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SMC2666

# relugolix, estradiol, norethisterone acetate film-coated tablets (Ryeqo®)

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**relugolix, estradiol, norethisterone acetate film-coated tablets (Ryeqo®)** is accepted for use within NHSScotland.

**Indication under review:** in adult women of reproductive age for symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis.

Relugolix, estradiol, norethisterone acetate film-coated tablets (Ryeqo®), compared with placebo, resulted in statistically and clinically significant improvements in treatment response (menstrual and non-menstrual pelvic pain) after 24 weeks in women with moderate-to-severe pain associated with endometriosis.

**Chair**
**Scottish Medicines Consortium**

# 1. Clinical Context

## 1.1. Medicine background

Ryeqo® (relugolix combination therapy [CT]) is a fixed-dose combination tablet containing the gonadotrophin releasing hormone (GnRH) antagonist, relugolix; the oestrogen receptor agonist, estradiol; and, the progestogen, norethisterone acetate. Relugolix inhibits GnRH receptors in the anterior pituitary gland, thereby decreasing release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from this gland. This reduction in FSH prevents follicular growth, thereby reducing estrogen production. Prevention of an LH surge inhibits ovulation and development of the corpus luteum, which precludes production of progesterone. Estradiol alleviates symptoms associated with a hypo-estrogenic state, such as vasomotor symptoms and bone mineral density (BMD) loss associated with the pharmacological action of GnRH inhibition. Norethisterone acetate reduces estrogen-induced risk of endometrial hyperplasia in non-hysterectomised patients.[1, 2]

SMC has accepted relugolix CT tablets for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age; restricted for use in patients who have failed or are unsuitable for conventional therapies (first-line treatments), such as tranexamic acid, hormonal contraceptives, and intrauterine delivery systems (SMC2442).

The recommended dose of relugolix CT is one tablet daily, containing 40 mg relugolix, 1 mg estradiol (as hemihydrate) and 0.5 mg norethisterone, with or without food. When starting treatment, the first tablet must be taken within 5 days of the onset of menstrual bleeding. If treatment is initiated on another day of the menstrual cycle, irregular and/or heavy bleeding may initially occur. Discontinuation should be considered when the patient enters menopause, as the symptoms of endometriosis are known to regress when menopause begins. A dual X ray absorptiometry (DXA) scan is recommended after 1 year of treatment. In patients with risk factors for osteoporosis or bone loss, a DXA scan is recommended prior to starting treatment. [1, 2]

## 1.2. Disease background

Endometriosis is a chronic inflammatory disease that is characterised by the growth of endometrial cells, which normally line the endometrium, outside the uterine cavity. These endometrial tissues remain sensitive to sex hormones (for example oestrogen) and break down during the normal menstrual cycle. Pelvic pain is very common with this condition but depending on the extent and location of the extrauterine tissue, pain can also occur with menses (dysmenorrhea), between menses (non-menstrual pelvic pain), and with sexual intercourse (dyspareunia). Some women also experience pain during urination and have painful bowel movements.[3, 4] Patients with endometriosis can also have impaired or outright infertility; affecting approximately one third of endometriosis patients.[5, 6] Endometriosis mainly occurs during the reproductive phase of life (defined as 15 to 49 years of age according to the World Health Organisation) and is estimated to affect roughly 10% of females worldwide (190 million) of reproductive age.[5, 7] However, endometriosis can also occur in the postmenopausal phase (estimated prevalence of 2% to 5%); there have also been reports of endometriosis in patients <15 years old (estimated prevalence of 0.05%).[8, 9] Definitive diagnosis of endometriosis can be difficult,

and it takes on average 8.5 years to receive a diagnosis of endometriosis in the UK.[10] This is complicated by the fact that many patients with endometriosis have a greater risk of presenting with uterine fibroids, which has many overlapping symptoms (such as pelvic pain and infertility).[11, 12]

### 1.3. Treatment pathway and relevant comparators

There is no cure for endometriosis. Treatment selection is based upon several factors including the predominant symptoms, patient preferences (for example maximising fertility), age, other co-morbidities (for example uterine fibroids), and the involvement of other organs (for example bowel and bladder). Given these factors can change over time, the treatment pathway should be fluid. First-line treatments consist of: a short-term trial (for example 3 months) of analgesia (including non-steroidal anti-inflammatory drugs or paracetamol, alone or in combination) to treat endometriosis-associated pain; neuromodulators (for example gabapentin or pregabalin) for neuropathic pain; and hormonal treatments (for example off-label use of a combined oral contraceptive pill or progestogen). However, all hormonal treatments are contraceptive and are not suitable for those wishing to conceive.[13, 14]

If these first-line treatments do not address symptoms, then GnRH agonists are recommended as a second-line treatment option but are only licensed for up to 6 months. Hormonal add-back therapy (ABT) is recommended to prevent BMD loss and hypo-oestrogenic symptoms associated with GnRH agonists and means that GnRH agonists may be used for more than 6 months in clinical practice; this is confirmed by some clinical experts contacted by SMC. GnRH agonists can sometimes delay the need for surgery and a 3-month course of these medicines could be used prior to surgery in patients with deep endometriosis (involving the bowel, bladder or ureter)[13]; but preoperative hormone treatment to improve the immediate outcome of surgery for pain is not recommended by the guidelines produced by the European Society of Human Reproduction and embryology (ESHRE).[14] GnRH antagonists are another potential second-line medical treatment option for these patients; relugolix CT is currently the only licensed GnRH antagonist option.[14]

Surgical treatments for endometriosis should also be considered to reduce endometriosis-associated pain.[13, 14] Conservative surgical options that are likely to be offered to those without deep endometriosis and who consider fertility to be a priority, include excision or ablation. Other surgical options include hysterectomy ; however, this is usually offered to those with heavy menstrual bleeding that is unresponsive to other treatments.[5, 13, 14]

It is unclear whether medical or surgical therapies are more effective at relieving pain in endometriosis but, regardless of the type of management, long-term treatment to inhibit ovulation or reduce oestrogen production is advised.[2, 5, 14] Approximately 50% of patients with endometriosis will have a recurrence of symptoms within 5 years, regardless of the treatment approach[2, 5]; this highlights the complexity of management and the need for multidisciplinary expertise.[13, 14] There is an unmet need for licensed, long-term, non-invasive and effective treatments to manage the symptoms of endometriosis.

The submitting company advise that there are no direct, long-term licensed comparators. GnRH agonists such as leuprorelin acetate, triptorelin acetate and goserelin acetate are all licensed in endometriosis for up to 6 months and are the most relevant comparators. ESHRE guidelines advise

that, based on current evidence, no specific GnRH agonist can be recommended over another for the treatment of endometriosis-associated pain.[14]

## 2. Summary of Clinical Evidence

### 2.1. Evidence for the licensed indication under review

Evidence to support the use of relugolix CT for this indication comes from the SPIRIT 1 and SPIRIT 2 studies; these were similar in design. Details are summarised in Table 2.1.

**Table 2.1. Overview of relevant studies**

| Criteria | SPIRIT 1 and SPIRIT 2 studies.[3, 15] |
|---|---|
| Study Design | International, multicentre, randomised, double-blind, phase III studies. |
| Eligible Patients | • Premenopausal females aged 18 to 50 years with a diagnosis of endometriosis and, within 10 years prior, surgical or direct visualisation and/or histopathologic confirmation.<br>• Self-reported moderate, severe, or very severe pain during their most recent menses and for non-menstrual pelvic pain (NMPP) in the month prior.<br>• During the 35-day run-in period: menstruated for ≥ 3 days; dysmenorrhea NRS score ≥ 4.0 on ≥ 2 days and mean NMPP NRS score ≥ 2.5, or mean NMPP NRS score ≥ 1.25 and NMPP NRS score ≥ 5.0 on ≥ 4 days.[a]<br>• No surgical procedures for the treatment of endometriosis within 3 months prior to screening.<br>• No hormonal contraception. |
| Treatments & randomisation | Patients were randomised equally to receive one of the following oral treatments taken once daily:<br>• Relugolix CT for 24 weeks (relugolix CT group) or<br>• relugolix 40 mg for 12 weeks, followed by relugolix CT for 12 weeks (delayed relugolix CT group) or<br>• placebo for 24 weeks (placebo group).<br><br>Patients were allowed to take ibuprofen as rescue analgesia for breakthrough pain. Additionally, only one stronger analgesic (tramadol, codeine or hydrocodone) could be administered to a given patient throughout the study. Randomisation was stratified according to geographical region (North America versus Rest of World) and time since surgical endometriosis diagnosis (<5 years or ≥5 years). |
| Co-primary outcomes | • Proportion of responders based on the dysmenorrhoea NRS score at week 24; defined as a reduction from baseline in dysmenorrhoea of at least 2.8 points over the last 35 days of treatment, without an increase in analgesic use (ibuprofen or opioid).<br>• Proportion of responders based on the NMPP NRS score at week 24; defined as a reduction from baseline in non-menstrual pelvic pain score of at least 2.1 points over the last 35 days of treatment, without an increase in analgesic use (ibuprofen or opioid). |
| Secondary outcomes | In both studies unless otherwise specified:<br>1. Change from baseline to week 24 in EHP-30 pain domain score.[b]<br>2. Change from baseline to week 24 in mean dysmenorrhoea NRS score.<br>3. Change from baseline to week 24 in mean NMPP NRS score.<br>4. Change from baseline to week 24 in mean overall pelvic pain NRS score.<br>5. Proportion of patients not using protocol-specified opioids for endometriosis-associated pain at week 24.<br>6. Change from baseline to week 24 in mean dyspareunia NRS score.<br>7. Proportion of patients not using protocol-specified analgesics for endometriosis-associated pain at week 24 (SPIRIT 1) or the change from baseline to week 24 in protocol-specified analgesic use for endometriosis-associated pain based on mean pill count (SPIRIT 2). |
| Statistical analysis | A hierarchical statistical testing strategy was applied in the studies where the co-primary outcomes and key secondary outcomes were tested sequentially for relugolix CT versus placebo. In each study, the co-primary outcomes were tested first, and if the p value was less than 0.05 for both, then the seven key secondary outcomes were tested sequentially in the order above.[c] The assessment of |

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| | outcomes in the delayed relugolix CT group compared with placebo group were made descriptively as it was not included in the hierarchical hypothesis testing. Efficacy analyses were performed in the mITT population which included all randomised patients who received at least one dose of study medicine. |

Abbreviations: CT = combination therapy; EHP-30 = Endometriosis Health Profile-30; mITT = modified intention to treat; MRI = magnetic resonance imaging; NETA = norethisterone acetate; NMPP = non-menstrual pelvic pain; NRS = Numerical Rating Scale; relugolix CT = relugolix 40 mg, estradiol 1 mg, norethisterone acetate 0.5 mg

[a] pain assessment was performed using the NRS score, which is a verbal numeric scale where the patient grades their own pain on a scale of 0 (no pain) to 10 (worst pain imaginable); these were patient-reported daily in an eDiary. Separate measures of dysmenorrhea and NMPP NRS were conducted since treatment can lead to amenorrhoea.
[b] EHP-30 assesses the effect of pain on normal daily activity including the ability to stand, sit, walk, exercise, sleep, to participate in social events and jobs, and the effect on appetite.
[c] following a study protocol amendment, the hierarchical testing order for the secondary outcomes (5 and 6) in SPIRIT 2 matched that for SPIRIT 1.

Results from the primary analysis of the co-primary and selected secondary outcomes in both studies (in the statistical testing hierarchy) are presented in table 2.2. These results indicated statistically significant improvements in response (except for the final secondary outcome in SPIRIT 2 that is assessing analgesic use) after 24 weeks, for relugolix CT compared with placebo.

**Table 2.2: Results for the co-primary and selected secondary outcomes in the mITT populations of SPIRIT 1 and SPIRIT 2 studies.[3, 15]**

| | SPIRIT 1 | | SPIRIT 2 | |
|---|---|---|---|---|
| | **Relugolix CT (n=212)** | **Placebo (n=212)** | **Relugolix CT (n=206)** | **Placebo (n=204)** |
| **Co-primary outcome: proportion of responders at the end of treatment (week 24) based on the dysmenorrhea NRS score.** | | | | |
| Proportion of responders, % | 75% | 27% | 75% | 30% |
| Difference for relugolix CT versus placebo (95% CI), p-value | 48% (39% to 56%), p<0.001 | | 45% (36% to 54%), p<0.001 | |
| **Co-primary outcome: proportion of responders at the end of treatment (week 24) based on the NMPP NRS score.** | | | | |
| Proportion of responders, % | 59% | 40% | 66% | 43% |
| Difference for relugolix CT versus placebo (95% CI), p-value | 19% (9.5% to 28%), p<0.001 | | 23% (14% to 33%), p<0.001 | |
| **Secondary outcome: change from baseline to week 24 in EHP-30 pain domain score.** | | | | |
| LS mean (SE) | -33.8 (1.8) | -18.7 (1.8) | -32.2 (1.7) | -19.9 (1.7) |
| Difference for relugolix CT versus placebo (95% CI), p-value | -15.1 (-19.7 to -10.5), p<0.001 | | -12.3 (-16.7 to -7.9), p<0.001 | |
| **Secondary outcome: change from baseline to week 24 in mean dysmenorrhoea NRS score.** | | | | |
| LS mean (SE) | -5.1 (0.2) | -1.8 (0.2) | -5.1 (0.2) | -2.0 (0.2) |
| Difference for relugolix CT versus placebo (95% CI), p-value | -3.3 (-3.8 to -2.8), p<0.001 | | -3.2 (-3.7 to -2.7), p<0.001 | |
| **Secondary outcome: change from baseline to week 24 in mean NMPP NRS score.** | | | | |
| LS mean (SE) | -2.9 (0.2) | -2.0 (0.2) | -2.7 (0.2) | -2.0 (0.2) |
| Difference for relugolix CT versus placebo (95% CI), p-value | -0.9 (-1.4 to -0.4), p=0.0002 | | -0.7 (-1.2 to -0.3), p=0.0012 | |
| **Secondary outcome: change from baseline to week 24 in mean overall pelvic pain NRS score.** | | | | |
| LS mean (SE) | -3.1 (0.2) | -1.9 (0.2) | -2.9 (0.2) | -2.0 (0.2) |
| Difference for relugolix CT versus placebo (95% CI), p-value | -1.1 (-1.6 to -0.7), p<0.001 | | -0.9 (-1.4 to -0.5), p<0.001 | |

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|---|---|---|---|---|
| **Secondary outcome: proportion of patients not using protocol-specified opioids for endometriosis-associated pain at week 24.** | | | | |
| Proportion of patients, % | 86% | 76% | 82% | 66% |
| Difference for relugolix CT versus placebo (95% CI), p-value | 9.4% (2.0% to 17%), p=0.0005 | | 16% (7.5% to 24%), p<0.001 | |
| **Secondary outcome: change from baseline to week 24 in mean dyspareunia NRS score.** | | | | |
| LS mean (SE) | -2.4 (0.2) | -1.7 (0.2) | -2.4 (0.2) | -1.9 (0.2) |
| Difference for relugolix CT versus placebo (95% CI), p-value | -0.7 (-1.3 to -0.1), p=0.0149 | | -0.5 (-1.0 to 0.0) p=0.0371 | |
| **Secondary outcome: proportion of patients not using protocol-specified analgesics for endometriosis-associated pain at week 24.** | | | | |
| Proportion of patients, % | 56% | 31% | 54% | 24% |
| Difference for relugolix CT versus placebo (95% CI), p-value | 26% (16% to 35%), p<0.001 | | 31% (22% to 40%)[a] | |
| **Secondary outcome: change from baseline to week 24 in protocol-specified analgesic use for endometriosis-associated pain based on mean pill count.** | | | | |
| LS mean (SE) | -0.5 (0.1) | -0.4 (0.1) | -0.5 (0.1) | -0.4 (0.1) |
| Difference for relugolix CT versus placebo (95% CI), p-value | -0.1 (-0.3 to 0.1)[b] | | -0.1 (-0.3 to 0.0), NSS | |

[a] this outcome was not multiplicity controlled in SPIRIT 2, therefore no p-value is reported.
[b] this outcome was not multiplicity controlled in SPIRIT 1, therefore no p-value is reported.

CI = confidence interval; CT = combination therapy; mITT = modified intention to treat; NSS = not statistically significant; SE = standard error

A secondary analysis was performed comparing the delayed relugolix CT group (n=211 in SPIRIT 1 and n=206 in SPIRIT 2) with the placebo group in terms of responder rates at week 24. In both studies, there was a similar treatment effect (to that in the primary analysis) in favour of the delayed relugolix CT group compared with the placebo group.[3, 15] The delayed relugolix CT group was included to compare BMD and vasomotor symptoms for relugolix monotherapy with relugolix CT at week 12.[15] It is noted that efficacy data for the delayed relugolix CT group were not included in the economic model, as the submitting company deemed these irrelevant to the submission population.

### 2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed, as an exploratory outcome, using the EuroQol five-dimensions five levels (EQ-5D-5L) at baseline and at 24 weeks for both studies. There were numerically greater improvements in the relugolix CT group compared with the placebo group in both studies across the domains for mobility, self-care, usual activities, pain/discomfort and anxiety/depression. However, these results are descriptive only, many of the improvements were marginal, and EQ-5D-5L was not designed specifically for use in endometriosis.[16-18] These results were used to generate utility values for the economic analysis.

### 2.3. Supportive studies

Patients who completed the SPIRIT 1 or 2 studies, were eligible to enrol in the open-label, single-arm extension study, SPIRIT EXTENSION, where all patients received relugolix CT once daily for up to 80 weeks.[19] In the pooled SPIRIT 1 and SPIRIT 2 study populations, the proportions of patients who completed the study were: 85% (355/420), 83% (347/420), and 81% (342/421), in the

relugolix CT, delayed relugolix CT, and placebo groups respectively and 66%, 59%, and 66% respectively entered the extension study. Of the 802 patients who were enrolled in the extension study, 85% completed to 52 weeks of treatment and 63% to 104 weeks. In patients originally randomised to the relugolix CT group (n=277), the improvements in endometriosis were sustained through to week 104 week (response rates of 85% and 76% for the dysmenorrhea and NMPP co-primary outcomes, respectively). Decreases in dyspareunia and improvement in Endometriosis Health Profile-30 (EHP-30) were also sustained, along with reduced analgesic use. For patients originally randomised to placebo who switched to relugolix CT, results at week 104 (that is after 80 weeks of relugolix CT treatment) were similar (80% and 73% respectively) to those of the relugolix CT group.[3, 19]

### 2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing relugolix CT with GnRH agonists, the submitting company presented a Bayesian network meta-analysis (NMA). Comparisons of relugolix CT were made with leuprorelin acetate (via network connections of placebo and dienogest) in premenopausal women with a clinically confirmed diagnosis of endometriosis. Efficacy outcomes included overall pelvic pain (OPP), total pelvic pain (TTP) and a pooled outcome combining OPP and TPP; these were used to inform the economic analyses. The submitting company concluded that, based on the NMA results, and the lack of statistical significance, there was no evidence of a difference between relugolix CT and placebo or leuprorelin acetate for the OPP and TPP outcomes. However, based on the limitations of this NMA, these conclusions are uncertain (see section 4.2).

**Table 2.3: Summary of indirect treatment comparison**

| Criteria | Overview |
|---|---|
| Design | Bayesian NMA. |
| Population | Premenopausal women with a clinically confirmed diagnosis of endometriosis and endometriosis-associated pain. |
| Comparators | Leuprorelin acetate (via network connections of placebo and dienogest). |
| Studies included | SPIRIT 1 and SPIRIT 2 studies (relugolix CT)[15];<br>TERRA study (leuprorelin acetate)[20]; Strowitzki *et al*., 2010 (leuprorelin acetate and dienogest)[21]; and Lang 2018 (dienogest).[22] |
| Outcomes | OPP and TTP, and a pooled outcome combining OPP and TPP. |
| Results | For the base case OPP results, presented at 12 weeks, there were wide credible intervals that crossed one and no evidence of a difference between relugolix CT versus placebo (OR: 0.52 [CrI: 0.044 to 6.4]) and versus leuprorelin acetate (OR: 1.1 [CrI: 0.032 to 41]).<br><br>For the base case TPP results, presented at 24 weeks, there were wide credible intervals that crossed one and no evidence of a difference between relugolix CT versus placebo (OR: 0.37 [CrI: 0.031 to 4.5]), dienogest (OR: 2.2 [CrI: 0.064 to 77]) and versus leuprorelin acetate (OR: 2.5 [CrI: 0.032 to 190]).<br><br>The submitting company also presented the combined evidence synthesis using OPP values from SPIRIT 1 and SPIRIT 2 at week 24. The results showed wide credible intervals with no evidence of a difference between relugolix CT versus placebo (OR: 0.44 [CrI: 0.047 to 4]), dienogest (OR: 2.1 [CrI: 0.12 to 36]) and leuprorelin acetate (OR: 1.8 [CrI: 0.097 to 31]). |

Abbreviations: CrI = credible interval; OPP = overall pelvic pain; OR = odds ratio; TPP = total pelvic pain.

## 3. Summary of Safety Evidence

In the SPIRIT 1 and SPIRIT 2 studies, the pattern of adverse events (AEs) with relugolix CT was consistent with that expected for a GnRH antagonist, and comparable with the safety profile that was observed in the initial marketing authorisation for the treatment of symptoms associated with uterine fibroids.[3]

Pooled data from the SPIRIT 1 and SPIRIT 2 studies indicated that within the respective relugolix CT (n=418), delayed relugolix CT (n=417), and placebo (n=416) groups the rates of AEs were: 76%, 79% and 70%; which were treatment-related in 47%, 58% and 38% of patients. The higher incidence of AEs in the delayed relugolix CT group was due to this group receiving relugolix monotherapy (without ABT) for the first 12 weeks of treatment, resulting in the higher number of postmenopausal symptoms. The incidence of treatment-related serious AEs were considered to be low: 1.2%, 0.7%, and 0.2%; as was the incidence of treatment-related grade 3 or higher AEs: 2.9%, 2.9%, and 1.9%. The most frequently reported treatment-related AEs (that affected ≥1% of patients in either the relugolix CT group or placebo group, and were more common in the relugolix CT group) were (presented as relugolix CT versus placebo): headache (17% versus 14%), hot flush (12% versus 6.5%), bone density decreased (3.8% versus 2.2%), libido decreased (3.8% versus 1.2%), nausea (3.6% versus 2.2%), menorrhagia (2.6% versus 1.4%), vulvovaginal dryness (2.2% versus 0.5%), arthralgia (2.2% versus 1.0%), and dizziness (2.2% versus 1.0%).[3]

The safety of relugolix CT over 52 weeks was consistent with that during the placebo-controlled 24 week period, and the rates of AEs (including serious and grade ≥3) did not disproportionately increase with further long term treatment up to 104 weeks in the SPIRIT EXTENSION study.[3] Overall, relugolix CT appeared to be generally well tolerated, with <10% of patients in the relugolix CT or delayed relugolix CT groups cumulatively discontinuing due to an adverse event after 104 weeks of treatment; these discontinuation rates did not increase disproportionately over these time periods.[3]

The effect of relugolix CT on BMD loss was of special interest. A slight increase in BMD loss initially, followed by stabilisation, at a level of approximately 1%, over a 2-year period was observed with relugolix CT and was not considered clinically meaningful. Loss in bone density was significantly greater in women treated with delayed relugolix CT than those treated with relugolix CT, suggesting that the dose of estradiol in relugolix CT might be adequate to maintain estradiol concentrations in a therapeutically effective range.[3, 15] Overall, it was concluded that the risk of BMD loss is manageable with the addition of estradiol and norethisterone acetate to relugolix.[3]

## 4. Summary of Clinical Effectiveness Considerations

### 4.1. Key strengths

- SPIRIT 1 and SPIRIT 2 were randomised, double-blind, phase III studies that appear to have been well-conducted, with stratification, and generally well-balanced baseline characteristics between the treatment groups; this makes it likely there is a low risk of bias, and provides reassurance about the internal validity of the studies.[3]

- In the SPIRIT 1 and SPIRIT 2 studies, when compared with placebo, relugolix CT resulted in statistically significant and clinically meaningful improvements in the co-primary and several secondary outcomes that assessed the effect of treatment response in the symptoms of endometriosis. Sensitivity and subgroup analyses further confirmed this benefit of relugolix CT over placebo.[3, 15] Data from the longer-term SPIRIT EXTENSION study suggested that these treatment effects are maintained for up to 104 weeks.[3, 19]
- Relevant to the licensed indication, nearly all patients in the SPIRIT 1 and SPIRIT 2 studies (pooled study populations, n=1,251) had a prior surgical procedure(s) and/or prior medical management for endometriosis; meaning this study assessed relugolix CT as a second-line treatment in the management of their disease. The majority (83%) had at least one prior surgery/procedure before study initiation. At baseline, 99% had used a prior medicine for endometriosis; whilst 93% used analgesia for pelvic pain, including 38% who used opioids.[3]
- Relugolix CT was well-tolerated and no new safety concerns were identified in patients with moderate-to-severe endometriosis in the SPIRIT 1 and SPIRIT 2 studies.[3]
- It was noted that relugolix CT provides adequate contraception after intake for at least one month. Experts contacted by SMC highlighted this as an advantage for some patients since existing GnRH mediators do not have this effect and require additional barrier contraception.[1, 3]

*Other data were also assessed but remain confidential.**

### 4.2. Key uncertainties

- The SPIRIT 1 and SPIRIT 2 studies provide direct evidence versus placebo only and these controlled data are limited to 24 weeks. Although evidence from the extension study suggests that the treatment effect is maintained to 104 weeks, this is uncontrolled.
- There are no direct data comparing relugolix CT with relevant comparators and there were several limitations with the NMA. The outcomes used (OPP and TPP), and the 12-week timepoint, differ from those assessed in the SPIRIT trials. The comparator studies included patients with no history of medication or surgery. There was noticeable variation in the results of the placebo arm, and cases where the placebo arm could not be compared between studies. There were no safety or patient reported outcomes presented. The NMA results suggested no benefit of relugolix CT over leuprorelin acetate, with extremely wide credible intervals crossing one, highlighting the uncertainty of the results. Statistician feedback for SMC had no major concerns over how the NMA was conducted and highlighted the uncertainty of the results is expected, given the limited evidence base. It appears to be reasonable to assume similar (not equal) efficacy between relugolix CT and leuprorelin.[3]

### 4.3. Clinical expert input

Experts contacted by SMC considered relugolix CT to be a therapeutic advancement and would fulfil an unmet need for this patient population as it provides an oral option.

### 4.4. Service implications

Experts contacted by SMC anticipate relugolix CT would displace the use of GnRH agonists and may delay or reduce the number of women who need subsequent surgical management for endometriosis. However, the requirement for a DXA scan after one year of treatment, and as clinically indicated thereafter,[1] may prove challenging for several boards in NHSScotland given the current high demand.

## 5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Endometriosis UK, which is a registered charity.
- Endometriosis UK has received 1.2% pharmaceutical company funding in the past two years, including from the submitting company.
- Endometriosis affects 1 in 10 women and those assigned female at birth from puberty to menopause, although the impact may be felt for life. The most common symptoms include chronic pelvic pain, painful periods that interfere with everyday life, heavy menstrual bleeding, pain during or after sex, painful bowel movements, pain with urination and fatigue. Endometriosis can also affect fertility, leading to difficulties getting pregnant. Patients interviewed by the patient group reported feeling as though their life was on hold, struggling with daily tasks, especially when they were suffering with pain.
- A benefit of this medicine over other treatments is that it is taken daily, so if side effects are deemed unmanageable it can be stopped quickly.
- The patient group reports that there was positive feedback from patients they interviewed about having an all-in-one treatment where the patient does not have to remember to additionally take HRT as a separate tablet.
- Respondents were also positive at the prospect of being able to have this treatment for a longer period of time than currently available treatments although it would not be suitable for those where HRT is contraindicated.

## 6. Summary of Comparative Health Economic Evidence

### 6.1. Economic case

**Table 6.1 Description of economic analysis**

| Criteria | Overview |
|---|---|
| Analysis type | Cost Utility Analysis |
| Time horizon | Lifetime horizon (66 years);starting age is 34 years, menopause is assumed at age 50 years. |
| Population | Adult pre-menopausal women with symptomatic endometriosis who have a history of previous medical or surgical treatment. |
| Comparators | GnRH agonists (treatment duration up to 1 year). A 50:50 split between short acting and long acting triptorelin is assumed in the base case for costs. Hormonal ABT is assumed to be used alongside GnRH agonists, with an equal split between tibolone and raloxifene.<br><br>BSC and surgery (conservative surgery and hysterectomy) are modelled as subsequent treatment options. |

| | |
|---|---|
| Model description | A Markov model with 15 unique health states. All patients start in "Initial treatment" and the cycle length is 3 months. At 6 months (2 cycles), treatment response for all patients is evaluated where patients can be in either complete response, partial response, or no response health states. If patients are in the partial response or no response health states, they spend 1 cycle in the no response state then undergo a treatment switch to BSC or surgery. There is a 6-month waiting period applied for surgery, where patients are assumed to receive BSC. Patients who chose BSC can opt for surgery after the treatment switch if there is no response. There are also post-surgery, menopause, and death states. The model does not allow for surgery to be an option 2 years before menopause. |
| Clinical data | The direct evidence was sourced from the phase III, double-blinded randomised controlled studies, SPIRIT 1 & 2.<br>The response rates for the relugolix CT arm were sourced from the SPIRIT 1 & 2 studies (combined total of 418 patients). There are two definitions of response: "change from baseline" and "threshold" which were used in the base case and scenario analysis respectively.<br>An indirect treatment comparison (ITC) was used to compare relugolix CT to GnRH agonists, using placebo as a common comparator. The odds ratio estimated for Overall Pelvic Pain (OPP) at 12 weeks between relugolix CT and leuprorelin acetate (1.1) was used to calculate the response rates for the GnRH agonist arm. This meant that in the model GnRH agonists are assumed to have a better response rate than relugolix CT.<br>Response for BSC as a subsequent treatment was sourced from the placebo arm of the SPIRIT 1 & 2 studies.<br>The SPIRIT open label EXTENSION study was used to estimate discontinuation rates and the proportion of patients who switch to BSC or surgery. The distribution between conservative surgery and hysterectomy was estimated based on an RWE study by Soliman et al (2016).[23] |
| Extrapolation | The SPIRIT 1 and 2 studies end at 24 weeks, and the extension study ends at 104 weeks. The model assumes patients will continue active treatment of relugolix CT (also applies to BSC as a subsequent treatment) until menopause, with treatment waning being captured in the discontinuation rates. GnRH agonists are limited to a treatment duration of 1 year, after which patients switch to BSC or surgery. Discontinuation rates from the SPIRIT EXTENSION study are applied to both the relugolix CT and GnRH agonist arms, where the discontinuation rate recorded at 24 months is used as a constant rate for relugolix CT arm until menopause.[24] |
| Quality of life | EQ-5D-5L data sourced from the SPIRIT 1 & 2 studies were mapped to 3L using the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU)[24] age-sex based mapping. Utilities were then derived using UK value set published by Dolan[25] for EQ-5D-3L.<br>Utilities were assigned to initial treatment (0.5838), response (0.8839), partial response (0.8014) and non-responder (0.7189) health states. Disutilities for adverse events are applied to the cycle in which the event occurs and were sourced from a literature review search. The model also accounts for disutilities related to surgery. |
| Costs and resource use | Costs included: medicine acquisition for relugolix CT, GnRH agonists (including add-back therapy) and BSC, administration costs, concomitant medication, resource use such as visits to health care professionals, tests and procedures, as well as adverse events and cost of surgery. |
| PAS | There was no Patient Access Scheme (PAS) included in this submission. |

Abbreviations: ABT = add-back therapy; BSC = best supportive care; CT = combination therapy; DSU = Decision Support Unit; GnRH = gonadotrophin releasing hormone; RWE = real world evidence

### 6.2. Results

The base case analysis estimated that the incremental cost-effectiveness ratio (ICER) between relugolix CT and GnRH agonists is £2,569 per quality adjusted life year (QALY) gained. The economic results showed a QALY gain of 0.7, which is driven by the duration of response in the relugolix CT arm and the influence of long term disutilities on the comparator arm, particularly those relating to surgery. The incremental costs are driven by the medicine acquisition costs for relugolix CT but off-set by costs of surgery in the GnRH agonists arm.

**Table 6.2 – base case results**

| Technologies | Total costs (£) | Total QALYs | Incr. costs (£) | Incr. LYGs | Incr. QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| Relugolix CT | £12,224 | 17.16 | - | | - | - |
| GnRH agonist | £10,416 | 16.46 | £1,808 | 0.01 | 0.70 | £2,569 |

Abbreviation: Incr. = incremental; QALYS = quality-adjusted-life years, ICER = incremental cost effectiveness ratio; LYG = life years gained

### 6.3. Sensitivity analyses

The sensitivity analysis included probabilistic, deterministic one-way and scenario analysis.

In the deterministic sensitivity analysis, the parameter with the greatest impact on the ICER was the health state utility for "response", followed by the health state utility for post-hysterectomy stable state. The incremental QALY gain displayed in table 6.2 stems from this health state due to the assumption that relugolix CT maintains a response over a longer treatment duration. Therefore, if the response health state utilities are changed, the QALY gain would change, which in turn would affect the ICER result.

A range of scenario analyses were performed and presented in tables 6.3 below.

**Table 6.3: Results of scenario analyses**

| | Parameter | Base-case | Scenario | Incremental costs | Incremental QALYs | ICER vs. relugolix CT (£/QALY) |
|---|---|---|---|---|---|---|
| **#** | **Base-case** | | | **£1,808** | **0.70** | **£2,569** |
| 1 | Definition of response | Change from baseline: NRS score reduction from baseline of both 2.8 for dysmenorrhea and 2.1 for NMPP and no increase of analgesic use | Threshold: Achieving or maintaining a threshold below 4 in NRS scale (mild pain) for both NMPP and dysmenorrhea and no increase of analgesic use | £1,990 | 0.75 | £2,652 |
| 2 | Timepoint for evaluation of complete response | 6 months | 3 months | £1,178 | 0.48 | £2,472 |
| 3 | Referral to surgery upon discontinuation of treatment | Referrals possible up until menopause (51 years of age) | No referrals within 2 years of menopause | £1,746 | 0.70 | £2,479 |
| 4 | | | No referrals within 5 years of menopause | £1,633 | 0.71 | £2,299 |
| 5 | Duration of GnRH agonist treatment | 12 months | 6 months | £1,948 | 0.73 | £2,678 |
| 6 | | | 24 months | £1,237 | 0.62 | £2,007 |
| 7 | GnRH agonist and HRT dose intensity | 100% | 50% | £1,841 | 0.70 | £2,616 |
| 8 | Relugolix CT treatment duration | Until menopause (16 years in the model) | 5 years | £885 | 0.29 | £3,037 |
| 9 | DXA scan | excluded from costs | all relugolix CT patients | £1,976 | 0.70 | £2,809 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | receive a DXA scan prior to treatment and at week 52. | | | |
| 10 | Long term disutility for hysterectomy | Base case uses WHO 2004 reference of 0.18 disutility | Assumption 0.05 | £1,808 | 0.26 | £6,849 |
| 11 | | | Assumption 0.01 | £1,808 | 0.13 | £14,054 |
| 12 | Combined scenario 1, 8, 9 | Relugolix CT treatment duration is until menopause in the model. DXA scan not included in the costs, change from baseline definition of response for utilities | Restricting relugolix CT treatment duration to 5 years, included DXA scan requirement, utilising conservative utility values for all health states (threshold definition of response) | £1,144 | 0.31 | £3,693 |

Abbreviations: DXA = Dual X-ray absorptiometry; QALYS = quality-adjusted-life years, ICER = incremental cost effectiveness ratio; HRT = hormone replacement therapy, NRS = numeric rating scale, NMPP = non menstrual pelvic pain

### 6.4. Key strengths

- The SPIRIT 1 and 2 studies are well-conducted phase III randomised controlled studies that directly compare relugolix CT to a placebo, which produced encouraging results. The SPIRIT EXTENSION study extends the follow-up period to 24 months, providing additional data to inform some of the clinical parameters.
- The utilisation of EQ-5D data from the SPIRIT 1 and 2 studies to derive health state-specific utilities is a key strength in the model.
- The Markov model used in the analysis is well-structured, with health states that accurately reflect the clinical pathway of endometriosis.

### 6.5. Key uncertainties

- The submission lacks direct head-to-head study data comparing relugolix CT to GnRH agonists. Therefore, the company conducted an ITC to estimate the comparative effectiveness of the treatments, using placebo as the common comparator in the network. Furthermore, several clinical parameters for the comparator, such as discontinuation rates and proportion of patients using analgesics, were assumed to mirror the relugolix CT arm in the SPIRIT 1, SPIRIT 2, and SPIRIT EXTENSION studies. The absence of direct comparative evidence introduces uncertainty into the model.
- While the SPIRIT studies suggested that relugolix CT is more effective than placebo, the ITC presented a different picture, showing no statistical difference between relugolix CT and placebo, or between relugolix CT and GnRH agonists. However, due to a numerical advantage, the response rate of GnRH agonists is assumed to be better than relugolix CT, which was informed by the ITC's odds ratios applied in the model. Yet, the model results showed a QALY gain for relugolix CT driven by the duration of response. Scenario 1 in table 6.3, illustrates a minimal change in the ICER when the more conservative definition of response is applied in the model. The lack of impact on the ICER results suggested the model's outcomes were primarily driven by treatment duration rather than the clinical data inputs from the SPIRIT studies and the ITC.

- The base case assumption is that GnRH agonists is administered for only one year, while the submitting company assumes that relugolix CT could be taken for as long as there is a response until menopause, a period extending up to 16 years in the model with a constant discontinuation rate applied. This assumption drives the QALY gains in the relugolix CT arm, as it accrues QALYS in the complete response health state over a much longer treatment duration. There were some reservations about whether relugolix CT would indeed be administered for as long a period as anticipated by the submitting company in actual clinical practice, given that the SPIRIT EXTENSION extends to only 2 years. However SMC clinical experts suggest that an extended treatment duration until menopause is plausible. Given the SMC experts feedback and the modest increase in the ICER in scenario 8, where the treatment duration was restricted to 5 years, the Committee agreed that the QALY gains from the extended treatment duration over GnRH agonists was reasonable.
- The model assumed that the long-term discontinuation rate for relugolix CT matched the rate observed at 24 months in the SPIRIT EXTENSION study. This assumption introduced uncertainty, as it is unclear whether the discontinuation rate would remain stable over such an extended duration.
- As a result of the extended treatment duration, patients in the relugolix CT arm remain in the complete response health state for an extended period avoiding transitioning to downstream health states, such as the subsequent treatment options (BSC or surgery). In contrast, patients in the comparator arm must transition after one year to these downstream health states, incurring additional costs and disutilities, particularly those associated with long-term surgical outcomes. This means that the long-term surgical disutilities, which were a key driver in the deterministic sensitivity analysis, affected the comparator arm more. Additionally, the source of the utility value for long term disutility following surgery was  from an older publication. The submitting company provided scenarios with arbitrary disutility values to show the impact of a reduced long-term disutility for hysterectomy on the ICER. While a reduced disutility value increased the ICER (scenario 10 & 11), the Committee noted that scenario 11 was too conservative and unlikely to reflect real world outcomes.
- The submitting company do not consider any impacts on fertility directly, which could be considered an issue if relugolix CT is taken over a long period of time compared to GnRH agonists. However, the submitting company state that since relugolix CT and GnRH agonists are contraceptives, the EQ-5D data and the long-term disutility associated with surgery has sufficiently captured fertility outcomes. The company explained that estimating fertility recovery impact would be challenging due to the uncertainty in predicting discontinuation rates and the time to full fertility post-treatment, a position the Committee deemed reasonable.
- SMC experts, and the Summary of Product Characteristics[1], have indicated that DXA scans are recommended for the intervention after one year of treatment, and prior to treatment for patients with risk factors for osteoporosis or bone loss. However, these costs were only accounted for in surgery outcomes. Scenario 9, which tests out this uncertainty, illustrates that there is only a minimal increase in the ICER when DXA scans are included in the analysis.

- The cost of GnRH agonists may be lower than the published price used in the model as a national contract framework price is in place. It is noted the price used in the base case is consistent with SMC process.

## 7. Conclusion

After considering all the available evidence, the Committee accepted relugolix CT for use in NHSScotland.

## 8. Guidelines and Protocols

The National Institute for Health and Care Excellence (NICE) published guideline (NG73) on the diagnosis and management of endometriosis in 2017, which was updated in April 2024.[13]

The European Society of Human Reproduction and Embryology (ESHRE) published guidance on the diagnosis and management of endometriosis in 2022.[14]

## 9. Additional Information

**9.1.**
**Product availability date**

12 September 2024

**Table 9.1 List price of medicine under review**

| Medicine | Dose regimen | Cost per year (£) |
|---|---|---|
| **Relugolix 40 mg, estradiol 1 mg, norethisterone acetate 0.5 mg tablets (Ryeqo®)** | **One tablet daily** | **936** |

*Costs from BNF online on 07 May 2024. Costs do not take any patient access schemes into consideration.*

## 10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 96 patients eligible for treatment with relugolix CT each year. The uptake rate was estimated to be 10% in year 1 and 60% in year 5. This resulted in 10 patients estimated to receive treatment in year 1 rising to 58 in year 5. SMC clinical expert responses indicate the number of eligible patients and the uptake rate is likely to be higher than estimated by the submitting company.

The gross impact on the medicines budget was estimated to be £9k in year 1 rising to £54.2k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be a saving of -£424 in year 1 and -£2.55k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 14 November 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

*No part of this advice may be used without the whole of the advice being quoted in full.*

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.