

Relugolix-estradiol-norethisterone acetate for treating symptoms of endometriosis

For committee and screen.
Slides contain no confidential
information

This is a single technology
appraisal topic.

Highly specialised technologies evaluation committee [6 February 2025], assessing ID3982 as a single technology appraisal

Chair: Paul Arundel

External assessment group: Kleijnen Systematic Reviews

Technical team: Victoria Gillis-Elliott; Nigel Gumbleton, Janet Robertson

Company: Gedeon Richter

© NICE 2025. All rights reserved. Subject to [Notice of rights](#).

Relugolix-estradiol-norethisterone acetate for treating symptoms of endometriosis

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

Key issues

Type	Issue	Impact
Clinical effectiveness	Is committee satisfied that the company's updated literature review and searches would have identified all potentially relevant studies on the relevant comparators?	Unclear
	<ul style="list-style-type: none">Are the committee satisfied that the company's updated ITC demonstrates effectiveness of relugolix CT compared with GnRH agonists?To what extent would the differences in pain rating scales contribute to inconsistent results?How reliable is the evidence for relugolix alone to assist committee's decisions for relugolix CT?	Unclear
Cost effectiveness	Are committee confident that the company's model structure reflects the treatment pathway?	Unclear
	Is it appropriate to exclude surgery as a comparator to relugolix CT?	Unclear
	Are committee satisfied with the definition of BSC?	Likely small
	<ul style="list-style-type: none">Would the treatment effect between relugolix CT compared with GnRH agonists decrease over time or stay the same?Would the pessimistic or optimistic scenario be more appropriate?	Likely small
	Do committee prefer the multiplicative approach or additive approach to applying disutilities?	Likely small
	Do committee prefer the disutility from infertility or from hysterectomy?	Unclear
	How long should GnRH agonists be used for?	Unclear
	Can counterintuitive results be explained?	Unclear

Technology (Ryeqo®, Gedeon Richter)

Marketing authorisation*	<p>Indicated in adult women of reproductive age for:</p> <ul style="list-style-type: none"> • Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis • European Medicines Agency reliance route and GBMA received
Mechanism of action	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • £72 per pack (28 tablets) to be taken once daily • ~£938.57 annually

Background on endometriosis

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

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

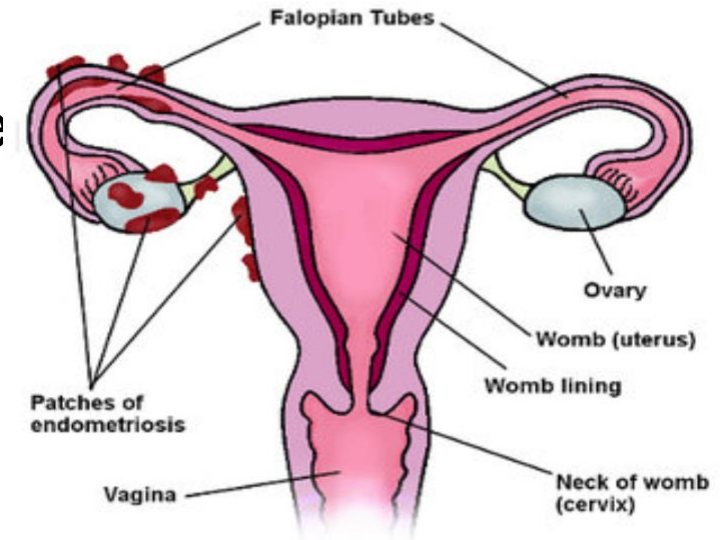
- “Approximately 1 in 10 women and those assigned female at birth in the UK”

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



Source: [Endometriosis UK](https://www.endometriosisuk.org/)

Patient perspectives (originally presented at ACM 1)

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

Clinical perspectives (originally presented at ACM 1)

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 which suggested relugolix CT has a lower risk than GnRH agonists; but 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”

Preliminary recommendation and conclusion

Relugolix–estradiol–norethisterone (relugolix combination therapy [CT]) is not recommended, within its anticipated marketing authorisation, for treating symptoms of endometriosis in adults who have had medical or surgical treatment for their endometriosis.

Rationale:

- It is not possible to determine the most likely cost-effectiveness estimates for relugolix CT
 - Relugolix CT has not been directly compared in a clinical trial with usual treatment.
 - Indirect comparisons suggest that it is likely to reduce pelvic pain almost as well as GnRH agonists, but this is uncertain. It is also uncertain how well relugolix CT works compared with surgery.
 - Because of uncertainty about the completeness of the clinical evidence and absence of evidence on other usual treatments, there are also concerns about the economic model.

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

Committee's requests at ACM 1 to address uncertainty

Committee requests from ACM 1	Included in company's response?	Resolved?
A systematic literature review addressing the methodological issues and including evidence for all relevant comparators	Yes	Yes
Evidence on the efficacy of relugolix CT compared with surgery	No	No
Clarity about best supportive care and how it is used in the model	Yes	No
An updated model that more accurately reflects the treatment pathway including relevant comparators and use of best supportive care	No	No
Full model validation and justification of any counterintuitive results	Yes	No
Scenario analyses: <ul style="list-style-type: none"> • considering the impact of changing values (baseline utility) • considering the impact of treatment effect waning • using longer treatment durations for GnRH agonists • applying a multiplicative approach to incorporate disutilities from adverse events • to capture the disutility from infertility 	Yes Yes Yes No Yes	Yes Yes No No No

Draft guidance consultation comments

Comments received from:

- **Professional group comments** Endometriosis, UK
- **Consultee comments**, Gedeon Richter (company). Response addressed most of committee's requests:
 - Provided a new systematic literature review and indirect treatment comparison
 - Provided a further response to support model validation and justification of counterintuitive results
 - Provided exploratory scenario analyses
 - using longer treatment durations for GnRH agonists
 - considering the impact of treatment waning
 - to further justify the utilities used in the model
 - to capture the disutility from infertility
 - Clarified treatments for best supportive care after relugolix CT
 - Consider the existing model structure does reflect the treatment pathway described in ACM1
 - Has not provided scenarios exploring a multiplicative approach for disutilities from adverse events

Draft guidance for consultation: Comments

Patient/ carer group comments from Endometriosis, UK

- Relugolix CT would be a benefit to help patients of endometriosis manage their symptoms due to the benefits that the drug has, whilst providing an alternative treatment option
- Treatment is longer compared to GnRH agonist treatments, (licensing limit of 6-months). As it is taken daily, those with unmanageable side effects can cease ingesting the drug immediately. This is much more effective than currently available treatments such as a 3 monthly injection, where patients must wait out the side effects until the medicine has left their body
- HRT is included in the tablet, this should mitigate the negative effects of menopause such as bone density. Feedback from community: Having an all-in-one treatment where the patient does not have to remember to additionally take HRT as a separate tablet would be helpful. Relugolix CT can be used as a contraceptive up until natural menopause
- It is positive that new treatments are becoming available, and it is an optimistic step into the future of endometriosis care.

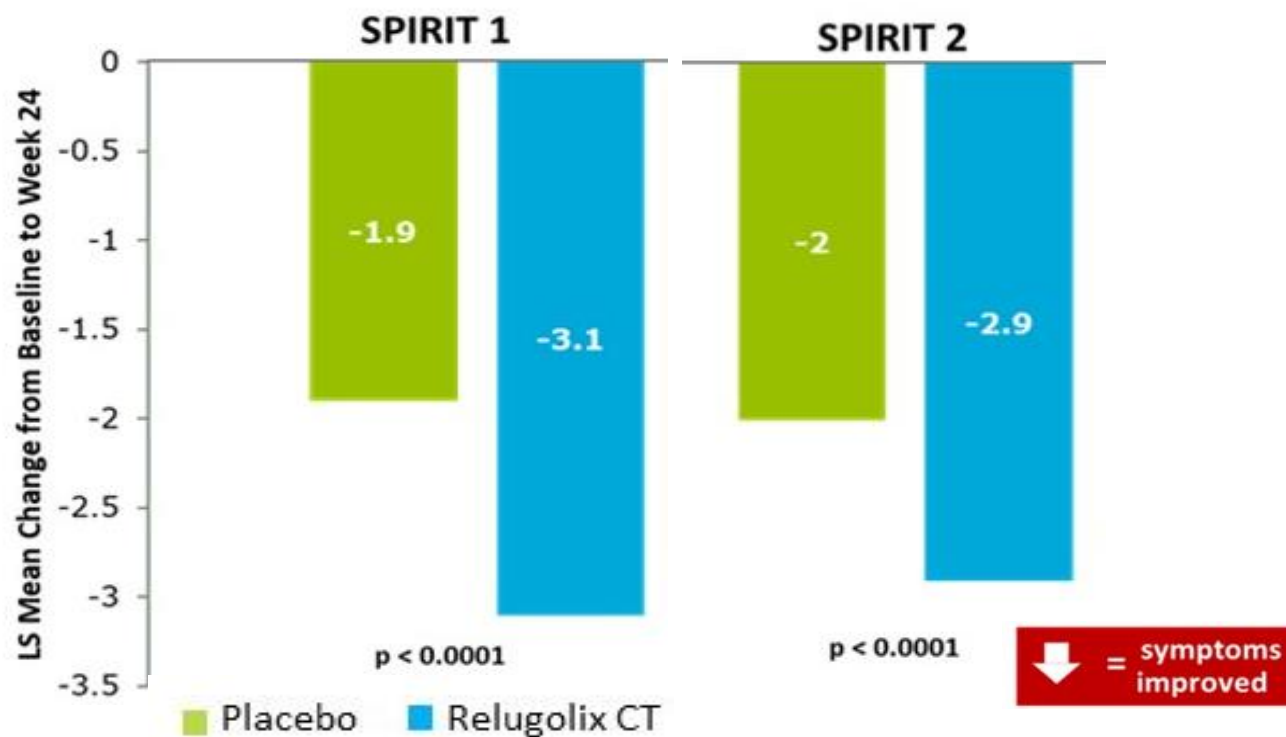
Relugolix-estradiol-norethisterone acetate for treating symptoms of endometriosis

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

SPIRIT 1 & 2, phase 3 RCTs: results- originally presented at ACM 1

Relugolix CT had significantly greater improvement in overall pelvic pain at 24 weeks than placebo; ITC including these studies 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
- TPP was not explicitly included as an outcome in the SPIRIT trials; ITC defined TPP as a composite of dysmenorrhoea, non-menstrual pelvic pain, dyspareunia

* [See appendix](#)

*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; ITC, indirect treatment comparison; NRS, numerical rating scale; relugolix CT, relugolix combination therapy, TPP, total pelvic pain

Key issue: Updated systematic literature review



ACM 1 background and conclusions

- EAG raised [concerns about robustness of company's literature review](#) and identified methodological errors. Company suggested [updating a Cochrane review](#) but EAG considered this unsuitable – it excluded surgical therapies and did not include some outcomes in scope
- Committee concluded an updated literature review was needed to ensure the relevant evidence base had been identified

Company response

- Carried out a [new systematic literature review](#) to address the committee's concerns

EAG comments

Overall EAG has no major concerns about the revised literature searches

- Key limitations had been addressed and revised searches were appropriate and fit for purpose
- Revised searches may have benefitted from separate adverse events searches to capture adverse events that are less likely to be retrieved by searches containing an RCT filter
- Update search includes research on buserelin, goserelin, leuprorelin, and triptorelin, and long-term efficacy from SPIRIT LTE. New review adds more studies for surgery, but company has stated that “no studies were identified that provide evidence for surgery as a comparator to Relugolix CT”
- New search identified 111 studies (139 publications) Original search identified 48 studies (58 publications)



Key issue: Company's indirect treatment comparison



ITC- Background

- In the original ITC's there was no significant difference between relugolix CT and GnRH agonists
- Company's model applied OR from ITC on overall pelvic pain to derive response rates for GnRH agonists. The EAG had various concerns with the company's ITC
- Committee concluded there was uncertainty:
 - unclear if all relevant evidence on GnRH agonists had been identified and
 - unclear about relative efficacy of surgery, - not in company's analyses but relevant comparator

Company response to draft guidance

- Carried out an updated ITC which found:
 - no evidence of a difference between Relugolix CT and leuprorelin acetate for overall pelvic pain, consistent with the original ITC
 - greater effect of leuprorelin acetate compared with relugolix CT for TPP, not consistent with original ITC
- Consider inconsistencies between the results for OPP and TPP are not unexpected
 - OPP uses numeric rating scale; TPP uses the Biberoglu and Behrman scale
 - Only the numeric rating scale has published MCIDs
- There is published data in several disease areas on the efficacy of relugolix alone (without estradiol and norethisterone) compared with GnRH agonists which suggests:
 - relugolix 40 mg non-inferior to leuprorelin acetate for treating endometriosis-associated pelvic pain
 - relugolix 40 mg non-inferior to leuprorelin acetate in reducing heavy bleeding from uterine leiomyomas
 - relugolix superior to leuprorelin acetate in people with prostate cancer achieving sustained castration rate

Key issue Indirect treatment comparison (continued)



EAG critique

Consider company's updated ITC still creates uncertainty

- Studies in the network for OPP were the same as those in the original ITC
 - Network included relugolix CT vs. placebo (SPIRIT 1 and 2) and leuprorelin vs placebo (D'Hooghe 2019) and data was considered as a single trial so unclear why results differed from clarification
 - Company's conclusion is unchanged (little difference between relugolix CT and leuprorelin acetate) – results are similar between the [company response and original ITC](#)
- Studies in the network for TPP were changed
 - TPP- included leuprorelin acetate vs. placebo (Osuga 2021) and excluded dienogest vs. placebo (Lang, 2018) and leuprorelin acetate vs. dienogest (Strowitzki et al. 2010) and data from each trial were considered separately (which is a more appropriate method)
 - Results suggest a clearer advantage to leuprorelin acetate which [differs from the original ITC](#)
 - Results of individual outcomes shows:
 - an advantage to leuprorelin acetate (dysmenorrhoea, non menstrual pelvic pain and pelvic pain)
 - similarity between relugolix CT and leuprorelin (dyspareunia)



- Are the committee satisfied that the company's updated ITC demonstrates effectiveness of relugolix CT compared with GnRH agonists?
- To what extent would the differences in pain rating scales contribute to inconsistent results?
- How reliable is the evidence for relugolix alone to assist committee's decisions for relugolix CT?

Relugolix-estradiol-norethisterone acetate for treating symptoms of endometriosis

- ☐ Background and key issues
- ☐ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**
- ☐ Other considerations
- ☐ Cost-effectiveness results
- ☐ Summary

Key issue: Company's model structure



Background

- At ACM 1 committee were concerned that the treatment pathway was more complex than that defined in the company [model structure](#); There is a fluctuating [treatment pathway](#) for endometriosis and relugolix CT could be used second or third line.
- EAG had noted several concerns
 - Fertility concerns guide clinical pathway. But this was not captured in the company's model structure
 - The population was unclear and treatment history, could affect appropriate comparators as well as the nature of subsequent treatment
 - BSC is part of the modelled treatment pathway (after treatment discontinuation with relugolix CT or GnRH agonists) but the company definition of BSC was not clear
- Committee concluded the model should reflect the treatment pathway, including the use of BSC and all relevant comparators, including surgery

Company response to draft guidance:

- Consider current model structure does reflect the treatment pathway, as it allows for further surgery after relugolix CT.
 - The model captures all possible avenues that may be taken after stopping treatment with either relugolix CT or GnRH agonist
 - After stopping relugolix CT/GnRH, a proportion can have surgery; but many choose not to
 - Model captures pain recurrence following surgery and subsequent treatment, either with BSC or further surgery (including hysterectomy)

Key issue: Company's model structure continued



EAG critique:

- Company has not changed model structure so the EAGs concerns at ACM1 (see previous slide) about the treatment pathway (defining the population, including all relevant comparators) and operationalising infertility in the model (see later issues) remains



Are committee confident that the company's model structure reflects the treatment pathway?

Key issue: Data informing the company model: Surgery



Background

- Committee concluded both GnRH agonists and surgery were relevant comparators.
- The modelled treatment pathway included relugolix CT, GnRH agonists, BSC and surgery (conservative surgery or hysterectomy). EAG highlighted that BSC and surgery after stopping relugolix CT was expected to have more impact on model results than response to GnRH agonists but it was unclear how these had been implemented in the company's model.

Company response to draft guidance:

1. Clarified differences in treatment pathway for surgery as a comparator and surgery as a treatment option after relugolix CT or GnRH agonists and how these were incorporated in the model structure ([see link](#))
2. Do not consider surgery is a comparator to relugolix CT
 - Different factors may lead to different treatment options based on patient preference and/or medical history - there may be clinically distinct populations eligible for each treatment modality
 - This is the first time assessment of relugolix CT has explored surgery as a potential comparator of interest. Evidence for surgery is limited and available studies are heterogeneous, so difficult to compare
 - Surgery was not a comparator in NICE evaluation of relugolix CT in uterine fibroids ([TA 832](#)) but scopes are similar ([see link](#))
3. Using current model, ICER for relugolix CT v surgery is low (surgery efficacy not informed by ITC)



EAG critique

- Surgery is included as a comparator in the company's model so this reinforces its relevance and EAG consider the company should provide stronger evidence or redefine the target population.
- Surgery is typically integrated into the overall treatment pathway and evaluation process should reflect local UK clinical practice, where surgery plays a significant role
- Surgery as a comparator is implemented in the same way as surgery as a follow-up treatment after relugolix CT or GnRH agonists except in first model cycle
- Unclear if model inputs (surgery costs, healthcare resource use, efficacy and health-related quality of life) for first line surgery can be generalised to follow-up surgery as not informed by a systematic review. But although impact is uncertain, it is expected to be minor



Is it appropriate to exclude surgery as a comparator to relugolix CT?

Key issue: Data informing the company model: The definition and role of BSC in the model should be clarified



Background

- The EAG had noted there was confusion about whether BSC in the model had included analgesics
- Clinical experts confirmed BSC would likely include analgesics and that BSC is used alongside all treatments
- Committee concluded that more clarity was needed on how best supportive care is defined and modelled

Company response to draft guidance

- BSC after relugolix CT is likely analgesics for pain management. Some patients may opt for surgery
- Patients would have already failed hormonal treatments before starting relugolix CT. So would not be expected to restart treatment with hormonal treatments at this stage.

EAG critique

- The EAGs original key issues (defining the population, including relevant comparators and identifying the role of BSC) are still unresolved and [the EAG suggestions to resolve have not been addressed](#)



Are committee satisfied with the definition of BSC?

Key issue: Treatment waning



Background

- Company assumed relugolix CT was taken until response, discontinuation or menopause and response was constant over time. EAG noted a 15-year sustained effect was a strong assumption and there had been no exploration of impact of treatment effect waning on model.
- Committee concluded scenarios examining the impact of treatment waning would be helpful

Company response to draft guidance:

- Does not anticipate any waning of treatment effect with relugolix CT
- Data from the open label extension showed response was maintained for 2 years of treatment
 - Week 104, the reduction in dysmenorrhoea was maintained (84% decrease from baseline).
 - Week 104, the reduction in non-menstrual pelvic pain was maintained (68.9% decrease from baseline).
 - No increase in discontinuation rates due to lack of efficacy between [SPIRIT 1 & 2 and SPIRIT OLE](#).
- Conducted scenario analyses applying alternative discontinuation rates at months 21 and 24 from SPIRIT
 - 'pessimistic' scenario using the upper value (maximum) of the discontinuation rate (0.033)
 - 'optimistic' scenario where the lower value (minimum) discontinuation rate(0) at months 21 and 24+.

EAG critique

- Scenario results had little impact on the model results- but consider the effect of waning could be captured by adjusting the response rates over time rather than treatment discontinuation



NICE

- Would the treatment effect of relugolix CT compared with GnRH agonists decrease over time or stay the same?
- Would the pessimistic or optimistic scenario be more appropriate?

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



Key issue: Long term utility

Background

- In company model utility values were based on SPIRIT trials (baseline utility 0.58 for both treatment arms)
- EAG considered long-term disutilities after surgery were a key driver.
- Company had used an additive approach to apply disutilities from adverse events and surgery-related complications
- [Section 4.3.7 of NICE health technology evaluations: the manual](#) states a multiplicative approach is preferred
- Older studies had been used to inform the disutility for adverse events from surgical complications, for hysterectomy were taken from Global Burden of Disease study(1990). But unclear if applicable to UK
- Committee concluded high level of uncertainty needed to be addressed - preferred multiplicative approach

Company response to draft guidance

- EQ-5D values were from SPIRIT so at the top of NICE's preferred evidence hierarchy for utility source.
- Utility values align with literature:
 - Original SLR identified utility values from 0.15 to 0.689 pre-surgery; highest value overall was 0.78 (Oppenheimer et al. 2021), but population was less severe than SPIRIT trials
 - In a population that aligned with SPIRIT, (moderate to severe endometriosis pain) SLR identified a baseline EQ-5D of 0.49 (Grundström et al. 2019)
- Endometriosis affects all dimensions of EQ-5D (noted a 2019, survey highlighting impact on quality of life)
- Sensitivity analysis where utility of non-responders (0.72) is set equal to the baseline utility value (0.58).



Key issue: Long term utility continued

Company response to draft guidance continued:

- A multiplicative approach to incorporate disutilities is not appropriate
 - a multiplicative approach is typically used for an age-related decrement and an additive approach is used for other disutilities.
 - Consider that a multiplicative approach to incorporating disutilities from adverse events would not have a significant impact upon the results so have not provided scenarios to explore this.

EAG critique

- Does not agree with company's interpretation but considers a multiplicative approach is likely to have a minor impact on the model result
 - Has concerns around the company's approach to assume the same utility value for non-responders and the same utility value for responders without considering their treatment path or consecutive episodes of non-response.
 - Has concerns about using relatively old studies to inform disutility values due to adverse events or surgical complications, (for example long-term disutility value for people having hysterectomy)



Do committee prefer the multiplicative approach or additive approach to applying disutilities?

Key issue: Modelling the disutility from infertility



Background

- Company model applies a utility decrement to all women after hysterectomy- it considered differences in disutility because of infertility between treatments were captured in EQ-5D from trial
- EAG considered company approach too simplistic, (fertility drives treatment choice) but had large impact on results. The model applied utility decrements to all people after hysterectomy, but decrement should be applied to only people who were actively seeking to have become pregnant
- Committee noted the uncertainty and concluded it would have preferred scenarios in which the disutility from infertility was explored separately to better capture a population that might not want to have children)

Company response to draft guidance

- Consider disutility from hysterectomy is most appropriate
- Does not agree that the decrement be applied to people who were actively seeking to become pregnant
 - It would assume disutility associated with hysterectomy is only limited to infertility, but hysterectomy can have a substantial impact on quality of life beyond this
 - Not plausible that only people who want a child would have a disutility after hysterectomy
 - Oophorectomy (where ovaries are removed as well as uterus) would trigger menopause, which also has a negative impact on health-related quality of life.
- Carried out scenario analyses to explore disutility associated with hysterectomy (disutility set at 0.05, 0.01 and 0.1)

Key issue: Modelling the disutility from infertility continued



EAG critique

- Company's approach (applying single utility decrement for all women) is simplistic and the estimated value, representing a disutility linked to infertility, is probably incorrect because company state the disutility is for hysterectomy but they still applied the value that they had used for infertility
- Company position (assuming hysterectomy can have a substantial impact on quality of life beyond infertility, and that it is not plausible that only people wishing to have a child would have a long-term disutility after a hysterectomy) is in contrast with its original position
- Company applied a disutility sourced from Global Burden of Disease report (1990) but EAG are unclear if this value is still representative and the company have applied the disutility they originally applied for infertility and not hysterectomy
- EAG reproduced company scenario (disutility for hysterectomy set at 0.05, 0.01 and 0.1) –
 - A lower disutility = higher ICER
- EAG carried out additional exploratory scenario analyses
 - no disutility,
 - including each disutility with surgery as a comparator
 - utility decrements from hysterectomy/infertility applied to a proportion up to a certain age



Key issue: Treatment duration of GnRH agonists



Background

- GnRH agonists are licensed for 6 months. But in clinical practice may be used for longer periods.
- The company model included relugolix CT for 16 years with GnRH agonists used for 1 year but the length of time GnRH agonists were used varied (in some cases up to 5 to 10 years)
- Committee requested sensitivity analyses varying duration of GnRH agonist use in clinical practice

Company response to draft guidance

- 2 out of 5 UK clinical experts consulted by company stated a small proportion had GnRH agonists for more than 2 years.
- Carried out scenarios including GnRH use up to 5, 7 and 10 years- relugolix CT dominated GnRH agonists

EAG comments

- Agrees with company scenarios – as duration for GnRH agonists increases, relugolix CT becomes less costly but incremental QALYs decrease (HR favours GnRH agonists).
- The longer GnRH agonists are taken the more effective they become compared to relugolix CT. But it would take 15 years (60 treatment cycles) until GnRH agonists are more effective than relugolix CT – results in ICER in SW quadrant (less costly, less effective)



Key issue: Model validation and counterintuitive results



Background

- Company had provided an adapted (global) model including parameters that were not in its submission but EAG had not been able to fully validate or critique
- Counterintuitive results had suggested that even if 100% stopped having relugolix CT at 9 or 12 months relugolix CT would have greater QALYs and fewer costs than GnRH agonists. Yet, GnRH agonists were more effective in the first year of treatment
- Committee concluded that full model validation and clear justification of counterintuitive results was needed

Company response to draft guidance

- Full details of model validation (both external and internal) were provided at clarification ([see link to summary](#))
- Explored sensitivity of utility values by including scenario- utility of non-response set equal to baseline utility
- Counterintuitive results explained by the ratio of costs pre-response compared with post-response:
 - Before response assessment, the costs of GnRH agonist are higher than relugolix CT
 - At response rates above 1%, there are higher total costs for relugolix CT (and more QALYs) due to longer duration of treatment post-response assessment, despite fewer passing response assessment
 - At response rates of 1% balance of costs switches as minimal relugolix CT costs generated post assessment. Lower costs are generated in the relugolix CT arm than the GnRH agonist arm because relugolix CT is cheaper pre-assessment than GnRH and there are minimal costs post-assessment
- Decreasing relugolix CT duration to 9 or 12 months results in lower QALYs and costs vs. GnRH agonist

Key issue: Model validation and counterintuitive results (continued)



EAG critique

- Unable to replicate results of company scenario analysis (utility of non-response was set equal to baseline) but EAG analysis resulted in an ICER in NE quadrant (more effective and more expensive)
- In the company results, the total QALYs are relatively insensitive to single changes in utilities because:
 - 88% of the overall gain in QALYs from relugolix CT compared with GnRH agonists is from lower level AEs and surgery-related complications for patients in the relugolix CT arm,
 - 86% of the overall QALY gains from lower level long-term surgery-related complications only (post-hysterectomy disutility).
- Regarding the counterintuitive results - understanding how the model works and how results are obtained is important but it does not imply that the results are valid.
- EAG still consider it would be reasonable to expect the cost-effectiveness of relugolix CT to increase in line with the proportion achieving complete response (the more response, the better), but this is not the case in the results



Can counterintuitive results be explained?

Other outstanding issues

Issue	Description	Company DG response
Probabilistic vs deterministic results	<ul style="list-style-type: none"> • Probabilistic results were similar to deterministic; so company stated the analysis was robust. • EAG had considered some important parameters were missing. Company provided at clarification but state they included but did not justify or explain which were included 	<ul style="list-style-type: none"> • Provided an updated model with missing probabilistic sensitivity analysis parameters at clarification • At response to DG provided full list of parameters added into the PSA
Clinical outcomes in the model	<ul style="list-style-type: none"> • EAG had noted several outcomes from the scope (endometriosis recurrence, hospital admission, fertility and complications) were not included in the model (see link). • Experts at ACM 1 had noted outcomes that affect quality of life and are important (pelvic pain, including chronic pain and dysmenorrhoea, and dyspareunia and psychological impact of endometriosis) • Committee concluded dimensions that are important to patients' quality of life should be included in the model. 	<p>Company provided a response at clarification stage</p> <p>EAG note this issue is unresolved</p>

Summary of preferences

	ACM1 committee preferences	Company	EAG response and Impact
Model structure	Alternative model structure to reflect treatment pathway and include BSC and surgery	Exploratory scenarios including surgery	Exploratory scenarios including surgery – Impact uncertain
Model validation	Scenarios considering impact of changing values, (baseline utility)	Scenario where utility of non-responders (0.72) set to baseline utility (0.58)	Impact small
Scenarios of longer durations for GnRH agonists	Scenarios considering longer treatment of GnRH agonist	Maintained GnRH use for 1 year Scenarios varying GnRH use (up to 5, 7 and 10 years)	GnRH use capped at 15 yrs Impact large
Scenarios considering disutility from infertility	Scenarios exploring disutility from infertility	Maintain disutility from hysterectomy Scenarios (disutility set at 0.05, 0.01 and 0.1)	Scenarios: <ul style="list-style-type: none"> no disutility, each disutility with surgery as a comparator utility decrements from hysterectomy/infertility for proportion and certain age Impact large
Scenarios considering the impact of treatment effect waning	Scenarios considering a waning of relugolix CT	Maintains no waning of relugolix CT Scenario at 21 and 24+ Months (0.033 discontinuation rate) (0 discontinuation rate)	Impact small
Disutilities from adverse events	A multiplicative approach to incorporating disutilities from adverse events	Maintains additive approach to incorporate disutility from adverse events	Impact likely small

Other benefits not captured- originally presented at ACM 1

- 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?

Relugolix-estradiol-norethisterone acetate for treating symptoms of endometriosis

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

Cost-effectiveness results

- All results presented include publicly available prices
- There are confidential comparator prices available, however they would not impact decision making in any scenarios in the cost-effectiveness results

Company base case results

Deterministic base case result: relugolix CT vs. GnRH agonists

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Relugolix CT	£11,487	17.165	-	-	-
GnRH agonists	£10,280	16.461	£1,207	0.704	£1,715

Deterministic base case results: relugolix CT vs. surgery

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Relugolix CT	£11,487	17.165	-	-	-
Surgery	£9,741	16.345	£1,746	0.820	£2,130*

*ICER in NE quadrant of CE plane (more costly, more effective)

Abbreviations: GnRH gonadotropin reuptake inhibitor, relugolix CT, relugolix combined therapy; Inc, incremental; ICER, incremental cost-effectiveness ratio; LYG , life years gained; QALY, quality-adjusted life year

Company scenario analyses (deterministic) relugolix CT vs. GnRH agonists (1)

Where GnRH agonists treatment duration is capped

Scenario (applied to company base case)	Inc costs (£)	Inc QALYs	ICER (£/QALY)
Company base case (deterministic)	£1,207	0.704	£1,715
GnRH agonists (capped at 5 years)	-£164	0.398	Relugolix CT dominates
GnRH agonists (capped at 7 years)	-£670	0.283	Relugolix CT dominates
GnRH agonists (capped at 10 years)	-£1,237	0.145	Relugolix CT dominates

Where utility of non-response was set equal to the baseline utility

Scenario (applied to company base case)	Inc costs (£)	Inc QALYs	ICER (£/QALY)
GnRH agonists	£1,207	0.717	£1,683

Company scenario analyses (deterministic) relugolix CT vs. GnRH agonists (2)

With alternative disutility of hysterectomy

Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case (deterministic)	£1,207	0.704	£1,715
Disutility of hysterectomy is 0.01	£1,207	0.129	£9,383
Disutility of hysterectomy is 0.05	£1,207	0.264	£4,573
Disutility of hysterectomy is 0.1	£1,207	0.433	£2,787

With alternative relugolix CT discontinuation rates

Scenario (applied to company base case)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Pessimistic scenario Maximum discontinuation rate (0.033)	£1,082	0.497	£2,178
Optimistic scenario Minimum discontinuation rate (0)	£1,166	0.906	£1,287

EAG exploratory analyses (deterministic) relugolix CT vs. GnRH agonists

Technologies	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Company base case (deterministic)	£1,207	0.704	£1,715
GnRH agonists treatment duration capped at 15 years	-£1,656	-0.002	£746,754*
No disutility of hysterectomy	£1,207	0.095	£12,731
Half disutility of hysterectomy applied to 50% following hysterectomy, 50% on treatment (relugolix CT and GnRH agonists), and up to 45 years	£1,207	0.039	£31,249
Base-case disutility of hysterectomy applied to 50% following hysterectomy, 50% on treatment (relugolix CT and GnRH agonists), and up to 45 years	£1,207	-0.018	GnRH agonists dominate

* ICER in SW quadrant of CE plane (less costly, less effective)

Abbreviations: GnRH gonadotropin reuptake inhibitor, relugolix CT, relugolix combined therapy; ICER, incremental cost-effectiveness ratio; inc, incremental; LYG , life years gained; QALY, quality-adjusted life year

EAG exploratory analyses (deterministic) relugolix CT vs. surgery

Technologies	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Company base case (deterministic)	£1,746	0.820	£2,130
Disutility of hysterectomy is 0.01	£1,746	0.076	£23,010
Disutility of hysterectomy is 0.05	£1,746	0.251	£6,959
Disutility of hysterectomy is 0.10	£1,746	0.470	£3,717
No disutility of hysterectomy	£1,746	0.032	£54,351
Half disutility of hysterectomy applied to 50% following hysterectomy, 50% on treatment (relugolix CT and GnRH agonists), and up to 45 years	£1,746	-0.005	Surgery dominates
Base-case disutility of hysterectomy applied to 50% following hysterectomy, 50% on treatment (relugolix CT and GnRH agonists), and up to 45 years	£1,746	-0.042	Surgery dominates

Abbreviations: GnRH gonadotropin reuptake inhibitor, relugolix CT, relugolix combined therapy; ICER, incremental cost-effectiveness ratio; inc, incremental; LYG , life years gained; QALY, quality-adjusted life year

Relugolix-estradiol-norethisterone acetate for treating symptoms of endometriosis

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

Key issues

Type	Issue	Impact
Clinical effectiveness	Is committee satisfied that the company's updated literature review and searches would have identified all potentially relevant studies on the relevant comparators?	Unclear
	<ul style="list-style-type: none">Are the committee satisfied that the company's updated ITC demonstrates effectiveness of relugolix CT compared with GnRH agonists?To what extent would the differences in pain rating scales contribute to inconsistent results?How reliable is the evidence for relugolix alone to assist committee's decisions for relugolix CT?	Unclear
Cost effectiveness	Are committee confident that the company's model structure reflects the treatment pathway?	Unclear
	Is it appropriate to exclude surgery as a comparator to relugolix CT?	Unclear
	Are committee satisfied with the definition of BSC?	Likely small
	<ul style="list-style-type: none">Would the treatment effect between relugolix CT compared with GnRH agonists decrease over time or stay the same?Would the pessimistic or optimistic scenario be more appropriate?	Likely small
	Do committee prefer the multiplicative approach or additive approach to applying disutilities?	Likely small
	Do committee prefer the disutility from infertility or from hysterectomy?	Unclear
	How long should GnRH agonists be used for?	Unclear
	Can counterintuitive results be explained?	Unclear

Thank you.

Relugolix-estradiol-norethisterone acetate for treating symptoms of endometriosis

Supplementary appendix

Decision problem

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

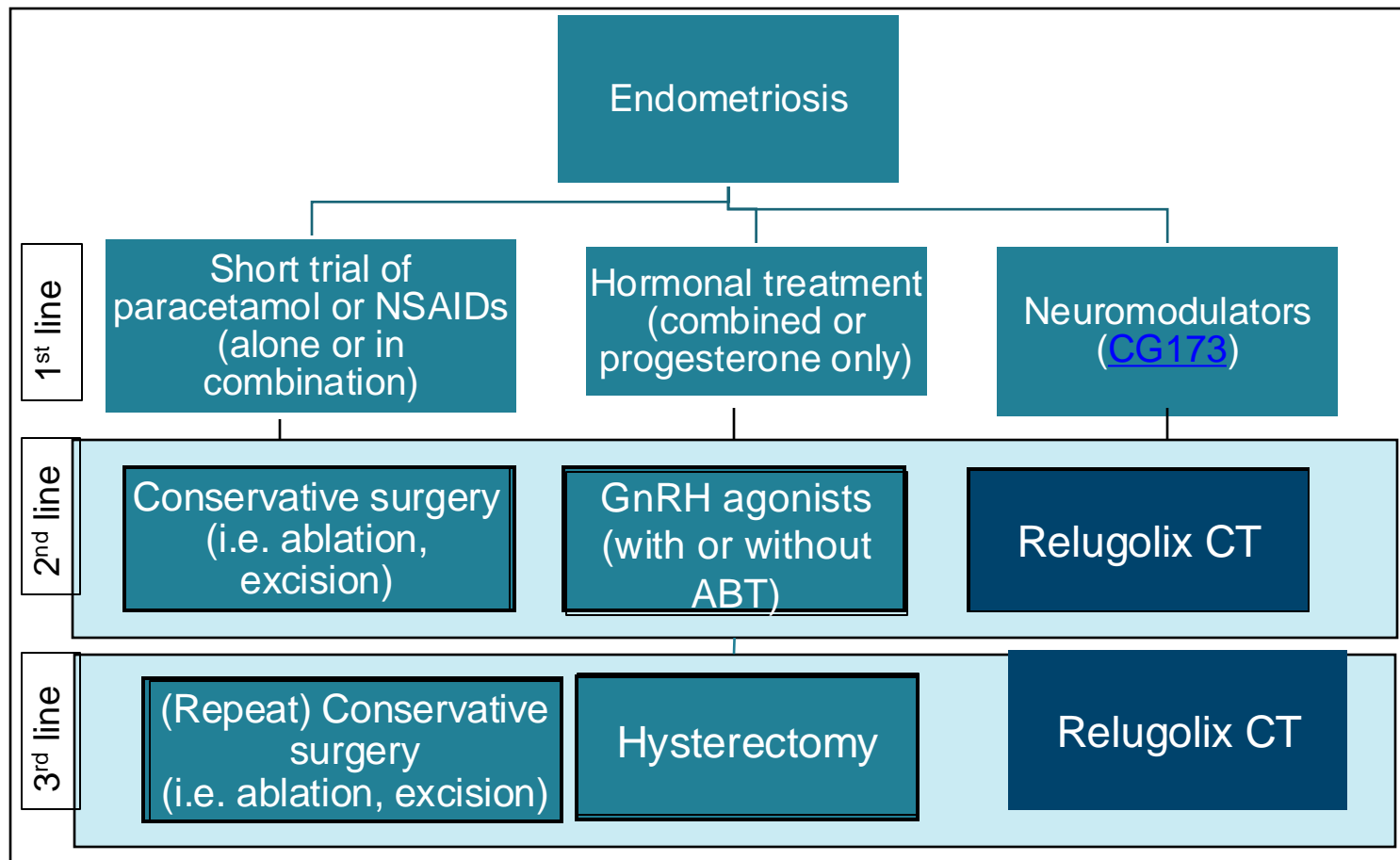
Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adults with symptoms of endometriosis	Focus on 2 nd 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: <ul style="list-style-type: none"> 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

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.

Company response to draft guidance: Model aligns with [ESHRE guidelines](#)

Key issue data to inform the model: Surgery



List of comparators in scope for current evaluation (ID3982) and list of comparators in scope for TA832

	Relugolix–estradiol–norethisterone acetate for treating symptoms of endometriosis [ID3982]	Relugolix with oestradiol and norethindrone acetate for treating uterine fibroids [TA832]
Comparators	<p>Established clinical management without relugolix in combination with oestradiol and norethindrone, including:</p> <ul style="list-style-type: none">• analgesics or NSAID alone or in combination with each other• neuromodulators• hormonal treatment such as<ul style="list-style-type: none">• combined hormonal contraception (off-label for some combined hormonal contraceptives),• oral progestogens,• GnRH agonists.	<p>Hormonal treatments, including:</p> <ul style="list-style-type: none">• LNGIUS (off-label for some LNG-IUSs)• Combined hormonal contraception (off-label for some combined hormonal contraceptives)• cyclical oral progestogens• gonadotrophin-releasing hormone analogues (off-label for some gonadotrophin-releasing hormone analogues)

Key issue: Data informing the company model: Best supportive care



EAG critique

- EAGs original key issues (defining the population, including relevant comparators and identifying the role of BSC) are still unresolved and the EAG suggestions to resolve have not been addressed

Key issue	Suggested approach
Population needs to be defined	The lack of clarity on precise line and previous treatment means there is uncertainty on the population eligible for relugolix CT, which could have profound implications including for relevant comparators and subsequent treatments.
Relevant comparators may be missing from the economic analyses	Include missing comparators in the model Update SLR and economic model to include relevant comparators
Definition and role of BSC in the model should be clarified	Provide a clear definition of BSC, placebo and analgesics, and how these are used in the model Update evidence synthesis and economic model to include effectiveness estimates of BSC in the correct population (BSC after treatment discontinuation)

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'*

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	<p>Company report search strategy was identical but update was performed for period from May 2022 to November 2023.</p> <p>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.</p> <p>Unclear why this differed as full search strategies not provided.</p>

Key issue Systematic literature review*

Aspect	EAG concerns with original literature search	Company's updated review
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	SR search in MEDLINE and EMBASE strategies may have mitigated against some loss of recall, but EAG unable to say impact
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	Searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews
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	New search adds more studies related to surgery
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 –seemed overly restrictive - should remove	Conditions facet Interventions facet and pain facet updated to address terms

EAG's concerns with company's original ITC



Issue
Clinical evidence had a minimal input on model results because GnRH agonists only applied for 1 year
Results driven by relative effect of relugolix CT compared with subsequent treatments (surgery and BSC) but unclear how the treatment effect was incorporated after GnRH agonists stop
The link between clinical effectiveness and economic evidence was weak and more clinical effectiveness parameters were needed in model
The same treatment stopping rates and transition to subsequent treatments had been applied for both arms
It was unclear if evidence for distribution between types of surgery was generalisable to UK
The probability of pain after surgery had not been taken from SPIRIT trials

[Link](#)

Published data relevant to relugolix (alone)

* [See link](#)



Head-to-head evidence comparing relugolix (alone) with GnRH agonists:

Endometriosis:

- **Osuga et al, (2021)** a phase 2 study in women with endometriosis-associated pain comparing relugolix 40 mg with leuprolide acetate 3.75 mg

Table Mean change from baseline in VAS scores for endometriosis-associated

	Mean (SD) change from baseline in mean VAS score (mm)	
	Relugolix 40 mg (n = 103)	Leuprolide 3.75 mg (n = 82)
Pelvic pain	-11.9 (11.26)	-12.7 (12.57)
Dysmenorrhea	-29.5 (17.54)	-27.2 (19.86)
Dyspareunia	-0.9 (12.04)	-4.6 (15.09)

- **Harada et al, (2022)** a phase 3, randomized, double-blind study assessing change in VAS (SE) for pelvic pain at 24 weeks for relugolix compared with leuprolide
relugolix (n = 171) mean change = -52.6 (SE= 1.3); leuprolide (n = 164) mean change = -57.5 (SE =1.4)

Uterine leiomyoma (fibroids)

- **Osuga et al (2019)**; double-blind, double-dummy study showed that relugolix 40 mg was non-inferior to leuprolide in reducing heavy bleeding associated with uterine leiomyomas
relugolix (n = 139) 82.2% had a total pictorial blood loss assessment chart score of less than 10
leuprolide (n = 142) 83.1%
relugolix–leuprolide difference -0.9%; 95% CI: -10.10 to 8.35; prespecified noninferiority margin -15%; P=.001).

Prostate cancer

- **Shore et al (2020)** a phase 3 study in advanced prostate cancer,
proportion achieving suppressed testosterone castration levels at 48 weeks - relugolix = 96.7% leuprolide = 88.8%
(between-group difference, 7.9 percentage points; 95% confidence interval, 4.1 to 11.8; P<0.001)

Abbreviations: GnRH, gonadotropin releasing hormone; SD, standard deviation; SE, standard error; VAS visual analogue scale

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

[* See link](#)

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

SPIRIT 1 & 2 trials: co-primary endpoint results

* [See link](#)

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

Figure. proportion responding - dysmenorrhoea *

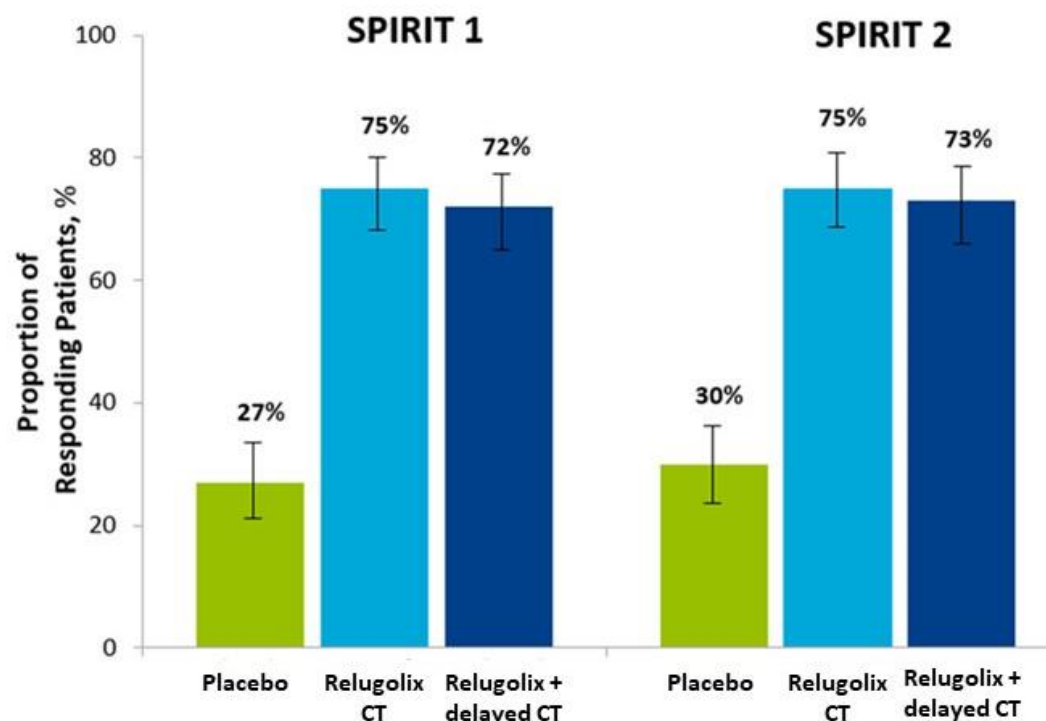
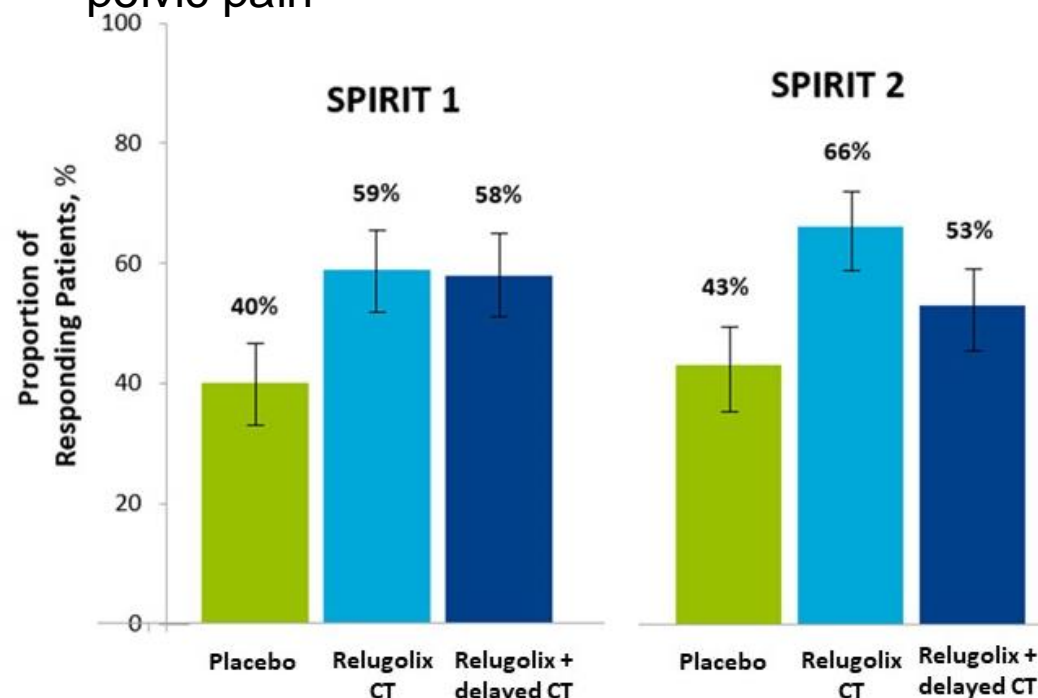


Figure. proportion responding – non-menstrual pelvic pain *



* 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)

SPIRIT 1 & 2, phase 3 trials: results

* [See link](#)

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

Pain scales used for outcomes in the ITC

[* See link](#)

Company consider inconsistencies between the results for OPP, using the NRS) and TPP, using Biberoglu and Behrman are not unexpected

NRS is a segmented version of the VAS, anchored by pain severity extremes. Patient selects a rating (0 to 10) that best reflects pain intensity

B&B based on pain symptoms (dysmenorrhea, pelvic pain and dyspareunia) classified as absent, mild, moderate or severe

- Modified versions combine pain symptoms into the ‘pelvic symptoms score’ or ‘endometriosis symptom severity scale’ and the clinical findings into the ‘physical symptoms score’. Both the pelvic symptoms score and the physical symptoms score can be combined with the ‘B&B total sum score’ .

Figure. Numeric rating scale

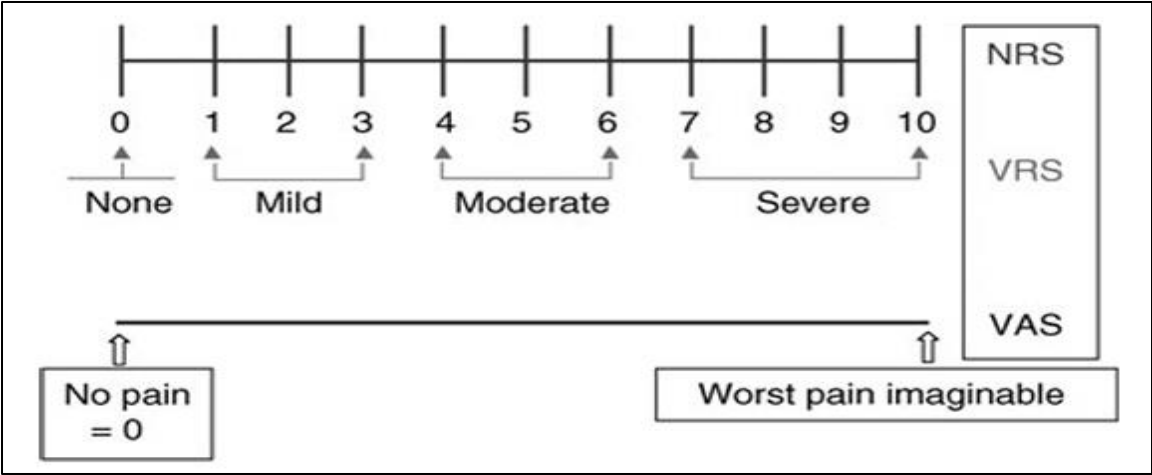


Table. Modified Biberoglu and Behrman Scale

Dysmenorrhea	Pelvic Pain	Dyspareunia	Numerical Score
No pain	No pain	No pain	0
Mild	Mild	Mild	1
Moderate	Moderate	Moderate	2
Severe	Severe	Severe	3
Did not menstruate	-	No intercourse	4

Updated ITC results 1

[* See link](#)

There are no significant differences between relugolix CT and leuprorelin acetate for OPP response

Table: mean difference of treatment effects for OPP at 12 weeks (fixed effects)*

Placebo	0.87 (0.24, 1.48)	0.89 (0.59, 1.2)
-0.87 (-1.48, -0.24), 0.997	Leuprorelin Acetate	0.02 (-0.66, 0.72)
-0.89 (-1.2, -0.59), >0.999	-0.02 (-0.72, 0.66), 0.517	Relugolix CT

Table: OR for OPP at 12 weeks (fixed effects)*

Placebo	0.47 (0.26, 0.8)	0.48 (0.37, 0.61)
2.33 (1.25, 3.82), 0.997	Leuprorelin Acetate 3.75 mg	1.11 (0.55, 1.94)
2.13 (1.63, 2.73), >0.999	0.99 (0.52, 1.81), 0.422	Relugolix CT

*Bold values indicate evidence of a difference. Mean difference < 0 favours row intervention over column intervention.

Evidence of a greater effect for TPP, and higher chance of TPP response for leuprorelin acetate than for Relugolix CT,

Table: mean difference of treatment effects for TPP at 12 weeks (fixed effects)*

Placebo	2.5 (2.14, 2.85)	1.15 (0.96, 1.34)
-2.5 (-2.85, -2.14), >0.999	Leuprorelin acetate 3.75 mg	-1.35 (-1.74, -0.95)
-1.15 (-1.34, -0.96), >0.999	1.35 (0.95, 1.74), <0.001	Relugolix CT

Table: OR for TPP at 12 weeks (fixed effects)*

Placebo	0 (0, 0.01)	0.06 (0.04, 0.09)
348.91 (139.28, 740.18), >0.999	Leuprorelin acetate 3.75 mg	21 (7.19, 48.79)
17.59 (10.6, 27.4), >0.999	0.06 (0.02, 0.14), <0.001	Relugolix CT

*. Values in bold indicate evidence of a difference. Mean difference < 0 favours row intervention over column intervention.

Updated ITC results (2)

* [See link](#)

Table: mean difference of treatment effects for OPP at 12 weeks– fixed effect model - ranking probabilities

Treatment	Probability	SUCRA	Mean rank (95%CrI)
Placebo	0	0.0016	3 (3, 3)
Leuprorelin acetate	0.483	0.7399	1.52 (1, 2)
Relugolix CT	0.517	0.7585	1.48 (1, 2)

For overall pelvic pain, leuprorelin acetate and Relugolix CT had similar ranking as being the most effective treatment

Table: OR for OPP at 12 weeks – fixed effect model - ranking probabilities

Treatment	Probability	SUCRA	Mean rank (95%CrI)
Placebo	0	0.0013	3 (3, 3)
Leuprorelin acetate	0.58	0.79	1.42 (1, 2)
Relugolix CT	0.42	0.71	1.58 (1, 2)

Updated ITC results (3)

[* See link](#)

Table: mean difference of treatment effects for TPP at 12 weeks– fixed effect model - ranking probabilities

Treatment	Probability	SUCRA	Mean rank (95%CrI)
Placebo	<0.001	0	3 (3, 3)
Leuprorelin acetate	>0.999	1	1 (1, 1)
Relugolix CT	<0.001	0.5	2 (2, 2)

For total pelvic pain, Leuprorelin acetate has highest probability (>0.999) of having best ranks compared with Relugolix CT (<0.001)

It is likely that leuprorelin acetate is the most effective treatment based on ranking of probabilities

Sensitivity analyses of TPP supported this

Table: OR for TPP at 12 weeks – fixed effect model - ranking probabilities

Treatment	Probability	SUCRA	Mean rank (95%CrI)
Placebo	<0.001	0	3 (3, 3)
Leuprorelin acetate 3.75 mg	>0.999	1	1 (1, 1)
Relugolix CT	<0.001	0.5	2 (2, 2)

NICE Abbreviations: Cr, credible interval; ITC, indirect treatment comparison; OR, odds ratio; OPP, overall pelvic pain; relugolix CT, relugolix combination therapy; TPP, total pelvic pain; LA, leuprorelin acetate;

Updated ITC results (4)

* [See link](#)

Table: mean difference of OPP - fixed effect model

Comparator	Company response to DG	Clarification
Placebo	-0.89 (-1.2 to -0.59)	-0.80 (-0.49 to -1.1)
Leuprorelin Acetate 3.75 mg	-0.02 (-0.72 to 0.66)	0.070 (-0.61 to 0.74)

OPP results are similar between the company response to the DG and to clarification

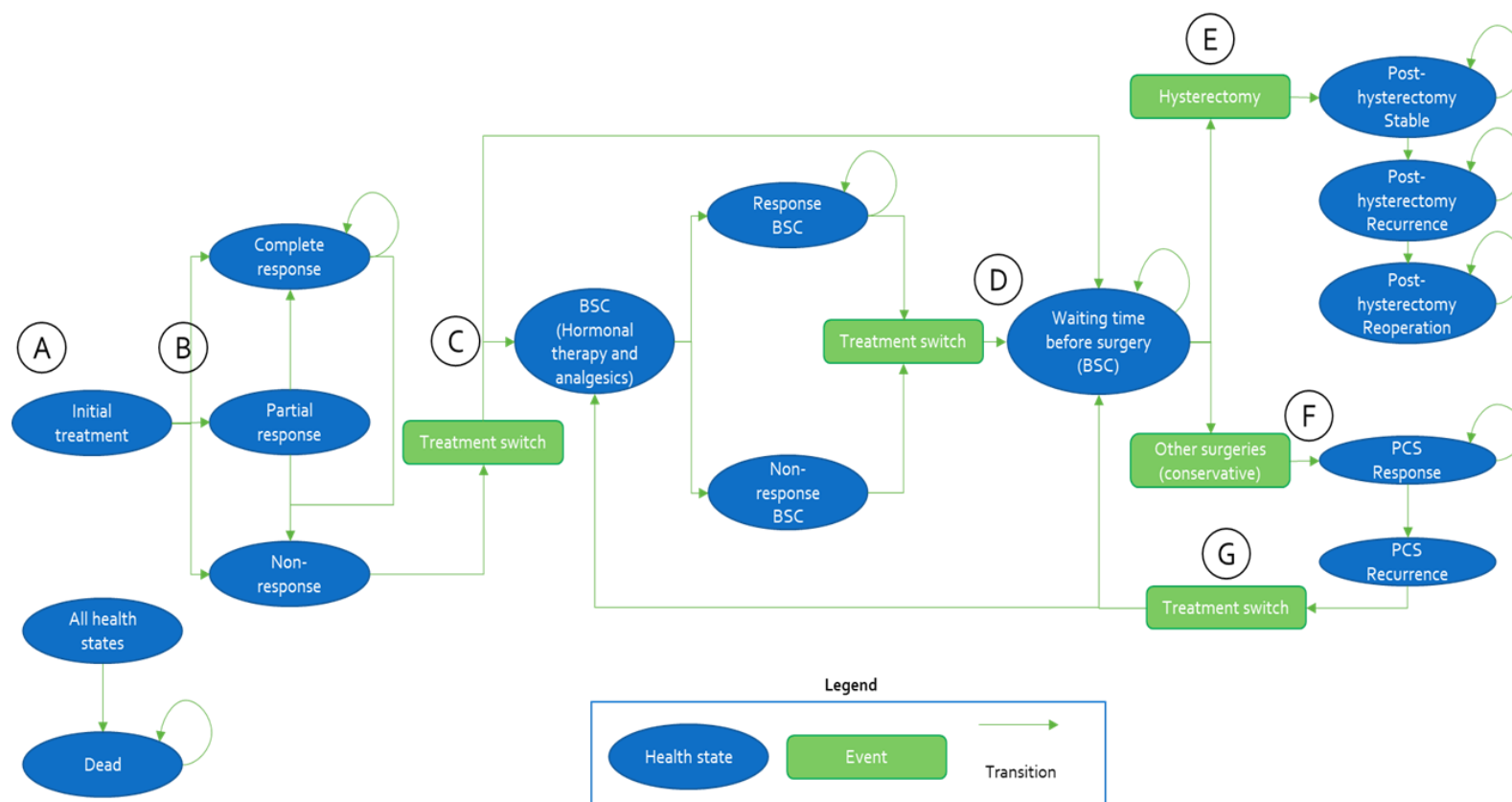
TPP results show much clearer advantage to leuprorelin acetate

Table: mean difference of TPP– fixed effect model

Comparator	Company response to DG	Clarification letter response
Placebo	-1.15 (-1.34 to -0.96)	-1.1 (-1.4 to -0.79)
Leuprorelin Acetate 3.75 mg	1.35 (0.95 to 1.74)	0.56 (0.017 to 1.1)

Company's model overview 1

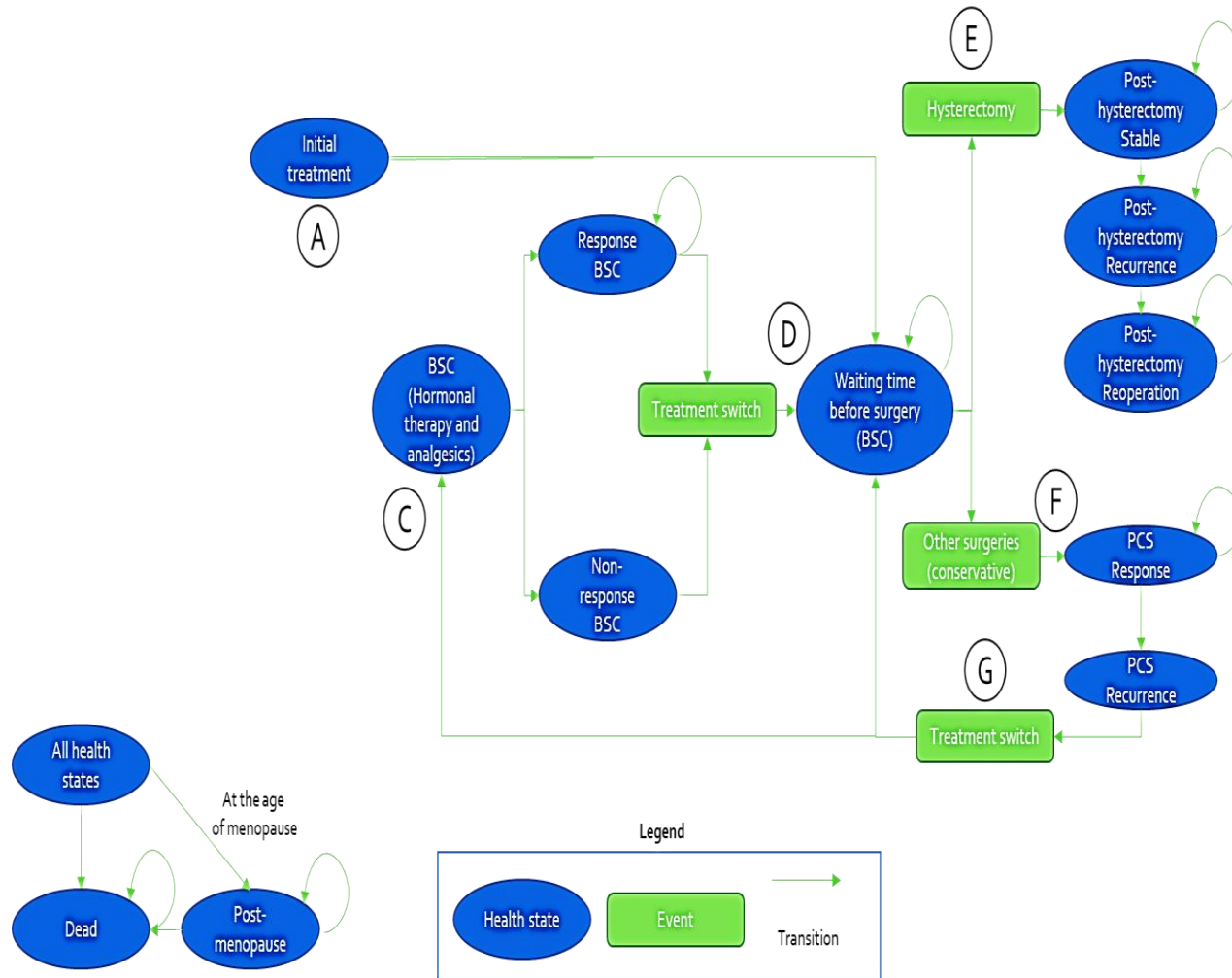
Model structure



- 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
- 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

Company's model with surgery as a comparator

Model structure with surgery as a comparator



Surgery as a comparator is implemented the same as surgery as a treatment after relugolix CT/GnRH agonist

Table: Distribution of strategies to manage pain recurrence after conservative surgery

Key issue Treatment waning



Table: Response rates at 24, 52 and 104 weeks of treatment with Relugolix CT

	Number (%) of patients who responded to treatment			
	Week 24		Week 52	Week 104
	SPIRIT 1 (n = 212)	SPIRIT 2 (n = 206)	SPIRIT OLE (n = 277)	SPIRIT OLE (n = 277)
Dysmenorrhoea	158 (75)	155 (75)	235 (85)	235 (85)
NMPP	124 (59)	136 (66)	204 (74)	210 (76)

* [See link](#)

Figure: Change from baseline in average dysmenorrhoea NRS score in SPIRIT trials

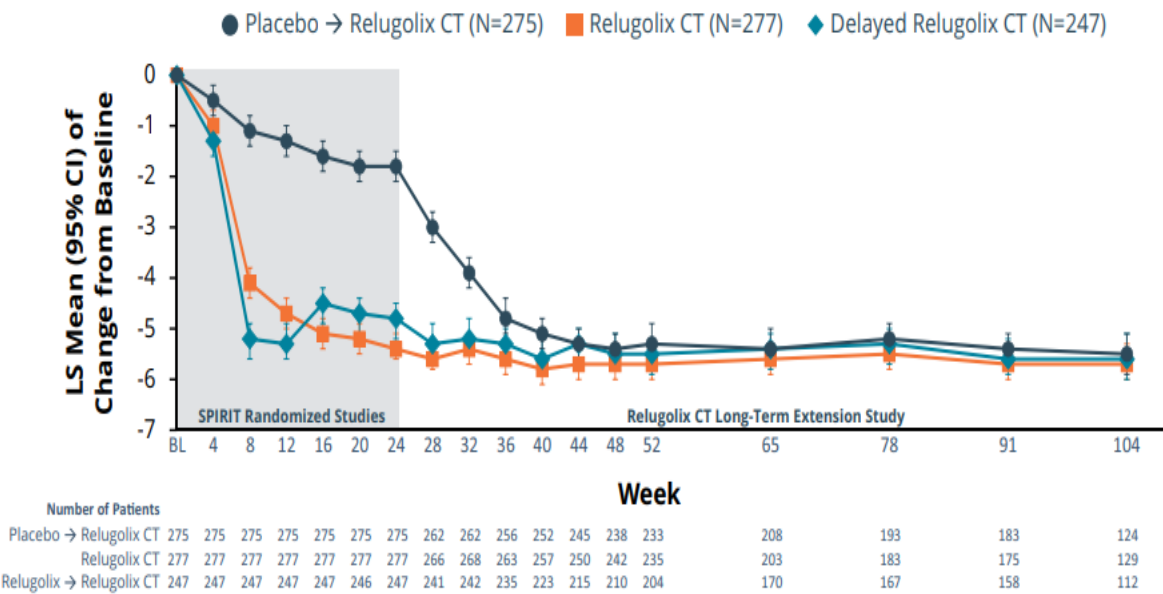
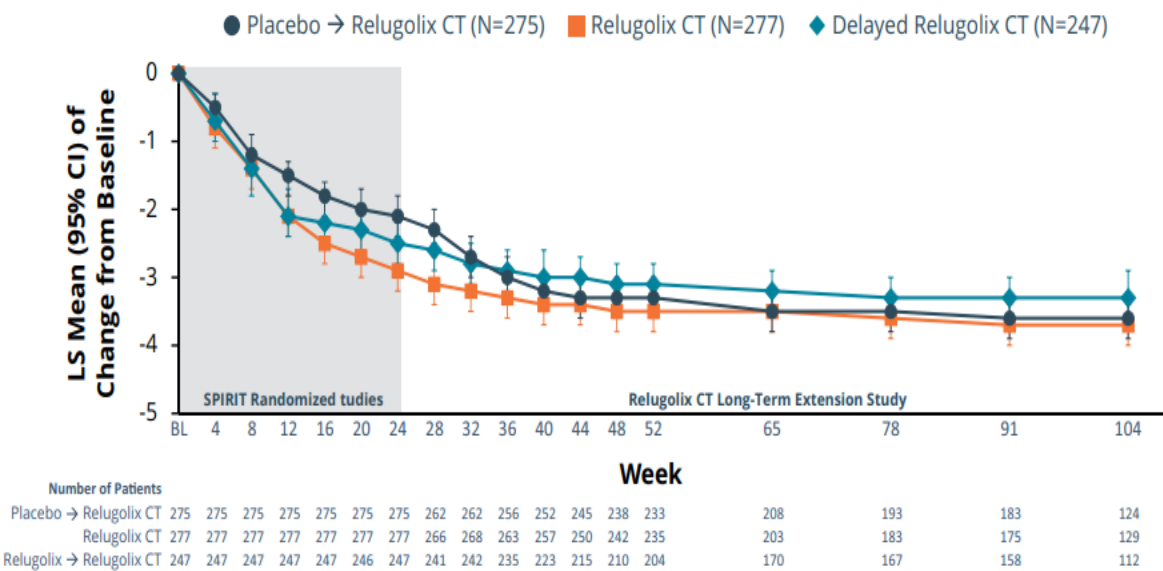


Figure: Change from baseline in average NMPP NRS score in SPIRIT trials



Model validation and counterintuitive results

Company's actions to validate its model:

- Validation of model structure, clinical/treatment pathway, and key assumptions with clinical experts at a global advisory board
- Use of pivotal trial data where possible to inform clinical and quality of life inputs
- Use of transparent and standard statistical approaches to translate clinical results to ultimate health outcomes
- Ensuring the modelled population corresponded to the population of the pivotal trial
- Use of the best available evidence from external sources to inform the input parameters and assumptions

Internal validation followed a formal technical quality control protocol and was conducted during the latter stages of model development. This was carried out by an experienced modeller and included several black-box tests and validation of the expected results

[See link](#)

Outcomes (originally presented at ACM 1)

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);

[See link](#)

** 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