.57 annually

* Already recommended for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age;
Abbreviations: GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; relugolix CT, relugolix combination therapy; LH, luteinising hormone

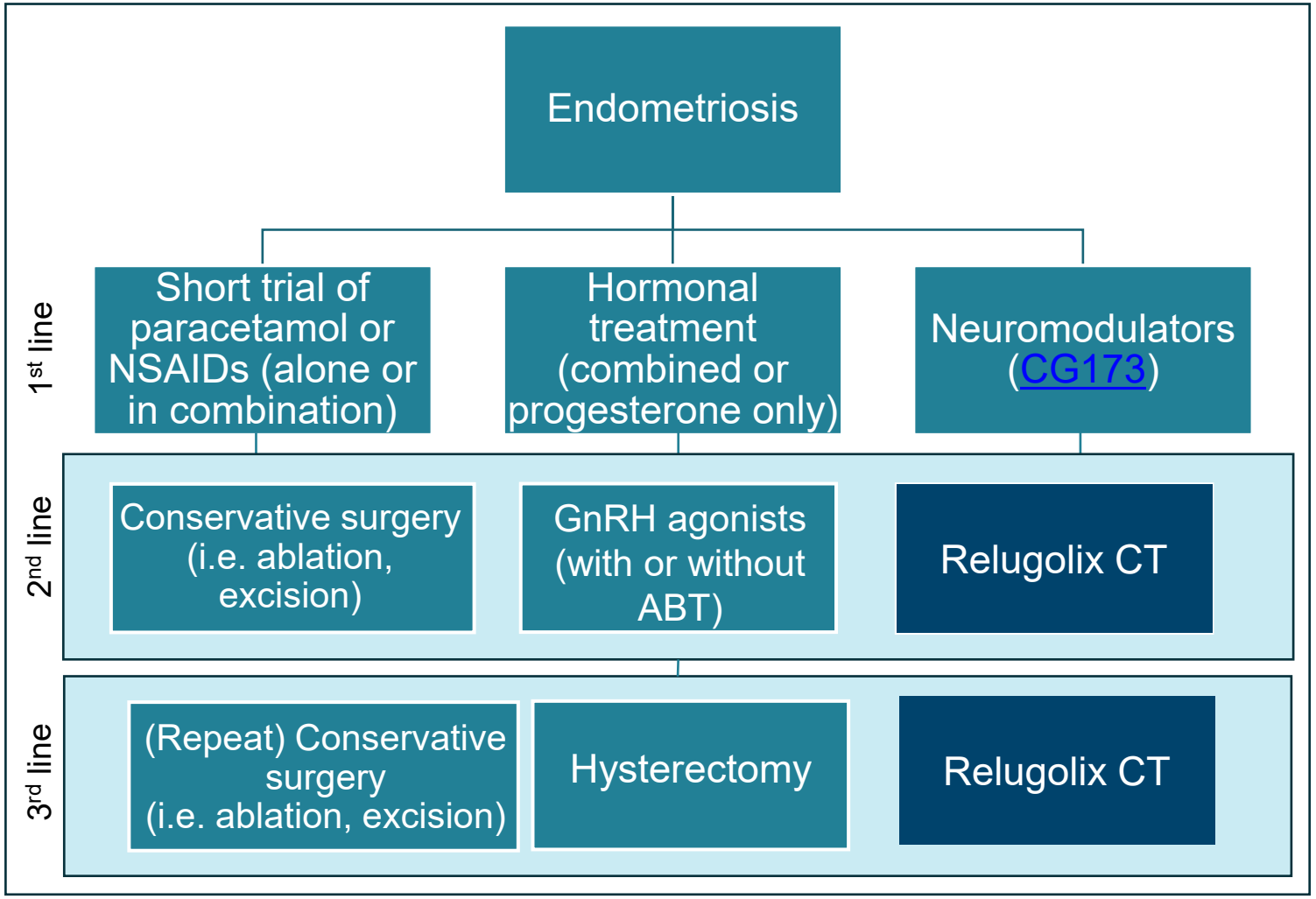
Key issues

Type of issue	Issue		Resolved?	Impact
Decision problem	1	Lack of clarity in positioning of relugolix CT and relevant comparators	No	Unclear
Clinical effectiveness	2	Methodological limitations in systematic literature review	No	Unclear
Cost effectiveness	3	Link between clinical and economic evidence		
	3a	ITC and other data in model	No	Unclear
	3b	Subsequent treatment after 1-year comparator and lack of clarity about BSC	No	Likely large
	3ci	Long-term utility / disutility	No	Likely large
	3cii	Operationalisation of infertility	No	Likely large
	3d	Treatment waning	No	Likely large
	4	Model validation and counterintuitive results	No	Unclear

Abbreviations: GnRH, gonadotropin releasing hormone; BSC, best supportive care; ITC, indirect treatment comparison; relugolix CT, relugolix combination therapy with estradiol and norethisterone acetate

Treatment pathway

Endometriosis



Best supportive care alongside all treatment options or if treatment fails as may improve quality of life:

- Physiotherapy
- Psychological support
- Acupuncture/osteopathy
- Nutrition/diet support
- Pain medication (i.e neuromodulators) for pain symptoms with neuropathic component used with hormonal treatment
- Analgesics*
- ? Hormonal treatment

(some of above is self-funded)

GnRH agonists are used as adjunct to surgery for deep endometriosis involving the bowel, bladder or ureter (3 months; NG73); it is possible relugolix CT may also be used in the short-term to provide symptom relief while waiting for surgery.

* Include paracetamol, codeine, NSAIDs, TENS, lidocaine patches, opiates, neuropathic medicine; Abbreviations: ABT, add-back therapy; GnRH, GnRH, gonadotropin-releasing hormone; NSAIDs, non-steroidal anti-inflammatory drug; relugolix CT, relugolix combination therapy with estradiol and norethisterone acetate

Key issue #1: Positioning of relugolix CT

EAG: company positioning unclear, impacts potential comparators and subsequent treatments

Background

- Proposed marketing authorisation specifies: '…a history of previous medical or surgical treatment'
- Company position treatment as second-line after NSAIDs, neuromodulators and surgery

EAG comments

- Lack of clarity in line of treatment, previous treatment(s), and population eligible for relugolix CT
- Clinical expert notes could be used 2nd or 3rd line – has implications for relevant comparator

Clinical expert

- Expect second or third-line use when hormonal contraceptive or progestogens, or surgery, ineffective
- In short-term (i.e. 3 months), may be included in combination treatment for symptom relief before surgery or before / after surgical excision of endometriosis if ovarian suppression considered beneficial
- Short-term use around surgery may be option for those wishing to conceive, but main use for those not wishing to conceive

Abbreviations: GnRH, gonadotropin releasing hormone; BSC, best supportive care; NSAIDs, non-steroidal anti-inflammatory drugs; relugolix CT, relugolix combination therapy with estradiol and norethisterone acetate

Key issue #1: Comparators

Company focus on GnRH agonists; EAG: relevant comparators may be missing

Background

- Company position second-line and include GnRH agonists as main comparator; consider NSAIDs, neuromodulators and surgery will be used before relugolix CT
- Clinical guideline (NG73) only refers to GnRH agonists as off-label use for 3 months before surgery
- GnRH agonists only licensed 6 months with ABT, but company notes used longer in the NHS

EAG comments

- Lack of clarity in treatment pathway so unclear on relevant comparators
- Agree GnRH agonist relevant, but other comparisons may be relevant; and could help make more connections within the indirect treatment comparisons
- Clinical expert: off-licence nasal or parenteral GnRH analogues used in practice

Clinical expert input

- GnRH agonists with ABT most appropriate comparator. Often used off licensed for > 6 months but then ABT particularly important for bone health
- Other alternatives: dienogest (licensed for endometriosis)

- Is treatment pathway accurate? What are appropriate comparators?
  - Is conservative surgery offered 1st line or 2nd line? (could it be a comparator at 2nd line?)
  - Could relugolix CT be used 3rd line in addition to 2nd line?
  - Is short-term use of relugolix CT an option? If so, what is the appropriate comparator?
- Are nasal (buserelin or nafarelin) or parenteral GnRH agonists used in the UK?

Abbreviations: ABT, add-back therapy; GnRH, gonadotropin releasing hormone; BSC, best supportive care; relugolix CT, relugolix combination therapy; NSAIDs, non-steroidal anti-inflammatory drugs

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Key issue 2: Systematic literature review*

EAG: serious concerns about robustness of search so not reviewed evidence; also, search may be missing studies on potentially relevant comparators

Background

- EAG raised concerns at clarification about searches and requested rerun and expanded search
- Because of time constraints, company updated Cochrane review on GnRH agonists for painful symptoms in endometriosis (Veth et al 2023) but additional studies not included in ITCs

EAG comments

- Systematic literature review not methodologically robust; a new, full SLR needed:
  - General poor reporting and lack of transparency. i.e. unclear on date span for Embase search, data extraction process or plan, search strategies for update to Cochrane review, quality assessment process and risk of bias assessment
  - Appropriateness of search methods questionable, resulting in unexpectedly small results for a common condition (~500 in Embase): no specific search for adverse events, no searches of Cochrane Library or CENTRAL, does not cover comparators in scope, and problems with 'conditions', 'interventions' and 'pain' facets
- Update to Cochrane review unsuitable: comparators and outcomes differ as does update search
- Not reviewed evidence: new SLR would likely identify different evidence base which could affect committee deliberations

Is committee confident the company's searches would have identified all potentially relevant studies on the relevant comparators?

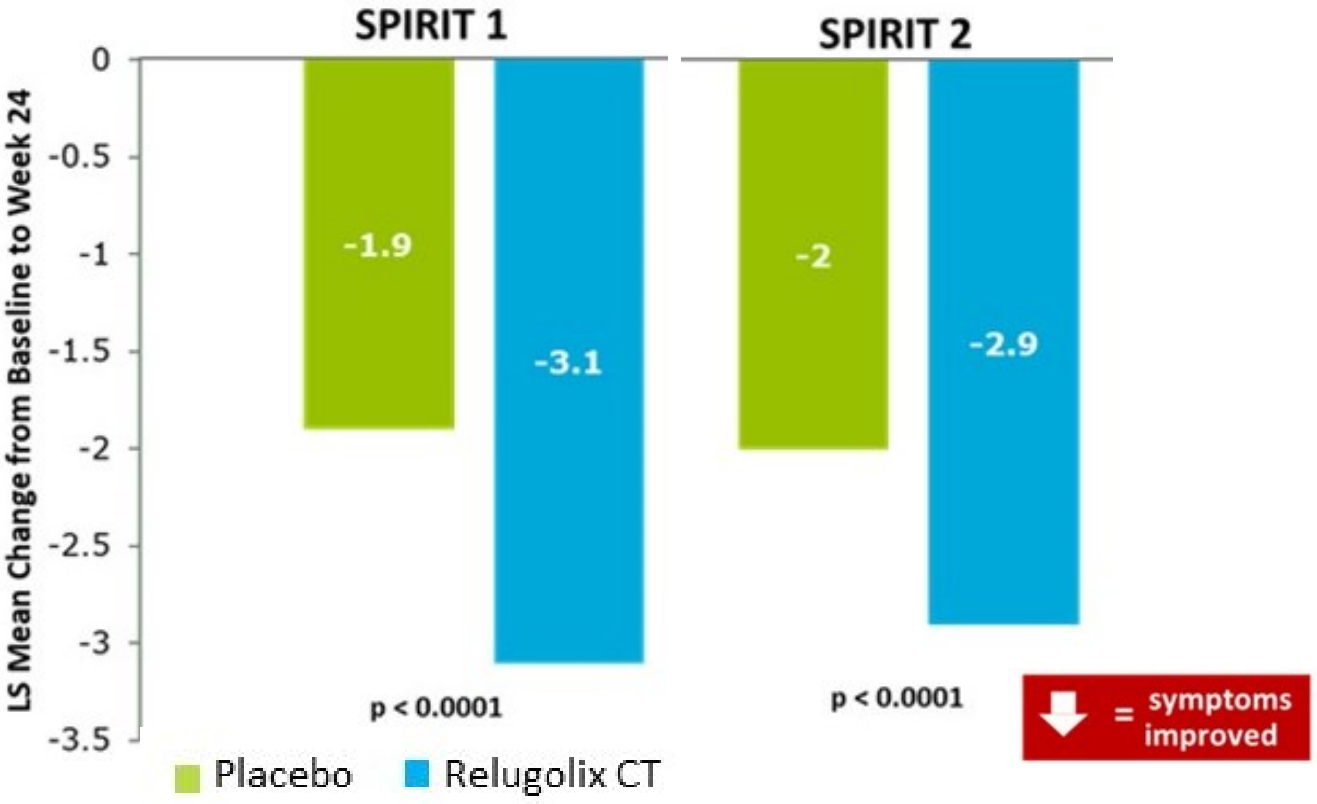
Abbreviations: ITC, indirect treatment comparison; GnRH, gonadotropin-releasing hormone; SLR, systematic literature review

* See appendix

SPIRIT 1 & 2 trial, phase 3 RCTs: results*

Relugolix CT had significantly greater improvement in overall pelvic pain at 24 weeks than placebo; informs GnRH agonist response rates in model

Figure. least squares change from baseline to 24 weeks in mean overall pelvic pain (NRS)*



- Overall pelvic pain was secondary endpoint in trial (dysmenorrhoea and non-menstrual pelvic pain co-primary endpoints); ITC on overall pelvic pain used in model to derive response rates for GnRH agonists
- Results from clinical evidence not presented in EAG report because of EAG concerns with completeness of systematic literature review

*Patients reported pelvic pain on 11-point NRS (0 = no pain to 10 = pain as bad as you can imagine) daily in an eDiary; Abbreviations: GnRH, gonadotropin-releasing hormone; NRS, numerical rating scale; relugolix CT, relugolix combination therapy

* See appendix

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Key issue 3a: ITC and other data in model

EAG: changes to clinical evidence has minor impact on results; model should incorporate more important clinical outcomes

Background

- ITCs: no significant differences between relugolix CT and GnRH agonists (all GnRH agonists assumed same)
- Model uses trial co-primary endpoints for response rates with relugolix CT and applies OR from ITC on overall pelvic pain to derive response rates for GnRH agonists
- Outcomes from scope not in model: endometriosis recurrence, hospital admission, fertility, complications

EAG comments

- Clinical evidence has minimal input on model results because only applied for one year until GnRH agonists stop (relugolix CT continues an additional 16 years); results driven by relative effect of relugolix CT compared with subsequent treatments (surgery and BSC); unclear how treatment effect compared to BSC and surgery incorporated in model after GnRH agonists stop
- Link between clinical effectiveness and economic evidence weak; more clinical effectiveness parameters needed in model (but clinical expert notes most important outcome is associated pelvic pain)
- Issues with other data in model: same treatment stopping rates and transition to subsequent treatments for both arms; unclear if evidence for distribution between types of surgery generalisable to UK, probability of pain after surgery not taken from SPIRIT trials

- How long are GnRH agonists used in clinical practice?
- Do committee consider sufficient clinical effectiveness parameters have been included in the model?
- Do committee require more information about the relative effect of relugolix CT with treatments taken after GnRH agonists stop?

Abbreviations: BSC, best supportive care; GnRH, gonadotropin releasing hormone; ITC, indirect treatment comparison; OR, odds ratio; relugolix CT, relugolix combination therapy

Key issue 3b: Subsequent treatment and BSC

EAG: further definition and use in model need clarification

Background

- BSC used in model after stopping initial treatment (see model structure); important because results driven by relative effect of relugolix CT compared with treatments after GnRH agonists, taken for most of time horizon
- Company submission: BSC = 'hormonal therapy with or without analgesics'; clarification response: does not include hormonal treatments: 'symptomatic treatment for pain management (NSAIDs, i.e., analgesics only)'. Note BSC is same as placebo in SPIRIT trials and assumed equivalency in model

EAG comment

- Unclear if placebo in SPIRIT includes NSAIDs (as company say) because trial aim was to reduce analgesic use; company also explain relugolix CT, GnRH agonists, BSC and surgery used with analgesics
- Clearer definition of BSC and use in model needed

Clinical expert input

- BSC usually multimodal (some self-funded): physiotherapy, psychological support, acupuncture/osteopathy, nutrition/dietary changes; analgesics: paracetamol, codeine, NSAIDs, TENS, lidocaine patches, opiates, neuropathic medicine used at any point in pathway alongside or after failed treatment as may improve QOL

Technical team

- The model structure explicitly includes hormonal treatment as part of BSC

- What is role of BSC in clinical practice? (i.e. when is it used and for how long) Does BSC include analgesics or hormonal therapy?
- Is more clarity needed on how BSC is defined and used in the model?

Abbreviations: BSC, best supportive care; GnRH, gonadotropin releasing hormone; NSAID, non-steroidal anti-inflammatory drug; relugolix CT, relugolix combination therapy; QoL: Quality of Life

Key issue 3ci: Utility / disutility impact in model

EAG note small changes to long-term utility / disutility have a big impact on results

Company approach

1. Patients with response have same utility irrespective of treatment arm
2. Utility values based on SPIRIT trials; baseline utility 0.58
3. Use additive approach to apply disutilities from adverse events and surgery-related complications

EAG comments

- Long-term disutilities after surgery key driver: model insensitive to changes in utility values for response or non-response health states, most QALY gain from disutilities after surgery (0.606 of 0.71) [note: any changes in model that decrease incremental QALYs increase ICER quickly]
- Studies used to inform disutility for adverse events or surgical complications old; company state impact negligible but may not be because long-term disutilities have big impact on results
- Unclear if disutility values used for hysterectomy applicable to UK; from Global Burden of Disease study published 1990. Decreasing by half doubles the ICER

1. Unclear if appropriate.
2. Insufficient* face validity check for utility values used; baseline utility seems low (0.58); outstanding uncertainty
3. Multiplicative approach for disutility from adverse events and complications usually preferred (NICE health technology evaluations: the manual section 4.3.7); company approach needs justification and exploration of impact with scenario analysis

Would committee wish to see clearer justification and validation of choices in model related to utilities?

* Text corrected after committee meeting. Abbreviations: ICER, incremental cost-effectiveness threshold; QALY, quality-adjusted life year

Key issue 3cii: Operationalisation of infertility in model

Company: no utility decrement from infertility modelled; EAG: big impact on results as relugolix CT taken 15 years longer, model structure needs changing

Company approach

1. Model applies utility decrement to all women after hysterectomy
2. Differences in disutility because of infertility between treatments captured in EQ-5D from trial
3. Utility benefit after stopping relugolix CT too uncertain to parameterise and likely little impact – difference in time to regain fertility between treatments likely months. People who stop treatment because of pregnancy or wishing to conceive excluded from discontinuation rates because BSC and surgery not feasible options

EAG comments

- Company approach simplistic, particularly since fertility drives treatment choice (as per clinical guideline)
- No scenario analysis of alternative approach – changes to model that result in less incremental QALYs can increase ICER quickly
- In current model structure, disutility from infertility is the only parameter with potential major impact on results

1. Model structure needs updating: decrement should only be applied to those actively seeking to have a family, be age-dependent and be based on a more recent estimate
2. Impact of infertility associated with relugolix CT likely greater than GnRH agonists because treatment longer; stopping GnRH agonist after 1 year and relugolix CT after 10 years may have different impact on fertility
3. Unclear if women stopping treatment because of pregnancy or wishing to become pregnant included in model at all; unclear why BSC and surgery not considered feasible options

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Does committee prefer the company or EAG approach to disutilities related to infertility?

Key issue 3d: Treatment waning

Company assumed constant response to treatment over time; EAG: needs exploration – 15-year sustained effect strong assumption

Background

- In base-case, patients take relugolix CT until response, discontinuation or menopause; response assumed constant over time
- Company cite SPIRIT OLE which reported a high response rates at week 52 and 104/end of treatment; concluded captured through discontinuation rate applied to model when patients move from complete to non-response

Response*	Week 52	Week 104/ end of trial
Dysmenorrhea	84.8% (95% CI: 80.06 to 88.85)	84.8% (80.06, 88.85)
NMPP	73.6% (95% CI: 68.04, 78.74)	75.8% (70.33, 80.74)

* Dysmenorrhoea: defined as mean reduction in NRS score of 2.8 points or more and no increase in analgesia; NMPP: defined as mean reduction in NRS score of 2.1 points or more and no increase in analgesia

EAG comments

- Unclear if captured through discontinuation rate because company assume constant discontinuation rate after 15 months, implying constant treatment effect after about 60 weeks (and BSC and surgery both effectively the comparator after 1 year)
- 15-year sustained effect is strong assumption
- No exploration of impact of treatment effect waning on model – changes to model that result in less incremental QALYs can increase ICER quickly

Would the treatment effect between relugolix CT compared with GnRH agonists decrease over time or stay the same?

Abbreviations: CI, confidence interval; GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; NMPP, non-menstrual pelvic pain; NRS, numerical rating scale; OLE, open-label extension; QALY, quality-adjusted life year; relugolix CT, relugolix combination therapy

Key issue 4: Model validation and counterintuitive results

EAG: changes to model inputs and structure needed to produce valid results; unfeasible to define base case

EAG comments

- **Validation**:
  - Model structure unclear, overly complex and unable to fully validate and critique (i.e. alternative comparators surgery and BSC from global model). Inefficient for EAG to check
  - Results likely invalid if another comparator relevant
  - Company probabilistic ICER similar to deterministic ICER but not because robust analysis. Lack of transparency on PSA which may be missing parameters and parameter-specific variation (see here)
- **Counterintuitive results:**
  - When proportion of patients with relugolix CT with complete response decreases, model results do not seem valid. For example, when 1% have complete response, there are 0.011 additional QALYs compared with GnRH agonists (possibly because no waning in long-term response). Because 99% stop relugolix CT due to no response, relugolix CT is cost saving compared with GnRH agonists.
  - If 100% of patients stop relugolix CT at 9 or 12 months, relugolix has more QALYs and less costs; this is counterintuitive since OR of 1.1 suggests GnRH agonists are more effective in the first year of model

Unfeasible to provide base case: assessing most uncertainties require major changes to model – not possible with current evidence

Can counterintuitive results be explained?

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Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; relugolix CT, relugolix combination therapy

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential discounts

- Company base case* ICERs are within the range normally considered an effective use of NHS resources
- Company scenarios do not have a substantial impact on results; however, EAG consider company does not provide enough scenarios on key assumptions
- No EAG results as consider it unfeasible to provide base case as major changes to model needed for valid results

*Company base case updated at clarification. Changes to the model include: introducing post-menopause state, extension of model to lifetime, using OR from ITC for relative effect, using age-related utility decrements, including functionality to input individual utility values for each state, correction in calculation error of life years; company also corrected aspects related to the sensitivity analyses.

Abbreviations: EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio

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Equality considerations

- Choice of treatment is postcode lottery: those available / offered are based on knowledge of individual medical professionals and what is available in certain areas / Trusts (Endometriosis UK)
- Evidence to suggest people from some ethnic minority backgrounds:
    - may be underdiagnosed and/or present later for help with endometriosis so have more severe symptoms (company)
    - may receive lower quality of care; this may be due to socioeconomic factors since people from some ethnic minority groups are more likely to live in areas of high deprivation, have lower incomes, experience language barriers and have poorer access to women's healthcare services (company)
- SPIRIT trials had few people from ethnic minority backgrounds (lead team)
- Underdiagnosis of endometriosis should be considered (EAG)
- Clear, culturally competent information needed to improve access (clinical expert)
- Convenience of relugolix CT over GnRH agonist injection may particularly benefit individuals with transportation barriers, mobility issues (clinical expert)
- Identified at scoping:
    - technology should be available to all eligible people, including transmen or non-binary people
    - contraceptive treatments may not be acceptable to people from some religious or ethnic groups
    - delaying childbearing, by choice or because of subfertility, may be a risk factor for endometriosis

Other benefits not captured

- An all-in-one daily tablet with HRT (relugolix CT) mean a person does not have to remember to take ABT
- Compared with GnRH agonist injections every 1 to 3 months :
  - Daily oral treatment less invasive than GnRH agonist injections
  - Can be used longer
  - Because of oral formulation and shorter half-life, return to normal hormonal levels and menstruation after stopping is faster – helpful to recover fertility or if side effects

Are there other potential uncaptured benefits that should be considered in decision-making?

Abbreviations: ABT, add-back therapy; GnRH, gonadotropin-releasing hormone; HRT, hormone replacement therapy; relugolix CT, relugolix combination therapy

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	3d	Treatment waning	No	Likely large
	4	Model validation and counterintuitive results	No	Unclear

Abbreviations: GnRH, gonadotropin releasing hormone; BSC, best supportive care; ITC, indirect treatment comparison; relugolix CT, relugolix combination therapy with estradiol and norethisterone acetate

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Thank you.

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Supplementary appendix

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Decision problem

Submission focused on 2nd line and one comparator, GnRH agonists

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adults with symptoms of endometriosis	Focus on 2nd line after hormonal therapy and prior surgery in line with MA	-
Intervention	Relugolix in combination with oestradiol and norethisterone acetate (relugolix CT)	-	-
Comparators	Established clinical management without relugolix CT, including: • analgesics or NSAID alone or in combination with each other • neuromodulators • hormonal treatment such as combined hormonal contraception, oral progestogens, GnRH agonists.	GnRH agonists All used first-line before relugolix CT: analgesics or NSAIDs, combined hormonal contraception, oral progestogens, neuromodulators	Some potentially relevant comparators missing
Outcomes	Overall pain, opioid use, analgesic use, recurrence, hospital admission, subsequent surgical treatment, fertility adverse effects or complications, HRQoL	See this slide	Not all outcomes included; inconsistent in submission sections

Abbreviations: GnRH, gonadotropin-releasing hormone; HRQoL, health-related quality of life; MA, marketing authorisation; NSAID, non-steroidal anti-inflammatory drug; relugolix CT, relugolix combination therapy

Reporting of systematic literature review

EAG concerned with general lack of clarity and transparency in process

- lack of clear and descriptive reporting about the systematic literature review, in general, but some specific concerns are reported below
- best practice states importance of well-conducted and reported search methods

Some specific elements EAG found lacking in transparency
Date span for Embase search unclear
Full search strategies for update to Cochrane review not provided
No details of data extraction process or plan: essential for robust SLR
Insufficient details of the quality assessment process and risk of bias assessment
Not enough details of update to search or of additional 'pragmatic literature review': no details provided other than '*searching the web using key words related to GnRH agonist therapies used to treat moderate-to-severe pain associated with endometriosis*'

Abbreviations: EAG, external assessment group; SLR, systematic literature review

EAG concerns with literature search

Aspect	Description
No specific search for adverse events	Main searches restricted to RCTs – when study design filter used, Centre for Reviews and Dissemination recommends additional searches to ensure long-term, rare or unanticipated adverse events not missed
No searches of Cochrane Library or CENTRAL	Company: Cochrane reviews and editorials would be picked up by PubMed. EAG: best practice for systematic reviews to search a range of databases; CENTRAL includes citations of randomised trials not included in other databases, are in many languages and includes citations only available in conference proceedings or other difficult to access sources, and trial registers beyond ClinicalTrials.gov or WHO portal
Search does not cover decision problem in scope	Analgesics not searched for Various types of surgery listed in search as a comparator but no studies included GnRH antagonists excluded as none available in UK
Search strategy problematic	'conditions' facet missing free text, use of Boolean operator NOT for subject headings for adenomyosis / uterus myoma / and ovary cancer to excluded from search (not recommended way) 'intervention facet missing subject heading and synonyms for relugolix, failure to explode some subject headings, missing free text and subject headings for named comparators 'pain' facet – inclusion seemed overly restrictive (low Embase results); should remove

EAG concerns with Cochrane review update

Aspect	Description
Comparators differ	Cochrane review does not include neuromodulators or NSAIDs and excluded surgical therapies, combined oral contraceptive pill, progesterone receptor modulators or selective oestrogen receptor modulators (SERMs) or GnRH antagonists
Outcomes differ	Outcomes in scope not in Cochrane review: opioid use, analgesic use, recurrence of endometriosis, admission to hospital, subsequent surgical treatment, fertility, complications of treatment and HRQoL
Conditions facet of search strategy	Only contained terms for GnRH analogues, not relugolix CT or other interventions in scope; should search relugolix CT in separate search
Update searches differ	Company report search strategy was identical but update was performed for period from May 2022 to November 2023. MEDLINE search seems low; EAG reran using different combinations of MEDLINE segments (i.e., Epub ahead of print, In-process etc.) with different date limits, and all yielded higher results. Unclear why this differed as full search strategies not provided.

Key clinical trials: SPIRIT 1 and SPIRIT 2

Clinical trial designs and outcomes

	SPIRIT 1 and SPIRIT 2
Design	Phase 3 double-blind RCTs
Population	Pre-menopausal people aged 18 to 50 years with moderate to severe pain associated with endometriosis
Intervention	Relugolix + oestradiol + norethisterone acetate
Comparator(s)	Placebo*
Duration	24 weeks
Co-primary outcomes	Proportion of responders with non-menstrual pelvic pain or dysmenorrhoea at 24 weeks
Key secondary outcomes	Non-menstrual pelvic pain, dysmenorrhoea, overall pelvic pain, dyspareunia (NRS), opioid use, analgesia use
Locations	Multicentre, global (excluding UK)
Used in model?	Yes

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* Trial had 3rd arm not presented in submission: relugolix alone (12 weeks) then relugolix + oestradiol + norethisterone acetate (12 weeks); Abbreviations: NRS, numerical rating scale

Outcomes

Scope	Clinical effectiveness section	Indirect treatment comparison	Included in model
overall pain, opioid use, analgesic use, endometriosis recurrence*, hospital admission*, subsequent surgical treatment, fertility*, adverse effects or complications*, HRQoL	OPP, opioid use, analgesic use, adverse effects, HRQoL (EQ-5D-5L) Other: dysmenorrhoea**, EHP-30 pain domain, NMPP**, dyspareunia	OPP TPP (sum of dysmenorrhoea, NMPP/PP and dyspareunia) (note: analgesic and opioid use reported but not in ITC because too much heterogeneity)	Response: dysmenorrhoea, NMPP, OPP (from ITC) Other: analgesic use, subsequent surgical or medical treatment, surgical complications, HRQoL

* Not collected in SPIRIT trials (but company note recurrence not relevant since relugolix CT is not disease modifying, hospital admission likely mostly related to procedures [based on Australian data] which are covered in the model, complications covered by adverse events);
** co-primary endpoints in SPIRIT trials; Abbreviations: HRQoL, health-related quality of life; ITP, indirect treatment comparison; NMPP, non-menstrual pelvic pain; OPP, overall pelvic pain; TPP, total pelvic pain

SPIRIT 1 & 2 trials: co-primary endpoint results

Relugolix CT had significant improvements in proportion of patients having improved dysmenorrhoea or non-menstrual pelvic pain at 24 weeks

Figure. proportion responding - dysmenorrhoea *

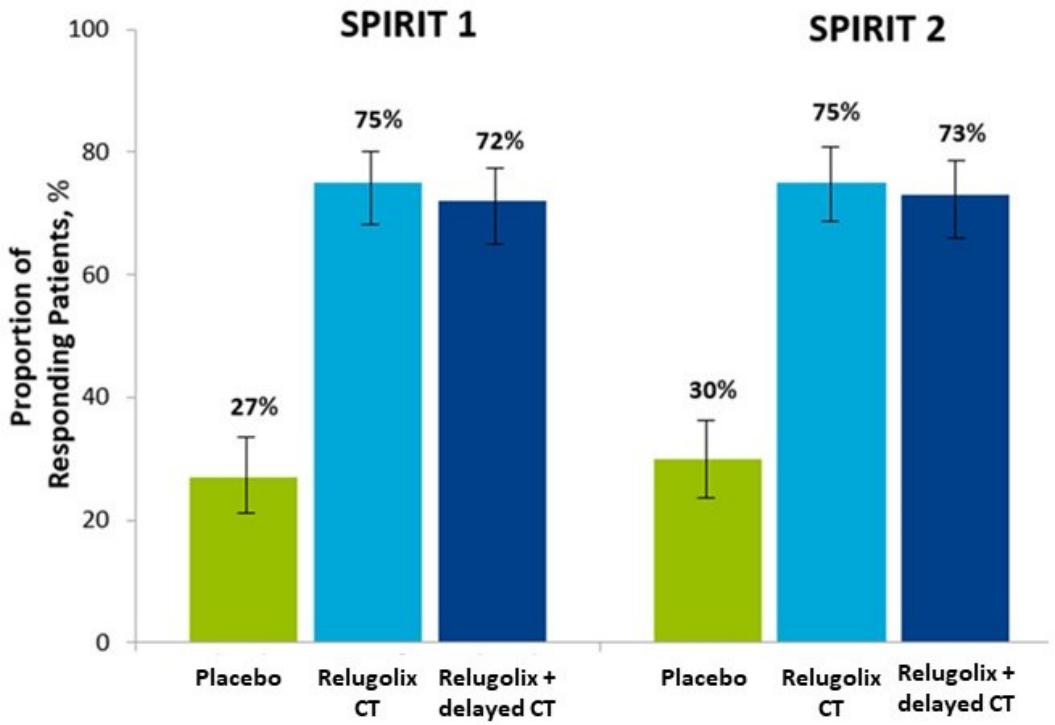
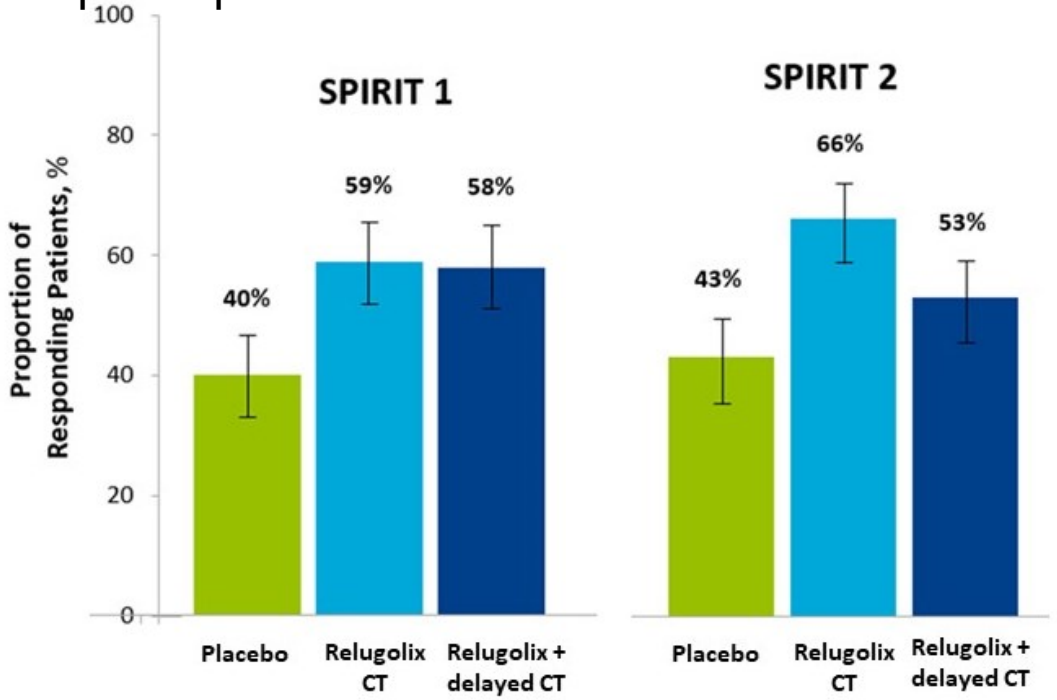


Figure. proportion responding – non-menstrual pelvic pain *



* Response in dysmenorrhoea defined as mean reduction in NRS score of 2.8 points or more and no increase in analgesia; response in non-menstrual pelvic pain defined as mean reduction in NRS score of 2.1 points or more and no increase in analgesia; Abbreviations: relugolix CT, relugolix combination therapy; NRS, numerical rating scale (relugolix + delayed CT arm not used in submission)

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SPIRIT 1 & 2, phase 3 trials: results

Relugolix CT showed significant improvements over placebo in most outcomes

Outcome at 24 weeks or end of trial: relugolix CT vs placebo, difference (CI) p-value	SPIRIT 1	SPIRIT 2
Proportion dysmenorrhoea responder (%)	75 vs 27, 47.6 (39.3 to 56) p<0.0001	75 vs 30, 44.9 (36.2 to 53.5) p<0.0001
Proportion non-menstrual pelvic pain responder (%)	59 vs 40, 18.9 (9.5 to 28.2) p<0.0001	66 vs 43, 23.4 (14 to 32.8) p<0.0001
Change from baseline in mean dysmenorrhea NRS score*	-5.1 vs -1.8, -3.3 (-3.8 to -2.8) p<0.0001	-5.1 vs -2.0, -3.2 (-3.7 to -2.7) p<0.0001
Change from baseline in mean NMPP NRS score*	-2.9 vs -2.0, -0.9 (-1.4 to -0.4) p=0.0002	-2.7 vs -2.0, -0.7 (-1.2 to -0.3) p<0.0001
Change from baseline in mean overall pelvic pain NRS score*	-3.1 vs -1.9, -1.1 (-1.6, -0.7) p<0.0001	-2.9 vs -2.0, -0.9 (-1.4, -0.5) p<0.0001
Proportion not using protocol-specified opioids for endometriosis-associated pain (%)	86 vs 76, 9.4 (2 to 16.8) p=0.0005	82 vs 66, 15.9 (7.5 to 24.2) p<0.0001
Change from baseline in mean dyspareunia NRS score*	-2.4 vs -1.7, -0.7 (-1.3 to -0.1) p=0.0149	-2.4 vs -1.9, -0.5 (-1.0 to 0.0) p=0.0371
Proportion not using analgesics for endometriosis-associated pain (%)	56 vs 31, 25.5 (16.4 to 34.6) p<0.0001	54 vs 24, 30.8 (21.9 to 39.8) p<0.0001

All outcomes used in economic model presented. *Outcomes used in indirect treatment comparison

Abbreviations: CI, confidence interval; NMPP, non-menstrual pelvic pain; NRS, numerical rating scale; relugolix CT, relugolix combination therapy

ITC missing relevant reported outcomes, unnecessary transformation of data, lack of clarity about source of some evidence*

Background

- Co-primary endpoints in SPIRIT trials (dysmenorrhoea and non-menstrual pelvic pain) not in scope (see here)
- Company: only possible to conduct ITCs on overall pelvic pain and total pelvic pain, the later which is a composite of dysmenorrhoea, non-menstrual pelvic pain, dyspaneuria (see here)

EAG comment

- Outcomes used in ITCs not directly measured in SPIRIT trials
- Unclear why company did transformation from continuous outcomes to odds ratio as difficult to interpret; requested at clarification and company provided
- Unclear where NRS values for SPIRIT trials came from
- ITCs should be conducted with all outcomes relevant including dysmenorrhoea and NMPP; scale as close to original, if possible, with any transformation adequately justified and with clear presentation of the original data, source and method of transformation

Abbreviations: ITC, indirect treatment comparison; NMPP, non-menstrual pelvic pain; NRS, numerical rating scale

* See appendix here and here

ITC methodology

Relugolix CT was compared with one GnRH agonist (leuprorelin acetate) in a network for 2 outcomes: overall and total pelvic pain

- No direct head-to-head trials so company conducted indirect treatment comparisons
- SPIRIT 1 and 2 pooled for relugolix CT
- Treatment effect from trials was converted from continuous measure to odds ratio because of how treatment effect was estimated in the model

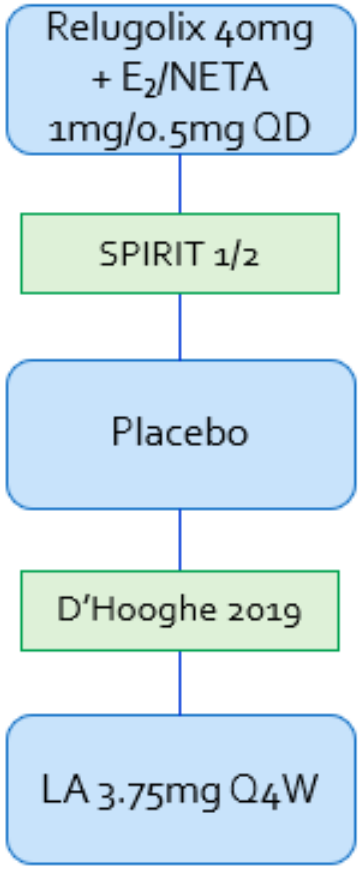
Comparators and outcomes in ITCs

Comparator /outcome	Included in ITC
GnRH agonists	• leuprorelin acetate Not able to connect in ITC: goserelin, triptorelin, nafarelin, buserelin
Outcomes	• overall pelvic pain • total pelvic pain (composite of dysmennorhoea, non-menstrual pelvic pain, dyspaneuria) Reported but not able to include in ITC: analgesic and opioid use (too much heterogeneity between studies)

Abbreviations: GnRH, gonadotropin releasing hormone; ITC, indirect treatment comparison; relugolix CT, relugolix combination therapy

ITC networks

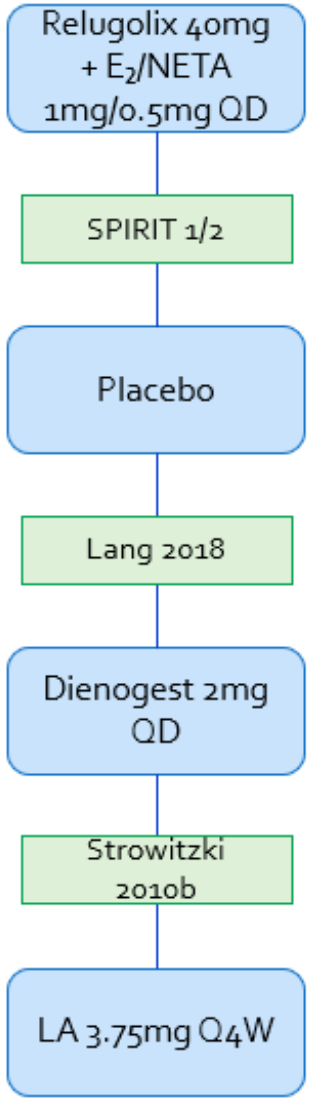
Figure. Evidence network diagram for OPP at 12 weeks



Characteristics of trials in ITCs

Trial in ITCs	Arms, duration	# patients, location
SPIRIT 1 & 2 (both ITCs)	Relugolix CT vs placebo; 24 weeks	N = 841 (combined), Global (not UK)
D'Hooghe 2019 (OPP ITC)	Leuprorelin acetate (no ABT) vs placebo; 12 weeks	N = 540, Europe and Japan
Lang 2018 (TPP ITC)	Dienogest vs placebo; 24 weeks	N = 255, China
Strowitzki 2010b (TPP ITC)	Leuprorelin acetate (no ABT) vs dienogest; 24 weeks	N = 252*, Europe (not UK)

Figure. Evidence network diagram for TPP at 24 weeks



* Value corrected after committee meeting. Abbreviations: CT, combination therapy; LA, leuprolide acetate; OPP, overall pelvic pain; TPP, total pelvic pain

ITC results

No significant differences found between relugolix CT and leuprorelin acetate

Figure. Forest plot of OR for overall pelvic pain at 12 weeks (random effects, weak priors)

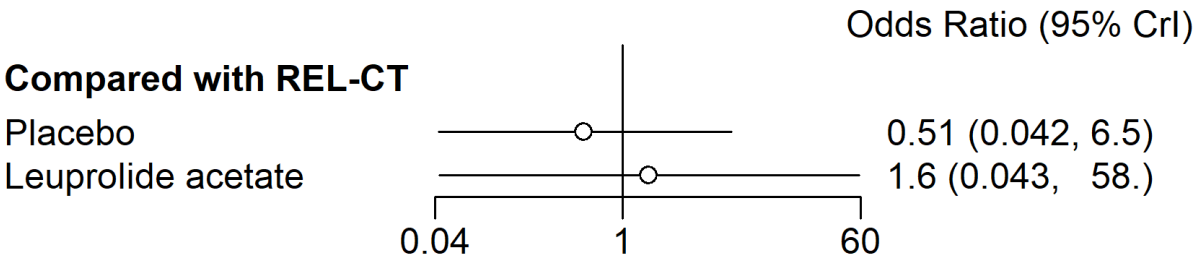
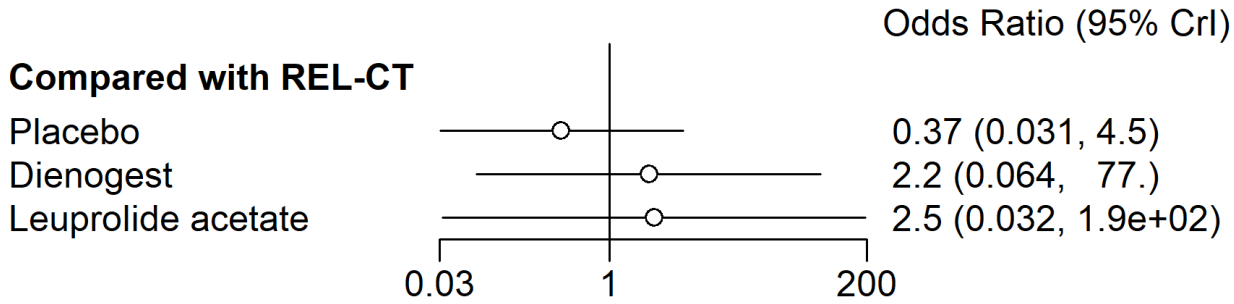


Figure. Forest plot of OR for total pelvic pain at 24 weeks (random effects, weak priors)



Only overall pelvic pain ITC results used in model

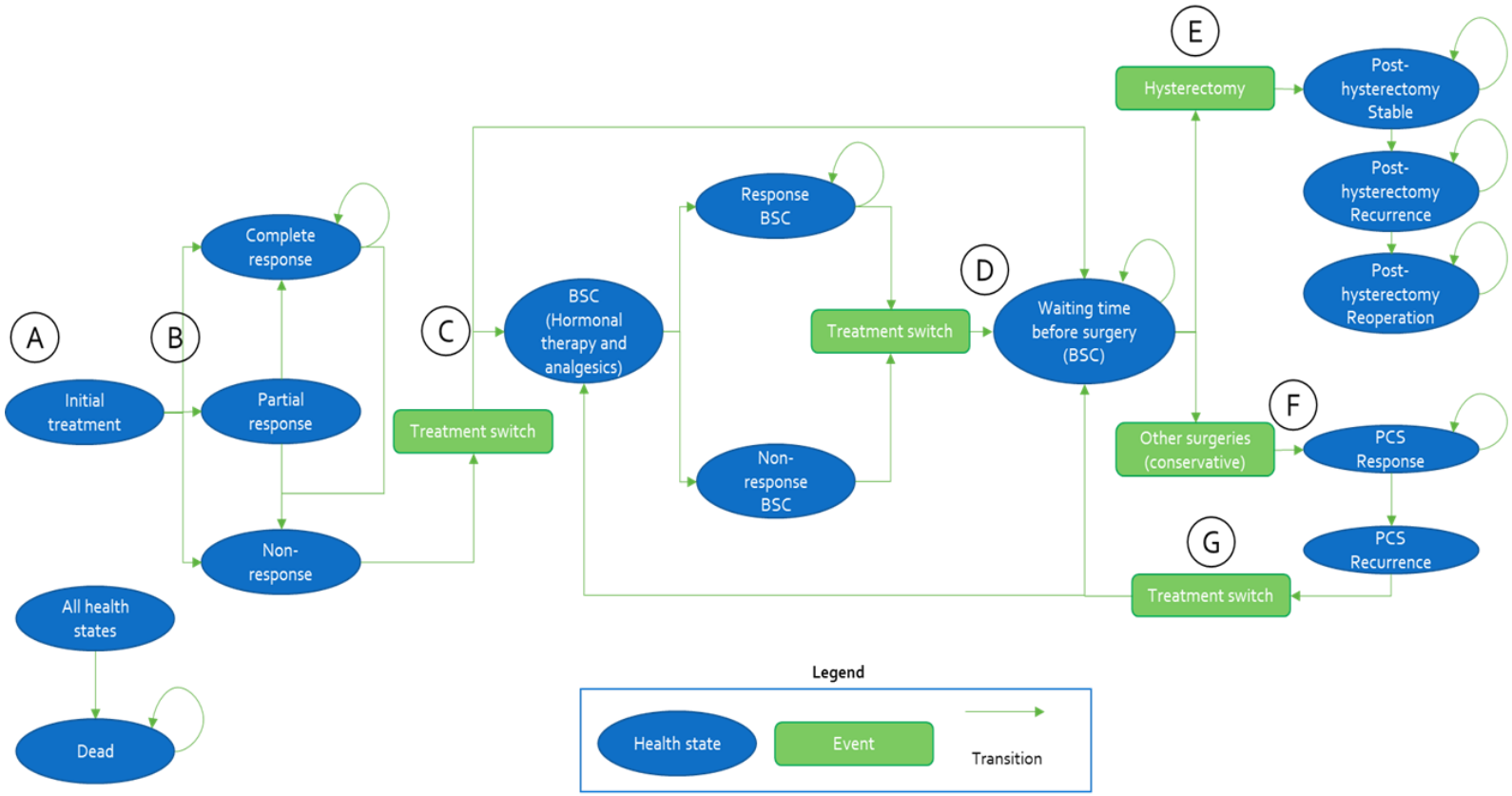
Sensitivity analyses with empirical priors or fixed effects had similar results except:

- For overall pelvic pain, the fixed effects model vs placebo showed relugolix CT better
- For total pelvic pain:
  - Fixed effects model vs dienogest or leuprorelin acetate show relugolix CT worse
  - Comparison vs placebo for both models showed relugolix CT better

Abbreviations: Cr, credible interval; ITC, indirect treatment comparison; OR, odds ratio; REL-CT, relugolix CT; relugolix CT, relugolix combination therapy

Company's model overview 1

Model structure



- Technology affects **costs** by:
  - Increasing QALYs in "response" health states
  - Reducing QALYs post-hysterectomy
  - In all other health states, difference in QALYs is not substantial
- Technology affects **QALYs** by:
  - Higher price
  - Less costs associated with surgery and health care visits
- Assumptions with greatest ICER effect:
  - Main gain in QALYs is due to long-term disutilities after surgery

Abbreviations: BSC, best supportive care; PCS, post-conservative surgery

How company incorporated evidence into model

Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	SPIRIT 1 & 2
Intervention efficacy	Response based on SPIRIT 1 & 2
Comparator efficacy	GnRH agonists (subcutaneous only) assumed equal efficacy; effectiveness compared with relugolix CT using ITC for overall pelvic pain: OR 1.1 (95% CrI 0.032, 41)
Utilities	EQ-5D-5L from SPIRIT 1 & 2 mapped to 3rd line using the age- and sex-specific NICE Decision Support Unit mapping tool; disutilities from safety from literature
Costs	List prices. GnRH agonists (subcutaneous only): 50/50 split amongst the cheapest short-acting GnRH agonist and the cheapest long-acting GnRH agonist ABT (starting after 3 months): 50/50 split between tibolone and raloxifene
Resource use	NHS Reference Costs, British National Formulary (BNF) and Personal Social Services Research Unit (PSSRU)
Adverse events	SPIRIT 1 & 2 (for relugolix CT and BSC and some events for GnRH agonists) and risk ratios applied to BSC based on Cochrane review (for GnRH agonists + ABT for some adverse events)

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Abbreviations: BSC, best supportive care; ABT, add-back therapy; CrI, credible interval; GnRH, gonadotropin releasing hormone; ITC, indirect treatment comparison; OR, odds ratio

Probabilistic vs deterministic results

Company: robust analysis indicated by probabilistic results being similar to deterministic results; EAG: problems with PSA

Background

- Probabilistic results similar to deterministic; all PSA outcomes show relugolix CT more clinically effective than GnRH agonists, more costly, and within £20,000 – 30,000 per QALY threshold
- Company conclude robust analysis

EAG comment

- Does not indicate robust analysis because:
  1. Input parameters missing from PSA: EAG requested at clarification and company state they included but did not explain which were or were not included or any justification
  2. Fixed 10% variation from mean (standard error) used for parameters: each parameter should have their own standard deviation, particularly if non-symmetric confidence intervals. At clarification, company state it replaced fixed SE if directly reported or could be calculated from confidence intervals but it was unclear for how many this was done

Abbreviations: GnRH, gonadotropin releasing hormone; relugolix CT, relugolix combination therapy; PSA, probabilistic sensitivity analysis; SE, standard error