Single Technology Appraisal

Relugolix–estradiol–norethisterone acetate for treating symptoms of endometriosis [ID3982]

Committee Papers

National Institute for Health and Care Excellence

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Single Technology Appraisal

Relugolix–estradiol–norethisterone acetate for treating symptoms of endometriosis [ID3982]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Gedeon Richter**
   a. Comments on the Draft Guidance
   b. Addendum to Draft Guidance response

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Endometriosis UK

3. **External Assessment Group critique of company comments on the Draft Guidance**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Relugolix–estradiol–norethisterone acetate for treating symptoms of endometriosis [ID3982]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 22 April 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Gedeon Richter

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Gedeon Richter is disappointed that the committee has not recommended Relugolix CT for the treatment of symptoms associated with endometriosis. As acknowledged by the committee, there is an unmet need for long-term, non-invasive, effective treatment options for women with this debilitating condition. We note the list of additional information requested by committee; responses to these requests are provided below.

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2	**Regarding the committee's request for a new systematic literature review:** **Gedeon Richter has performed an updated literature review, which we believe has thoroughly captured the evidence base** Gedeon Richter has conducted a new systematic literature review to address the committee's concerns that the evidence had not been identified systematically. The searches covered the period from database inception to 29th April 2024. Following deduplication and screening, 139 reports representing 111 unique studies were identified. Of note, no studies were identified that provide evidence for surgery as a comparator to Relugolix CT. Full details of the systematic literature review are provided in the accompanying document *'ID3982_RelugolixCT_Addendum_13.12.24 [NoCON].docx'.* **Gedeon Richter has also performed an updated indirect treatment comparison; the results of which do not impact the model** An updated indirect treatment comparison found no evidence of a difference between Relugolix CT and leuprorelin acetate 3.75 mg in terms of overall pelvic pain (OPP). This is consistent with the indirect treatment comparison in our original submission. There was evidence for a greater effect of leuprorelin acetate 3.75 mg compared with Relugolix CT on total pelvic pain (TPP), which is not consistent with the original ITC. However, according to the published literature, inconsistencies between the results for OPP, which uses the Numeric rating scale (NRS) and TPP, which uses the Biberoglu and Behrman (B&B), are not unexpected. The B&B, which is scored out of a total of 15, has been stated to be "*confusing and potentially hazardous because combining physical examination with symptomatology can induce wrong conclusions. Patients describe symptomatology and gynaecologists evaluate tenderness and induration during physical examination with an exceedingly high risk of bias and inconsistent reproducibility*". Notably, the NRS has published Minimal Clinically Important Change Scores (MCIDs) whereas the B&B does not (1). Furthermore, modified versions of the B&B score combine the three pain symptoms into a 'pelvic symptoms score' or 'endometriosis symptom severity scale'. Combined scores can be misleading on account of the way in which they are estimated. For example, individuals reporting only moderate pain may record combined scores that are higher than those with severe dyspareunia combined with mild dysmenorrhea and no pelvic pain (1). Full details of the updated ITC are provided in the accompanying document *'ID3982_RelugolixCT_Addendum_13.12.24 [NoCON].docx'.* **In addition, relugolix is a well-studied molecule, with head-to-head data vs. GnRH agonist available in several indications** Although there are no studies directly comparing Relugolix CT with gonadotropin-releasing hormone (GnRH) agonists in endometriosis, there are published data in several disease areas on the efficacy of relugolix alone (i.e. without estradiol and norethisterone) vs GnRH agonists. As GnRH agonists are also used with hormonal 'add-back therapy', any effect modification from hormonal therapy might to some extent be cancelled out. Examples of head-to-head studies for relugolix vs GnRH agonists are given below. <u>Endometriosis</u> In a Phase 2, randomised, open-label study conducted in Japan, women treated with relugolix 40 mg for 24 weeks had similar reductions in endometriosis-associated pelvic pain and dysmenorrhoea to those who received GnRH agonist (Table 1) (2). **Table 1: Mean change from baseline in VAS scores for endometriosis-associated pain** **Mean (SD) change from baseline in mean VAS score (mm)** **Relugolix 40 mg (n = 103)** **Leuprolide 3.75 mg (n = 82)**

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	<table><tr><td>Pelvic pain</td><td>-11.9 (11.26)</td><td>-12.7 (12.57)</td></tr><tr><td>Dysmenorrhea</td><td>-29.5 (17.54)</td><td>-27.2 (19.86)</td></tr><tr><td>Dyspareunia</td><td>-0.9 (12.04)</td><td>-4.6 (15.09)</td></tr></table> SD, standard deviation; VAS, visual analogue scale Source: Osuga Y, et al. BMC Women's Health 2021;21:250 (2) Similarly, in a Phase 3, randomised, double-blind study conducted in Japan, relugolix 40 mg was shown to be non-inferior to leuprolide for treating endometriosis-associated pelvic pain over 24 weeks of treatment (3). The mean (standard error) change from baseline in maximum VAS score for pelvic pain at Week 24 was -52.6 (1.3) in the relugolix group (n = 171) and -57.5 (1.4) in the leuprolide group (n = 164). <u>Uterine leiomyoma</u> A double-blind, double-dummy study conducted in Japan showed that relugolix 40 mg was non-inferior to leuprolide in reducing heavy bleeding associated with uterine leiomyomas (4). At Weeks 6-12, 82.2% of patients in the relugolix group (n = 139) had a total pictorial blood loss assessment chart score of less than 10 compared with 83.1% in the leuprolide group (n = 142) (relugolix−leuprolide difference −0.9%; 95% CI: −10.10 to 8.35; prespecified noninferiority margin −15%; *P*=.001). <u>Prostate cancer</u> In a global Phase 3 study of 934 men with advanced prostate cancer, the sustained castration rate (defined as the proportion of patients achieving supressed testosterone to castration levels) of relugolix through 48 weeks of treatment was superior to that of leuprolide: 96.7% vs. 88.8% (between-group difference, 7.9 percentage points; 95% confidence interval, 4.1 to 11.8; P<0.001) (5). **The updated indirect treatment comparison results do not affect the conclusions of the economic modelling** Updating the economic model with the least favourable (random effects) odds ratios from the updated ITC (1.12 and 27.75 for OPP and TPP, respectively) still results in cost effective results for Relugolix CT (£1,821 and £1,716 per QALY for OPP and TPP respectively), as the benefit is underpinned by the long duration of treatment with Relugolix CT vs. GnRH agonist.
3	**Regarding the committee's request for evidence on the efficacy of Relugolix CT compared with surgery:** **Gedeon Richter does not consider that surgery is a comparator to Relugolix CT** The European Society of Human Reproduction and Embryology (ESHRE) guidelines recommend that the decision to perform surgery vs. medical therapy should be guided by the presence or absence of pain symptoms, patient age and preferences, history of previous surgery, presence of other infertility factors, ovarian reserve and the estimated endometriosis fertility index (6). This suggests that different patient factors are likely to lead to different treatment options for reasons of patient preference and/or medical history. A recent publication of a (non-randomised) study comparing surgery vs. medical management of endometriosis-related pain during the COVID-19 pandemic concluded that *"how one compares to the other is still unclear due to <u>systematic differences</u> between study cohorts"*, supporting the view that there may be clinically distinct populations eligible for each treatment modality (7). To date, Relugolix CT has been submitted for reimbursement in 15 countries (England, Scotland, the Netherlands, Australia, Hungary, Denmark, Germany, Sweden, Belgium, Norway, Finland, Spain, France, Italy and Slovenia); in each submission GnRH agonists were considered the relevant comparator. Official evaluations have been received from Australia, Denmark, Germany, Sweden, Belgium and Scotland; none of these evaluations considered surgery as a comparator. To date, this is the first time any health technology assessment of Relugolix CT in either endometriosis or uterine fibroids has explored surgery as a potential comparator of interest.

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At the committee meeting, the clinical expert stated that the evidence for surgery is limited and the available studies are heterogeneous, making them difficult to compare. A 2020 Cochrane review of laparoscopic surgery for endometriosis found just 14 randomised controlled trials and concluded that it was uncertain whether laparoscopic surgery reduces endometriosis pain when compared with diagnostic laparoscopy only (8). Furthermore, there is no conclusive evidence on whether medical or surgical treatments are more effective in managing pain. Only a handful of studies have directly compared the two and found no significant differences in treatment satisfaction (9).

We are not aware of any other analogues where surgery was considered a comparator
While endometriosis is clinically distinct from uterine fibroids, the treatment pathway is similar between both indications, with surgery being an alternative to medical treatment at each step of the pathway. Despite the NICE uterine fibroids scope sharing many similarities with that of endometriosis in the list of comparators, specifically with respect to hormonal treatment, surgery was not proposed as a comparator at any stage of the NICE appraisal of Relugolix CT in uterine fibroids (TA832). Both scopes, similarly, include surgery as an outcome (see Table 2 below) (10, 11).

Furthermore, surgery is used as a treatment approach alongside medical management in a number of other indications. Examples include Crohn's disease (CD) and ulcerative colitis (UC). As per the scopes of endometriosis and uterine fibroids, recent scopes for CD and UC include surgery in the list of outcomes, but not in the list of comparators (12-16).

Table 2: Comparison of comparators and outcomes listed in endometriosis vs. uterine fibroids scopes

	Relugolix–estradiol–norethisterone acetate for treating symptoms of endometriosis [ID3982]	**Relugolix with oestradiol and norethindrone acetate for treating uterine fibroids [TA832]**
Comparators	Established clinical management without relugolix in combination with oestradiol and norethindrone, including: • analgesics or non-steroidal anti-inflammatory drug (NSAID) alone or in combination with each other • neuromodulators • hormonal treatment such as combined hormonal contraception (off-label for some combined hormonal contraceptives), oral progestogens, gonadotropinreleasing hormone (GnRH) agonists.	Hormonal treatments, including: • levonorgestrel-releasing intrauterine system (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)
Outcomes	The outcome measures to be considered include: • overall pain • opioid use • analgesic use • recurrence of endometriosis • admission to hospital • subsequent surgical treatment • fertility • adverse effects of treatment • complications of treatment • health-related quality of life	The outcome measures to be considered include: • change in menstrual blood loss volume • time to menstrual blood loss response • pain • uterine fibroid volume • haemoglobin levels • change in bone mineral density • rates and route of surgery

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			• impact on fertility and pregnancy and teratogenic effects • mortality • adverse effects of treatment, including but not limited to vasomotor symptoms, incontinence and pelvic organ prolapse • health-related quality of life

Relugolix CT is likely to be cost effective against surgery
The economic model submitted for this appraisal was designed at a global level with surgery as a comparator to Relugolix CT. This was done in the event that surgery may be considered a comparator in any of the markets in which Relugolix CT has been submitted for reimbursement. None of these markets considered surgery to be a relevant comparator.

Using the current model, we can see that the incremental cost-effectiveness ratios for Relugolix CT vs. surgery are extremely low. It should be noted that the current model has the functionality for a pairwise comparison of Relugolix CT vs. surgery; however, the efficacy inputs for the surgery arm are not informed by the indirect treatment comparison that informs the Relugolix CT and GnRH agonist arms. A description of how surgery efficacy is parameterised in the model is given in the appendix at the end of this document.

Table 3: Preliminary cost-effectiveness results, Relugolix CT vs. surgery

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Relugolix CT	£11,487	23.105	17.165	-	-	-	-
Surgery	£9,741	23.095	16.345	£1,746	0.010	0.820	£2,130

GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

4 **Regarding the committee's request for clarity on what constitutes best supportive care:**

Best supportive care after treatment with Relugolix CT is likely to be analgesics for pain management. Some patients may opt for surgery at this stage, and this is considered separately. Hormonal treatments are not considered best supportive care at this point in the treatment pathway as patients would have already failed these before moving on to Relugolix CT. Patients would therefore not be expected to restart treatment with hormonal treatments.

The original submitted model was developed at a global level and included hormonal treatments as best supportive care. However, these were subsequently removed as their inclusion was not reflective of best supportive care in England and Wales. An updated model that included only analgesics as best supportive care was submitted at clarification in November 2023.

5 **Regarding the committee's request for a model that more accurately reflects the treatment pathway:**

Gedeon Richter believes that the current model structure does reflect the treatment pathway as described by the clinical expert during the committee meeting, as it allows for patients to receive further surgeries after Relugolix CT. The model spans a lifetime horizon and captures all possible avenues that may be taken by a patient upon discontinuation of active treatment (Relugolix CT or GnRH agonist). Following discontinuation from Relugolix CT/GnRH, a proportion of patients can have surgery; however, as alluded to by the clinical expert, many choose not to. As explained by the clinical

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<tr><td></td><td>expert, not all patients respond to surgery, therefore the model also captures pain recurrence following surgery. Pain recurrence in the model leads to the initiation of a subsequent treatment, either with best supportive care or additional surgeries. The model captures the fact that some patients will opt for a radical surgery i.e. hysterectomy. We also believe that the model is in line with current European Society of Human Reproduction and Embryology guidelines (6), which were published in 2022 and are often used over the NICE Guideline NG73.</td></tr>
<tr><td>6</td><td>Regarding the committee’s request for scenarios using longer treatment durations for GnRH agonists:

Relugolix CT becomes increasingly cost-effective against GnRH agonists with longer GnRH agonist use
GnRH agonists are licenced for use for up to 6 months. However, we are aware that they are used off-licence for longer periods of time. In a survey of five UK clinical experts conducted during development of our submission, two responded that a small proportion of their patients have received GnRH agonists for more than 2 years. The original company submission included a scenario with GnRH treatment duration capped at 2 years. At the committee meeting, the clinical expert indicated that GnRH agonists are prescribed by some clinicians for longer than 5 years and in some cases, for up to 10 years. Based on this, we have run scenarios including GnRH use up to 5, 7 and 10 years. The results are shown below. It can be seen that Relugolix CT becomes increasingly cost-effective against GnRH agonists when agonists are used for longer durations. Relugolix CT dominates GnRH agonists in all 3 of the alternative treatment duration scenarios explored as it is less costly whilst also being more effective. These scenarios reiterate the base-case cost effectiveness model results which show that Relugolix CT is highly cost-effective against GnRH agonists.

At the committee meeting, the clinical expert stated that some general practitioners are not comfortable prescribing GnRH agonists for longer than 6 months, so patients then have to move to secondary care to continue treatment. The expert’s opinion was that a treatment that is licensed for long-term use would therefore be beneficial. This further highlights that Relugolix CT would be meeting an area of high unmet need.

Table 4: Cost-effectiveness results, scenario where GnRH treatment duration is capped at 5 years
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>Relugolix CT</td><td>£11,487</td><td>23.105</td><td>17.165</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>GnRH agonist</td><td>£11,651</td><td>23.101</td><td>16.766</td><td>-£164</td><td>0.004</td><td>0.398</td><td>Relugolix CT dominates</td></tr>
</table>
GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Table 5: Cost-effectiveness results, scenario where GnRH treatment duration is capped at 7 years
<table>
<tr><th>Technologies</th><th>Total costs (£)</th><th>Total LYG</th><th>Total QALYs</th><th>Incremental costs (£)</th><th>Incremental LYG</th><th>Incremental QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>Relugolix CT</td><td>£11,487</td><td>23.105</td><td>17.165</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>GnRH agonist</td><td>£12,157</td><td>23.103</td><td>16.882</td><td>-£670</td><td>0.002</td><td>0.283</td><td>Relugolix CT dominates</td></tr>
</table>
GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year</td></tr>
</table>

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Table 6: Cost-effectiveness results, scenario where GnRH treatment duration is capped at 10 years

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Relugolix CT	£11,487	23.105	17.165	-	-	-	-
GnRH agonist	£12,724	23.104	17.020	-£1,237	0.001	0.145	Relugolix CT dominates

GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

7

Regarding the committee's request for further validation and justification of the utilities used in the model and scenarios considering the impact of changing these values:

The model utility values were derived using NICE's preferred methods and align with the literature

The utility values were informed by EQ-5D values collected in the SPIRIT trials and are thus at the top of NICE's preferred evidence hierarchy for source of utility. Furthermore, we reiterate, as per response at clarification, that the baseline utility values are within the range of those identified in the SLR, which ranged from 0.15 to 0.689 pre-surgery. In a study by Grundström et al. of biopsy-confirmed endometriosis in women with moderate to severe pelvic pain, the baseline EQ-5D was 0.49 (17). The highest baseline value observed in the SLR was 0.78 in a prospective observational study in France (18). However, no pain scores were specified for eligibility, and participants were eligible for high-dose progestin, thus these participants can be considered less severe than those in the SPIRIT studies, which required participants to have moderate-severe endometriosis-associated pain.

A low baseline utility score reflects the devastating impact that endometriosis has on patients' lives

A low baseline utility score is not unexpected, as endometriosis affects all dimensions of the EuroQoL-5D. A 2019 survey carried out by the BBC in conjunction with Endometriosis UK highlighted the devastating impact that endometriosis can have on patients' lives. More than 13,500 women with endometriosis took part and nearly all said that endometriosis has affected their career, sex life and mental health. Most felt their education had been affected and most said they relied on prescription painkillers (including opioids). One respondent described the pain as *"like barbed wire wrapped around your insides and someone's pulling at it while at the same time an animal is trying to eat its way through you"*. In addition, around half the respondents said they had considered taking their own life.

Details of the survey are available at https://www.bbc.co.uk/news/health-49897873 and https://www.endometriosis-uk.org/press-release-new-bbc-research-wake-call-provide-better-care

The model is relatively insensitive to the choice of utility values applied to key health states

To explore the sensitivity of the model to the utility values, we have explored a scenario where the utility of non-responders (0.72) is set equal to the baseline utility value (0.58). The results for this scenario are presented below. Applying the baseline health state utility to the non-response health state results in a slight increase (0.013) in the incremental quality-adjusted life years associated with Relugolix CT vs. GnRH agonists compared to the base-case. This leads to a lower incremental cost-effectiveness ratio of £1,683 compared to the base-case lower incremental cost-effectiveness ratio of £1,715, showing that the model is relatively insensitive to the choice of utility values applied to key health states.

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Table 7: Cost-effectiveness results, scenario where utility of non-response is set equal to baseline utility

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Relugolix CT	£11,487	23.105	17.112	-	-	-	-
GnRH agonist	£10,280	23.098	16.395	£1,207	0.007	0.717	£1,683

GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Gedeon Richter note the committee's concern about small differences in the utility values for response and non-response. A possible explanation for this is that in the SPIRIT studies, patients had access to analgesics. Non-responders to Relugolix CT may therefore have experienced some benefit from these analgesics, which had an impact on their utility scores.
</td></tr>
<tr><td>8</td><td>

Regarding the committee's request for a multiplicative approach to incorporating disutilities from adverse events:

Gedeon Richter are of the understanding that a multiplicative approach is typically used for an age-related decrement and an additive approach is used for other disutilities. The company consider that opting for a multiplicative approach to incorporating disutilities from adverse events would not have a significant impact upon the results and have thus not incorporated any scenarios around this.
</td></tr>
<tr><td>9</td><td>

Regarding the committee's request for scenarios considering the EAG's approach to capturing disutility from infertility:

Disutility from hysterectomy is a more appropriate description than disutility from infertility

The draft guidance states that '*the EAG also noted that the model applied utility decrements to all people after hysterectomy, but it preferred that the decrement only be applied to people who were actively seeking to have become pregnant'.* Gedeon Richter do not agree with this approach because it would assume that the disutility associated with a hysterectomy is only limited to infertility, when in fact hysterectomy can have a substantial impact on quality of life beyond this. It is not plausible that only those who wish to have a child would experience a disutility after having a hysterectomy. Women may feel a sense of loss or sadness, a loss of femininity and in some cases, hysterectomy can trigger depression (19). Furthermore, feedback from gynaecologists who were interviewed as part of the submission development process was that women who have endometriosis and opt for a hysterectomy would typically have an oophorectomy as part of the procedure (i.e. the ovaries are removed alongside the uterus). This would then also trigger menopause, which also has a negative impact on health-related quality of life. Furthermore, research shows that women who experience premature menopause (before age 40 years) or early menopause (between ages 40 and 45 years) experience an increased risk of overall mortality, cardiovascular diseases, neurological diseases, psychiatric diseases, osteoporosis, and other sequelae. The risk of adverse outcomes increases with earlier age at the time of menopause (20, 21).

Scenario analyses show that Relugolix CT remains cost-effective regardless of the magnitude of the disutility associated with hysterectomy

We have conducted a range of scenario analyses to explore the uncertainty around the disutility associated with hysterectomy. It can be seen that the incremental cost-effectiveness ratios across all scenarios explored are well below the £20,000 to £30,000 per quality-adjusted life year threshold, irrespective of whether a very small or more sizeable impact of hysterectomy on health-related quality of life is assumed.
</td></tr>
</table>

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Table 8: Cost-effectiveness results, scenario where disutility of hysterectomy is 0.01

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Relugolix CT	£11,487	23.105	17.976	-	-	-	-
GnRH agonist	£10,280	23.098	17.847	£1,207	0.007	0.129	£9,383

GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Table 9: Cost-effectiveness results, scenario where disutility of hysterectomy is 0.05

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Relugolix CT	£11,487	23.105	17.785	-	-	-	
GnRH agonist	£10,280	23.098	17.521	£1,207	0.007	0.264	£4,573

GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Table 10: Cost-effectiveness results, scenario where disutility of hysterectomy is 0.1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Relugolix CT	£11,487	23.105	17.547	-	-	-	-
GnRH agonist	£10,280	23.098	17.113	£1,207	0.007	0.433	£2,787

GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

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10

Regarding the committee's request for scenarios considering the impact of treatment waning:

Gedeon Richter does not anticipate any waning of treatment effect with Relugolix CT

At the committee meeting, the clinical expert stated that there is no waning of effect with GnRH agonists. We therefore see no reason to expect that there would be a waning of effect with Relugolix CT.

As described in the company submission, data from the SPIRIT OLE trial show that response was maintained during 2 years of treatment with Relugolix CT (Table 11).

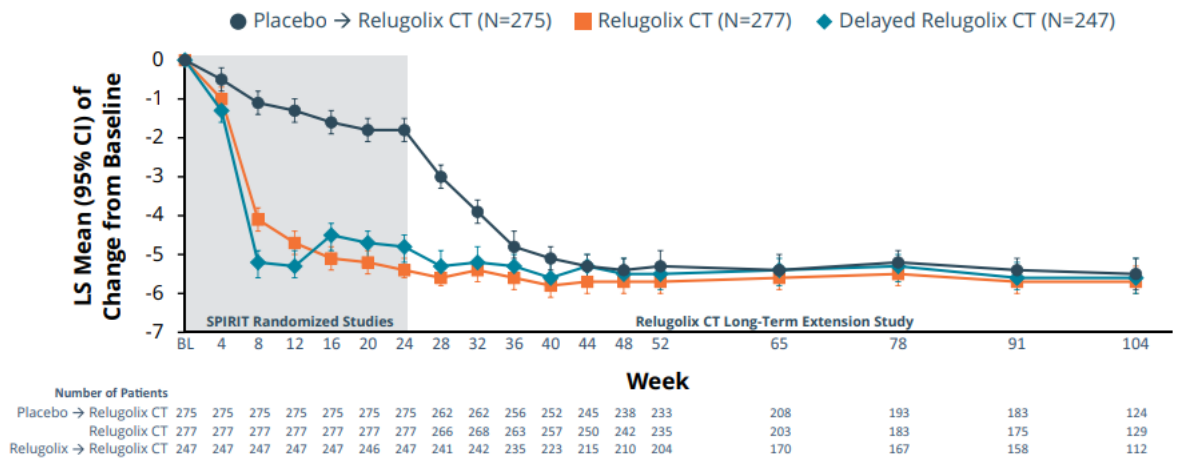
Table 11: Response rates at 24, 52 and 104 weeks of treatment with Relugolix CT

	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)

NMPP, non-menstrual pelvic pain; OLE, open-label extension
Source: Giudice et al. Lancet 2022;399:2267-79 (22); Becker et al. Hum Reprod 2024;39:526-37 (23).

At Week 52, patients receiving Relugolix CT had an 83.9% reduction from baseline in mean dysmenorrhoea numerical rating scale scores and a reduction in pain scores from severe to mild (see Figure 1). At Week 104, the reduction in dysmenorrhoea was maintained (84% decrease from baseline).

Figure 1: Change from baseline in average dysmenorrhoea NRS score



CI, confidence interval; LS mean, least squares mean; NRS, numerical rating scale
Source: Becker et al. Hum Reprod 2024;39:526-37 (23).

At Week 52, patients receiving Relugolix CT had a 63.5% decrease from baseline in mean non-menstrual pelvic pain numerical rating scale scores, with a reduction in pain from moderate to mild (see Figure 2). At Week 104, the reduction in non-menstrual pelvic pain was maintained (68.9% decrease from baseline).

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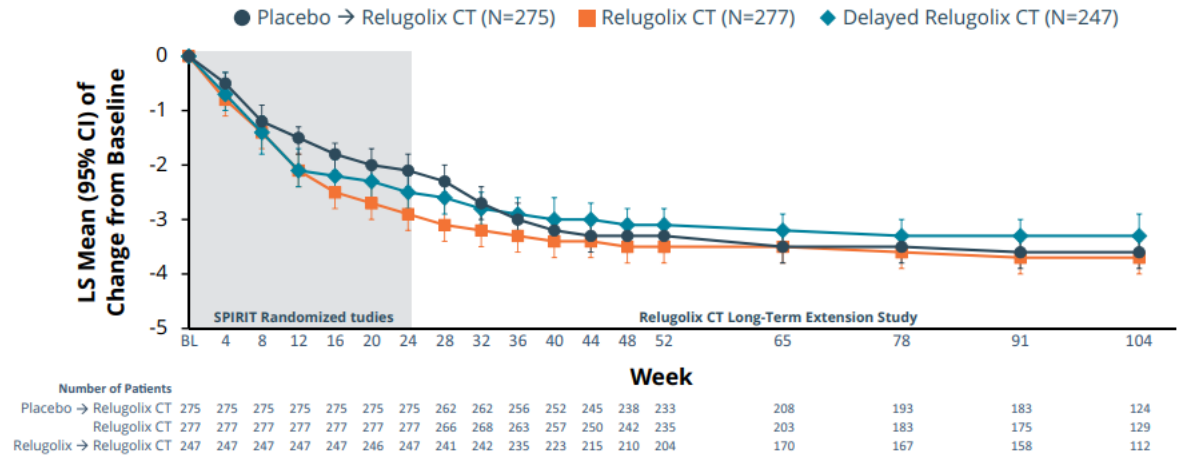
Figure 2: Change from baseline in average NMPP NRS score



CI, confidence interval; LS mean, least-squared mean; NMPP, non-menstrual pelvic pain; NRS, numerical rating scale
Source: Becker et al. Hum Reprod 2024;39:526-37 (23).

In addition, there was no increase in the rate of discontinuation owing to lack of efficacy between SPIRIT 1 & 2 and SPIRIT OLE. Of the 420 patients randomised to Relugolix CT in SPIRIT 1 & 2, eight (2%) discontinued because of lack of efficacy (22). Of the 802 patients enrolled in SPIRIT OLE, 16 (2%) discontinued because of lack of efficacy; four of whom had received Relugolix CT in SPIRIT 1 & 2 (23).

Altering the discontinuation rates in the model does not affect the base-case ICER
Despite there being no increase in discontinuation rates over time in the SPIRIT trials, Gedeon Richter have conducted scenario analyses where alternative discontinuation rates are applied at months 21 and 24+. We firstly explored a 'pessimistic' scenario using the upper value (maximum) of the discontinuation rate which was 0.033. We then explored an 'optimistic' scenario where the lower value (minimum) discontinuation rate of 0 was applied at months 21 and 24+. The results of these scenarios are reported below. It can be seen that under both scenarios, the incremental cost-effectiveness ratio does not differ very much from the base-case and lies well below UK thresholds.

Table 12: Cost-effectiveness results, scenario where maximum discontinuation rate is applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Relugolix CT	£11,361	23.103	16.958	-	-	-	-
GnRH agonist	£10,280	23.098	16.461	£1,082	0.005	0.497	£2,178

GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

Table 13: Cost-effectiveness results, scenario where minimum discontinuation rate is applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Relugolix CT	11,446	23.107	17.367	-	-	-	-
GnRH agonist	10,280	23.098	16.345	£1,166	0.009	0.906	£1,287

GnRH, gonadotropin-releasing hormone; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year

11	**Regarding the committee's request for full model validation and justification of counterintuitive results:**

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	The model underwent full external and internal validation during development Gedeon Richter were surprised to see this request, given that full details of model validation (both external and internal) were provided at clarification. In summary, the external validation comprised the following: • 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, including: • Turn off mortality ➔ Life-years equal in both comparators and equal to model horizon (undiscounted) • Equal efficacy and AEs for all comparators ➔ QALYs equal in both comparators • Increase treatment cost of Relugolix CT ➔ The total cost of Relugolix CT increases and the ICER of Relugolix CT increases • Costs of treatments and health care resource use set to £0 ➔ Costs equal to £0 in all comparators • Increase/decrease of model horizon ➔ Increase/decrease of life years in all comparators • Increase/decrease of utility-values for all health states ➔ Increase/decrease of QALYs in all comparators **Counterintuitive results in scenarios where Relugolix CT response rate is decreased** As described during the committee meeting, the seemingly counterintuitive results can be explained by the ratio of costs pre-response vs post-response: • Firstly, Relugolix CT is less expensive per patient per year than GnRH agonist, once administration costs are taken into account. Thus, prior to response assessment, the costs of GnRH agonist are higher than those of Relugolix CT. • At response rates above 1%, there are higher total costs in the Relugolix CT arm (and more QALYs) due to a longer duration of treatment post-response assessment, even though fewer patients pass the response assessment. • At a 1% response rate, the balance of costs switches round, as minimal Relugolix CT costs are now generated post assessment. As Relugolix CT is cheaper pre-assessment than GnRH

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	and there are minimal costs post-assessment, lower costs are now generated in the Relugolix CT arm than the GnRH agonist arm.
	
	The EAG then stated that "*if 100% of people stopped relugolix CT at 9 or 12 months, having relugolix CT resulted in more QALYs and fewer costs*." This statement is incorrect. If these are the only changes made to the model, decreasing the duration of treatment on relugolix CT to 9 or 12 months results in both lower QALYs and lower costs vs. GnRH agonist. Lower costs are to be expected, as relugolix CT is cheaper per unit time, fewer patients respond vs GnRH agonist AND duration of treatment is lower. Fewer QALYs are generated because response rate on relugolix CT is lower than GnRH agonist AND duration of treatment is now lower for responders.
	
	Probabilistic sensitivity analysis
	The draft guidance states *'the EAG stated that there was a lack of transparency about the probabilistic sensitivity analysis and noted that there may have been some missing parameters and parameter-specific variation.'* Gedeon Richter are surprised to see that this statement has been included in the draft guidance given that an updated model with missing probabilistic sensitivity analysis parameters was provided at the clarification stage, specifically in response to clarification question B31. A list of parameters that were added into the probabilistic sensitivity analysis at the clarification stage is provided below:
	• SPIRIT baseline characteristics (rows 37-44 in "*Variable bank*")
	  ○ Age (years)
	  ○ Weight (kg)
	  ○ Total cholesterol (mg/dL)
	  ○ HDL (mg/dL)
	  ○ Systolic blood pressure (mmHg)
	  ○ Smoker (%)
	  ○ Diabetes (%)
	• Odds ratio of response (GnRH-agonist vs Relugolix CT) (row 68)
	• Proportion of patients treated with Relugolix CT using analgesics before response (rows 78-83)
	• Proportion of patients treated with Relugolix CT using analgesics after response
	• Proportion of patients treated with best supportive care using analgesics before response
	• Proportion of patients treated with best supportive care using analgesics after response
	• Proportion of patients treated with GnRH-agonist using analgesics before response
	• Proportion of patients treated with GnRH-agonist using analgesics after response
	• Subsequent treatment following discontinuation of intervention/comparator - Proportion of patients treated with Relugolix CT who switch to best supportive care following discontinuation of treatment (rows 96-104)
	• Subsequent treatment following discontinuation of intervention/comparator - Proportion of patients treated with Relugolix CT who switch to conservative surgery following discontinuation of treatment
	• Subsequent treatment following discontinuation of intervention/comparator - Proportion of patients treated with Relugolix CT who switch to hysterectomy following discontinuation of treatment

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	• Subsequent treatment following discontinuation of intervention/comparator - Proportion of patients treated with best supportive care who switch to best supportive care following discontinuation of treatment • Subsequent treatment following discontinuation of intervention/comparator - Proportion of patients treated with best supportive care who switch to conservative surgery following discontinuation of treatment • Subsequent treatment following discontinuation of intervention/comparator - Proportion of patients treated with best supportive care who switch to hysterectomy following discontinuation of treatment • Subsequent treatment following discontinuation of intervention/comparator - Proportion of patients treated with GnRH-agonist who switch to best supportive care following discontinuation of treatment • Subsequent treatment following discontinuation of intervention/comparator - Proportion of patients treated with GnRH-agonist who switch to conservative surgery following discontinuation of treatment • Subsequent treatment following discontinuation of intervention/comparator - Proportion of patients treated with GnRH-agonist who switch to hysterectomy following discontinuation of treatment • Proportion of patients who switch to conservative surgery following treatment discontinuation with 2nd line best supportive care(rows 111-112) • Proportion of patients who switch to hysterectomy surgery following treatment discontinuation with 2nd line best supportive care • Proportion of patients treated with conservative surgery who undergo another conservative surgery following recurrence of pain (rows 117-119) • Proportion of patients treated with conservative surgery who switch to best supportive care following recurrence of pain • Proportion of patients treated with conservative surgery who undergo a hysterectomy following recurrence of pain • Long-term disutility following surgery - Post-hysterectomy (row 436) • CV and fracture risk - Log of Age (rows 721-727) • CV and fracture risk - Log of Total cholesterol • CV and fracture risk - Log of HDL • CV and fracture risk - Log of Systolic blood pressure (SBP) • CV and fracture risk - Treated [with statin] SBP • CV and fracture risk - Smoker • CV and fracture risk - Diabetes • Fracture risk model - RR per unit decrease in BMD (rows 743-744) • Fracture risk model - Mean bone mass (g/cm^2)

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Insert extra rows as needed

Appendix: Parameterisation of surgery as a comparator in the cost-effectiveness model

Apart from the first model cycles, surgery as a comparator is implemented in the same way as surgery as a treatment option following treatments with Relugolix CT/GnRH agonist. Surgery costs, healthcare resource use, efficacy and health-related quality of life inputs are described in the model technical report.

This appendix highlights the differences in treatment pathway between surgery as a comparator and surgery as a treatment option following Relugolix CT or GnRH agonist.

The model structure for surgery as a comparator in described in the figure below.

The surgical comparator includes conservative surgery or hysterectomy. Patients enter the model in the health state "*Initial treatment*" where they stay only one cycle before moving to health state "*Waiting time before surgery*" (D). To account for waiting time until surgery, patients in the surgical comparator arm remain in the health state "*Waiting time before surgery*" for one to four model cycles i.e., three to twelve months depending on the selected waiting time (**Input sheet$D123**). During that time, patients receive BSC. Upon completion of the waiting time, patients undergo either conservative surgery (F) or hysterectomy/oophorectomy (E) based on the user defined split between those two interventions (**Input sheet$D42:43**).

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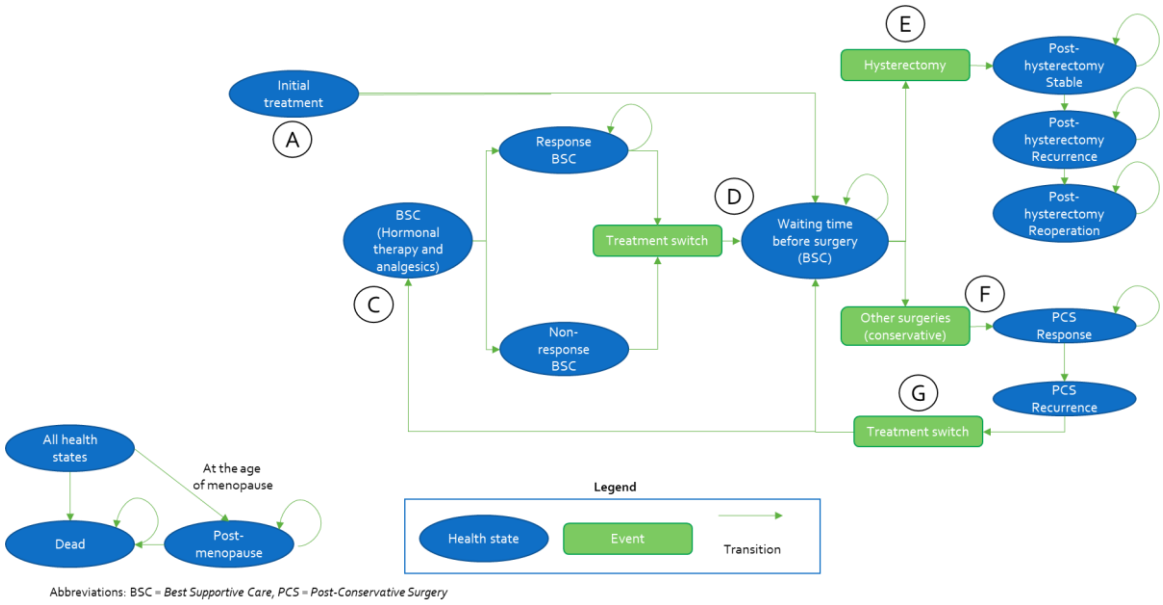
Figure 3 Cost-effectiveness model structure with surgery as a comparator



Abbreviations: BSC = *Best Supportive Care*, PCS = *Post-Conservative Surgery*

Patients who undergo surgery in the model face a risk of recurrence of pain (see Section 3.2.4 in the technical report for further details). This will lead to initiation of a subsequent treatment, either with BSC or additional surgeries. Probabilities of pain recurrence in patients who underwent conservative surgery or hysterectomy are defined in **Input sheet$D147:148**.

- Following hysterectomy (E), the share of patients undergoing reoperation is defined in **Input sheet$D153.**
- Following conservative surgery (F), the transitions probabilities to respective treatment (hysterectomy, conservative surgery, or BSC) following recurrence of pain are defined in **Input sheet$D131:133** and correspond to point (G) in the model diagram. For patients who transit to BSC (point (C) in the model diagram), probabilities of response to BSC are defined in **Input sheet$E70.**

The probability of death from surgery (conservative or hysterectomy/oophorectomy) can be defined by the user in **Input sheet$D156:158**. In the base case analysis, the three months probability of death following conservative surgery is 0.003% and 0.038% following hysterectomy/oophorectomy and is applied in conjunction with the respective surgery, i.e., during the model cycle when surgery is performed (see Section 2.13 of technical report).

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Single technology appraisal

Relugolix–estradiol–norethisterone acetate for treating symptoms of endometriosis [ID3982]

Addendum

Updated clinical SLR and ITC

December 2024

File name	Version	Contains confidential information	Date
ID3982_RelugolixCT_Addendum_amended 08.01.25 [NoCON]	**Final (amended)**	**No**	**08.01.25**

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Abbreviations

Abbreviation	Definition
AIC	Akaike information criterion
B&B	Biberoglu and Behrman scale
CFB	Change from baseline
CrI	Credible interval
DIC	Deviance information criterion
EHP-30	Endometriosis Health Profile-30
GnRH	Gonadotropin-releasing hormone
ITC	Indirect treatment comparison
mB&B	Modified Biberoglu and Behrman scale
MCMC	Markov Chain Monte Carlo
mITT	Modified intention to treat
NMA	Network meta-analysis
NMPP	Non-menstrual pelvic pain
NRS	Numerical rating scale
OPP	Overall pelvic pain
OR	Odds ratio
SD	Standard deviation
SLR	Systematic literature review
SMD	Standardised mean difference
SUCRA	Surface under the cumulative ranking
TPP	Total pelvic pain
VAS	Visual analogue scale

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1. Systematic literature review

1.1. Methods

The SLR methodology followed NICE guidelines on how to conduct a systematic literature review (SLR). The data selection process followed the Centre for Reviews and Dissemination (CRD) guidelines and Cochrane methodology (1). Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed when reporting this SLR (2).

1.1.1. Database searches

Relevant studies were identified by searching the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), and Cochrane Central Register of Controlled Trials to identify primary reports of RCTs and open label extensions (OLEs); MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews to identify relevant SLRs and meta-analyses. To ensure all relevant evidence was captured, a combination of applicable Emtree subject headings (Embase), medical subject headings (MeSH) and free text terms were used to retrieve all relevant publications. The searches were conducted from inception to April 29th, 2024 (Table 1, Table 2 and Table 3).

Table 1 Search strategy Embase (via Elsevier)

No.	Query	Results
1	'endometriosis'/exp OR 'endometriosis' OR 'endometriosis'/exp OR endometriosis OR 'dyspareunia'/exp OR 'dyspareunia' OR 'dyspareunia'/exp OR dyspareunia OR 'dysmenorrhea'/exp OR 'dysmenorrhea' OR 'dysmenorrhea'/exp OR dysmenorrhea	80352
2	endometrio* OR dyspareunia OR dysmenorrhea* OR (pain* NEAR/3 (cycl* OR menstru* OR catamenia OR pelvic OR pelvis)) OR (pain NEAR/3 (coital OR postcoital OR intercourse OR sex OR coitus)) OR 'adenomyosis externa' OR coitalgia	123937
3	#1 OR #2	123978
4	'elagolix'/exp OR 'relugolix'/exp	726
5	elagolix OR relugolix OR linzagolix OR deslorelin	1446
6	tak385 OR 'tak 385' OR t1331285 OR 't 1331285' OR 'rvt 601' OR rvt601 OR relumine OR orgovyx OR mvt601 OR 'mvt601'	53
7	'abt 620' OR abt620 OR orilissa OR nbi OR 56418 OR nbi56418	5471
8	#4 OR #5 OR #6 OR #7	6881
9	'laparoscopy'/exp OR peritoneoscop*:ti,ab,kw OR celioscop*:ti,ab,kw OR laparoscop*:ti,ab,kw OR 'pelvic edocscop*':ti,ab,kw	306293

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10	'diathermy'/exp OR diatherm*:ti,ab,kw OR 'elecro diathermy':ti,ab,kw OR inductothermy:ti,ab,kw OR 'endo diathermy':ti,ab,kw OR electrodiatherm*:ti,ab,kw OR endodiatherm*:ti,ab,kw	9393
11	luna:ti,ab,kw	2064
12	presacral AND neurectomy*:ti,ab,kw	145
13	'laser'/exp OR laser*:ti,ab,kw	396575
14	plasmajet*:ti,ab,kw OR 'plasma jet*':ti,ab,kw	921
15	'minimally invasive surgery'/exp OR microlaparoscopic*:ti,ab,kw OR minilaparoscopic*:ti,ab,kw	57465
16	'computer assisted surgery'/exp OR 'robotics'/exp OR (((('computer aid*' OR 'computer assist*') NEAR/2 surg*):ti,ab,kw)	91064
17	'da vinci':ti,ab,kw	8272
18	'robot*':ti,ab,kw OR 'remote surg*':ti,ab,kw OR 'microsur*':ti,ab,kw OR 'micro surg*':ti,ab,kw OR 'mini-invasive surg*':ti,ab,kw OR 'minimally invasive surg*':ti,ab,kw OR 'minimal access surg*':ti,ab,kw	182802
19	('uterine nerve' NEAR/3 ablat*):ti,ab,kw	45
20	'ablation':ti,ab,kw OR 'resect*':ti,ab,kw OR 'ablative':ti,ab,kw	843699
21	'hysterectomy'/exp OR 'cystectomy'/exp OR 'ablation therapy'/exp OR ((uterus NEAR/2 (amputa* OR extirpate*)):ti,ab,kw) OR hysterectomy*:ti,ab,kw OR cystectom*:ti,ab,kw OR pericystectom*:ti,ab,kw OR ((bladder NEAR/2 (remov* OR resect* OR excis* OR extirpate*)):ti,ab,kw)	224925
22	'salpingectomy'/exp OR 'ovariectomy'/exp OR salpingectom*:ti,ab,kw OR tubalplasty:ti,ab,kw OR tubectom*:ti,ab,kw OR oophorectom*:ti,ab,kw OR oophorotom*:ti,ab,kw OR ovarectom*:ti,ab,kw OR ovariotom*:ti,ab,kw OR ovariectomy*:ti,ab,kw OR ((ovar* NEAR/2 (amputat* OR resect*)):ti,ab,kw) OR ((tubal NEAR/2 excision*):ti,ab,kw)	65140
23	'salpingooophorectomy'/de OR adnexectom*:ti,ab,kw OR annexectom*:ti,ab,kw OR ((salpingo* NEXT/1 oophorectomy*):ti,ab,kw) OR salpingoophorectom*:ti,ab,kw	23306
24	'oral contraceptive agent'/exp OR 'hormonal contraceptive agent'/exp OR anti$conceptive*:ti,ab,kw OR 'birth control pill*':ti,ab,kw OR contracepti*:ti,ab,kw OR 'oral ovulation inhibit*':ti,ab,kw	181118
25	dienogest:ti,ab,kw	1162
26	'danazol'/exp OR danazol:ti,ab,kw OR bonzol:ti,ab,kw OR chronogyn:ti,ab,kw OR cyclomen:ti,ab,kw OR danatrol:ti,ab,kw OR danocrine:ti,ab,kw OR danokrin:ti,ab,kw OR danol:ti,ab,kw OR ladogal:ti,ab,kw OR ladogar:ti,ab,kw OR mastodanatrol:ti,ab,kw OR winobanin:ti,ab,kw	9932
27	'levonorgestrel releasing intrauterine system'/exp OR ((levonorgestrel* NEAR/2 'intra$uterine system*'):ti,ab,kw) OR ((levonorgestrel* NEAR/2 'intra$uterine device*'):ti,ab,kw) OR ((levonorgestrel* NEAR/2 (system* OR device*)):ti,ab,kw) OR ((levonorgestrel* NEXT/1 (iud OR iuds)):ti,ab,kw) OR 'lng ius':ti,ab,kw OR 'lng iud':ti,ab,kw OR fibroplant:ti,ab,kw OR jaydess:ti,ab,kw OR kyleena:ti,ab,kw	4319
28	'intrauterine contraceptive device'/exp OR (('homone releas*' NEAR/2 (intrauterine OR iud OR iuds)):ti,ab,kw) OR (('progesterone releas*' NEAR/2 (intrauterine OR iud OR iuds)):ti,ab,kw) OR 'medicated intra$uterine device*':ti,ab,kw	24181
29	'intrauterine device*':ti,ab,kw OR 'intrauterine coil*':ti,ab,kw OR 'margulie* coil*':ti,ab,kw OR 'marguiles spiral':ti,ab,kw OR 'dalkon shield*':ti,ab,kw OR 'dana device*':ti,ab,kw OR ((intraperitoneal NEAR/2 (iud OR iuds)):ti,ab,kw) OR 'intracervical device*':ti,ab,kw	9561

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30	'buserelin'/exp OR 'goserelin'/exp OR 'leuprolide'/exp OR 'triptorelin'/exp OR 'nafarelin'/exp OR 'leuprorelin'/exp OR 'busrelin acetate' OR 'nafarelin acetate'/exp OR 'gonadorelin acetate'/exp	27988
31	buserelin:ti,ab,kw OR goserelin:ti,ab,kw OR leuprolide:ti,ab,kw OR triptorelin:ti,ab,kw OR nafarelin:ti,ab,kw OR leuprorelin:ti,ab,kw OR naferelin:ti,ab,kw OR suprecur:ti,ab,kw OR suprefact:ti,ab,kw OR zoladex:ti,ab,kw OR lupron:ti,ab,kw OR prostap:ti,ab,kw OR enantone:ti,ab,kw OR lucrin:ti,ab,kw OR trenantone*:ti,ab,kw OR synarel:ti,ab,kw OR synarella:ti,ab,kw OR decapeptyl:ti,ab,kw OR gonapeptyl:ti,ab,kw OR luliberin:ti,ab,kw OR cystorelin:ti,ab,kw OR dirigestran:ti,ab,kw OR factrel:ti,ab,kw	9950
32	'gonadorelin'/exp OR gonadorelin:ti,ab,kw OR gonadoliberin:ti,ab,kw OR 'gonadotropin-releasing hormone*':ti,ab,kw OR gnrh*:ti,ab,kw OR 'gn rh*':ti,ab,kw OR 'luteini$ing hormone release':ti,ab,kw OR pulstim:ti,ab,kw OR relisorm:ti,ab,kw OR lutal:ti,ab,kw OR ludoran:ti,ab,kw OR kryptocur:ti,ab,kw OR cryptocur:ti,ab,kw OR factrell:ti,ab,kw OR fetagyl:ti,ab,kw OR feiral:ti,ab,kw	63951
33	analog*:ti,ab,kw OR agonist*:ti,ab,kw OR antagonist*:ti,ab,kw	1275624
34	#32 AND #33	26234
35	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #34	2003615
36	#8 OR #35	2007598
37	'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/exp OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de	1893940
38	'randomi$ed controlled trial?':ti,ab OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR ((allocated NEAR/2 random):ti,ab) OR 'single blind?':ti,ab OR 'double blind?':ti,ab OR (((treble OR triple) NEXT/1 blind?):ti,ab) OR placebo?:ti,ab OR 'prospective study'/de	1162834
39	(systematic:ti,ab,kw OR 'meta analys*':ti,ab,kw OR metaanalys*:ti,ab,kw) AND (review AND it OR 'review'/exp)	459408
40	#37 OR #38 OR #39	3113041
41	'case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de	2762462
42	'animal'/exp NOT ('human'/de AND 'animal'/exp)	6269919
43	#3 AND #36 AND #40	8009
44	#43 NOT (#41 OR #42)	7723

Table 2 Search strategy Cochrane (via Wiley)

ID	Search	Hits
#1	MeSH descriptor: [Endometriosis] explode all trees	1224
#2	MeSH descriptor: [Dyspareunia] explode all trees	310
#3	MeSH descriptor: [Dysmenorrhea] explode all trees	907
#4	(endometrio* or dyspareunia or dysmenorrhea* or (pain* near (cycl* or menstru* or catamenia or pelvic or pelvis)) or (pain near (coital or postcoital or intercourse or sex or coitus)) or adenomyosis externa or coitalgia)	13262
#5	[OR #1-#4]	13262
#6	Elagolix or relugolix or linzagolix or deslorelin	365
#7	tak385 or "tak 385" or t1331285 or "t 1331285" or "rvt 601" or rvt601 or relumine or orgovyx or mvt601 or "mvt601"	29
#8	("abt 620" or abt620 or orilissa or nbi 56418 or nbi56418)	11
#9	[OR #6-#8]	382
#10	MeSH descriptor: [Laparoscopy] explode all trees	9140
#11	peritoneoscop* or celioscop* or laparoscop* or pelvic edocscop*	28760

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#12	MeSH descriptor: [Diathermy] explode all trees	1533
#13	(diatherm* or elecro-diathermy or inductothermy or endo-diathermy or electrodiatherm* or endodiatherm*)	1163
#14	LUNA	726
#15	presacral neurectom*	26
#16	MeSH descriptor: [Lasers] explode all trees	3774
#17	Laser*	26218
#18	Plasmajet* or plasma jet*	176
#19	MeSH descriptor: [Minimally Invasive Surgical Procedures] explode all trees	3774
#20	Microlaparoscopic* or minilaparoscopic*	84
#21	MeSH descriptor: [Surgery, Computer-Assisted] explode all trees	2104
#22	MeSH descriptor: [Robotics] explode all trees	1962
#23	(computer aid* or computer assist*) near surg*	9169
#24	Da vinci	530
#25	(Robot* or Remote surg* or Microsur* or micro surg* or mini-invasive surg* or minimally invasive surg* or minimal access surg*)	22627
#26	(Uterine nerve near ablati*)	24
#27	Ablation or resect* or ablative	47393
#28	MeSH descriptor: [Hysterectomy] explode all trees	2482
#29	MeSH descriptor: [Cystectomy] explode all trees	554
#30	MeSH descriptor: [Ablation Techniques] explode all trees	8317
#31	(uterus near (amputa* or extirpate*)) or (hysterectom* or cystectom* or pericystectom*) or (bladder near (remov* or resect* or excis* or extirpat*))	12797
#32	MeSH descriptor: [Salpingectomy] explode all trees	106
#33	MeSH descriptor: [Ovariectomy] explode all trees	418
#34	(Salpingectom* or tubalplasty or tubectom* or Oophorectom* or oophorotom* or ovarectom* or ovariotom* or ovariectom*) or (ovar* near (amputat* or resect*)) or (tubal near excision*)	2869
#35	(adnexectom* or annexectom* or (salpingo* oophorectomy*) or salpingoophorectom*)	513
#36	MeSH descriptor: [Contraceptives, Oral] explode all trees	2336
#37	MeSH descriptor: [Contraceptives, Oral, Combined] explode all trees	1083
#38	MeSH descriptor: [Contraceptives, Oral, Hormonal] explode all trees	386
#39	MeSH descriptor: [Contraceptive Agents, Female] explode all trees	3229
#40	(anticonceptive* or anti conceptive* or birth control pill* or contracepti* or oral ovulation inhibit*)	19316
#41	MeSH descriptor: [Norethindrone Acetate] explode all trees	389
#42	MeSH descriptor: [Norethindrone] explode all trees	933
#43	(Norethindrone acetate or aminor or aygestin or errin or millgynon or norlutane or norlutate or norlutin or primolut nor or primolutnor or primosistan)	811
#44	Dienogest	382
#45	Danazol or bonzol or chronogyn or cyclomen or danatrol or danocrine or danokrin or danol or ladogal or ladogar or mastodanatrol or winobanin	578
#46	MeSH descriptor: [Levonorgestrel] explode all trees	1238
#47	(levonorgestrel* near intra?uterine system*) or (levonorgestrel* near intra?uterine device*) or (levonorgestrel* near (system* or device*)) or (levonorgestrel* near (iud or iuds)) or (LNG-IUS or lng-iud or fibroplant or jaydess or Kyleena)	1012
#48	MeSH descriptor: [Intrauterine Devices, Medicated] explode all trees	662
#49	(homone releas* near (intrauterine or iud or iuds)) or (progesterone releas* near (intrauterine or iud or iuds)) or medicated intra?uterine device*	626
#50	(intrauterine device* or intrauterine coil* or margulie* coil* or marguiles spiral or dalkon shield* or dana device* or (intraperitoneal near (iud or iuds)) or intracervical device*)	3526
#51	MeSH descriptor: [Buserelin] explode all trees	339
#52	MeSH descriptor: [Goserelin] explode all trees	671
#53	MeSH descriptor: [Leuprolide] explode all trees	819
#54	MeSH descriptor: [Triptorelin Pamoate] explode all trees	537
#55	MeSH descriptor: [Nafarelin] explode all trees	91
#56	buserelin or goserelin or leuprolide or triptorelin or nafarelin or leuprorelin or naferelin or suprecur or suprefact or Zoladex or lupron or prostap or enantone or lucrin or trenantone* or synarel or synarella or decapeptyl or gonapeptyl or luliberin or cystorelin or dirigestran or factrel or gonadoliberin	4038
#57	[OR #10-#56]	179589
#58	MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees	3320

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#59	(gonadorelin or gonadoliberin or Gonadotropin-Releasing Hormone* or GnRH* or Gn-RH*) or luteini?ing hormone release or (pulstim or relisorm or lutal or ludoran or kryptocur or cryptocur or factrell or fetagyl or feiral)	9300
#60	#58 or #59	10083
#61	analog* or agonist* or antagonist*	212192
#62	#60 and #61	6470
#63	#9 or #57 or #62	183048
#64	#5 and #63	4507
#65	#5 and #63 in Trials	4088

Table 3 Search strategy MEDLINE (via PubMed)

#	Query	Hits
1	endometriosis/ or dyspareunia/ or dysmenorrhea/	32,390
2	(endometrio* or dyspareunia or dysmenorrhea* or (pain* adj3 (cycl* or menstru* or catamenia or pelvic or pelvis)) or (pain adj3 (coital or postcoital or intercourse or sex or coitus)) or adenomyosis externa or coitalgia).af.	74,817
3	1 or 2	74,817
4	(Elagolix or relugolix or linzagolix or deslorelin).af.	675
5	(tak385 or "tak 385" or t1331285 or "t 1331285" or "rvt 601" or rvt601 or relumine or orgovyx or mvt601 or "mvt601").af.	17
6	("abt 620" or abt620 or orilissa or nbi 56418 or nbi56418).af.	10
7	4 or 5 or 6	676
8	exp Laparoscopy/ or (peritoneoscop* or celioscop* or laparoscop* or pelvic edocscop*).ti,ab,kw,kf.	179,562
9	exp Diathermy/ or (diatherm* or elecro-diathermy or inductothermy or endo-diathermy or electrodiatherm* or endodiatherm*).ti,ab,kw,kf.	20,481
10	LUNA.ti,ab,kw,kf.	1,149
11	presacral neurectomy*.ti,ab,kw,kf.	110
12	exp lasers/ or Laser*.ti,ab,kw,kf.	343,386
13	(Plasmajet* or plasma jet*).ti,ab,kw,kf.	886
14	exp Minimally invasive surgical procedures/ or (Microlaparoscopic* or minilaparoscopic*).ti,ab,kw,kf.	618,584
15	exp Surgery, computer-assisted/ or exp robotics/ or ((computer aid* or computer assist*) adj2 surg*).ti,ab,kw,kf.	65,355
16	Da vinci.ti,ab,kw,kf.	4,396
17	(Robot* or Remote surg* or Microsur* or micro surg* or mini-invasive surg* or minimally invasive surg* or minimal access surg*).ti,ab,kw,kf.	130,524
18	(Uterine nerve adj3 ablati*).ti,ab,kw,kf.	30
19	(Ablation or resect* or ablative).ti,ab,kw,kf.	564,463
20	exp Hysterectomy/ or exp cystectomy/ or exp ablation techniques/ or (uterus adj2 (amputa* or extirpate*)).ti,ab,kw,kf. or (hysterectom* or cystectom* or pericystectom*).ti,ab,kw,kf. or (bladder adj2 (remov* or resect* or excis* or extirpat*)).ti,ab,kw,kf.	212,588
21	exp salpingectomy/ or exp ovariectomy/ or (Salpingectom* or tubalplasty or tubectom* or Oophorectom* or oophorotom* or ovarectom* or ovariotom* or ovariectom*).ti,ab,kw,kf. or (ovar* adj2 (amputat* or resect*)).ti,ab,kw,kf. or (tubal adj2 excision*).ti,ab,kw,kf.	53,784
22	(adnexectom* or annexectom* or (salpingo* adj oophorectomy*) or salpingoophorectom*).ti,ab,kw,kf.	7,351
23	exp contraceptives, oral/ or exp Contraceptives, Oral, Combined/ or exp Contraceptives, Oral, Hormonal/ or exp Contraceptive Agents, Female/ or (anti?conceptive* or "birth control pill*" or contracepti* or "oral ovulation inhibit*").ti,ab,kw,kf.	123,697
24	exp norethindrone acetate/ or exp norethindrone/ or (Norethindrone acetate or aminor or aygestin or errin or millgynon or norlutane or norlutate or norlutin or primolut nor or primolutnor or primosistan).ti,ab,kw,kf.	4,555
25	Dienogest.ti,ab,kw,kf.	650
26	exp danzol/ or (Danazol or bonzol or chronogyn or cyclomen or danatrol or danocrine or danokrin or danol or ladogal or ladogar or mastodanatrol or winobanin).ti,ab,kw,kf.	2,635

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27	exp levonorgestrel/ or (levonorgestrel* adj2 intra?uterine system*).ti,ab,kw,kf. or (levonorgestrel* adj2 intra?uterine device*).ti,ab,kw,kf. or (levonorgestrel* adj2 (system* or device*)).ti,ab,kw,kf. or (levonorgestrel* adj (iud or iuds)).ti,ab,kw,kf. or (LNG-IUS or lng-iud or fibroplant or jaydess or Kyleena).ti,ab,kw,kf.	5,575
28	exp intrauterine devices, medicated/ or (homone releas* adj2 (intrauterine or iud or iuds)).ti,ab,kw,kf. or (progesterone releas* adj2 (intrauterine or iud or iuds)).ti,ab,kw,kf. or medicated intra?uterine device*.ti,ab,kw,kf.	3,830
29	(intrauterine device* or intrauterine coil* or margulie* coil* or marguiles spiral or dalkon shield* or dana device* or (intraperitoneal adj2 (iud or iuds)) or intracervical device*).ti,ab,kw,kf.	7,091
30	exp buserelin/ or exp goserelin/ or exp leuprolide/ or exp triptorelin pamoate/ or exp nafarelin/	8,251
31	(buserelin or goserelin or leuprolide or triptorelin or nafarelin or leuprorelin or naferelin or suprecur or suprefact or Zoladex or lupron or prostap or enantone or lucrin or trenantone* or synarel or synarella or decapeptyl or gonapeptyl or luliberin or cystorelin or dirigestran or factrel or gonadoliberin).ti,ab,kw,kf.	6,756
32	exp Gonadotropin-Releasing Hormone/ or (gonadorelin or gonadoliberin or Gonadotropin-Releasing Hormone* or GnRH* or Gn-RH*).ti,ab,kw,kf. or luteini?ing hormone release.ti,ab,kw,kf. or (pulstim or relisorm or lutal or ludoran or kryptocur or cryptocur or factrell or fetagyl or feiral).ti,ab,kw,kf.	47,947
33	(analog* or agonist* or antagonist*).ti,ab,kw,kf.	1,004,840
34	32 and 33	19,690
35	or/8-31,34	1,856,634
36	7 or 35	1,856,752
37	(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.tw. or clinical trials as topic.sh. or randomly.ab. or trial.ti. or (crossover or cross-over or cross over).tw.	1,680,964
38	((systematic or meta-analys* or metaanalys*).ti,ab,kw,kf. and Review.pt.) or (meta-analysis or systematic review).pt.	446,232
39	37 or 38	1,997,988
40	(Case reports or comment or editorial or published erratum or letter).pt.	4,561,902
41	animals/ not (humans/ and animals/)	5,181,854
42	3 and 36 and 39	2,725
43	42 not (40 or 41)	2,584

Additionally, the US National Institutes of Health Clinical Trial Registry (http://www.clinicaltrials.gov) was searched to identify completed clinical trials not yet published or active clinical trials not yet completed, that meet the criteria.

1.1.2. Study selection and data collection

The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (3). The evidence for the review was based on pre-defined eligibility criteria and followed the population, intervention, comparators, outcomes, study design, timeframe, and study language framework (PICO). The key criteria for inclusion and exclusion of studies for this clinical SLR is presented in Table 4.

Table 4. PICO criteria for study selection

Criterion	Inclusion criteria	Exclusion criteria

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Disease	Premenopausal women with a clinically confirmed diagnosis of endometriosis who are experiencing EM-associated pain (no restrictions on definitions of pain severity).	Women without a clinically confirmed diagnosis of endometriosis
Intervention	**Relugolix with add back therapy**	No intervention of interest evaluated
Comparators	**Hormonal:** • Combined and progestin-only contraceptives • LNG-IUS • GnRH agonists with or without add-back therapies **Surgical treatments**: • Any laparoscopic or robotic intervention • Endometrial ablation/excision techniques **Placebo or best supportive care**	• GnRH antagonists (Elagolix, Linzagoliz, Oligolix etc) • Any other class of drugs for eg: anaesthetics, hemorheological agents etc
Outcomes	**Efficacy outcomes** • Dysmenorrhea (DYS) • Dyspareunia (DYSP) • Non-menstrual pelvic pain (NMPP), • Overall pelvic pain (OPP), • Endometriosis health profile (EHP), overall and by domain subscale • Health-related quality of life (HRQoL) using the generic measures (like SF-36, EQ-5D, NHP, WHOQOL-BREF, The DukeHealth Profile, 15D, QLI) or endometriosis specific measures (like EHP-30, EHP-5) or self developed specific scales like Colwell scale, Bodner scale, etc) **Safety outcomes** • Prevalence of adverse events (AEs), • Prevalence of serious adverse events (SAEs), • Prevalence of fatal AEs, • Bone mineral density (BMD) loss,	

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	• Prevalence of hot flashes, • Change in low-density lipoprotein cholesterol (LDL-C) from baseline **Tolerability outcomes** • Discontinuation (all-cause), • Discontinuation due to AEs	
Study design	Randomised controlled trials and open-label extensions (OLE) Systematic literature reviews and meta-analyses of RCTs (for hand-searching of references only)	Observational studies Retrospective studies Case series/case studies Editorials, commentary, letters, narrative reviews Pharmacokinetic or pharmacodynamics studies Animal or in vitro studies
Publication date	1974 to date	Prior to 1974
Language	Eligible language publications only	Studies published in language other than English

1.1.3. Screening and data extraction

Citations were uploaded onto the systematic review web app, Rayyan.ai, (4) for deduplication and were subsequently exported into Microsoft Excel for title and abstract screening. Two independent reviewers conducted the initial screening of titles and abstracts according to the predefined PICOS criteria. Records selected at first pass were then screened at second pass (full-text stage) by the same 2 reviewers. Any discrepancies between reviewers at screening was resolved by a third independent reviewer. The full texts of studies meeting inclusion criteria at this stage were included in the review and progressed to data extraction and critical appraisal.

1.1.4. Quality Assessment

The quality of the included studies was evaluated using the Cochrane Risk of Bias 2.0 tool.

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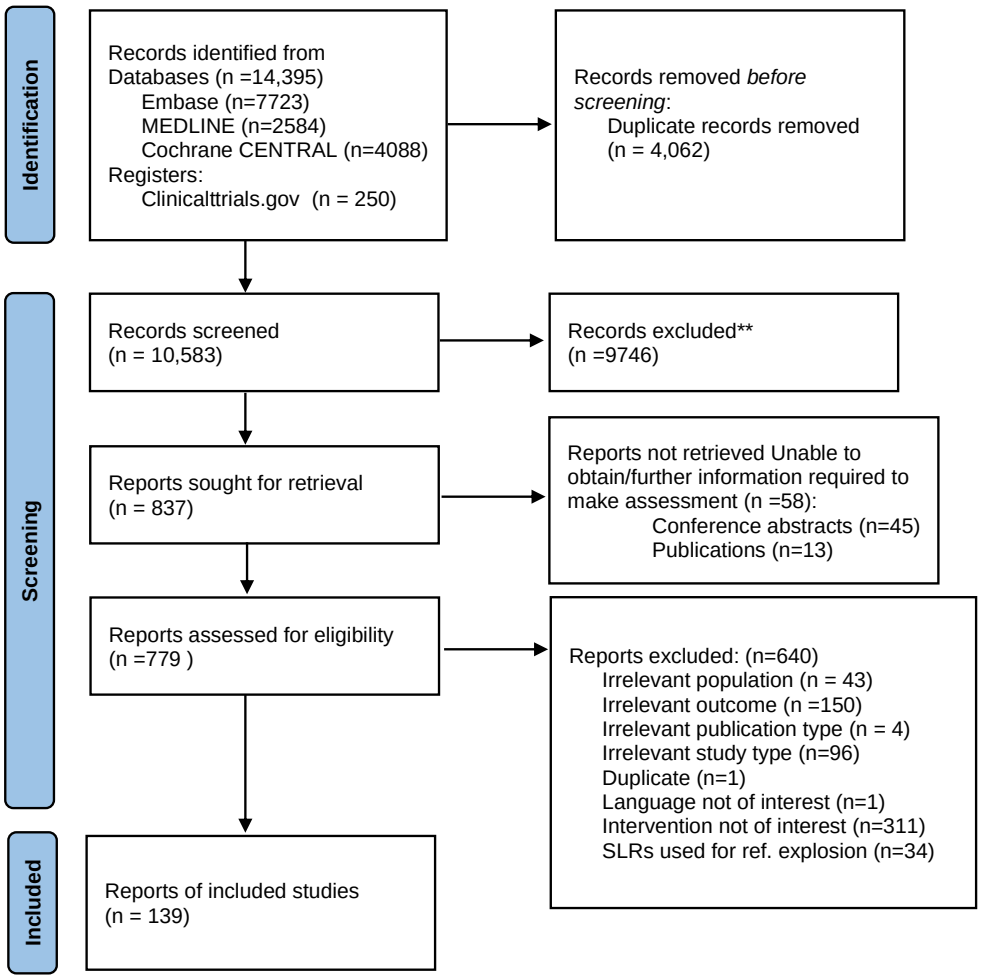
1.2. Results

1.2.1. Study selection results

The process of study identification is summarised in Figure 1. A total of 14,645 records were identified by bibliographic database searches and trial registries. Of those, 4,062 duplicates were identified and excluded. Following de-duplication, 10,583 unique records were screened at first pass, 9746 were excluded and 837 were eligible for full-text screening. Of the remaining reports, 45 conference abstracts and 13 full-length papers were not accessible because not enough information was available to retrieve them. Of the 779 reports retrieved for full-text screening, 640 were subsequently excluded and 137 reports were included, together with 2 trial records that did not have associated publications.

Figure 1 PRISMA flow diagram



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Papers excluded at this second stage of the screening process (along with the reasons for exclusion) are listed in Table 5.

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Table 5 List of excluded studies (n=640)

Author, Year/Sponsor, Year	Title	Reason for exclusion
Publications (n= 358)		
Yunker, 2018	Minimally invasive surgery and chronic pelvic pain	Irrelevant study type
Ouyang, 2022	Efficacy of excision versus ablation for improving endometriosis related pain: A systematic review and meta-analysis	Intervention not of interest
Kalafat, 2022	ORAL GONADOTROPIN-RELEASING HORMONE ANTAGONISTS IN THE TREATMENT OF ENDOMETRIOSIS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS OF EFFICACY PARAMETERS AND ADVERSE EFFECTS	Intervention not of interest
Kitawaki, 2011	Maintenance therapy with dienogest following gonadotropin-releasing hormone agonist treatment for endometriosis-associated pelvic pain	Irrelevant outcome
Won, 2010	Optimal management of chronic cyclical pelvic pain: An evidence-based and pragmatic approach	Irrelevant study type
Kitawaki, 2012	Long-term suppression of endometriosis-associated pelvic pain with sequential administration of a gonadotropinreleasing hormone agonist followed by danazol, oral contraceptives or dienogest	Irrelevant outcome
Hornstein, 1998	Leuprolide acetate depot and hormonal add-back in endometriosis: A 12- month study	Intervention not of interest

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Cope, 2020	Nonsurgical radiologic intervention for management of abdominal wall endometriosis: A systematic review and meta-analysis	Intervention not of interest
van Hoesel, 2021	Selective oestrogen receptor modulators (SERMs) for endometriosis	Intervention not of interest
Yeung, 2017	Endometriosis in adolescents: A systematic review	Irrelevant study type
Hornstein, 1997	Retreatment with nafarelin for recurrent endometriosis symptoms: Efficacy, safety, and bone mineral density	Irrelevant study type
Bedaiwy, 2006	Treatment with leuprolide acetate and hormonal add-back for up to 10 years in stage IV endometriosis patients with chronic pelvic pain	Irrelevant study type
Shangold, 2023	ORAL LEUPROLIDE (Ovarest¬Æ) ACHIEVES PROFOUND SUPPRESSION OF ESTRADIOL AND PAIN RELIEF COMPARABLE TO THAT OF APPROVED INJECTABLE LEUPROLIDE FORMULATIONS IN WOMEN WITH ENDOMETRIOSIS AND PELVIC PAIN	Irrelevant study type
Van Barneveld, 2022	Depression, Anxiety, and Correlating Factors in Endometriosis: A Systematic Review and Meta-Analysis	Intervention not of interest
Mira, 2020	Hormonal treatment isolated versus hormonal treatment associated with electrotherapy for pelvic pain control in deep endometriosis: Randomized clinical trial	Intervention not of interest
Mitchell, 2022	Progestins in the symptomatic management of endometriosis: a meta-analysis on their effectiveness and safety	Intervention not of interest

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J Obst Gynaecol, 2010	Medical Management of Pain Associated With Endometriosis	Irrelevant Publication type
Learman, 2005	Chronic pelvic pain - Part 2: An integrated management approach	Irrelevant study type
Artukoglu, 2017	Efficacy of palmitoylethanolamide for pain: A meta-analysis	Intervention not of interest
Leonardi, 2021	Surgical Interventions for the Management of Chronic Pelvic Pain Syndrome in Women	Intervention not of interest
Litta, 2014	Risk of recurrent menorrhagia after hydrothermoablation: Role of GnRH analogues neoadjuvant treatment in long term successful rate	Irrelevant population
van den Beukel, 2017	Surgical treatment of adhesion-related chronic abdominal and pelvic pain after gynaecological and general surgery: A systematic review and meta-analysis	Intervention not of interest
Jensen, 2018	Use of combined hormonal contraceptives for the treatment of endometriosis-related pain: a systematic review of the evidence	Intervention not of interest
Yarmolinskaya, 2016	Modern trends in combined treatment of genital endometriosis	Irrelevant study type
Kanti, 2024	Transvaginal ultrasound and magnetic resonance imaging in the diagnosis of endometrioma: a systematic review and meta-analysis of diagnostic test accuracy studies	Irrelevant outcome
Bravi, 2014	BMJ open tobacco smoking and risk of endometriosis: A systematic review and meta-analysis	Intervention not of interest

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Bergeron, 2020	Endometrial Ablation or Resection Versus Levonorgestrel Intra-uterine System for the Treatment of Women with Heavy Menstrual Bleeding and a Normal Uterine Cavity: A Systematic Review with Meta-analysis	Intervention not of interest
Chaichian, 2017	Comparing the efficacy of surgery and medical therapy for pain management in endometriosis: A systematic review and meta-analysis	Intervention not of interest
Kettel, 1994	Clinical efficacy of the antiprogesterone RU486 in the treatment of endometriosis and uterine fibroids	Intervention not of interest
Al-Hendy, 2021	ASSESSMENT OF COMMON ADVERSE EVENTS OF RELUGOLIX COMBINATION THERAPY IN PREMENOPAUSAL WOMEN TREATED FOR SYMPTOMATIC ESTROGEN-DRIVEN CONDITIONS: LIBERTY AND SPIRIT STUDIES	Irrelevant outcome
Haberland, 2018	Psychometric validation of the Endometriosis Symptom Diary (ESD) and Endometriosis Impact Scale (EIS): Findings from an interventional study	Irrelevant outcome
Becker, 2021	The Effect of Time Since Surgical Diagnosis of Endometriosis on Treatment Outcomes with Relugolix Combination Therapy: Spirit Program	Irrelevant outcome
Becker, 2024	Two-year efficacy and safety of relugolix combination therapy in women with endometriosis-associated pain: SPIRIT open-label extension study	Irrelevant study type
Biswas, 2024	Evaluation of Efficacy and Safety of 2 mg vs 4 mg Dienogest in Endometriosis: A Randomised Single-blind Dose-ranging Trial	Intervention not of interest

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Manetta, 2008	Uterine Ultrasonographic Changes During Endometriosis Treatment: A Comparison Between Levonorgestrel-Releasing Intrauterine Devices and a Gonadotropin-Releasing Hormone Agonist	Irrelevant outcome
Loverro, 2008	A randomized study comparing triptorelin or expectant management following conservative laparoscopic surgery for symptomatic stage III-IV endometriosis	Irrelevant outcome
Winzenborg, 2020	Effect of Elagolix Exposure on Clinical Efficacy End Points in Phase III Trials in Women With Endometriosis-Associated Pain: An Application of Markov Model	Intervention not of interest
Pados, 2010	Laparoscopic management of endometriotic cysts: Cystectomy or ‚Äúthree-stage' technique‚Äù?	Intervention not of interest
Gibbons, 2021	Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery: a Cochrane systematic review	Intervention not of interest
As-Sanie, 2022	TIME TO MINIMAL OR NO PELVIC PAIN WITH RELUGOLIX COMBINATION THERAPY IN WOMEN WITH ENDOMETRIOSIS-ASSOCIATED PAIN: RESULTS FROM THE SPIRIT PROGRAM	Irrelevant study type
Strowitzki, 2010	Dienogest 2 mg/day for the treatment of endometriosisassociated pain: A double-blind placebo-controlled study investigating efficacy	Intervention not of interest
Johnson, 2022	EVALUATION OF THE EFFECT OF RELUGOLIX COMBINATION THERAPY ON BONE MINERAL DENSITY (BMD) OVER TWO YEARS IN WOMEN WITH ENDOMETRIOSIS-ASSOCIATED PAIN: SPIRIT LONG-TERM EXTENSION (LTE) STUDY	Irrelevant study type

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Conz, 2020	Levonorgestrel-releasing intrauterine system and breast cancer risk: A systematic review and meta-analysis	Irrelevant study type
As-Sanie, 2021	Sustained efficacy and safety of relugolix combination therapy in women with endometriosis-associated pain: SPIRIT 52-week data	Irrelevant study type
Shi, 2022	Effect and safety of drospirenone and ethinylestradiol tablets (II) for dysmenorrhea: A systematic review and meta-analysis	Intervention not of interest
McClung, 2022	EVALUATION OF RELUGOLIX COMBINATION THERAPY (REL-CT) AND BONE MINERAL DENSITY (BMD) IN WOMEN WITH ENDOMETRIOSIS-ASSOCIATED PAIN THROUGH 52 WEEKS: SPIRIT LONG-TERM EXTENSION (LTE) STUDY	Irrelevant study type
Moray, 2021	A systematic review on clinical effectiveness, side-effect profile and meta-analysis on continuation rate of etonogestrel contraceptive implant	Intervention not of interest
Becker, 2022	SPIRIT long-term extension study: two-year efficacy and safety of relugolix combination therapy in women with endometriosis-associated pain	Irrelevant Publication type
Peitsidis, 2023	A Systematic Review of Systematic Reviews on the Use of Aromatase Inhibitors for the Treatment of Endometriosis: The Evidence to Date	Intervention not of interest
Penotti, 1996	Gonadotropin-releasing hormone agonist-induced hypoestrogenism and blood flows in cerebral arteries	Irrelevant outcome
Moufawad, 2023	Obstructed hemivagina and ipsilateral renal anomaly syndrome: A systematic review about diagnosis and surgical management	Intervention not of interest

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Richard, 2022	Effect of Postoperative Hormonal Suppression on Fertility in Patients With Endometriosis After Conservative Surgery: A Systematic Review and Meta-analysis	Irrelevant outcome
Parodi, 2023	Complete Uterine Septum, Double Cervix and Vaginal Septum (U2b C2 V1): Hysteroscopic Management and Fertility Outcomes,ÄîA Systematic Review	Irrelevant study type
Nnoaham, 2012	Is early age at menarche a risk factor for endometriosis? A systematic review and meta-analysis of case-control studies	Irrelevant study type
Younis, 2019	Impact of unilateral versus bilateral ovarian endometriotic cystectomy on ovarian reserve: A systematic review and meta-analysis	Intervention not of interest
Beelen, 2019	Prognostic Factors for the Failure of Endometrial Ablation: A Systematic Review and Meta-analysis	Intervention not of interest
Agarwal, 1997	Nafarelin vs. Leuprolide acetate depot for endometriosis: Changes in bone mineral density and vasomotor symptoms	Irrelevant outcome
Muzii, 2014	The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: A systematic review and meta-analysis	Intervention not of interest
Moustafa, 2014	Systematic review of the outcome associated with the different surgical treatment of bowel and rectovaginal endometriosis	Intervention not of interest
Pantou, 2023	The role of non-coding RNAs in endometriosis diagnosis: A systematic review and meta-analysis	Irrelevant outcome
Bendifallah, 2021	Surgical Outcomes after Colorectal Surgery for Endometriosis: A Systematic Review and Meta-analysis	Irrelevant outcome

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Zhang, 2022	Impact of cystectomy versus ablation for endometrioma on ovarian reserve: a systematic review and meta-analysis	Intervention not of interest
Amini, 2016	The effect of Foeniculum vulgare on dysmenorrhea; A systematic review	Irrelevant outcome
Pergialiotis, 2017	A systematic review on vaginal laser therapy for treating stress urinary incontinence: Do we have enough evidence?	Intervention not of interest
Festin, 2016	A prospective, open-label, single arm, multicentre study to evaluate efficacy, safety and acceptability of pericoital oral contraception using levonorgestrel 1.5 mg	Intervention not of interest
Hafermann, 2024	Efficacy and safety of V-Loc,Ñ¢ barbed sutures versus conventional suture techniques in gynecological surgery: a systematic review and meta-analysis	Intervention not of interest
Gerges, 2021	Optimal imaging modality for detection of rectosigmoid deep endometriosis: systematic review and meta-analysis	Irrelevant outcome
de Sá Rosa, 2006	The levonorgestrel-releasing intrauterine device reduces CA-125 serum levels in patients with endometriosis	Irrelevant outcome
Zakhari, 2020	Dienogest and the Risk of Endometriosis Recurrence Following Surgery: A Systematic Review and Meta-analysis	Irrelevant study type
Somigliana, 2019	Ovarian stimulation and endometriosis progression or recurrence: a systematic review	Irrelevant study type
Noventa, 2015	Ultrasound techniques in the diagnosis of deep pelvic endometriosis: Algorithm based on a systematic review and meta-analysis	Intervention not of interest

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Vlek, 2016	Laparoscopic Imaging Techniques in Endometriosis Therapy: A¬†Systematic Review	Intervention not of interest
Marchand, 2021	Systematic review, meta-analysis and statistical analysis of laparoscopic supracervical hysterectomy vs. endometrial ablation	Intervention not of interest
Ibrahim, 2021	Surgical modalities for the treatment of recto-vaginal deep infiltrating endometriosis: systematic review and meta-analysis	Intervention not of interest
Alborzi, 2019	The success of various endometrioma treatments in infertility: A systematic review and meta-analysis of prospective studies	Intervention not of interest
Ugur, 1996	Combined use of a long-acting gonadotropin-releasing hormone agonist and low-dose danazol in advanced stage endometriosis	Irrelevant study type
Edelman, 2006	Continuous versus cyclic use of combined oral contraceptives for contraception: Systematic Cochrane review of randomized controlled trials	Irrelevant population
Prodromidou, 2021	Endometriosis of the canal of nuck: A systematic review of the literature	Irrelevant study type
Wen, 2009	Comparative safety and effectiveness of TCu380A versus MLCu375: A systematic review of randomized trials	Intervention not of interest
de Oliveira, 2017	Hysteropreservation versus hysterectomy in the surgical treatment of uterine prolapse: systematic review and meta-analysis	Irrelevant population
Zhou, 2021	Accuracy of transvaginal ultrasound for diagnosis of deep infiltrating endometriosis in the uterosacral ligaments: Systematic review and meta-analysis	Intervention not of interest

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Rahn, 2011	Systematic review highlights difficulty interpreting diverse clinical outcomes in abnormal uterine bleeding trials	Irrelevant population
Ayhan, 2021	Malignant struma ovarii: From case to analysis	Irrelevant population
Ohlsson Teague, 2010	The role of microRNAs in endometriosis and associated reproductive conditions	Irrelevant outcome
Gao, 2023	Systematic Review and Meta-Analysis: Impact of Various Hemostasis Methods on Ovarian Reserve Function in Laparoscopic Cystectomy for Ovarian Endometriomas	Intervention not of interest
Vercellini, 2013	Long-term adjuvant therapy for the prevention of postoperative endometrioma recurrence: A systematic review and meta-analysis	Irrelevant study type
Carr, 2003	Effect of gonadotropin-releasing hormone agonist and medroxyprogesterone acetate on calcium metabolism: A prospective, randomized, double-blind, placebo-controlled, crossover trial	Irrelevant outcome
Angioni, 2016	Endometrial ablation: First-vs. second-generation techniques	Irrelevant population
Surrey, 1995	Prolonged gonadotropin-releasing hormone agonist treatment of symptomatic endometriosis: The role of cyclic sodium etidronate and low-dose norethindrone 'add-back' therapy	Intervention not of interest
Wieser, 2007	Evolution of medical treatment for endometriosis: Back to the roots?	Intervention not of interest
Acien, 2002	Use of intraperitoneal interferon Œ±-2b therapy after conservative surgery for endometriosis and postoperative medical treatment with depot gonadotropin-releasing hormone analog: A randomized clinical trial	Irrelevant outcome

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Sorensen, 1997	Pre- and postoperative therapy with GnRH agonist for endometrial resection. A prospective, randomized study	Irrelevant population
Georgiou, 2019	Long-term gonadotrophin-releasing hormone agonist (GnRHa) therapy before in vitro fertilisation (IVF) for improving fertility outcomes in women with endometriosis: a Cochrane systematic review and meta-analysis	Irrelevant outcome
Stabile, 2021	Postcoital vaginal perforation and evisceration in women with no prior pelvic surgery: Laparoscopic management and systematic review of the literature	Intervention not of interest
Vlesko, 2024	Comparison of Combined Parenteral and Oral Hormonal Contraceptives: A Systematic Review and Meta-Analysis of Randomized Trials	Intervention not of interest
Csirzo, 2024	Robot-assisted laparoscopy does not have demonstrable advantages over conventional laparoscopy in endometriosis surgery: a systematic review and meta-analysis	Intervention not of interest
Amama, 1998	The effect of gonadotropin-releasing hormone agonist on type I collagen C-telopeptide and N-telopeptide: The predictive value of biochemical markers of bone turnover	Irrelevant study type
Nirgianakis, 2022	Effectiveness of Dietary Interventions in the Treatment of Endometriosis: a Systematic Review	Intervention not of interest
Duffy, 2014	Laparoscopic surgery for endometriosis	Intervention not of interest

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Raffone, 2022	The Use of near Infra-Red Radiation Imaging after Injection of Indocyanine Green (NIR-ICG) during Laparoscopic Treatment of Benign Gynecologic Conditions: Towards Minimalized Surgery. A Systematic Review of Literature	Irrelevant outcome
Franck, 2018	Questionnaire-based evaluation of sexual life after laparoscopic surgery for endometriosis: a systematic review of prospective studies	Intervention not of interest
Giampaolino, 2019	Role of Ovarian Suspension in Preventing Postsurgical Ovarian Adhesions in Patients with Stage III-IV Pelvic Endometriosis: A Systematic Review	Intervention not of interest
Henzl, 1989	Role of nafarelin in the management of endometriosis	Irrelevant outcome
Celik, 2017	Surgery for Benign Gynecological Disorders Improve Endometrium Receptivity: A Systematic Review of the Literature	Intervention not of interest
Hansen, 2021	Impact of exercise on pain perception in women with endometriosis: A systematic review	Intervention not of interest
Henzl, 1990	Efficacy and safety of nafarelin in the treatment of endometriosis	Irrelevant study type
Damm, 2019	Continuous vs. cyclic combined hormonal contraceptives for treatment of dysmenorrhea: a systematic review	Intervention not of interest
Yang, 2014	Effects of laparoscopic ovarian endometriosis cystectomy combined with postoperative GnRH-a therapy on ovarian reserve, pregnancy, and outcome recurrence	Irrelevant outcome
Wilson, 2007	Leuprolide acetate: A drug of diverse clinical applications	Irrelevant Publication type

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Ozaksit, 1995	Serum CA 125 levels before, during and after treatment for endometriosis	Irrelevant study type
Zhu, 2020	Effects of postoperative medical treatment and expectant treatment on dysmenorrhea after conservative laparoscopic surgery for deep-infiltrating endometriosis accompanied by dysmenorrhea	Irrelevant study type
Hosseinimousa, 2022	Can Laparoscopic Cystectomy Improve Pregnancy Outcomes in Endometrioma? A Prospective Clinical Trial Study	Irrelevant outcome
Sharma, 2021	To compare the effect of GnRH agonist versus human chorionic gonadotropin (HCG) trigger on clinical pregnancy rate in intrauterine insemination cycle	Irrelevant study type
De Cicco, 2021	Bowel resection for deep endometriosis: A systematic review	Irrelevant outcome
Cardoso, 2020	Systematic review of genome-wide association studies on susceptibility to endometriosis	Irrelevant outcome
Matsuzaki, 2020	Quantitative analysis of estrogen receptor alpha and beta messenger ribonucleic acid levels in normal endometrium and ovarian endometriotic cysts using a real-time reverse transcription-polymerase chain reaction assay	Irrelevant outcome
Maple, 2023	Ultrasound Characteristics and Scanning Techniques of Uterosacral Ligaments for the Diagnosis of Endometriosis: A Systematic Review	Intervention not of interest
Batioglu, 1997	Comparison of GnRH agonist administration before and after laparoscopic drainage of endometriomas	Irrelevant outcome
Olsarova, 2020	Early life factors for endometriosis: A systematic review	Intervention not of interest

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Tsai, 2004	Short-term postoperative GnRH analogue or danazol treatment after conservative surgery for stage III or IV endometriosis before ovarian stimulation: A prospective, randomized study	Irrelevant outcome
Seckin, 2019	Preoperative serum anti-mullerian hormone levels in women with ovarian endometriosis compared to women with peritoneal endometriosis	Irrelevant study type
Karaer, 2004	Aromatase inhibitors: Possible future applications	Intervention not of interest
Ansaripour, 2022	Comparison of Triggering Final Oocyte Maturation with Follicle Stimulating Hormone Plus Human Chorionic Gonadotropin, versus Human Chorionic Gonadotropin Alonein Normoresponder Women Undergoing Intracytoplasmic Sperm Injection: A Randomized Clinical Trial	Intervention not of interest
Zhu, 2019	2604 A Comparison of Efficacy Between Postoperative Medical Treatment and Expectant Treatment in Relieving Dysmenorrhea After Conservative Laparoscopic Surgery for Deep-Infiltrating Endometriosis Accompanied by Dysmenorrhea	Irrelevant outcome
Cantineau, 2021	Agents for ovarian stimulation for intrauterine insemination (IUI) in ovulatory women with infertility	Intervention not of interest
Matsushita, 2014	Unexpected ovarian malignancy following laparoscopic excision of adnexal masses	Irrelevant study type
Esber, 2024	Clinical Outcomes after the Use of Antiadhesive Agents in Laparoscopic Reproductive Surgery	Intervention not of interest
Burla, 2022	Intraoperative Appearance of Endosalpingiosis: A Single-Center Experience of Laparoscopic Findings and Systematic Review of Literature	Irrelevant population

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Dedden, 2023	Hysterectomy and sexual function: a systematic review and meta-analysis	Intervention not of interest
Wolthuis, 2014	Laparoscopic natural orifice specimen extraction-colectomy: A systematic review	Intervention not of interest
Latthe, 2007	Surgical interruption of pelvic nerve pathways in dysmenorrhea: A systematic review of effectiveness	Intervention not of interest
Wright, 1995	Short-term lupron or danazol therapy for pelvic endometriosis	Irrelevant outcome
Carvalho, 2012	Minimal and mild endometriosis negatively impact on pregnancy outcome	Intervention not of interest
Hughes, 1993	A quantitative overview of controlled trials in endometriosis-associated infertility	Irrelevant outcome
Cieri-Hutcherson, 2021	Systematic review of l-arginine for the treatment of hypoactive sexual desire disorder and related conditions in women	Irrelevant outcome
Takenaka, 2017	An exploratory, parallel-group, comparative study of pre-surgicaltherapy with dienogest or leuprorelin in laparoscopic cystectomy of endometrial cysts; 5 years of follow-up	Irrelevant outcome
Erian, 1998	The effects of danazol after endometrial resection. Results of a randomized, placebo-controlled, double-blind study	Intervention not of interest
Choktanasiri, 1996	Long-acting triptorelin for the treatment of endometriosis	Irrelevant study type
Frankowska, 2024	The Efficacy and Safety of Transvaginal Ethanol Sclerotherapy in the Treatment of Endometrial Cysts,ÄîA Systematic Review	Irrelevant study type

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Moore, 1981	Management of pelvic endometriosis with low-dose danazol	Intervention not of interest
Ho, 2017	Sphenopalatine ganglion: block, radiofrequency ablation and neurostimulation -¬†a systematic review	Intervention not of interest
Metwally, 2022	Endometrial scratch to increase live birth rates in women undergoing first-time in vitro fertilisation: RCT and systematic review	Irrelevant outcome
Georgiou, 2019	Long-term GnRH agonist therapy before in vitro fertilisation (IVF) for improving fertility outcomes in women with endometriosis	Duplicate
Muneyyirci-Delale, 2016	Effect of norethindrone vs leuprolide treatment on breakthrough bleeding of women with symptomatic endometriosis	Irrelevant outcome
Oliveira, 2023	Robotic Surgery for Bladder Endometriosis: A Systematic Review and Approach	Intervention not of interest
Sattler, 2021	Plasma cell vulvitis: A systematic review	Irrelevant study type
Rocca, 2021	Safety and benefits of contraceptives implants: A systematic review	Intervention not of interest
Bartiromo, 2021	Endometriosis and phytoestrogens: Friends or foes? a systematic review	Intervention not of interest
Pastor, 2013	The influence of combined oral contraceptives on female sexual desire: A systematic review	Irrelevant population

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Vogell, 2018	Novel imaging technologies in laparoscopic gynecologic surgery: A systematic review	Irrelevant outcome
Barbara, 2017	When love hurts. A systematic review on the effects of surgical and pharmacological treatments for endometriosis on female sexual functioning	Irrelevant outcome
May, 2010	Peripheral biomarkers of endometriosis: A systematic review	Irrelevant outcome
Gkegkes, 2023	Pancreatic endometriosis: a systematic review	Irrelevant study type
Palla, 2017	Ureteral endometriosis: A systematic literature review	Irrelevant study type
Al-Taher, 2018	Intraoperative enhanced imaging for detection of endometriosis: A systematic review of the literature	Irrelevant outcome
Singh, 2020	Surgical Outcomes in Patients With Endometriosis: A Systematic Review	Irrelevant outcome
Bonocher, 2014	Endometriosis and physical exercises: A systematic review	Irrelevant outcome
Wood, 2020	Women‚Äôs sexual experiences as a side effect of contraception in low- and middle-income countries: evidence from a systematic scoping review	Irrelevant outcome
May, 2011	Endometrial alterations in endometriosis: A systematic review of putative biomarkers	Irrelevant outcome
Korom, 2004	Catamenial pneumothorax revisited: Clinical approach and systematic review of the literature	Irrelevant study type
Stefanopol, 2022	Clinical, Imaging, Histological and Surgical Aspects Regarding Giant Paraovarian Cysts: A Systematic Review	Intervention not of interest

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Ianieri, 2018	Recurrence in Deep Infiltrating Endometriosis: A Systematic Review of the Literature	Intervention not of interest
Gorgy, 2022	Evaluating the educational quality of surgical YouTube¬Æ videos: A systematic review	Intervention not of interest
Prodromidou, 2020	Diagnosis, surgical treatment and postoperative outcomes of hepatic endometriosis: A systematic review	Intervention not of interest
Hirsch, 2018	Diagnosis and management of endometriosis: a systematic review of international and national guidelines	Irrelevant outcome
Incognito, 2023	Interleukin-6 as A Useful Predictor of Endometriosis-Associated Infertility: A Systematic Review	Intervention not of interest
Somigliana, 2012	Surgical excision of endometriomas and ovarian reserve: A systematic review on serum antim√ºllerian hormone level modifications	Intervention not of interest
Walker, 2021	Development of a core outcome set for effectiveness studies of breech birth at term (Breech-COS): A systematic review on variations in outcome reporting	Irrelevant population
Dragoman, 2016	The safety of subcutaneously administered depot medroxyprogesterone acetate (104¬†mg/0.65¬†mL): A systematic review	Intervention not of interest
Giulioni, 2024	Pudendal Nerve Neurolysis in Patients Afflicted With Pudendal Nerve Entrapment: A Systematic Review of Surgical Techniques and Their Efficacy	Intervention not of interest
Munro, 2021	A systematic review of the menstrual experiences of university students and the impacts on their education: A global perspective	Irrelevant outcome

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Matteo, 2006	Pituitary desensitization for eight weeks after the administration of two distinct gonadotrophin-releasing hormone agonists	Irrelevant outcome
Rai, 2000	Is endometrial pre-treatment of value in improving the outcome of transcervical resection of the endometrium?	Irrelevant outcome
Fernandez, 2004	One year comparison between two add-back therapies in pateints treated with a GmRH agonist for symptomatic endometriosis: A randomized double-blind trial	Intervention not of interest
Jelley, 1986	The effect of LHRH agonist therapy in the treatment of endometriosis (English experience).	Irrelevant outcome
Almeida Jr., 2005	Microlaparoscopy and a GnRH agonist: a combined minimally invasive approach for the diagnosis and treatment of occlusive salpingitis isthmica nodosa associated with endometriosis.	Irrelevant outcome
Bhattacharya, 2017	Effect of gonadotrophin releasing hormone agonist (GNRHA)-induced pseudomenopauseon serum25-hydroxyvita mind3 level and health related quality of life (HRQOL) in endometriosis	Irrelevant study type
Uemura, 1999	Low-dose GnRH agonist therapy for the management of endometriosis	Irrelevant study type
Anastasilakis, 2023	Lipid Profile after Pharmacologic Discontinuation and Restoration of Menstruation in Women with Endometriosis: A 12-Month Observational Prospective Study	Irrelevant study type
Han, 2013	The incidence and characteristics of uterine bleeding during postoperative GnRH agonist treatment combined with estrogen-progestogen add-back therapy in endometriosis patients of reproductive age	Irrelevant outcome

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Dmowski, 1996	Excretion of urinary N-telopeptides reflects changes in bone turnover during ovarian suppression and indicates individually variable estradiol threshold for bone loss	Irrelevant study type
Bartley, 2013	Long term treatment with Letrozole after GnRH‚Äëa down-regulation in premenopausal patients with moderate and severe endometriosis: a safety and efficacy study	Irrelevant outcome
Anastasilakis, 2022	Bmd and bone turnover markers alterations in women with endometriosis during menstrual cessation due to GnRH therapy and after menstrual restoration	Irrelevant study type
Polatti, 1995	Long term evaluation of bone loss in patients treated with GnRH Analogues	Irrelevant study type
Batioglu, 1996	The use of GnRH agonists in the treatment of endometriomas with or without drainage	Irrelevant outcome
Hsu, 1997	Immunomodulation in women with endometriosis receiving GnRH agonist	Irrelevant outcome
Marshall, 1996	Urinary N-telopeptides to monitor bone resorption while on GnRH agonist therapy	Irrelevant study type
Zhao, 2012	Effects of progressive muscular relaxation training on anxiety, depression and quality of life of endometriosis patients under gonadotrophin-releasing hormone agonist therapy	Intervention not of interest
McClung, 2023	BONE MINERAL DENSITY AFTER TWO YEARS OF TREATMENT WITH RELUGOLIX COMBINATION THERAPY AND ONE-YEAR POST-TREATMENT FOLLOW-UP IN WOMEN WITH ENDOMETRIOSIS: SPIRIT PROGRAM	Irrelevant study type
Vuckovic, 2012	Laparoscopic treatment of endometrioma	Intervention not of interest

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Compston, 1995	The effects of gonadotrophin-releasing hormone agonists on iliac crest cancellous bone structure in women with endometriosis	Irrelevant study type
Latthe, 2014	Dysmenorrhoea	Irrelevant population
Rachon, 2016	Safety of the isopropanolic Cimicifuga racemosa extract (iCR) on the endometrium	Irrelevant population
Dietrich, 2014	Obstructive Reproductive Tract Anomalies	Irrelevant population
Mullarkey, 2021	Deeply infiltrating endometriosis masquerading as a sigmoid adenoma	Irrelevant study type
Alborzi, 2006	Management of ovarian endometrioma	Irrelevant study type
Horton, 2008	Abdominal wall endometriosis: a surgeon's perspective and review of 445 cases	Irrelevant study type
Glazewska, 2018	Complications of surgery in CEMIG UK	Intervention not of interest
Bosteels, 2011	Is reproductive surgery effective in the treatment of female subfertility: An evidence-based approach?	Intervention not of interest
Lessey, 2000	Medical management of endometriosis and infertility	Irrelevant study type
Seyhan, 2018	Do endometriomas grow during ovarian stimulation for assisted reproduction? A three-dimensional volume analysis before and after ovarian stimulation	Irrelevant outcome
Mahutte, 2003	Inverse correlation between peritoneal fluid leptin concentrations and the extent of endometriosis	Irrelevant study type
Rock, 1995	The revised American Fertility Society classification of endometriosis: Reproducibility of scoring	Irrelevant study type

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Marino, 2023	A prospective, observational, multivariate study to evaluate the best predictor of ovarian response, between AMH measured with fully automated assay and AFC	Intervention not of interest
Cunha-Filho, 2022	Final Follicular Phase LH, estradiol and progesterone secretion in Long-acting FSH versus daily FSH administration for controlled ovarian stimulation for In Vitro Fertilization	Intervention not of interest
Cunha-Filho, 2022	Testosterone and antioxidants supplementation before controlled ovarian stimulation for in vitro fertilization: A prospective non-randomized study	Intervention not of interest
Shi, 2016	Gper mediated action of estrogen in edometrial receptivity of women with high serum estradiol level on HCG day	Irrelevant outcome
Navarro, 2013	Impact of hypophyseal suppression and controlled ovarian stimulation on anti-mullerian serum levels in patients with and without endometriosis submitted to ICSI	Irrelevant outcome
Tomassetti, 2022	The Ultra-Long Study: A Randomized Controlled Trial Evaluating Long-Term GnRH Downregulation Prior to ART in Women With Endometriosis	Irrelevant outcome
Lo, 1997	The use of gonadotrophin-releasing hormone analogues in gynaecology	Irrelevant study type
Takeuchi, 2000	A prospective randomized study comparing endocrinological and clinical effects of two types of GnRH agonists in cases of uterine leiomyomas or endometriosis	Irrelevant outcome
Tsai, 2016	Low-dose add-back therapy during postoperative GnRH agonist treatment	Irrelevant study type
Lim, 2015	A pilot study: short term danazol in adjunct with GNRH agonist to reduce flare ups for treatment of endometriosis	Irrelevant outcome

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Rickes, 2002	Increased pregnancy rates after ultralong postoperative therapy with gonadotropin-releasing hormone analogs in patients with endometriosis	Irrelevant outcome
Gallagher, 2018	Long-Term Effects of Gonadotropin-Releasing Hormone Agonists and Add-Back in Adolescent Endometriosis	Irrelevant study type
Waller, 1993	Gonadotropin-releasing hormone analogues for the treatment of endometriosis: long-term follow-up	Irrelevant outcome
Zawin, 1990	Monitoring therapy with a gonadotropin-releasing hormone analog: utility of MR imaging	Irrelevant outcome
Maouris, 1990	The effect of danazol and the LHRH agonist analogue goserelin (Zoladex) on the biological activity of luteinizing hormone in women with endometriosis	Irrelevant outcome
Maged, 2018	Effect of Prolonged GnRH Agonist Downregulation on ICSI Outcome in Patients With Endometriomas of Less Than 5 cm: a Randomized Controlled Trial	Irrelevant outcome
Velasco, 2005	Changes in cytokine levels of patients with ovarian endometriosis after treatment with gonadotropin-releasing hormone analogue, ultrasound-guided drainage, and intracystic recombinant interleukin-2	Irrelevant outcome
Poiraudeau, 1997	Circulating insulin-like growth factor system changes in women with acute estrogen deficiency induced by GnRH agonist	Intervention not of interest
Khalifa, 2021	Role of suppression of endometriosis with progestins before IVF-ET: a non-inferiority randomized controlled trial	Irrelevant outcome
Winkel, 2001	Medical and surgical therapies for pain associated with endometriosis	Irrelevant study type

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Venturella, 2011	CA 125 modifications throughout menstrual cycle and following gnrh-analog administration to diagnose endometriosis as cause of chronic pelvic pain. A prospective controlled study	Irrelevant outcome
Tomassetti, 2021	The ultra-long study: a randomized controlled trial evaluating long-term GnRH downregulation prior to ART in women with endometriosis	Irrelevant outcome
Sesti, 2009	Recurrence rate of endometrioma after laparoscopic cystectomy: a comparative randomized trial between post-operative hormonal suppression treatment or dietary therapy vs. placebo	Irrelevant outcome
Roux, 1995	Bone loss during gonadotropin releasing hormone agonist treatment and use of nasal calcitonin	Irrelevant outcome
Pohl, 2022	A model-based analysis to guide gonadotropin-releasing hormone receptor antagonist use for management of endometriosis	Intervention not of interest
Moscarini, 2014	Ovarian stripping versus cystectomy: recurrence of endometriosis and pregnancy rate	Intervention not of interest
Lagana, 2013	Control of symptoms relapse after conservative surgery for endometriosis: advantages of using dienogest plus estradiol valerate	Irrelevant outcome
Bansal, 2018	The Role of GnRH Analogues in Improving Outcome in Women Undergoing Superovulation and Intrauterine Insemination after Surgical Correction of Mild Endometriosis: a Randomized Controlled Trial	Irrelevant outcome
el-Roeiy, 1988	Danazol but not gonadotropin-releasing hormone agonists suppresses autoantibodies in endometriosis	Irrelevant outcome

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Ah, 2016	Raloxifene administration in women treated with long-term gonadotropin-releasing hormone agonist for severe endometriosis: effects on bone mineral density	Irrelevant study type
Ouladsahebmadarek, 2011	Hysterectomy versus GnRH agonist for dysfunctional uterine bleeding in premenopausal women	Irrelevant population
Shaw, 1994	A risk benefit assessment of drugs used in the treatment of endometriosis	Irrelevant study type
Petraglia, 2012	Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment	Intervention not of interest
Buendgen, 2013	Initiation of ovarian stimulation independent of the menstrual cycle: a case-control study	Intervention not of interest
Bonner, 2024	Osteopathic Manipulative Treatment in Dysmenorrhea: A Systematic Review.	Intervention not of interest
Steele, 2024	When you see nothing at all: Outcomes following a negative laparoscopy. A systematic review.	Intervention not of interest
Qing, 2024	Systematic review and meta-analysis on the effect of adjuvant gonadotropin-releasing hormone agonist (GnRH-a) on pregnancy outcomes in women with endometriosis following conservative surgery.	Irrelevant outcome
AbuMusa, 2019	Efficacy of Dienogest versus oral contraceptive pills (OCPs) on pain associated with endometriosis: randomized Controlled Trial	Intervention not of interest
Cervantes, 2023	Sexual Function of Patients with Deep Endometriosis after Surgical Treatment: A Systematic Review.	Irrelevant outcome

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Ronsini, 2023	The Efficiency of Sclerotherapy for the Management of Endometrioma: A Systematic Review and Meta-Analysis of Clinical and Fertility Outcomes.	Intervention not of interest
Wang, 2022	Levonorgestrel-releasing intrauterine system vs. systemic medication or blank control for women with dysmenorrhea: Systematic review and meta-analysis of randomized controlled trials.	Intervention not of interest
Lee, 2002	Gonadotrophin releasing hormone agonist (GnRHa)-Zoladex (Goserelin) and hormonal add-back therapy in endometriosis: a 12 month study	Irrelevant study type
Liu, 2021	Dienogest as a Maintenance Treatment for Endometriosis Following Surgery: A Systematic Review and Meta-Analysis.	Intervention not of interest
Ronsini, 2023	Liquid Biopsy in Endometriosis: A Systematic Review.	Irrelevant outcome
Ye, 2023	Endometriosis of the skeletal muscular system (ESMS): a systematic review.	Irrelevant study type
Johnstone, 2023	Pain, pain management and related outcomes following pelvic exenteration surgery: a systematic review.	Irrelevant population
Hooker, 2022	The link between intrauterine adhesions and impaired reproductive performance: a systematic review of the literature.	Irrelevant population
Vercellini, 1999	A gonadotrophin-releasing hormone agonist compared with expectant management after conservative surgery for symptomatic endometriosis	Irrelevant outcome
Yin, 2022	The effect of medication on serum anti-mullerian hormone (AMH) levels in women of reproductive age: a meta-analysis.	Irrelevant outcome

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Darici, 2022	Different segmental resection techniques and postoperative complications in patients with colorectal endometriosis: A systematic review.	Intervention not of interest
Caruso, 2022	Randomized study on the effectiveness of nomegestrol acetate plus 17beta-estradiol oral contraceptive versus dienogest oral pill in women with suspected endometriosis-associated chronic pelvic pain.	Intervention not of interest
Moreno-Sepulveda, 2022	The Effect of Laparoscopic Endometrioma Surgery on Anti-Mullerian Hormone: A Systematic Review of the Literature and Meta-Analysis.	Irrelevant outcome
Garcia-Garcia, 2022	Recurrence Rate and Morbidity after Ultrasound-guided Transvaginal Aspiration of Ultrasound Benign-appearing Adnexal Cystic Masses with and without Sclerotherapy: A Systematic Review and Meta-analysis.	Irrelevant population
Travaglino, 2022	Prognostic value of the TCGA molecular classification in uterine carcinosarcoma.	Irrelevant population
Kiesel, 1989	Treatment of endometriosis	Language not of interest
Perino, 2004	A randomized comparison of endometrial laser intrauterine thermotherapy and hysteroscopic endometrial resection	Intervention not of interest
Ball, 2021	Systematic review of patient-specific pre-operative predictors of pain improvement to endometriosis surgery.	Intervention not of interest
Popoutchi, 2021	SURGICAL TECHNIQUES FOR THE TREATMENT OF RECTAL ENDOMETRIOSIS: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND OBSERVATIONAL STUDIES.	Intervention not of interest

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Muraoka, 2021	Impact of perioperative use of GnRH agonist or dienogest on ovarian reserve after cystectomy for endometriomas: a randomized controlled trial.	Irrelevant outcome
Acien, 2021	Anastrozole and levonorgrestrel-releasing intrauterine device in the treatment of endometriosis: a randomized clinical trial.	Intervention not of interest
Toczek, 2021	Endometriosis: New Perspective for the Diagnosis of Certain Cytokines in Women and Adolescent Girls, as Well as the Progression of Disease Outgrowth: A Systematic Review.	Irrelevant outcome
Ianieri, 2021	Indocyanine green in the surgical management of endometriosis: A systematic review.	Intervention not of interest
Surrey, 2001	The effect of prolonged GnRH agonist (GnRHa) therapy on in vitro fertilization-embryo transfer (IVF-ET) cycle outcome in endometriosis (ENDO) patients: a multicenter randomized trial	Irrelevant outcome
Surrey, 2003	Management of endometriosis-associated infertility	Irrelevant study type
Nankali, 2020	The effect of unilateral and bilateral laparoscopic surgery for endometriosis on Anti-Mullerian Hormone (AMH) level after 3 and 6 months: a systematic review and meta-analysis.	Irrelevant outcome
Vesale, 2020	Voiding Dysfunction after Colorectal Surgery for Endometriosis: A Systematic Review and Meta-analysis.	Irrelevant outcome
Popivanov, 2020	Perirectal Hematoma and Intra-Abdominal Bleeding after Stapled Hemorrhoidopexy and STARR-A Proposal for a Decision-Making Algorithm.	Irrelevant population

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Cao, 2020	The effectiveness of different down-regulating protocols on in vitro fertilization-embryo transfer in endometriosis: a meta-analysis.	Irrelevant study type
Ssentongo, 2020	Pain and Dysfunction with Sexual Activity after Inguinal Hernia Repair: Systematic Review and Meta-Analysis.	Irrelevant population
Leonardi, 2020	When to Do Surgery and When Not to Do Surgery for Endometriosis: A Systematic Review and Meta-analysis.	Intervention not of interest
Kyal, 2018	Does cabergoline help in decreasing chronic pelvic pain due to endometriosis compared to medroxyprogesterone acetate? A prospective randomized study	Intervention not of interest
Giudice, 2023	A Plain Language Summary to learn about relugolix combination therapy for the treatment of pain associated with endometriosis	Irrelevant study type
Strowitzki, 2012	Efficacy and safety of dienogest in the treatment of endometriosis	Irrelevant study type
Carroquino-Garcia, 2019	Therapeutic Exercise in the Treatment of Primary Dysmenorrhea: A Systematic Review and Meta-Analysis.	Irrelevant outcome
Candiani, 2018	Assessment of ovarian reserve after cystectomy versus 'one-step' laser vaporization in the treatment of ovarian endometrioma: a small randomized clinical trial.	Intervention not of interest
Balla, 2018	Outcomes after rectosigmoid resection for endometriosis: a systematic literature review.	Irrelevant outcome
Szubert, 2018	Conservative treatment of deep infiltrating endometriosis: review of existing options.	Irrelevant study type
Cohen, 2017	Sclerotherapy in the management of ovarian endometrioma: systematic review and meta-analysis.	Intervention not of interest

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Muzii, 2016	Continuous versus cyclic oral contraceptives after laparoscopic excision of ovarian endometriomas: a systematic review and metaanalysis.	Irrelevant study type
Zorbas, 2015	Continuous versus cyclic oral contraceptives for the treatment of endometriosis: a systematic review.	Intervention not of interest
Gurbuz, 2023	Preliminary results of the DINE Study (Dienogest vs. Norethindrone Acetate in Endometriosis Treatment)	Intervention not of interest
Agarwal, 2002	Pilot study evaluating the efficacy of deslorelin with add-back low-dose sex steroids for the treatment of pelvic pain secondary to laparoscopically confirmed endometriosis	Irrelevant study type
Chong, 2014	The role of cystectomy for non-malignant bladder conditions: a review.	Irrelevant population
Latthe, 2014	Dysmenorrhoea.	Intervention not of interest
Kodama, 2014	Feto-maternal outcomes of pregnancy complicated by ovarian malignant germ cell tumor: a systematic review of literature.	Irrelevant population
Muzii, 2014	The effect of surgery for endometrioma on ovarian reserve evaluated by antral follicle count: a systematic review and meta-analysis.	Irrelevant outcome
Vercellini, 2014	Adenomyosis and reproductive performance after surgery for rectovaginal and colorectal endometriosis: a systematic review and meta-analysis.	Irrelevant outcome
Panicker, 2014	Evolution of extended use of the combined oral contraceptive pill.	Intervention not of interest

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Fritzer, 2014	Dyspareunia and quality of sex life after surgical excision of endometriosis: a systematic review.	Intervention not of interest
As-Sanie, 2022	SUSTAINED IMPROVEMENT IN PHYSICAL FUNCTION AND QUALITY OF LIFE IN WOMEN WITH ENDOMETRIOSIS-ASSOCIATED PAIN TREATED WITH RELUGOLIX COMBINATION THERAPY OVER 104 WEEKS: SPIRIT LONG-TERM EXTENSION STUDY	Irrelevant study type
Gemzell-Danielsson, 2013	Management of pain associated with the insertion of intrauterine contraceptives.	Intervention not of interest
Matteson, 2013	Nonsurgical management of heavy menstrual bleeding: a systematic review.	Irrelevant population
Platteau, 2009	Interplay between infertility diagnosis and type of gonadotropin with respect to treatment outcome of controlled ovarian stimulation	Irrelevant study type
Raffi, 2012	The impact of excision of ovarian endometrioma on ovarian reserve: a systematic review and meta-analysis.	Intervention not of interest
Laschke, 2012	Anti-angiogenic treatment strategies for the therapy of endometriosis.	Intervention not of interest
Brown, 2012	Progestagens and anti-progestagens for pain associated with endometriosis.	Intervention not of interest
Bosteels, 2010	The effectiveness of reproductive surgery in the treatment of female infertility: facts, views and vision.	Intervention not of interest

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DiVasta, 2021	Nonhormonal therapy for endometriosis: a randomized, placebo-controlled, pilot study of cabergoline versus norethindrone acetate	Intervention not of interest
Sesti, 2011	Dietary therapy: a new strategy for management of chronic pelvic pain.	Intervention not of interest
Xiaoting, 2010	Interventions for pain during fixed orthodontic appliance therapy. A systematic review.	Irrelevant population
Acien, 2010	Treatment of endometriosis with transvaginal ultrasound-guided drainage and recombinant interleukin-2 left in the cysts: a third clinical trial.	Intervention not of interest
Nave, 2019	Absence of Drug-Drug Interaction of Anastrozole on Levonorgestrel Delivered Simultaneously by an Intravaginal Ring: results of a Phase 2 Trial	Irrelevant study type
Harada, 2008	Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial.	Intervention not of interest
Attar, 2006	Aromatase inhibitors: the next generation of therapeutics for endometriosis?.	Irrelevant study type
Cagnacci, 2005	Effect on insulin sensitivity of Implanon vs. GnRH agonist in women with endometriosis.	Irrelevant outcome
Naz, 2005	Recent advances in contraceptive vaccine development: a mini-review.	Irrelevant study type
Donnez, 2004	Equivalence of the 3-month and 28-day formulations of triptorelin with regard to achievement and maintenance of medical castration in women with endometriosis.	Irrelevant study type
Agarwal, 2002	Impact of six months of GnRH agonist therapy for endometriosis. Is there an age-related effect on bone mineral density?.	Irrelevant outcome

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Selak, 2000	Danazol for pelvic pain associated with endometriosis.	Intervention not of interest
Bianchi, 1999	Effects of 3 month therapy with danazol after laparoscopic surgery for stage III/IV endometriosis: a randomized study.	Intervention not of interest
Audebert, 1998	Pre or post-operative medical treatment with nafarelin in stage III-IV endometriosis: a French multicenter study.	Irrelevant outcome
Gentile, 1998	Is there any evidence for a post-tubal sterilization syndrome?.	Irrelevant population
Vercellini, 1997	Progestins for symptomatic endometriosis: a critical analysis of the evidence.	Intervention not of interest
Zamberlan, 1997	Intermittent Etidronate partially prevents bone loss in hirsute hyperandrogenic women treated with GnRH agonist.	Irrelevant study type
Kiesel, 1996	Should add-back therapy for endometriosis be deferred for optimal results?.	Irrelevant outcome
Paoletti, 1996	Spontaneous reversibility of bone loss induced by gonadotropin-releasing hormone analog treatment.	Irrelevant study type
Newton, 1996	Memory complaints associated with the use of gonadotropin-releasing hormone agonists: a preliminary study.	Irrelevant outcome
Fraser, 1996	Depot goserelin and danazol pre-treatment before rollerball endometrial ablation for menorrhagia.	Irrelevant population
Howell, 1995	Endocrine effects of GnRH analogue with low-dose hormone replacement therapy in women with endometriosis.	Irrelevant outcome

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Ylikorkala, 1995	Decrease in symptoms, blood loss and uterine size with nafarelin acetate before abdominal hysterectomy: a placebo-controlled, double-blind study.	Irrelevant outcome
Halbe, 1995	Updating the clinical experience in endometriosis--the Brazilian perspective.	Intervention not of interest
Adamson, 1994	Pain of endometriosis: effects of nafarelin and danazol therapy.	Irrelevant outcome
Surrey, 1993	Effects of sodium etidronate in combination with low-dose norethindrone in patients administered a long-acting GnRH agonist: a preliminary report.	Irrelevant population
Barbieri, 1993	Gonadotropin-releasing hormone agonists: treatment of endometriosis.	Irrelevant study type
Kauppila, 1993	Changing concepts of medical treatment of endometriosis.	Irrelevant study type
Rock, 1993	Zoladex (goserelin acetate implant) in the treatment of endometriosis: a randomized comparison with danazol. The Zoladex Endometriosis Study Group.	Irrelevant outcome
Overton, 1993	The effect of nafarelin on human plasma adrenocorticotrophic hormone and cortisol concentrations.	Irrelevant outcome
Hickok, 1991	Medical treatment of endometriosis: a comparison of the suppressive effects of danazol and nafarelin on reproductive hormones.	Irrelevant outcome
Telimaa, 1989	Circulating lipid and lipoprotein concentrations during danazol and high-dose medroxyprogesterone acetate therapy of endometriosis.	Intervention not of interest
Ronnberg, 1989	Efficacy of gonadotropin-releasing hormone agonist (buserelin) in the treatment of endometriosis.	Irrelevant study type

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Chaudhuri, 1984	Clinical trial of a long-acting injectable contraceptive: NET-EN.	Intervention not of interest
Bergquist, 1990	Effects of nafarelin versus danazol on lipids and calcium metabolism	Irrelevant outcome
Henzl, 1988	Administration of nasal nafarelin as compared with oral danazol for endometriosis. A multicenter double-blind comparative clinical trial	Irrelevant outcome
DiVasta, 2015	Hormonal Add-Back Therapy for Females Treated With Gonadotropin-Releasing Hormone Agonist for Endometriosis: a Randomized Controlled Trial	Intervention not of interest
Donnez, 1989	Administration of nasal Buserelin as compared with subcutaneous Buserelin implant for endometriosis	Irrelevant outcome
Ferrero, 2007	Dyspareunia and quality of sex life after laparoscopic excision of endometriosis and postoperative administration of triptorelin	Irrelevant study type
Mukherjee, 1996	A randomized, placebo-controlled study on the effect of cyclic intermittent etidronate therapy on the bone mineral density changes associated with six months of gonadotropin-releasing hormone agonist treatment	Intervention not of interest
Hardt, 1983	Sustained gonadal suppression in fertile women with the LHRH agonist buserelin	Irrelevant population
Takenaka, 2015	Exploratory study of pre-surgical medications with dienogest or leuprorelin in laparoscopic cystectomy of endometrial cysts	Irrelevant study type
Sillem, 1999	Add-back medrogestone does not prevent bone loss in premenopausal women treated with goserelin	Intervention not of interest

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Fedele, 1992	Superovulation with human menopausal gonadotropins in the treatment of infertility associated with minimal or mild endometriosis: a controlled randomized study	Irrelevant outcome
Nezhat, 1996	Is hormonal treatment efficacious in the management of ovarian cysts in women with histories of endometriosis?	Intervention not of interest
Zhu, 2018	Comparison of Outcomes of Different Postoperative Hormone Therapy in the Treatment of Ovarian Endometriosis: a Brief Report	Irrelevant study type
Fedele, 1989	Gestrinone versus danazol in the treatment of endometriosis	Intervention not of interest
Seiler, 1986	Laparoscopic cauterization of endometriosis for fertility: a controlled study	Intervention not of interest
Carpenter, 1995	The effect of regular exercise on women receiving danazol for treatment of endometriosis	Intervention not of interest
Cicinelli, 2019	Unified diagnostic criteria for chronic endometritis at fluid hysteroscopy: proposal and reliability evaluation through an international randomized-controlled observer study	Irrelevant study type
Moore, 1985	Management of pelvic endometriosis with low-dose danazol	Intervention not of interest
Vilos, 2010	Randomized comparison of goserelin versus suction curettage prior to Thermachoice II balloon endometrial ablation: one-year results	Irrelevant population

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Uemura, 1994	Effect of gonadotropin-releasing hormone agonist on the bone mineral density of patients with endometriosis	Irrelevant study type
Shaw, 2001	A prospective randomized open study comparing goserelin (Zoladex) plus surgery and surgery alone in the management of ovarian endometriomas	Irrelevant outcome
Sakata, 1994	The hypothalamic-pituitary-ovarian axis in patients with endometriosis is suppressed by leuprolide acetate but not by danazol	Irrelevant outcome
Giorgino,1991	Goserelin versus danazol in the treatment of endometriosis	Irrelevant study type
Maouris, 1991	Psudomenopause Treatment for Endometriosis: the Endocrine Effects of Danazol Compared with the use of the LH-RH Agonist Goserelin	Irrelevant outcome
Yang, 2015	Effects of danchi decoction on P450arom, survivin of eutopic endometrium of patients with endometriosis after conservative surgery	Irrelevant outcome
Clinical trials (n= 248)		
University Hospital, Gasthuisberg, 2011	CO2 Absorption During Laparoscopy	Irrelevant population
PregLem SA, 2014	PGL2001 Proof of Concept Study in Symptomatic Endometriosis	Intervention not of interest
Uludag University, 2023	The Effect of Dienogest vs. Norethindrone Acetate Treatment in Endometriosis	Intervention not of interest
Sumitomo Pharma Switzerland GmbH, 2024	A Phase 3B Study to Evaluate Bone Mineral Density With Long-Term Use of Relugolix Combination Tablet in Women With Uterine Fibroids or Endometriosis	Irrelevant outcome

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University Hospital, Lille, 2020	Impact of Complete Surgery of Colorectal Deep Infiltrating Endometriosis on Fertility	Irrelevant outcome
Qilu Pharmaceutical (Hainan) Co., Ltd., 2022	A Study to Evaluate Safety and Efficacy of Elagolix in Patients With Moderate to Severe Endometriosis-Associated Pain	Intervention not of interest
Kissei Pharmaceutical Co., Ltd., 2024	Extension to Study on Efficacy and Safety of Linzagolix for the Treatment of Endometriosis-associated Pain (EDELWEISS 6)	Intervention not of interest
University Hospital, Ghent, 2023	The Use of plasmaJet During Operative Laparoscopy for Endometriosis	Intervention not of interest
AbbVie, 2019	A Study to Evaluate Safety and Efficacy of Elagolix in Participants With Endometriosis With Associated Moderate to Severe Pain	Intervention not of interest
University of Cagliari, 2024	Evaluation of Ovarian Reserve and Recurrence Rate After DWLS Diode Laser OMA Vaporization	Intervention not of interest
ObsEva SA, 2022	A Phase 3 Study to Confirm the Efficacy and Safety of Linzagolix to Treat Endometriosis-associated Pain	Intervention not of interest
Boston Children's Hospital, 2023	IUD and Norethindrone Acetate for Treatment of Endometriosis	Intervention not of interest
Hospices Civils de Lyon, 2023	Percutaneous Posterior Tibial Nerve Stimulation in Post-operative Voiding Dysfunction After Deep Endometriosis Surgery	Intervention not of interest
The University of Hong Kong, 2024	Letrozole in Preventing Recurrence of Endometrioma Following Laparoscopic Ovarian Cystectomy	Intervention not of interest

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Mereo BioPharma, 2020	A Safety & Efficacy Study of BGS649 in Women With Refractory Endometriosis	Intervention not of interest
Chen Chunlin, 2020	The Application of Real-Time Near-infrared Imaging in Gynecological Surgery	Intervention not of interest
Scientific Institute San Raffaele, 2017	The Impact on Ovarian Reserve of Ovarian Cystectomy Versus Laser Vaporization in the Treatment of Ovarian Endometrioma: a Randomized Clinical Trial	Intervention not of interest
Universitaire Ziekenhuizen KU Leuven, 2017	Gonadotropin-releasing Hormone (GnRH) Downregulation Versus Oral Anticonception Prior to ART in Postoperative Endometriosis Patients	Irrelevant outcome
Catholic University of the Sacred Heart, 2017	Near-infrared Fluorescence Imaging as a Supportive Tool for Localisation of Deep Infiltrating Endometriosis During Laparoscopy	Intervention not of interest
Yale University, 2024	Pre-IVF Treatment With a GnRH Antagonist in Women With Endometriosis	Intervention not of interest
Takeda, 2014	Efficacy and Safety of TAK-385 in the Treatment of Endometriosis	Irrelevant outcome
Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, 2022	IVF Versus Surgery for Endometriosis Related Infertility	Irrelevant outcome
University Magna Graecia, 2009	Continuous Postoperative Use of Low-Dose Combined Oral Contraceptivesfor for Endometriosis-Related Chronic Pelvic Pain	Intervention not of interest
Acibadem University, 2019	a Novel Surgical Approach for Endometriosis Surgery	Intervention not of interest

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Colorado Center for Reproductive Medicine, 2021	Endometrial Markers and Response of Endometriosis Patients to Prolonged GnRH Agonist Prior to IVF	Irrelevant population
Women's Hospital School Of Medicine Zhejiang University, 2022	Aspirin for the Management of Endometriosis-associated Pelvic Pain	Intervention not of interest
University College London Hospitals, 2013	Post-operative Ovarian Adhesion Study in Women With Endometriosis	Intervention not of interest
Bayer, 2023	Study to Gather Information How Well Three Different Doses of BAY1817080 Given Twice Daily Over 12 Weeks Work in Comparison to an Inactive Pill (Placebo) and Elagolix in Women Suffering From Pain Related to a Condition Where the Tissue That Usually Grows Inside the Womb Grows Outside of the Womb	Intervention not of interest
Assistance Publique - Hôpitaux de Paris, 2019	Efficacy of Cryoablation of Abdominal Wall Endometriosis	Intervention not of interest
Catholic University of the Sacred Heart, 2019	Comparison of Laparoscopic Endometrioma Stripping Versus Ethanol Sclerotherapy(CLESS)	Intervention not of interest
Hospices Civils de Lyon, 2024	Developing a Complex ex Vivo Endometrial Tissue Model to Improve Endometriosis Care	Irrelevant study type
Hospital Universitari de Bellvitge, 2024	Anti-mullerian Hormone (AMH) After Treatment of Endometriomas With Alcohol Sclerotherapy Versus Surgery: Clinical Trial	Intervention not of interest

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Mansoura University, 2011	Efficacy of Letrozole and CC Alone in an IUI Program in Cases With Surgically Treated Minimal to Mild Endometriosis	Intervention not of interest
CryoLife Europa, 2017	PerClot Compared to Usual Care in Gynaecology Procedures	Irrelevant study type
IRCCS Azienda Ospedaliero-Universitaria di Bologna, 2019	Endometriosis and Psychological Support	Intervention not of interest
Shanghai First Maternity and Infant Hospital, 2021	Assessment of Ovarian Reserve After Laparoscopic Cystectomy Versus Aspiration/Electrocoagulation in the Treatment of Ovarian Endometrioma	Intervention not of interest
Meir Medical Center, 2015	Efficacy of Aspiration and Sclerotherapy During Laparoscopy Using 95% Ethanol for the Treatment of Endometriomas	Intervention not of interest
University of Athens, 2014	Continuous Versus Cyclic Oral Contraceptives for Endometriosis	Intervention not of interest
AbbVie, 2018	Efficacy and Safety Study of Elagolix Versus Placebo or Leuprorelin Acetate in Endometriosis	Intervention not of interest
University of Aarhus, 2023	Intraoperative Clonidine for Postoperative Pain Management in Patients Undergoing Surgical Treatment for Endometriosis	Intervention not of interest
American University of Beirut Medical Center, 2022	Dienogest Versus GnRH-a Pre-treatment in Women With Endometriosis Undergoing IVF	Irrelevant outcome
Science Valley Research Institute, 2024	Subdermal Implant-bioabsorbable Gestrinone Pellet for Endometriosis Pelvic Pain Treatment	Intervention not of interest

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AbbVie, 2023	A Clinical Study to Evaluate the Safety and Efficacy of Elagolix in Participants With Moderate to Severe Endometriosis-Associated Pain	Intervention not of interest
Rijnstate Hospital, 2023	Cognitive Behavioral Therapy in Endometriosis	Intervention not of interest
The University of Hong Kong, 2015	Comparing the Use of Dienogest and Combined Oral Contraceptive Pills (Microgynon) to Reduce the Risk of Recurrence of Endometriotic Cyst After Conservative Surgery	Intervention not of interest
Colorado Center for Reproductive Medicine, 2024	Comparison Elagolix vs Depot Leuprolide Prior to Frozen Embryo Transfers in Patients With Endometriosis	Irrelevant population
Ain Shams University, 2017	Induction of Ovulation by Clomiphene Citrate Following Laparoscopic Surgery for Endometriosis Stage 1 and Stage 2 With and Without Suppression by Dienogest	Intervention not of interest
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), 2016	The Safety and Effectiveness of Surgery With or Without Raloxifene for the Treatment of Pelvic Pain Caused by Endometriosis	Intervention not of interest
University of Ioannina, 2013	GnRH-a and Pregnancy Rate in In Vitro Fertilization (IVF) Cycles.	Irrelevant population
University of Texas Southwestern Medical Center, 2024	Outcomes on Abdominal Versus Vaginal Morcellation At Time of Hysterectomy	Intervention not of interest

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AbbVie, 2018	An Efficacy and Safety Study of Elagolix (NBI-56418) in Women With Endometriosis	Intervention not of interest
Adana City Training and Research Hospital, 2023	Comparison of Thyroid Volumes in Patients With and Without Endometrioma	Irrelevant outcome
Stony Brook University, 2020	Deep Versus Moderate Neuromuscular Blockade During Laparoscopic Surgery	Intervention not of interest
University Hospital, Gasthuisberg, 2016	Peritoneal Cavity Conditioning Decreases Pain, Inflammation and Adhesions	Intervention not of interest
Centre Hospitalier Universitaire Vaudois, 2023	The Role of Preoperative Immunonutrition on Morbidity and Immune Response After Cystectomy (INCyst Trial)	Intervention not of interest
Ankara University, 2011	Comparison of Hemostatic Matrix and Bipolar Coagulation in Surgical Treatment of Endometriomas	Intervention not of interest
Milton S. Hershey Medical Center, 2024	Feasibility of a Mindfulness Intervention for Endometriosis Surgery	Intervention not of interest
Mercy Research, 2022	Ultravision,Ñ¢ System to Facilitate Low Impact Laparoscopic Surgery for Endometriosis	Intervention not of interest
ZIWIG, 2023	Analytical Evaluation of the Endotest¬Æ Diagnostic	Irrelevant outcome
Istanbul University, 2016	Assessment of Telomerase Activity in Endometrial Tissue and Serum in Endometriosis Patients	Irrelevant study type

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Myovant Sciences GmbH, 2023	SPIRIT EXTENSION: Efficacy and Safety Extension Study of Relugolix in Women With Endometriosis-Associated Pain	Irrelevant study type
AbbVie, 2024	Study Of Oral Elagolix Tablets In Combination With Combined Oral Contraceptive Capsules/Tablets To Assess Dysmenorrhea Response In Adult Female Participants With Endometriosis And Associated Moderate To Severe Pain	Intervention not of interest
University Hospital, Rouen, 2017	Functional Outcomes of Surgical Management of Deep Endometriosis Infiltrating the Rectum	Intervention not of interest
Myovant Sciences GmbH, 2021	SPIRIT 2: Efficacy and Safety Study of Relugolix in Women With Endometriosis-Associated Pain	Irrelevant outcome
Università degli Studi dell'Insubria, 2021	Suture of the Ovary After Enucleation of Ovarian Endometrioma	Intervention not of interest
Kissei Pharmaceutical Co., Ltd., 2014	A Phase II Randomized Open Label Study of KLH-2109 in Patients With Endometriosis	Intervention not of interest
IRCCS Azienda Ospedaliero-Universitaria di Bologna, 2019	Indocyanine Green and Rectosigmoid Endometriosis	Intervention not of interest
Viramal Limited, 2020	Study to Determine Intraperitoneal,Tissue, Serum Concentrations of VML-0501 Following Five Days of Daily Vaginal Single Dose of VML-0501 (100 mg Danazol), in Comparison to Oral Danazol Capsules Daily 600 mg), in Women With Signs and Symptoms of Endometriosis Undergoing Laparoscopy	Intervention not of interest

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AbbVie, 2018	Efficacy and Safety Study of Elagolix in Women With Endometriosis	Intervention not of interest
General Hospital Pula, 2019	The Influence of TAP Block in the Control of Postoperative Pain After Laparotomy for Gynecological Procedures	Intervention not of interest
Yale University, 2023	Cardiovascular Disease Risk in Women With Endometriosis	Intervention not of interest
Insel Gruppe AG, University Hospital Bern, 2020	Diagnostic Value of ICG in Endometriosis	Irrelevant outcome
Mediterranea Medica S. L., 2014	Mifepristone 2.5, 5, 10 mg Versus Placebo in the Treatment of Endometriosis	Intervention not of interest
AbbVie, 2018	Elagolix Versus Subcutaneous Depot Medroxyprogesterone Acetate for the Treatment of Endometriosis	Intervention not of interest
University of Aarhus, 2023	Is Laparoscopic Excision for Peritoneal Endometriosis Helpful or Harmful?	Intervention not of interest
Nanjing Chia-tai Tianqing Pharmaceutical, 2023	A Clinical Trial to Evaluate Efficacy and Safety of Elagolix Tablets in Women With Moderate or Severe Endometriosis-associated Pain	Intervention not of interest
Ain Shams University, 2016	Three Different Laparoscopic Approaches for Ovarian Endometrioma and the Effect on Ovarian Reserve	Intervention not of interest
Kissei Pharmaceutical Co., Ltd., 2013	A Randomized Open Label Study of KLH-2109 in Patients With Endometriosis(1)	Intervention not of interest

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IRCCS Azienda Ospedaliero-Universitaria di Bologna, 2022	Robot-assisted Versus Standard Laparoscopic Approach for the Surgical Treatment of Deep Infiltrating Endometriosis	Intervention not of interest
University of Cagliari, 2021	Psychological Impact of Amenorrhea in Women With Endometriosis	Irrelevant outcome
GCS Ramsay Santé pour l'Enseignement et la Recherche, 2024	SUPerficial ENDometriosis In Magnetic Resonance Imaging	Intervention not of interest
Enteris BioPharma Inc., 2022	A Study of Pharmacokinetic/Pharmacodynamic Profile of Orally Administered Leuprolide in Healthy Female Volunteers	Irrelevant population
KU Leuven, 2009	Effects of Extensive Abdominal Lavage on Postoperative Inflammation Following Full Thickness Excision of Deep Endometriosis	Intervention not of interest
Medical University of Vienna, 2022	Conventional Laparoscopy Versus Robotic Surgery for Pain Relief in Patients With Deep Infiltrating Endometriosis	Intervention not of interest
Milton S. Hershey Medical Center, 2023	Cannabidiol and Management of Endometriosis Pain	Intervention not of interest
University of Oklahoma, 2013	Post Operative Continuous Active Combination Sex Steroids for the Prevention of Recurrent Endometrioma Formation	Intervention not of interest
Kissei Pharmaceutical Co., Ltd., 2023	Extension to Study on Efficacy and Safety of Linzagolix for the Treatment of Endometriosis-associated Pain	Intervention not of interest

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Millennium Pharmaceuticals, Inc., 2016	A Phase 1 Study to Evaluate the Effects of Fluconazole and Atorvastatin on the Pharmacokinetics of TAK-385 in Healthy Subjects	Irrelevant population
Hopital Foch, 2023	Benefit of GnRH Agonist Before Frozen Embryo Transfer in Patients With Endometriosis and/or Adenomyosis	Irrelevant population
University Hospital, Angers, 2018	Assessment of Performance of [18F]-FES for Endometriosis Diagnosis	Intervention not of interest
Milton S. Hershey Medical Center, 2017	Robotic Surgical Management of Endometriosis: Excision Versus Ablation	Intervention not of interest
Hospital de Clinicas de Porto Alegre, 2016	Resveratrol for Pain Due to Endometriosis	Intervention not of interest
IRCCS Azienda Ospedaliero-Universitaria di Bologna, 2019	Surgical Eradication of Deep Infiltrating Endometriosis of the Vagina	Intervention not of interest
University of Cagliari, 2016	Efficacy of Palmitoylethanolamide-polydatin Combination on Chronic Pelvic Pain in Patients With Endometriosis	Intervention not of interest
Mr Andrew Kent, 2019	Carbon Dioxide-laser Versus Harmonic Scalpel in the Treatment of Pelvic Pain Due to Endometriosis	Intervention not of interest
University of Texas Southwestern Medical Center, 2017	Surgical Success After Laparoscopic vs Abdominal Hysterectomy	Intervention not of interest

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Insel Gruppe AG, University Hospital Bern, 2023	ICG for Visualization of the Ureters in DIE	Intervention not of interest
Poznan University of Medical Sciences, 2008	Efficacy Study of Atorvastatin in Pelvic Pain Relief in Women With Endometriosis	Irrelevant population
University Magna Graecia, 2014	AMH Levels Change During Treatment With GnRh Agonist	Irrelevant outcome
Astellas Pharma Europe B.V., 2019	A Study to Assess the Effectiveness and Safety of Different Doses of ASP1707 Compared to Placebo for Endometriosis Associated Pelvic Pain	Intervention not of interest
Stryker Orthopaedics, 2021	Objective to Evaluate the Safety and Effectiveness of LED Light Source System for Endoscopy in Ureteral Radiography	Intervention not of interest
National Research Centre, Egypt, 2020	Role of Suppression of Endometriosis With Progestins Before IVF-ET	Irrelevant outcome
Universitas Diponegoro, 2023	Comparing the Safety and Efficacy in the Use of Hormonal Therapy on Endometriosis Patients After Conservative Surgery	Irrelevant Publication type
AbbVie (prior sponsor, Abbott), 2013	An Open-label Study of the Effects of Elagolix in Adult Premenopausal Females	Intervention not of interest
University Hospital, Clermont-Ferrand, 2023	Using INDOcyanine Green to Analyse Ovarian Vascularization After Ovarian Laparoscopic CYStectomy	Intervention not of interest
Hera Biotech, Inc., 2023	Proof of Concept Study to Eval MetriDx Lab-developed Test to Identify Endometriosis-specific Bio Markers	Irrelevant study type

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Boston Children's Hospital, 2020	Dopamine Receptor Agonist Therapy for Pain Relief in Women Suffering From Endometriosis: A Pilot Study	Intervention not of interest
Francisco Carmona, 2018	Microparticle Generation After Laparoscopic Surgical Treatment for Endometrioma.	Intervention not of interest
Centre for Endocrinology and Reproductive Medicine, Italy, 2016	Anastrazole Plus GnRH-agonist in the Treatment of Endometriosis Recurrence	Irrelevant outcome
Northwestern University, 2024	Ulipristal for Endometriosis-related Pelvic Pain	Intervention not of interest
Benha University, 2023	Relation Between MicroRNA 203 and 210 and Sparing the Laparoscopic Examination in Cases of Unexplained Infertility	Intervention not of interest
NorthShore University HealthSystem, 2023	Chronic Pain Risk Associated With Menstrual Period Pain	Irrelevant population
Bagcilar Training and Research Hospital, 2018	Effects of Dienogest and Dienogest Plus Estradiol Valerate in Ovarian Endometrioma	Intervention not of interest
Institute for the Care of Mother and Child, Prague, Czech Republic, 2024	Laparoscopic Therapy of Endometrioma: Sclerotherapy vs Cystectomy in Patients With Unfinished Reproductive Plans	Intervention not of interest
Horsens Hospital, 2023	Impact of Operation on Fertility for Women With Severe Endometriosis	Irrelevant outcome

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Hospital Clinic of Barcelona, 2019	Impact on Ovarian Reserve According to the Type of Ovarian Endometrioma Excision: Laser Versus Conventional Cystectomy	Intervention not of interest
Instituto Valenciano de Infertilidad, IVI VALENCIA, 2009	Endometriosis Patients Undergoing Quinagolide Treatment	Intervention not of interest
The Cleveland Clinic, 2014	Study Comparing Conventional vs. Robotic-assisted Laparoscopic Hysterectomy	Intervention not of interest
Centre Hospitalier Universitaire de la Réunion, 2020	Evaluation of a Subcutaneous Progestogen Implants in the Medical Management of Painful Endometriosis	Intervention not of interest
Charles University, Czech Republic, 2020	Endometrioma Treatment and Ovarian Function	Intervention not of interest
Kissei Pharmaceutical Co., Ltd., 2023	Efficacy and Safety of Linzagolix for the Treatment of Endometriosis-associated Pain.	Intervention not of interest
Aljazeera Hospital, 2016	Barbed Sutures Versus Conventional Sutures in Laparoscopic Excision of Endometrioma	Intervention not of interest
The Cleveland Clinic, 2017	Laparoscopy vs. Robotic Surgery for Endometriosis (LAROSE): a Prospective Randomized Controlled Trial	Intervention not of interest
Azienda Ospedaliero-Universitaria di Modena, 2023	Adenomyosis and ART	Irrelevant outcome

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Cairo University, 2018	Trans-vaginal Aspiration of Small Ovarian Endometrioma. Comparison of Two Different Techniques Before ICSI	Intervention not of interest
Wake Forest University Health Sciences, 2024	Elagolix for Fertility Enhancement Clinical Trial	Intervention not of interest
Bayer, 2015	Phase 3 Study of Dienogest for the Treatment of Endometriosis in Chinese Patients	Intervention not of interest
Mahidol University, 2015	Postoperative Desogestrel for Endometriosis Related Pain	Intervention not of interest
Oulu University Hospital, 2024	LTAP Block in Endometriosis Surgery - a Randomised Controlled Double-blind Trial	Intervention not of interest
Universitaire Ziekenhuizen KU Leuven, 2023	Conservative Endometrioma Surgery	Intervention not of interest
Saad Amer, 2011	The Impact of Surgical Treatment of Endometriomas on Ovarian Reserve	Intervention not of interest
University of Oulu, 2023	Robotic Versus Laparoscopic Surgery for Deep Endometriosis	Intervention not of interest
Faculdade de Ciências Médicas da Santa Casa de São Paulo, 2020	Ovarian Function After Use of Various Hemostatic Techniques During Treatment for Endometrioma	Intervention not of interest
Jagiellonian University, 2023	Endometriosis and Peritoneal Dysbiosis	Irrelevant study type

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AbbVie, 2021	Global Study to Evaluate the Long-Term Safety and Efficacy of Elagolix in Women With Moderate to Severe Endometriosis-associated Pain	Intervention not of interest
Zhejiang University, 2011	Randomized Study of Gonadotropin-releasing-hormone Agonist (GnRH-a) or Expectant Management for Endometriosis	Irrelevant outcome
Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, 2022	Didroxyprogesterone Promotes Natural Pregnancy in Infertile Patients With Endometriosis	Irrelevant outcome
Kissei Pharmaceutical Co., Ltd., 2014	A Randomized, Placebo-controlled, Double-blind Study of KLH-2109 in Patients With Endometriosis (2)	Intervention not of interest
American University of Beirut Medical Center, 2021	Efficacy of Dienogest Versus Oral Contraceptive Pills on Pain Associated With Endometriosis	Irrelevant outcome
University of Cagliari, 2016	Impact on Ovarian Reserve of Diode Laser vs Bipolar Coagulation of Endometriomas	Intervention not of interest
Sumitomo Pharma Switzerland GmbH, 2024	Study of the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women With Uterine Fibroids or Endometriosis Who Are at Risk for Pregnancy	Irrelevant outcome
Plasma Surgical Inc, 2012	Ovarian Endometrioma Ablation Using Plasma Energy Versus Cystectomy	Intervention not of interest
Takeda, 2014	A Long-term Extension Study of TAK-385 in the Treatment of Endometriosis	Irrelevant outcome
AdventHealth, 2017	Fluorescence Imaging + ICG Dye for Use in the Visual Diagnosis of Endometriosis	Intervention not of interest

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ASKA Pharmaceutical Co., Ltd., 2020	Clinical Study to Evaluate Efficacy and Safety of TAK-385 40 mg Compared With Leuprorelin in Patients With Endometriosis	Irrelevant outcome
Sheffield Teaching Hospitals NHS Foundation Trust, 2019	Decapeptyl SR With Livial Add Back Therapy in the Management of Chronic Cyclical Pelvic Pain in Pre Menopausal Women	Irrelevant outcome
Shaimaa Mostafa Mohammed Refaay El shemy, 2019	Laparoscopic Ovarian Cystectomy Versus Aspiration and Coagulation in Ovarian Endometrioma	Intervention not of interest
Kasr El Aini Hospital, 2018	Effect of Prolonged GnRh Agonists on Results of Intracytoplasmic Sperm Injection (ICSI) in Endometrioma Patients	Irrelevant population
University of Patras, 2023	GnRH-a on Angiogenesis of Endometriosis	Irrelevant study type
Bayer, 2017	Effect of Concomitant Use of an Antimycotic, an Antibiotic, a Spermicide or Tampons on Pharmacokinetics of Anastrozole and Levonorgestrel Released From Intra-vaginal Ring	Intervention not of interest
University Hospital, Tours, 2018	Effect of Salpingectomy During Conservative Hysterectomy	Intervention not of interest
Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, 2023	Microbiota and Immunoassay in Women With and Without Endometriosis: a Pilot Study	Irrelevant study type
University Hospitals Cleveland Medical Center, 2014	Random Comparison of LigaSure and Disposable Staples for Laparoscopic Surgery	Intervention not of interest

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Ain Shams University, 2018	The Impact of Electrocoagulation on Ovarian Reserve After Laparoscopic Excision of Ovarian Cysts.	Intervention not of interest
University of Edinburgh, 2019	The Effectiveness of Laparoscopic Treatment of Superficial Endometriosis for Managing Chronic Pelvic Pain	Intervention not of interest
Uludag University, 2024	Pelvic Neuro-Angiogenesis in Deep Endometriosis	Intervention not of interest
Dr. Ofir Harnoy MD, 2017	The Application of Probe-based Confocal Laser Endomicroscopy in the Diagnosis of Deep Endometriosis	Intervention not of interest
University of Oxford, 2013	Pituitary Down-regulation Before IVF for Women With Endometriosis	Irrelevant outcome
Nobelpharma, 2010	Efficacy and Safety Study of Low Dose Oral Contraceptive Pill to Treat Dysmenorrhea	Intervention not of interest
Seoul National University Hospital, 2023	Comparison of Hemostatic Agent to Suture in Terms of Hemostatic Function and Preservation of Ovarian Function	Intervention not of interest
University Medical Center Groningen, 2017	Feasibility Study of Using Molecular Fluorescence Guided Surgery in Endometriosis	Intervention not of interest
Myovant Sciences GmbH, 2021	SPIRIT 1: Efficacy and Safety Study of Relugolix in Women With Endometriosis-Associated Pain	Irrelevant outcome
Hospices Civils de Lyon, 2023	Percutaneous Radiofrequency Ablation of Parietal Endometriosis (PRFA)	Intervention not of interest

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Pius-Hospital Oldenburg, 2015	Study to Compare Peritoneal Ablation by Excision Only and Excision With the Use of an Adhesion Barrier	Intervention not of interest
AbbVie, 2018	A Global Phase 3 Study to Evaluate the Safety and Efficacy of Elagolix in Subjects With Moderate to Severe Endometriosis-Associated Pain	Intervention not of interest
Novartis Pharmaceuticals, 2012	Letrozole in the Treatment of Severe and Recurrent Endometriosis	Intervention not of interest
Mansoura University, 2021	Goserline Acetate VS Dienogest in Endometriosi	Irrelevant outcome
Prince of Songkla University, 2014	Efficacy of Injectable Contraceptive and Oral Contraceptive Administered After Surgical Treatment of Endometriosis With Pain	Intervention not of interest
Ain Shams University, 2015	Laparoscopic Ovarian Cystectomy of Endometrioma vs Deroofing and Ovarian Reserve	Intervention not of interest
St. Louis University, 2023	Characteristics of Patient Population With Endometriosis	Irrelevant study type
Mercy Medical Center, 2020	A Comparison of Narrow Band Imaging (NBI) and Standard White Light Laparoscopy to Detect Endometriosis	Intervention not of interest
Universit√† degli Studi dell'Insubria, 2021	Surgery and ART For Endometrioma	Intervention not of interest
M.S.T. Medical Surgery Technology LTD., 2016	Evaluation of the Follow Me Mode of the AutoLap System - A Feasibility Study	Intervention not of interest
Indonesia University, 2021	Effects of Sulawesi Propolis Extract on Lesion Growth, Apoptotic and Inflammatory Activity of the Rat Endometriosis Tissue	Intervention not of interest

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The First Affiliated Hospital of Zhengzhou University, 2016	Effect of Shorten Gonadotropin-releasing Hormone Agonist Therapy on the Outcome of in Vitro Fertilization-Embryo Transfer in Patients With Endometriosis	Irrelevant outcome
Assistance Publique - Hôpitaux de Paris, 2022	Adenomyosis and Ulipristal Acetate	Irrelevant population
IRCCS Azienda Ospedaliero-Universitaria di Bologna, 2021	Intraoperative Assessment of Ureteral Perfusion in Women With Endometriosis	Intervention not of interest
Ponce Medical School Foundation, Inc., 2023	Enriched Environments in Endometriosis	Intervention not of interest
Instituto de Investigacion Sanitaria La Fe, 2015	The Effect of Pre-treatment With GnRH Analogues Prior in Vitro Fertilization in Patients With Endometriosis	Irrelevant outcome
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), 2014	Medical Treatment of Endometriosis-Associated Pelvic Pain	Irrelevant outcome
Medical University of Vienna, 2022	Evaluating Ovarian Reserve After Conventional Laparoscopy Versus Robotic Surgery for Bilateral Endometrioma	Intervention not of interest
Cairo University, 2019	Surgicel Reduces Ovarian Endometriomas Recurrence	Intervention not of interest

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Milton S. Hershey Medical Center, 2022	Low-Dose Naltrexone in Combination With Standard Treatment in Women With Endometriosis	Intervention not of interest
HaEmek Medical Center, Israel, 2023	Endothelial Dysfunction Among Woman With Endometriosis	Irrelevant study type
Lebanese University, 2023	Comparative Study on the Efficacy of Ovarian Stimulation Protocols on the Success Rate of ICSI in Female Infertility	Irrelevant outcome
Enteris BioPharma Inc., 2022	Study to Evaluate the Pharmacodynamics and Efficacy of Leuprolide Tablets (Ovarest¬Æ) in Women With Endometriosis	Irrelevant study type
Catholic University of the Sacred Heart, 2020	Prospective Evaluation of Near-infrared Fluorescence Imaging Use as a Supportive Tool in Deep Infiltrating Endometriosis Surgery	Intervention not of interest
Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), 2012	Treatment of Endometriosis With Norethindrone Acetate (NA) VS. Gonadotropin-Releasing Hormone (GnRH) Agonist (Lupron Depot 11.25 mg)	Irrelevant outcome
University Hospital, Clermont-Ferrand, 2019	Estimation of Vascularization After Treatment of Deep Rectovaginal Endometriosis Node by Rectal Shaving	Intervention not of interest
Kissei Pharmaceutical Co., Ltd., 2019	Late Phase II Clinical Study of KLH-2109 in Patients With Endometriosis	Irrelevant outcome
Tanta University, 2022	The Relation Between MiR-125b-5p and Staging of Endometriosis	Intervention not of interest

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University Hospital, Montpellier, 2015	Infertility and Endometriosis Cohort	Irrelevant outcome
Yonsei University, 2020	Vasopressin Injection Technique to Preserve Ovarian Reserve in Surgery for Unilateral Ovarian Endometriomas	Intervention not of interest
Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, 2022	Metabolomic Profile in Women With and Without Endometriosis	Irrelevant study type
Mahidol University, 2013	Effect of Pre-operative Depo Medroxyprogesterone Acetate on Serum Anti-mullerian Hormone Level After Laparoscopic Ovarian Cystectomy of Endometriomas	Intervention not of interest
AZ Jan Palfijn Gent, 2015	The Influence of Adjuvant Medical Treatment of Peritoneal Endometriosis on the Outcome of IVF. A Prospective Randomized Analysis.	Irrelevant outcome
University Hospital, Rouen, 2017	MEdical Versus SUrgical Treatments of Rectal Endometriosis	Irrelevant outcome
IRCCS Sacro Cuore Don Calabria di Negrar, 2024	ENDS (ENDometriosis & FuSobacterium) Unveiling the Contribution of Fusobacterium Infection to the Development of Endometriosis	Irrelevant study type
Hospital Clinic of Barcelona, 2009	Randomized Study on Endometrioma Treatment	Intervention not of interest
Guang'anmen Hospital of China Academy of Chinese Medical Sciences, 2016	Traditional Chinese Medicine Sequential Treatment for Endometriosis Associated Infertility	Intervention not of interest

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Centre for Endocrinology and Reproductive Medicine, Italy, 2024	Degarelix in the Treatment of Endometriosis Recurrence	Irrelevant outcome
King Chulalongkorn Memorial Hospital, 2017	Effectiveness of Levonorgestrel-intrauterine System (LNG-IUS) Versus Depot Medroxyprogesterone Acetate (DMPA) in Treatment of Pelvic Pain in Clinically Diagnosed Endometriotic Patients	Intervention not of interest
Taipei Veterans General Hospital, Taiwan, 2010	Maintenance Therapy of Levonorgestrel-releasing Intrauterine System (LNG-IUS) to Prevent the Recurrence of Symptomatic Endometriosis After Conservative Surgery	Irrelevant outcome
OMRIX Biopharmaceuticals, 2009	Evaluation of Adhexil Safety and Efficacy in Prevention and/or Reduction of Adhesions in Gynecological Surgery	Intervention not of interest
University Hospital Muenster, 2021	Ovariopexy for Adhesion Prevention After Laparoscopic Removal of Endometriosis of the Pelvic Side Wall or the Ovary	Intervention not of interest
Yonsei University, 2022	Catheter-directed Sclerotherapy Versus Surgical Resecction: Randomized Controlled Trial Comparing Ovarian Function and Therapeutic Efficacy After Treatment of Ovarian Endometrioma	Intervention not of interest
Assistance Publique - Hôpitaux de Paris, 2022	Deferred Versus Fresh Embryo Transfers	Irrelevant population
Rajavithi Hospital, 2022	Desogestrel for the Preoperative Treatment of Endometrioma Compared With Placebo	Intervention not of interest
AbbVie, 2021	Study to Evaluate the Long-Term Safety and Efficacy of Elagolix in Adults With Moderate to Severe Endometriosis-Associated Pain	Intervention not of interest

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Mahidol University, 2011	The Effectiveness of Lng IUD for Treatment of the Patient Undergone Conservative Surgery for Pelvic Endometriosis	Intervention not of interest
University of Tennessee, Chattanooga, 2021	Postoperative Narcotic Use After Laparoscopic Gynecologic Surgery	Intervention not of interest
Boston Children's Hospital, 2015	The Effect of Hormonal Add-Back Therapy in Adolescents Treated With a GnRH Agonist for Endometriosis: A Randomized Trial	Intervention not of interest
University of Sao Paulo, 2024	Cannabidiol for the Treatment of Pelvic Pain in Endometriosis (DREAMLAND)	Irrelevant population
Peking University People's Hospital, 2016	Reproductive Outcome of EM Treated by GnRH-a Associated With Laparoscopy	Irrelevant outcome
University of Louisville, 2023	The Use of Low Dose Metronidazole to Decrease Postoperative Pain After Endometriosis Surgery	Intervention not of interest
Yale University, 2024	Pre-IVF Treatment With a GnRH Antagonist in Women With endometriosis_temp	Irrelevant outcome
AbbVie (prior sponsor, Abbott), 2018	A Clinical Study to Evaluate the Safety and Efficacy of Elagolix in Subjects With Moderate to Severe Endometriosis-Associated Pain	Intervention not of interest
Hospices Civils de Lyon, 2021	Sexual Health After Endometriosis Surgery	Intervention not of interest
Cairo University, 2018	Mini Laparotomy With Laparoscopy for Management of Endometrioma	Intervention not of interest
Jagiellonian University, 2023	Endometriosis and Chronic Endometritis	Irrelevant study type

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Bayer, 2016	Comparative Study of BAY86-5300 With an Extended Flexible Regimen for Endometriosis	Intervention not of interest
Jagiellonian University, 2023	Organic Pollutants in Pelvic Endometriosis	Irrelevant outcome
Far Eastern Memorial Hospital, 2023	Comparisons of the Therapeutic Effects of Dienogest and Danazol on Endometriosis	Intervention not of interest
Semmelweis University, 2022	The Impact of NOSE-colectomy on Fertility and Quality of Life Among Patients With Colorectal Endometriosis	Intervention not of interest
Nobelpharma, 2010	Efficacy and Safety,Long-term Study of Low-dose Oral Contraceptive Pill to Treat Dysmenorrhea.	Intervention not of interest
Northwestern University, 2023	ICG to Assess Ovarian Perfusion	Intervention not of interest
Fundación Santa Fe de Bogota, 2016	Impact vs. Dienogest: A Combined Oral Contraceptive in the Size of Endometriomas	Intervention not of interest
Medstar Health Research Institute, 2023	Transvaginal Low-level Laser Therapy to Improve Pelvic Pain and Sexual Function in Patients With Endometriosis.	Intervention not of interest
Rigshospitalet, Denmark, 2007	Use of Arimidex and Zoladex as Pretreatment to IVF in Women With Ovarian Endometriosis	Irrelevant outcome
TriHealth Inc., 2024	Histologic Comparison of Ablative Techniques for Endometriosis - a Randomized Trial	Intervention not of interest

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Hospital Clinic of Barcelona, 2008	Pentoxifylline and Endometriosis	Intervention not of interest
Mayo Clinic, 2024	Comparison of Proton or Intensity Modulated Radiation Therapy After Surgery for Endometrial or Cervical Cancer	Irrelevant population
Asian Institute of Gastroenterology, India, 2023	The Use of MicroRNAs Dysregulation as Potential Biomarkers for Effective Diagnosis of Endometriosis	Intervention not of interest
Indonesia University, 2023	Effect of Propolis Administration for Dysmenorrhea in Endometriosis Patient With Levonorgestrel Implant Therapy	Intervention not of interest
University of Campinas, Brazil, 2017	Clinical Trial the Use of Levonorgestrel-releasing Intrauterine System Versus Etonogestrel Implant in Endometriosis	Intervention not of interest
Hospices Civils de Lyon, 2024	Optical Biopsy in Gynecological Surgery	Intervention not of interest
Uludag University, 2020	Surgery Before Embryo Transfer in ERROR (Endometrioma Related Reduction in Ovarian Reserve)	Intervention not of interest
Tenon Hospital, Paris, 2009	Laparoscopy Versus Laparotomy for Colorectal Endometriosis	Intervention not of interest
Bakirkoy Dr. Sadi Konuk Research and Training Hospital, 2021	New Cross Linked Hyaluronan Gel After Deep Infiltrating Endometriosis Surgery	Intervention not of interest

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NYU Langone Health, 2023	The Using Postoperative Ketamine and Exploring the Effect on Endometriosis Pain (UPKEEEP) Study	Intervention not of interest
Ruby Hall IVF and Endoscopy Centre, 2015	Case Report of Endometrioma in Layers of Broad Ligament.	Intervention not of interest
Dr Afchine Fazel, 2022	EndoSearch : Endometriosis Biomarkers	Irrelevant study type
Milton S. Hershey Medical Center, 2017	Study of Conventional Laparoscopic Hysterectomy Versus Robot-Assisted Laparoscopic Hysterectomy at a Teaching Institution	Intervention not of interest
Kanuni Sultan Suleyman Training and Research Hospital, 2020	The Effect of Dydrogesterone on Sexual Function in Women With Endometriosis	Intervention not of interest
University of Sao Paulo, 2015	Levonorgestrel-releasing Intrauterine System in Patients With Endometriosis	Irrelevant outcome
National Center for Complementary and Integrative Health (NCCIH), 2008	Endometriosis : Traditional Medicine vs Hormone Therapy	Intervention not of interest
Seoul National University Hospital, 2017	Trial Comparing Preoperative Dienogest Therapy Followed by Surgery vs. Upfront Surgery to Save Ovarian Reserve in Young Women With Ovarian Endometrioma	Intervention not of interest
The Cleveland Clinic, 2018	SO+IUI After Operative Laparoscopy in Patients With Advanced Stage Endometriosis	Intervention not of interest

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SLRs reference explosion (n= 34)		
Lata, 2014	Effectiveness of conservative surgery and adjunctive hormone suppression therapy versus surgery alone in the treatment of symptomatic endometriosis: A systematic review with meta-analysis	SLR for reference explosion, not included in review
Wong, 2011	Hormonal treatment for endometriosis associated pelvic pain	SLR for reference explosion, not included in review
Yan, 2022	Oral gonadotropin-releasing hormone antagonists for treating endometriosis-associated pain: a systematic review and network meta-analysis	SLR for reference explosion, not included in review
Xin, 2023	Efficacy and safety of oral gonadotropin-releasing hormone antagonists in moderate-to-severe endometriosis-associated pain: a systematic review and network meta-analysis	SLR for reference explosion, not included in review
Eberle, 2024	Medical Management of Ovarian Endometriomas: A Systematic Review and Meta-analysis	SLR for reference explosion, not included in review
Jia, 2012	Health-related quality of life in women with endometriosis: A systematic review	SLR for reference explosion, not included in review

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Muzii, 2023	The Efficacy of Dienogest in Reducing Disease and Pain Recurrence After Endometriosis Surgery: a Systematic Review and Meta-Analysis	SLR for reference explosion, not included in review
Zajec, 2022	Current status and challenges of drug development for hormonal treatment of endometriosis: a systematic review of randomized control trials	SLR for reference explosion, not included in review
Yeung, 2009	Laparoscopic Management of Endometriosis: Comprehensive Review of Best Evidence	SLR for reference explosion, not included in review
Hodgson, 2020	Interventions for endometriosis-related infertility: a systematic review and network meta-analysis	SLR for reference explosion, not included in review
Lan, 2013	Analysis of the levonorgestrel-releasing intrauterine system in women with endometriosis	SLR for reference explosion, not included in review
Brown, 2010	Gonadotrophin-releasing hormone analogues for pain associated with endometriosis.	SLR for reference explosion, not included in review
Jones, 2024	A systematic review to determine use of the Endometriosis Health Profiles to measure quality of life outcomes in women with endometriosis	SLR for reference explosion, not included in review

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Yap, 2004	Pre and post operative medical therapy for endometriosis surgery.	SLR for reference explosion, not included in review
Brown, 2014	Endometriosis: An overview of Cochrane Reviews	SLR for reference explosion, not included in review
Tan, 2013	Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding	SLR for reference explosion, not included in review
Soares, 2012	Pharmacologic therapies in endometriosis: A systematic review	SLR for reference explosion, not included in review
Becker, 2017	Reevaluating response and failure of medical treatment of endometriosis: a systematic review	SLR for reference explosion, not included in review
D,ÄôAlterio, 2021	Medical and surgical interventions to improve the quality of life for endometriosis patients: A systematic review	SLR for reference explosion, not included in review
Veth, 2023	Gonadotropin-releasing hormone analogues for endometriosis.	SLR for reference explosion, not included in review

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Gibbons, 2021	Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery.	SLR for reference explosion, not included in review
Zakhari, 2021	Endometriosis recurrence following post-operative hormonal suppression: a systematic review and meta-analysis.	SLR for reference explosion, not included in review
Wattanayingcharoenchai, 2021	Postoperative hormonal treatment for prevention of endometrioma recurrence after ovarian cystectomy: a systematic review and network meta-analysis.	SLR for reference explosion, not included in review
Song, 2018	Efficacy of levonorgestrel releasing intrauterine system as a postoperative maintenance therapy of endometriosis: A meta-analysis.	SLR for reference explosion, not included in review
Fu, 2017	Progesterone receptor modulators for endometriosis.	SLR for reference explosion, not included in review
Marqui, 2015	Evaluation of endometriosis-associated pain and influence of conventional treatment: a systematic review.	SLR for reference explosion, not included in review
Ferrero, 2015	Endometriosis: the effects of dienogest.	SLR for reference explosion, not included in review

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Andres, 2015	Dienogest in the treatment of endometriosis: systematic review.	SLR for reference explosion, not included in review
Gerlinger, 2012	Treatment of endometriosis in different ethnic populations: a meta-analysis of two clinical trials.	SLR for reference explosion, not included in review
Ferrero, 2010	Endometriosis.	SLR for reference explosion, not included in review
Vercellini, 2009	Medical treatment for rectovaginal endometriosis: what is the evidence?.	SLR for reference explosion, not included in review
Johnson, 2007	Endometriosis.	SLR for reference explosion, not included in review
Abou-Setta, 2006	Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery.	SLR for reference explosion, not included in review
Sagsveen, 2003	Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density.	SLR for reference explosion, not included in review

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1.2.2. Evidence base overview

In total, 139 reports representing 111 unique studies (RCTs) met the eligibility criteria and were included in the SLR. Of the 139 reports, 114 were full-length journal publications, 23 were available as conference abstracts, and two were identified from a trial registry. The year of publication, based on the primary study reports, ranged from 1988 to 2023. The number of participants in each trial ranged from 10 to 2019 (5, 6). Out of the 139 studies extracted, 15 primary studies are associated with 28 secondary publications (a total of 43 studies), while 95 primary studies were unlinked. The characteristics of included studies are listed in Table 6**.**

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Table 6 Characteristics of included studies

Author, Year	Study name, Trial ID	Study location	Sample size	Intervention	Comparator(s)	Study Endpoints
Journal articles: Relugolix (n= 4)						
Osuga, 2021 (7)	NCT01458301	Japan	487	Relugolix	Placebo Leuprorelin Acetate	DYS; DYSP; Miscellaneous Pelvic pain; EHP; Safety
Osuga, 2021 (8)	NCT01452685	Japan	397	Relugolix	Placebo	DYS; DYSP; Miscellaneous Pelvic pain; EHP; Safety
Giudice, 2022 (Primary study) (9)	SPIRIT 1; NCT03204318 SPIRIT 2; NCT03204331	SPIRIT1 - Multinational SPIRIT 2 - Multinational	1251	Relugolix combination therapy Delayed relugolix combination therapy	Placebo	DYS; DYSP; NMPP; OPP; TPP; EHP; Safety; BMD; Change in LDL-C/HDL-C
Harada, 2022 (10)	NCT03931915	Japan	335	Relugolix	Leuprorelin	DYS; NMPP; DYSP; EHP; Miscellaneous Pelvic pain; Safety; HRQoL
Conference abstracts: Relugolix (n= 7)						

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As-Sanie, 2020 (Linked to Giudice, 2022) (11)	SPIRIT; NCT03204318	Multinational	507	Relugolix combination therapy Delayed relugolix combination therapy	Placebo	DYS; NMPP; EHP; BMD
As-Sanie, 2021 (Linked to Giudice, 2022) (12)	SPIRIT 1; NCT03204318 SPIRIT 2; NCT03204331	Multinational	1261	Relugolix combination therapy Delayed relugolix combination therapy	Placebo	EHP
Becker, 2021 (Linked to Giudice, 2022) (13)	SPIRIT 1; NCT03204318 SPIRIT 2; NCT03204331	USA	834	Relugolix combination therapy Delayed relugolix combination therapy	Placebo	DYS; NMPP; EHP
McClung, 2021 (Linked to Giudice, 2022) (6)	LIBERTY SPIRIT 1; NCT03204318 SPIRIT 2; NCT03204331	USA	2019	Relugolix combination therapy Delayed relugolix combination therapy	Placebo	BMD

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McClung, 2022 (Linked to Giudice, 2022) (14)	LIBERTY SPIRIT 1; NCT03204318 SPIRIT 2; NCT03204331	USA	1251	Relugolix combination therapy Delayed relugolix combination therapy	Placebo	BMD
As-Sanie, 2022 (Linked to Giudice, 2022) (15)	SPIRIT 1; NCT03204318 SPIRIT 2; NCT03204331	Multinational (North American and overall)	1251	Relugolix combination therapy Delayed relugolix combination therapy	Placebo	DYS; NMPP; Safety; BMD
Becker, 2023 (Linked to Giudice, 2022) (16)	SPIRIT 1; NCT03204318 SPIRIT 2; NCT03204331	USA	255	Relugolix combination therapy Delayed relugolix combination therapy	Placebo	DYS; NMPP
Journal articles: Buserelin (n= 11)						
Tummon,1988 (17)		USA	38	Leuprolide or buserelin IN or buserelin SC	Danazol	BMD

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Dlugi, 1988 (18)		USA	19	Buserelin acetate plus luteinizing hormone-releasing hormone ethyl amide	Danazol	Change in LDL-C/HDL-C
Matta, 1988 (19)		UK	13	Buserelin	Danazol	Safety outcomes, BMD
Lemay,1988 (20)		Canada	13	Intranasal buserelin	Subcutaneous buserelin	DYS, DYSP, Miscellaneous Pelvic Pain, Safety outcomes
Dawood, 1989 (21)		USA	31	Buserelin	Danazol	BMD
Fedele, 1989 (22)	NR	Italy	62	Buserelin	Danazol	DYSP, Miscellaneous Pelvic Pain, Safety outcomes
Fedele, 1993 (23)		Italy	35	Buserelin acetate	Expectant Management	DYS, Safety outcome
Fukushima, 1993 (Primary study) (24)		Japan	28	Buserelin	Danazol	BMD
Fukushima, 1995 (Linked to		Japan	19	Buserelin	Danazol	BMD

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Fukushima, 1993) (25)						
Nieto, 1996 (26)		Spain	43	Gestrinone	Buserelin	Miscellaneous pelvic pain, Safety outcomes, HRQoL
Harada, 2009 (27)	NR	Japan	271	Dienogest	Buserelin acetate	DYSP, Miscellaneous pelvic pain, Safety outcomes, BMD, HRQoL
Journal articles: Goserelin (n= 20)						
Lemay, 1991 (28)		Canada	39	Goserelin	Danazol	Safety outcomes, Change in LDL-c/HDL-c
Shaw,1992 (29)		Europe,18 centres	307	Goserelin	Danazol	Miscellaneous pelvic pain, Safety outcomes
Vercellini, 1993 (30)	NR	Italy	57	Goserelin	Cyclic oral contraceptive	DYS, DYSP, NMPP, Safety outcomes
Magini,1993 (31)		Italy	24	Goserelin	Goserelin	DYS, DYSP, NMPP, Miscellaneous Pelvic Pain, Safety outcomes
Damario, 1994 (32)		USA	315	Goserelin	Danazol	Safety outcomes, BMD

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Howell, 1995 (33)	NR	UK	50	Goserelin	Goserelin plus HRT	Safety outcomes, BMD, Change in HDL-C/ LDL/C
Kiilholma, 1995 (34)		Finland	93	Goserelin acetate plus a combination of 17 β-E2 and norethisterone acetate	Goserelin acetate plus placebo	Miscellaneous pelvic pain
Makarainen, 1996 (35)		Finland	29	Goserelin acetate plus medroxyprogesterone acetate	Goserelin acetate plus placebo	Only Qualitative Data
Wingfield, M., 1996 (36)		Australia, New Zealand	71	Goserelin	Danazol	Safety outcomes
Taskin, 1997 (37)		Turkey	58	Goserelin acetate plus tibolone	Goserelin acetate plus iron pill	Miscellaneous pelvic pain
Sowter, 1997 (38)		United Kingdom	77	Neo-adjuvant goserelin	No preoperative endometrial preparation and surgery	DYS, Miscellaneous pelvic pain, HRQoL
Moghissi, 1998 (39)	NR	USA	345	Goserelin	Goserelin plus estrogen and medroxyprogesterone acetate	Miscellaneous pelvic pain, BMD
Franke, 2000 (40)		Multiple centers in Netherlands	41	Goserelin plus placebo	Goserelin plus HRT (17b-E2 and norethisterone acetate)	Miscellaneous pelvic pain, BMD

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Pierce, 2000 (41)		United Kingdom	45	Goserelin acetate plus estradiol and norethisterone acetate	Goserelin acetate	BMD
Bergqvist, 2000 (42)	NR	Sweden, Norway, Denmark and Finland	213	Goserelin	Nafarelin	Miscellaneous pelvic pain, Safety outcomes
Soysal, 2004 (43)		Turkey	80	Adjuvant goserelin plus anastrozole	Adjuvant goserelin plus placebo	DYS, DYSP, Miscellaneous pelvic pain, BMD
H Akram, 2006 (44)		Pakistan	40	Goserelin	Danazol	Miscellaneous pelvic pain, Safety outcomes
Gong, 2015 (45)		China	64	Adjuvant goserelin initiated 3–5 day	Adjuvant goserelin initiated on days 1–5 of menstruation	Miscellaneous pelvic pain, BMD
Takaesu, 2016 (46)		Japan	190	Adjuvant dienogest	Adjuvant goserelin	Safety outcomes
Ozaki, 2020 (47)		Japan	74	Neo-adjuvant goserelin acetate	Neo-adjuvant dienogest	Miscellaneous pelvic pain, Safety outcomes
Conference abstract: Goserelin (n= 1)						
Scarpellini, 2010 (48)		Italy	45	Anastrazole plus goserelin	Goserelin	Miscellaneous pelvic pain

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Journal articles: Leuprorelin (n= 38)						
Tummon, 1989 (49)		USA	15	Leuprolide	Danazol	Miscellaneous pelvic pain
Dlugi, 1990 (50)	NR	USA	63	Leuprolide acetate	Placebo	DYS, DYSP, NMPP, Change in LDL-C/HDL-C
Wheeler, 1992 (Primary study) (51)		USA	270	Leuprolide acetate	Danazol	DYS, DYSP
Wheeler, 1993 (Linked to Wheeler, 1992) (52)		USA	270	Leuprolide acetate	Danazol	Safety outcomes, BMD, Change in LDL-C/ HDL-C
Surrey, 1992 (53)		USA	20	Leuprolide acetate plus Norethindrone	Leuprolide acetate plus Placebo	Miscellaneous pelvic pain, BMD, Change in LDL-C/HDL-C
Vercellini,1994 (54)		Italy	42	Danazol	Leuprolide acetate plus danazol	DYS, DYSP, NMPP, Safety outcomes, Change in LDL-C/HDL-C
Dawood, 1995 (55)		USA	12	Leuprolide acetate plus placebo	Danazol plus placebo	BMD

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Crosignani, 1996 (56)		Italy	30	Leuprorelin acetate (11.25 mg)	Leuprorelin acetate (3.75 mg)	DYSP, NMPP
Vercellini,1996 (57)		Six centres in Italy	55	Gestrinone	Leuprolide acetate	DYS, DYSP, NMPP, Safety outcomes, BMD, Change in LDL-C/HDL-C
Freundl, 1998 (Primary study) (58)		Germany	27	Leuprorelin acetate depot + Ethinyloestradiol + Desogestrel	Leuprorelin acetate depot + Placebo	DYS, DYSP, NMPP, Safety outcomes, BMD
Somekawa, 1999 (59)		Japan	110	Leuprolide acetate	Leuprolide acetate plus menatetrenone Leuprolide acetate plus menatetrenone Leuprolide acetate plus menatetrenone plus 1,25-(OH)2D3	BMD
Gnoth, 1999 (Linked to Freundl, 1998) (60)		Germany	27	Leuprorelin acetate depot + Ethinyloestradiol + Desogestrel	Leuprorelin acetate depot + Placebo	BMD

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Ling, 1999 (61)		USA	100	Leuprolide	Placebo	TPP
Hurst, 2000 (62)		USA	13	Leuprolide acetate plus oral estradiol	Leuprolide acetate plus placebo	Only Qualitative Data
Cheung, 2000 (63)		China	48	Triptorelin plus leuprorelin acetate	Leuprorelin acetate plus triptorelin	Safety outcomes, Change in LDL-C/HDL-C
Miller,2000 (64)		USA	120	Leuprolide acetate	Placebo	Miscellaneous pelvic pain, HRQoL
Busacca, 2001 (65)		Italy	89	Adjuvant leuprolide acetate	Patients with no adjuvant therapy	Miscellaneous pelvic pain, Safety outcomes
Regidor, 2001 (Primary study) (66)		Germany	48	Leuprorelin acetate	Gestagen lynestrenol	DYS, DYSP, Miscellaneous pelvic pain, Safety outcomes
Irahara, 2001 (67)		Japan	21	Leuprolide acetate plus conjugated Estrogens plus medroxyprogesterone Acetate	Leuprolide acetate	BMD
Rotondi, 2002 (68)		Italy	81	Leuprolide acetate	Danazol	Safety outcomes

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Zupi, 2004 (69)	NR	Italy	133	Leuprolide acetate plus transdermal E2 (Esclima) and daily oral norethindrone	Oral ethinyl E2 (Esclima) plus gestodene daily	DYS, DYSP, Miscellaneous pelvic pain, Safety outcomes, BMD, HRQoL
Petta, 2005 (70)		Brazil	82	Levonorgestrel-releasing intrauterine system	Leuprolide	Miscellaneous pelvic pain, Safety outcomes
Crosignani, 2006 (71)		Multinational	299	Depot medroxyprogesterone acetate	Leuprolide acetate	Safety outcomes, BMD, HRQoL
Gomes, 2007 (5)		USA	10	Levonorgestrel-releasing intrauterine system	Leuprorelin	Miscellaneous pelvic pain
Sesti, 2007 (72)		Italy	222	Adjuvant triptorelin or leuprorelin	Adjuvant placebo or continuous low-dose monophasic oral contraceptive (ethynyl estradiol plus gestoden) or with continuative dietary therapy (vitamins, minerals salts, lactic ferments, fish oil)	DYS, DYSP, NMPP
Ferreira, 2010 (Linked to		Brazil	44	Levonorgestrel intrauterine system	Leuprolide acetate	Miscellaneous pelvic pain, Change in LDL-C/HDL-C

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Vieira, 2007) (73)						
Strowitzki, 2010 (Linked to Strowitzki, 2009) (74)	NR	Multinational	252	Dienogest	Leuprolide acetate	TPP, Miscellaneous pelvic pain, Safety outcomes, BMD. HRQoL
Guzick, 2011 (75)		USA	47	Leuprolide plus norethindrone	Levlen plus normal saline	Miscellaneous pelvic pain, HRQoL
Strowitzki, 2012 (Linked to Strowitzki, 2009) (76)		Germany	252	Dienogest	Leuprolide acetate	DYS, DYSP, TPP, Miscellaneous pelvic pain, change in LDL-C/HDL-C, HRQoL
Mettler, 2014 (77)		Germany	450	Leuprorelin acetate	Surgical laparoscopy alone Adjuvant leuprolide acetate treatment	DYS, DYSP, Miscellaneous pelvic pain
Granese, 2015 (78)		Italy	78	Adjuvant dienogest + estradiol valerate	Adjuvant leuproline acetate	EHP, Safety outcomes
Tang, 2017 (79)		China	50	Leuprorelide acetate	Leuprorelide acetate (one dose)	BMD

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Shen, 2017 (80)		China	100	Leuprolide acetate plus 1.25mg tibolone	Leuprolide acetate plus 2.5 mg tibolone	BMD
Abdou, 2018 (81)		Egypt	284	Dienogest	Leuprolide acetate	DYSP, Miscellaneous pelvic pain, safety outcomes
D'Hooghe, 2019; (82)	NCT01767090	Europe and Japan	540	ASP1707 (3 mg) ASP1707 (5 mg) ASP1707 (10 mg) ASP1707 (15 mg)	Placebo Leuprorelin	DYS, DYSP, NMPP, OPP, Safety outcomes, BMD, HRQoL
Ceccaroni, 2021 (83)		Italy	170	Adjuvant triptorelin plus leuprorelin	Adjuvant dienogest	DYS, DYSP, Miscellaneous pelvic pain, safety outcomes
Bala, 2022 (84)	NR	Pakistan	360	Adjuvant leuprorelin acetate	Laparoscopy with no hormonal therapy or any medical therapy Laparoscopy with hormonal therapy or any medical therapy	DYS, DYSP, Miscellaneous pelvic pain
Yu, 2022 (85)		China	158	Adjuvant leuprorelin	Adjuvant dydrogestone	Safety outcomes
Data obtained from Clinical trials.gov (NCT02203331): Leuprorelin (n= 1)						
		Multinational	319	Levonorgestrel		

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Bayer,2023; (86)	NCT02203331			Anastrozole 300 µg/d plus levonorgestrel Anastrozole 600 µg/d plus levonorgestrel Anastrozole 1050 µg/d plus levonorgestrel Leuprolide acetate	Placebo Comparator: Placebo intravaginal ring plus placebo depot injection	Miscellaneous pelvic pain, safety outcomes
Conference abstract: Leuprorelin (n= 13)						
Regidor, 2002 (Linked to Regidor, 2001) (87)		Germany	55	Leuprorelin acetate	Gestagen lynestrenol	Miscellaneous pelvic pain
Archer, 2004 (Primary study) (88)		USA and Canada	274	Leuprolide acetate	Depot medroxyprogesterone acetate subcutaneous	Miscellaneous pelvic pain, safety outcomes, BMD
Carson, 2005 (Linked to Archer, 2004) (89)		USA and Canada	274	Leuprolide acetate	Depot medroxyprogesterone acetate subcutaneous	Miscellaneous pelvic pain, BMD

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Vieira, 2007 (Primary study) (90)		Brazil	44	Levonorgestrel Intra-uterine system	Leuprolide acetate	Change in LDL-C/HDL-C
Strowitzki, 2009 (Primary study) (91)		Germany	252	Dienogest	Leuprolide acetate	Miscellaneous pelvic pain
Muneyyirci-Delale, 2012 (Primary study) (92)		USA	62	Leuprolide acetate depot	Norethindrone acetate	Miscellaneous pelvic pain
Muneyyirci-Delale, 2013 (Linked to Muneyyirci-Delale, 2012) (93)		USA	62	Leuprolide acetate depot	Norethindrone acetate	BMD
Muneyyirci-Delale, 2013 (Linked to Muneyyirci-Delale, 2012) (94)		USA	62	Leuprolide acetate depot	Norethindrone acetate	NMPP, Miscellaneous pelvic pain,

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Muneyyirci-Delale,2014 (Linked to Muneyyirci-Delale, 2012) (95)		USA	62	Leuprolide acetate depot	Norethindrone acetate	HRQoL
Muneyyirci-Delale, 2015 (Linked to Muneyyirci-Delale, 2012) (96)		USA	62	Leuprolide acetate depot	Norethindrone acetate	DYS, NMPP
Charles, 2015 (Linked to Muneyyirci-Delale, 2012) (97)		USA	62	Leuprolide acetate depot	Norethindrone acetate	Change in LDL-C/HDL-C
Muneyyirci-Delale, 2017 (Linked to Muneyyirci-Delale, 2012) (98)		USA	62	Leuprolide acetate depot	Norethindrone acetate	Miscellaneous pelvic pain

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Jain, 2021 (Linked to Kachhawa, 2018) (99)		India	50	Leuprolide acetate	Cabergoline	Miscellaneous pelvic pain
Journal articles: Nafarelin (n= 19)						
Valimaki, 1989 (100)		Finland	18	Nafarelin	Danazol	Change in LDL-C/HDL-C
Burry, 1989 (101)		USA	53	800 µg/day Nafarelin acetate	800 mg/day Danazol	Safety outcomes, Change in LDL-C/HDL-C
				400 µg/day Nafarelin acetate	600 mg/day Danazol	
Kennedy, 1990 (Primary study) (102)		UK	82	Nafarelin acetate	Danazol	Miscellaneous pelvic pain, Safety outcomes
Shaw, 1990 (Linked to Kennedy, 1990) (103)		United Kingdom	82	Nafarelin acetate	Danazol	DYS, DYSP, Miscellaneous pelvic pain
Rolland, 1990 (104)		13 centres in seven	194	Nafarelin plus danazol placebo	Danazol plus nafarelin placebo	Safety outcomes

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		European countries				
Fraser, 1991 (105)		Australia	40	Nafarelin acetate	Danazol	DYSP, Miscellaneous pelvic pain
The Nafarelin European Endometriosis Trial Group (NEET), 1992 (106)		UK	307	Nafarelin	Danazol	DYS, DYSP, Miscellaneous pelvic pain, Safety outcomes, HRQoL
Eldred, 1992 (107)		UK	94	Nafarelin plus norethisterone	Nafarelin plus matching placebo capsule	Safety outcomes, BMD
Parazzini,1994 (108)		Italy	75	Adjuvant nafarelin	Adjuvant placebo	Miscellaneous pelvic pain
Finkelstein, 1994 (Primary study) (109)		USA	50	Nafarelin	Nafarelin and parathyroid hormone	Safety outcomes, BMD, Change in LDL-C/HDL-C
Orwoll, 1994 (Linked to Hornstein, 1995) (110)		USA	173	Nafarelin	Nafarelin plus placebo	BMD

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Hornstein, 1995 (Primary study) (111)		USA	179	Nafarelin plus placebo	Nafarelin	DYS, DYSP, Miscellaneous pelvic pain
Hornstein, 1997 (112)		USA	93	Adjuvant nafarelin	Adjuvant placebo	TPP
Bergqvist, 1997 (113)		UK	49	Nafarelin plus norethisterone	Nafarelin plus placebo Nafarelin 400 µg plus placebo	Safety outcomes
Finkelstein, 1998 (Linked to Finkelstein, 1994) (114)		USA	43	Nafarelin acetate	Nafarelin and parathyroid hormone	Safety outcomes, BMD
Finkelstein, 1999 (Linked to Finkelstein, 1994) (115)		USA	38	Nafarelin	Nafarelin and parathyroid hormone	BMD
Tahara, 2000 (116)		Japan	15	Nafarelin (full dose) plus nafarelin (half dose)	Nafarelin (full dose)	TPP, Safety outcomes, BMD
Bergqvist, 2001 (117)		Sweden	30	Nafarelin	Medroxyprogesterone acetate	DYS, DYSP, Miscellaneous pelvic pain, HRQoL

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Cheng, 2005 (118)		Taiwan	59	Nafarelin	Danazol	DYS, DYSP, Miscellaneous pelvic pain, safety outcomes, Change in LDL-C/HDL-C
Journal articles: Triptorelin (n= 12)						
Cirkel, 1995 (119)		Germany	55	Triptorelin	Danazol	DYS, DYSP, Miscellaneous pelvic pain, Safety outcomes, Change in LDL-C/HDL-C
Lindsay, 1996 (120)		Netherlands	29	Triptorelin plus tibolone	Triptorelin plus placebo	Safety outcomes, BMD
Bergqvist, 1998 (121)		Sweden	49	Triptorelin depot	Placebo	DYSP, Miscellaneous pelvic pain, safety outcome
Morgante,1999 (122)		Italy	28	Adjuvant triptorelin plus by danazol	Adjuvant triptorelin alone	Miscellaneous pelvic pain, safety outcomes, BMD
Parazzini, 2000 (123)		Italy	101	Gestroden plus ethynlestradiol	Triptorelin	DYS, NMPP
Cosson, 2002 (124)		France	142	Adjuvant dienogest	Adjuvant triptorelin	DYS, DYSP, Miscellaneous pelvic pain, Safety

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						outcomes, Change in LDL-C/HDL-C
Wong, 2004 (125)		Hong Kong	40	Adjuvant danazol	Adjuvant triptorelin	Miscellaneous pelvic pain, safety outcomes
Ferrero, 2011 (126)		Italy	35	Letrozole plus triptorelin	Letrozole plus norethisterone acetate	DYSP, NMPP, Safety outcomes, BMD
Angioni, 2015 (127)		Italy	159	Adjuvant triptorelin	Surgery alone	HRQoL
Yang, 2019 (128)		China	130	Adjuvant triptorelin acetate	No treatment after surgery	Safety outcomes
Li, 2022 (Linked to Ipsen, 2016); (NCT03232281) (129)		China	300	Neo-adjuvant triptorelin pamoate	Neo-adjuvant triptorelin acetate	Miscellaneous pelvic pain, Safety outcomes
Ti, 2023 (130)		China	94	Adjuvant levonorgestrel-releasing intrauterine system + Triptorelin	Adjuvant triptorelin	DYS
Data obtained from Clinical trials.gov (NCT03232281): Triptorelin (n= 1)						

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Ipsen, 2016 (Primary study); (131)		China	300	Neo-adjuvant triptorelin pamoate	Neo-adjuvant triptorelin acetate	Miscellaneous pelvic pain, Safety outcomes
Journal articles: Other (n= 10)						
Acién, 2003 (Primary study) (132)		Spain	24	Decapeptyl plus dextrose	Decapeptyl plus dextrose plus recombinant Interleukin-2 (rIL-2)	Miscellaneous pelvic pain, Safety outcomes
Acién, 2005 (Linked to Acién, 2003) (133)		Spain	24	Decapeptyl plus dextrose plus rIL-2, 3 million IU	Decapeptyl plus dextrose plus rIL-2, 2 X 3 million IU	Miscellaneous pelvic pain
Al-Azemi, 2009 (134)		U.K.	25	HRT and tibolone + Zoladex (Immediate; Group 1)	Placebo (first 6-months) + Tibolone + Zoladex (Delayed: Group 2)	Miscellaneous pelvic pain, EHP, BMD
Bayoglu, 2011 (135)		Turkey	40	Adjuvant levonorgestrel-releasing intrauterine system	Adjuvant zoladex	TPP, Miscellaneous pelvic pain, safety outcomes
Almassinokiani, 2013 (136)		Iran	60	Adjuvant decapeptyl	Adjuvant simvastatin	DYS, DYSP, Miscellaneous pelvic pain

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Agarwal, 2015 (137)		USA	20	Deslorelin (D) plus low-dose estradiol add-back (D+E2 transdermal)	Deslorelin (D) plus E2 combined with testosterone (Estradiol ± Testosterone) nasal spray (D + E2 + T nasal)	DYS, DYSP, Miscellaneous pelvic pain, safety outcomes, BMD, Change in LDL-C/HDL-C, HRQoL
Gallagher, 2017 (138)	NCT00474851	USA	50	Norethindrone acetate plus conjugated estrogens	Norethindrone acetate plus placebo	HRQoL
Huang, 2018 (139)		China	100	Adjuvant GnRH-a	Standard laparoscopic surgical procedure alone	DYS, DYSP, Miscellaneous pelvic pain, safety outcomes
Fenghua, 2022 (140)		China	80	Adjuvant GnRH-a plus Mirena intrauterine device	Adjuvant GnRH-a	DYS
Tang, 2023 (141)		China	81	Adjuvant GnRH-a	Adjuvant dienogest	Miscellaneous pelvic pain
Conference abstracts: Other (n= 2)						
Cirstoiu, 2013 (142)		Romania	80	GnRH-a	Danazol plus gestrinone	BMD
Kachhawa, 2018 (Primary study) (143)		India	50	Cabergoline	GnRH-a	Miscellaneous pelvic pain

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Abbreviations: BDM, Bone Mineral Density; CEE, Conjugated Estrogens; D, Deslorelin; DMPA-SC, Depot Medroxyprogesterone Acetate - Subcutaneous; DNG, Dienogest; DYS, Dysmenorrhea; DYSP, Dyspareunia; E2, Estradiol; EHP, Endometriosis Health profile; GnRH-a, Gonadotropin-Releasing Hormone Agonist; HRQoL, Health-related quality of life, HRT, Hormone Replacement Therapy; IN, Intranasal; IU, International Units; IUD, Intrauterine Device; LA, Leuprolide Acetate; LDL-C/HDL-C, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol; LH-RH, NMPP, Non-Menstrual Pelvic Pain, OPP, Overall Pelvic Pain, Luteinizing Hormone-Releasing Hormone; LNG-IUS, Levonorgestrel-Releasing Intrauterine System; MPA, Medroxyprogesterone Acetate; NA, Norethindrone Acetate; NET, rIL-2, Recombinant Interleukin-2; SC, Subcutaneous Norethisterone Acetate;

Miscellaneous Pelvic Pain = pelvic pain that does not align with the definitions of Overall Pelvic Pain (OPP) or Total Pelvic Pain (TPP). MPP encompasses two main categories: the first includes cumulative or summed pain symptoms across dysmenorrhoea, dyspareunia, and non-menstrual pelvic pain (NMPP), but did not use the NRS, B&B, or modified B&B scales. The second category involves pelvic pain reported by study authors that is not specifically defined within the article (e.g. non-menstrual).

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1.3. Quality of included studies

A summary of the risk of bias assessment for each trial included in this review is presented in Table 7

The randomization process (D1) was consistently reported across trials; 65 out of 111 studies (58%) were considered low risk. 45 studies (41%) were judged to have some concerns because there was not enough information to determine if the allocation sequence was concealed until participants were enrolled and assigned to their intervention. One open label study (Fenghua 2022 (140)) was judged as high risk for D1 because it was unlikely that the allocation sequence was concealed from participants enrolled in the study. For D2, 33 studies were considered as having a high risk of bias because the studies were open label, whereas 24 studies were judged as having some concerns because there was not enough information to determine if participants were aware of their assigned intervention. Six studies were considered to have a high risk of bias for D3 because of missing outcome data but overall, this domain was consistently reported across trials; 105 out of 111 studies (95%) were considered as having a low risk of bias. Sixteen studies were judged as high risk for D4 because it was likely that outcome assessors were aware of the intervention received by study participants, whereas for 42 studies it was not reported if outcome assessors were blinded. For D5, only 58 out of 111 studies reported that the results were analysed in accordance with a pre-specified analysis plan, whereas 52 studies were judged as having some concerns because there was not enough information to determine if the analysis plan was pre-specified and one study (19) was judged as high risk. Overall, 35 out of 111 studies (32%) were judged as low risk, 38 out of 111 studies (34%) as having some concerns and 38 out of 111 (34%) as high risk.

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Table 7 Cochrane Risk of Bias Assessment

Study ID	Risk of Bias domains					
	D1	D2	D3	D4	D5	Overall
Giudice 2022 (SPIRIT 1) (9)	Low	Low	Low	Low	Low	Low
Giudice 2022 (SPIRIT 2) (9)	Low	Low	Low	Low	Low	Low
Zupi 2004 (69)	Low	High	Low	Some concerns	Low	High
Vercellini 1996 (57)	Low	Low	Low	Low	Low	Low
Tahara 2000 (116)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Osuga 2021 (8)	Low	Low	Low	Low	Low	Low
Crosignani 2006 (71)	Low	High	Low	Low	Low	High
Osuga 2021 (7)	Low	Low	Low	Low	Low	Low
Angioni 2015 (127)	Low	High	Low	High	Low	High
Fenghua 2022 (140)	High	High	Low	Some concerns	Some concerns	High
Dlugi 1988 (18)	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Hornstein 1997 (112)	Low	Low	Low	Low	Low	Low
Vercellini 1994 (54)	Low	High	Low	Some concerns	Some concerns	High
Ferrero 2011 (126)	Low	High	Low	Low	Low	High
Bayoglu 2011 (135)	Low	High	Low	Some concerns	Some concerns	High
Fedele 1993 (23)	Some concerns	High	Low	Some concerns	Some concerns	High
Gomes 2007 (5)	Low	High	Low	Low	Low	High
Cheng 2005 (118)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Shaw 1992 (29)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Wong 2004 (125)	Some concerns	High	Low	Some concerns	Some concerns	High
Parazzini 2000 (123)	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Morgante 1999 (122)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Parazzini 1994 (108)	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Tummon 1988 (17)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Cirkel 1995 (119)	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Howell 1995 (33)	Some concerns	High	Low	Some concerns	Some concerns	High
Vercellini 1993 (30)	Some concerns	High	Low	High	Some concerns	High

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Study ID	Risk of Bias domains					
	D1	D2	D3	D4	D5	Overall
Busacca 2001 (65)	Some concerns	High	Low	Some concerns	Some concerns	High
Regidor 2001 (66)	Low	High	Low	High	Some concerns	High
Crosignani 1996 (56)	Some concerns	High	Low	High	Some concerns	High
Hurst 2000 (62)	Low	Low	Low	Low	Low	Low
Akram 2006 (44)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Finkelstein 1994 (109)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Dlugi 1990 (50)	Low	Low	Low	Low	Low	Low
Franke 2000 (40)	Low	Low	Low	Low	Low	Low
Moghissi 1998 (39)	Low	Low	Low	Low	Low	Low
Makarainen 1996 (35)	Some concerns	Low	Low	Low	Low	Some concerns
Dawood 1995 (55)	Low	Low	Low	Low	Low	Low
Kennedy 1990 (102)	Some concerns	Low	Low	Low	Low	Some concerns
Tummon 1989 (49)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Bala 2022 (84)	Some concerns	High	Low	High	Some concerns	High
Pierce 2000 (41)	Low	Some concerns	Low	High	Some concerns	High
Rotondi 2002 (68)	Some concerns	Some concerns	High	Some concerns	Some concerns	High
Bergqvist 1998 (121)	Low	Some concerns	Low	Low	Low	Some concerns
Dawood 1989 (21)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Cheung 2000 (63)	Low	Low	Low	Low	Low	Low
Gallagher 2017 (138)	Low	Low	Low	Low	Low	Low
Takaesu 2016 (46)	Low	High	Low	Some concerns	Low	High
Gong 2015 (45)	Some concerns	High	Low	High	Some concerns	High
Tang 2017 (79)	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Damario 1994 (32)	Some concerns	High	High	High	Some concerns	High
Wingfield 1996 (36)	Low	High	High	High	Some concerns	High
Miller 2000 (64)	Low	Low	Low	Low	Low	Low
Irahara 2001 (67)	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns

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Study ID	Risk of Bias domains					
	D1	D2	D3	D4	D5	Overall
Soysal 2004 (43)	Low	Low	Low	Low	Low	Low
Taskin 1997 (37)	Low	Low	Low	Low	Low	Low
Lindsay 1996 (120)	Low	Low	Low	Low	Low	Low
Ferreira 2010 (73)	Low	High	Low	High	Low	High
Tang 2023 (141)	Some concerns	High	Low	High	Some concerns	High
Sesti 2007 (72)	Low	Low	Low	Low	Low	Low
Somekawa 1999 (59)	Some concerns	High	Low	Some concerns	Some concerns	High
Kiilholma 1995 (34)	Low	Low	Low	Low	Low	Low
Hornstein 1995 (111)	Low	Low	Low	Low	Low	Low
NEET (106)	Low	Low	Low	Low	Low	Low
Agarwal 2015 (137)	Low	High	High	High	Some concerns	High
Yu 2022 (85)	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Li 2022 (129)	Low	High	Low	High	Low	High
Surrey 1992 (53)	Low	Low	Low	Low	Low	Low
Bergqvist 1997 (113)	Low	Low	Low	Low	Low	Low
Abdou 2018 (81)	Low	High	Low	Some concerns	Some concerns	High
Petta 2005 (70)	Low	High	High	High	Some concerns	High
Cosson 2002 (124)	Low	High	Low	Low	Low	High
Harada 2009 (27)	Low	Low	Low	Low	Low	Low
Gnoth 1999 (60)	Low	Low	Low	Low	Low	Low
Orwoll 1994 (110)	Some concerns	Low	Low	Low	Low	Some concerns
Fedele 1989 (22)	Some concerns	Low	Low	Low	Low	Some concerns
Mettler 2014 (77)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Ceccaroni 2021 (83)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Magini 1993 (31)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Yang 2019 (128)	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Al-Azemi 2009 (134)	Low	Some concerns	Low	Some concerns	Some concerns	High
Granese 2015 (78)	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Ti 2023 (130)	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns

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Study ID	Risk of Bias domains					
	D1	D2	D3	D4	D5	Overall
Freundl 1998 (58)	Low	Low	Low	Low	Low	Low
Bergqvist 2000 (42)	Some concerns	Low	Low	Low	Low	Some concerns
Bergqvist 2001 (117)	Some concerns	Low	Low	Low	Low	Some concerns
Almassinokiani 2013 (136)	Some concerns	Low	Low	Low	Low	Some concerns
Shaw 1990 (103)	Some concerns	Low	Low	Low	Low	Some concerns
Harada 2022 (10)	Low	Low	Low	Low	Low	Low
Huang 2018 (139)	Some concerns	High	Low	High	Low	High
Acién 2003 (132)	Low	Low	Low	Low	Low	Low
Guzick 2011 (75)	Low	Low	Low	Low	Low	Low
Eldred 1992 (107)	Low	Low	Low	Low	Low	Low
Matta 1988 (19)	Some concerns	High	Low	Some concerns	High	High
Fraser 1991 (105)	Some concerns	Low	Low	Low	Low	Some concerns
Fukushima 1993 (24)	Some concerns	Some concerns	Low	Low	Low	Some concerns
Wheeler 1992 (51)	Low	Low	Low	Low	Low	Low
Valimaki 1989 (100)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concens
Sowter 1997 (38)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Strowitzki 2010 (74)	Low	High	Low	Some concerns	Some concerns	High
Rolland 1990 (104)	Low	Some concerns	High	Low	Low	High
Ozaki 2020 (47)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Lemay 1991 (28)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Burry 1989 (101)	Low	Low	Low	Low	Low	Low
Lemay 1988 (20)	Low	High	Low	High	Some concerns	High
Ling 1999 (61)	Low	Low	Low	Low	Low	Low
Bayer 2023 / NCT02203331 (86)	Low	Low	Low	Low	Low	Low
Shen 2017 (80)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Nieto 1996 (26)	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Ipsen 2016 / NCT03232281(131)	Low	High	Low	Low	Some concerns	High
D'Hooge 2019 (82)	Low	Low	Low	Low	Low	Low

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Domains: D1: Bias arising from the randomization process. D2: Bias due to deviations from intended intervention. D3: Bias due to missing outcome data. D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result.

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2. Indirect treatment comparison

2.1. Summary of trials included in indirect or mixed treatment comparisons

Four trials were included in the indirect treatment comparison (Table 8). Figure 2 and Figure 3 show the network diagrams for the outcomes included in the indirect treatment comparison: overall pelvic pain (OPP) and total pelvic pain (TPP) (see Section 2.2.4 for further details on these outcomes).

Table 8 Summary of the trials used to carry out the indirect or mixed treatment comparison

	Relugolix CT	Placebo	Leuprorelin acetate (3.75 mg)
SPIRIT 1 (9)	Yes	Yes	
SPIRIT 2 (9)	Yes	Yes	
D'Hooghe 2019 (82)		Yes	Yes
Osuga, 2021 (8)		Yes	Yes

Table footnote

Figure 2 Network diagram of overall pelvic pain outcome. Studies included SPIRIT 1, SPIRIT 2 and D'Hooghe 2019

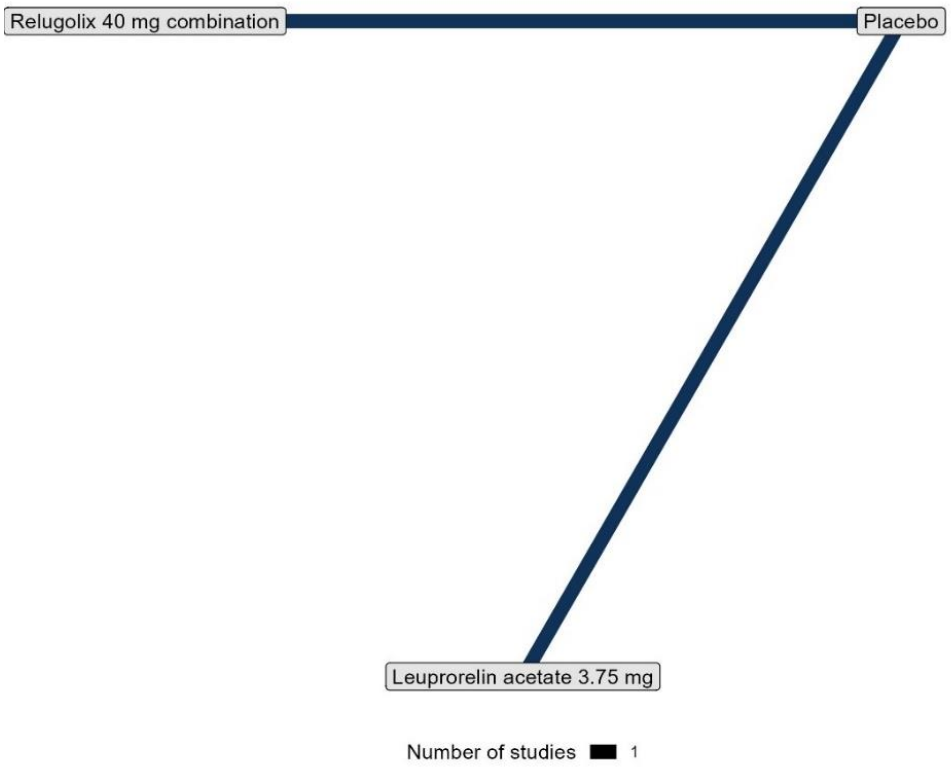

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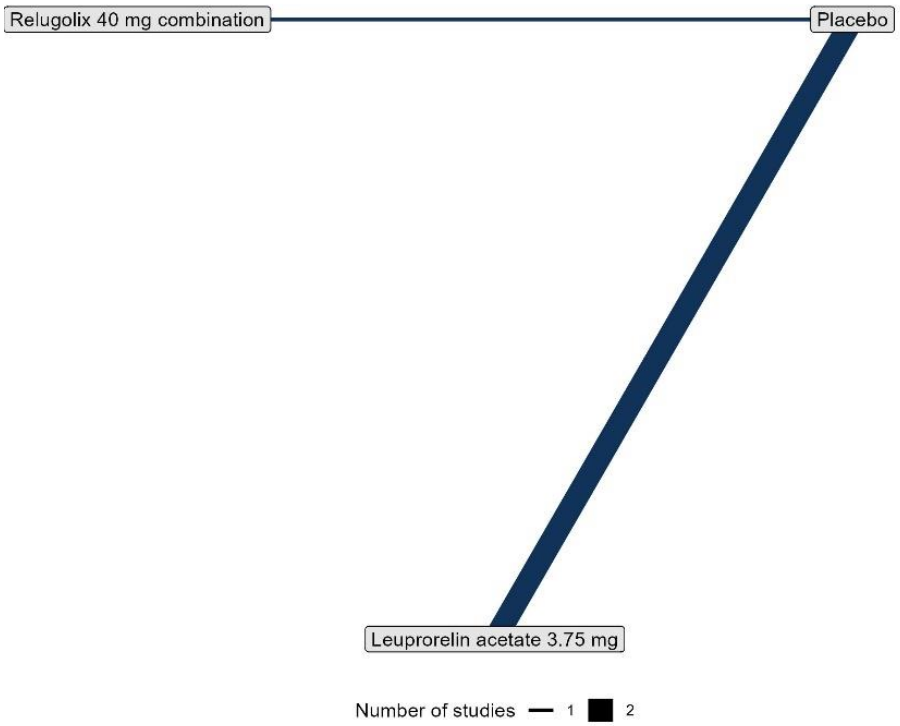
Figure 3 Network diagram of total pelvic pain outcome from individual outcomes of Non-menstrual pelvic pain (NMPP), Dyspareunia, Dysmenorrhea. Studies included SPIRIT 1, SPIRIT 2, Dough 2019, Osuga 2021



The rationale for excluding trials or treatments identified as having either overall or total pelvic pain (either composite outcome made up of the individual outcomes of non-menstrual pelvic pain (NMPP), dyspareunia, dysmenorrhea, or non-composite TPP outcome) outcomes is given below:

- Hornstein 1997 (112) reported the composite TPP outcome, however this trial was not included in the network as the interventions (nafarelin plus placebo, placebo) were administered for six-months after reductive laparoscopic surgery. This was the same exclusion as in the prior NMA.

- D'Hooghe 2019 (82) trial intervention ASP1707 (10 mg, 15 mg, 3 mg and 5 mg) is not included as this was an investigational compound that was terminated after initial trial and is a GnRH antagonist.

- SPIRIT 1 and SPIRIT 2 (9) trial intervention delayed Relugolix combination therapy (relugolix 40 mg monotherapy for 12 weeks followed by relugolix combination therapy for 12-weeks) is not of interest and is not included.

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- Harada 2022 (10) trial intervention leuprorelin acetate 3.75 or 1.88 mg is not included as it is not a compound of interest.

- Osuga 2021 (8) trial interventions relugolix 10 mg, 20 mg, 40 mg monotherapy are not included as relugolix monotherapy is not of interest.

- Bayoglu 2011 (135) trial interventions adjuvant levonorgestrel intra-uterine system (dose NR) and adjuvant zoladex (goserelin, dose NR) are disconnected for the non-composite TPP outcome.

- Tahara 2000 (116) trial interventions nafarelin (200 µg, twice daily) and nafarelin (200 µg, twice daily) plus nafarelin (200 µg once daily) are disconnected for the non-composite TPP outcome.

2.2. Methods and outcomes of studies included in indirect or mixed treatment comparisons

2.2.1. Comparison of populations

Comparison of the trials' target populations are detailed in Table 9, inclusion and exclusion criteria in Table 10, previous surgery for endometriosis in Table 11, and outcomes reported by studies in Table 12.

Giudice, 2022 (SPIRIT 1 & 2) (9) and D'Hooghe, 2019 (82) recruited in multiple countries, whereas Osuga, 2021 (8) only recruited in Japan. All studies were double-blinded, multicentre studies. Largest studies, by number randomised, were Giudice, 2022 (SPIRIT 1 & 2) (9) (N = 638 and 623 overall, 424 and 410 to treatments of interest) then in order of size; D'Hooghe, 2019 (82) (N = 540 overall, 177 to treatments of interest), Osuga, 2021 (8) (N = 487 overall, 181 to treatments of interest). Most studies recruited patients aged between 18 or 20 to 45 or 50 years. Osuga, 2021 (8) did not have an upper age limit. All studies included patients with regular menstrual cycles.

Most studies' inclusion was moderate-to-severe endometriosis-associated pain. Each study scored using different measures, for different types of pain, and varied if self-reported or physician reported. All studies required surgical confirmed endometriosis and excluded patients with previous surgery for endometriosis.

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Table 9 Comparison of trials' target populations

Reference	Countries	Design	Intervention/Comparator
Giudice, 2022 (9); (N=834) SPIRIT 1 (N=424) SPIRIT 2 (N=410)	SPIRIT 1 - Argentina, Belgium, Bulgaria, Canada, Czech Republic, Finland, Hungary, Poland, Portugal, South Africa, Spain, Ukraine, USA SPIRIT 2 - Australia, Brazil, Chile, Czech Republic, Georgia, Italy, New Zealand, Poland, Romania, Sweden, USA	Replicate, phase 3, multicentre, randomised, double-blind, placebo-controlled studies	Relugolix combination therapy: Relugolix (40mg) + Estradiol 1mg (once daily) + Norethisterone acetate 0.5mg (once daily) for 24-weeks; SPIRIT 1 (N=212) SPIRIT 2 (N=206) Placebo (once-daily oral); SPIRIT 1 (N=212) SPIRIT 2 (N=204)
D'Hooghe, 2019; (82) (N=177)	Europe and Japan	Phase 2, multinational, multicentre, double-blind, randomized, parallel-group, placebo-controlled study	Leuprorelin acetate (3.75 mg, injection for 24 weeks); (N=89) Placebo (12-weeks); (N=88)
Osuga, 2021; (8) (N=181)	Japan	Phase 2, multicentre, randomized, double-blind, placebo-controlled trial	Leuprorelin acetate (3.75 mg injection every 4-weeks for 12-weeks); (N=82) Placebo (Daily oral dose for 12 weeks); (N=99)

Table 10 Comparison of inclusion and exclusion criteria

Reference	Inclusion criteria	Exclusion criteria
Giudice, 2022; (9) SPIRIT 1 SPIRIT 2	Premenopausal women aged 18–50 years with endometriosis that was surgically or directly visualised with or without histological confirmation, or histological diagnosis alone, within the past 10 years were eligible to participate. Patients who self-reported moderate, severe, or very severe dysmenorrhea during their most recent menses, and moderate, severe, or very severe non-menstrual pelvic pain during the past month using the Endometriosis Associated Pain Severity score, could enter the run-in period. To be eligible for randomisation, patients were required to have a dysmenorrhea Numerical Rating Scale (NRS; 0=no pain; 10=pain as bad	Had a history of chronic pelvic pain not caused by endometriosis (e.g., vaginismus, chronic pelvic infection, symptomatic hydrosalpinx, symptomatic dermoid, symptomatic corpus lutea, persistent symptomatic ovarian cyst, suspected ovarian torsion, or pelvic floor disorders). Had 4 or more prior laparoscopic or open abdominal or pelvic surgical procedures for endometriosis. During the Run-In Period, reports non-menstrual pelvic pain is "much better" on the PGIC for non-menstrual pelvic pain. Has a transvaginal ultrasound during the Screening or Run-In Period demonstrating pathology other than endometriosis that could be responsible for or contributing to the patient's chronic pelvic pain or a clinically significant gynaecological disorder determined by the investigator to require further evaluation and/or

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	as you can imagine) score of 4.0 or higher for at least 2 days during the run-in period together with a mean non-menstrual pelvic pain score of at least 2.5, or a mean non-menstrual pain score of 1.25 with a score of at least 5.0 on 4 or more days. Participants were required to have menstruated for at least 3 days during the run-in period. Non-hormonal contraception was required during study participation.	treatment during the study. Has any chronic pain or frequently recurring pain condition, other than endometriosis, that is treated with opioids or requires analgesics for ≥7 days per month; Has had a surgical procedure for treatment of endometriosis within the 3 months prior to the Screening visit; a bone mineral density by dual energy x-ray absorptiometry Z score of less than –2.0 at the lumbar spine, total hip, or femoral neck; history of chronic pelvic pain not caused by endometriosis; or having a contraindication to use of combined hormonal therapy.
D'Hooghe, 2019 (82)	Eligible subjects were women aged 18–45 years with moderate-to-severe endometriosis-associated dysmenorrhea and non-menstrual pelvic pain (NMPP), a surgically confirmed diagnosis of endometriosis, and a confirmed regular menstrual cycle of 24–35 days.	Exclusion criteria included treatments that alter gynaecological endocrinology, surgery for endometriosis within 4 weeks of study initiation, and the presence of pelvic or gynaecological abnormalities
Osuga, 2021 (8)	The inclusion criteria for the study were Japanese premenopausal women over 20 years of age with regular menstrual cycles, a diagnosis of endometriosis within the previous 5 years (confirmed by laparotomy, laparoscopy, or magnetic resonance imaging detection of ovarian chocolate cyst(s), and experiencing dysmenorrhea and pelvic pain due to endometriosis of at least moderate severity as determined by the investigator using the Biberoglu and Behrman scale	The exclusion criteria for the study included measurable uterine fibroids with the longest diameter greater than 3 cm, lower abdominal pain due to irritable bowel syndrome or severe interstitial cystitis, thyroid dysfunction, pelvic inflammatory disease, a positive Papanicolaou smear test result, history of hysterectomy or bilateral oophorectomy, and serious cardiovascular, hepatic, renal, or hematologic disorders

Table 11 Previous surgery for endometriosis

Reference	Surgically confirmed endometriosis	Surgery as an exclusion reason	Inclusion/Exclusion Comments
Giudice, 2022; (9) SPIRIT 1 SPIRIT 2	Yes	Yes	Inclusion: "endometriosis that was surgically or directly visualised with or without histological confirmation, or histological diagnosis alone, within the past 10 years were eligible to participate" Exclusion: "Had 4 or more prior laparoscopic or open abdominal or pelvic surgical procedures for endometriosis…Has had a surgical procedure for treatment of endometriosis within the 3 months prior to the Screening visit."
D'Hooghe, 2019 (82)	Yes	Yes	Inclusion: "a surgically confirmed diagnosis of endometriosis" Exclusion: "surgery for endometriosis within 4 weeks of study initiation"
Osuga, 2021 (8)	Yes	Yes	Inclusion: "a diagnosis of endometriosis within the previous 5 years confirmed by laparotomy, laparoscopy, or magnetic resonance imaging" Exclusion: "history of hysterectomy"

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Table 12 Outcomes reported

Reference	Outcome	Timepoint	Absolute value or change from baseline (CFB)	Scale	Definition
Giudice, 2022; (9) SPIRIT 1	Overall pelvic pain (OPP)	12 weeks	CFB	numeric rating scale (NRS)	Average overall pelvic pain numeric rating scale (NRS) Patients rated their worst pelvic pain in the past 24 hours on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine.
	Dyspareunia	12 weeks	CFB	modified Biberoglu and Behrman scale (mB&B)	modified Biberoglu and Behrman scale (mB&B), subset of patients who were sexually active with NRS >0 The daily average mB&B scores for each patient were assessed on a continuous scale with the pain categories as follows: none = 0, mild = 1, moderate = 2, severe = 3.
Giudice, 2022; (9) SPIRIT 2	OPP	12 weeks	CFB	NRS	Average overall pelvic pain NRS score. Patients rated their worst pelvic pain in the past 24 hours on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine.
	Dyspareunia	12 weeks	CFB	mB&B	mB&B modified Biberoglu and Behrman scale, subset of patients who were sexually active with NRS >0 The daily average mB&B scores for each patient were assessed on a continuous scale with the pain categories as follows: none = 0, mild = 1, moderate = 2, severe = 3
Giudice, 2022; (9) Pooled modified Intention to Treat population (SPIRIT 1 & 2) (144)	Dysmenorrhea	12 weeks	CFB	mB&B	mB&B modified Biberoglu and Behrman scale
	Non-menstrual pelvic pain (NMPP)	12 weeks	CFB	mB&B	mB&B modified Biberoglu and Behrman scale

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D'Hooghe, 2019; (82)	OPP	12 weeks	CFB	NRS	NRS in subjects who were treated with the same dose for the full 24-week study. Scale from 0, no pain to 10, worst imaginable pain.
	Dyspareunia	12 weeks	CFB	modified Biberoglu and Behrman (mB&B)	modified Biberoglu and Behrman (mB&B) (i.e. dysmenorrhea, NMPP and dyspareunia, pelvic tenderness & induration).
	Dysmenorrhea	12 weeks	CFB	mB&B	modified Biberoglu and Behrman
	NMPP	12 weeks	CFB	mB&B	modified Biberoglu and Behrman
Osuga, 2021; (8)	Dysmenorrhea	12 weeks	CFB	Biberoglu and Behrman scale (B&B)	Biberoglu and Behrman scale (B&B) reported by the investigator through interviews with the patient to evaluate pain symptoms
	Dyspareunia	12 weeks	CFB	B&B	B&B score reported by the investigator through interviews with the patient to evaluate pain symptoms. Only in patients who engaged in intercourse during the study period, and some patients with dyspareunia possibly avoided sexual intercourse
	Pelvic pain	12 weeks	CFB	B&B	B&B score reported by the investigator through interviews with the patient to evaluate pain symptoms

2.2.2. Comparison of baseline characteristics

Baseline characteristics are detailed in Table 13. The studies were similar in size and included 478 to 635 participants. The populations appeared comparable on the baseline characteristics. Mean ages of participants ranged from 33.1 to 36.1 years. The majority of studies included a majority white population: Giudice 2022 (SPIRIT 1 and 2) (9) ≥90% and D'Hooghe 2019 (82) ≥73%. D'Hooghe 2019 (82) also included a substantial proportion of Asian patients (27%), and Osuga 2021 (8) only took place in Japan, therefore assumed to be majority Asian participants recruited.

Time since diagnosis, high and low density lipoprotein, and bone mineral density were not reported in studies other than SPIRIT 1 and SPIRIT 2 (9).

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Table 13 Comparison of baseline characteristics

Reference	Intervention	Age Mean (SD)	Race	Time since diagnosis Mean (SD)	High/low density lipoprotein Mean (SD)	Bone mineral density Mean (SD)
Giudice, 2022; SPIRIT 1 (9)	Relugolix CT (N=212)	33.9 (6.3)	White: 92% Black: 6% Asian: NA Other: 2%	3.8 (3.2)	LDL-C: 2.619 (0.7643) HDL-C: 1.654 (0.3569)	Lumbar spine Z score: 0.17 (1.1) Total hip Z score: 0.01 (0.9)
	Placebo (N=212)	34.2 (6.6)	White: 91% Black: 6% Asian: NA Other: 3%	3.8 (3.3)	LDL-C: 2.634 (0.6997) HDL-C: 1.697 (0.4454)	Lumbar spine Z score: 0.18 (1.1) Total hip Z score: 0.05 (0.9)
Giudice, 2022; SPIRIT 2 (9)	Relugolix CT (N=206)	33.8 (6.7)	White: 90% Black: 7% Asian: NA Other: 3%	4.1 (3.5)	LDL-C: 2.599 (0.7627) HDL-C: 1.557 (0.3725)	Lumbar spine Z score: 0.23 (1.1) Total hip Z score: 0.1 (1)
	Placebo (N=204)	33.6 (6.5)	White: 90% Black: 6% Asian: NA Other: 4%	3.8 (3)	LDL-C: 2.557 (0.7486) HDL-C: 1.561 (0.3697)	Lumbar spine Z score: 0.35 (1) Total hip Z score: 0.12 (1)
D'Hooghe, 2019 (82)	Leuprorelin acetate (3.75 mg) (N=89)	33.1 (19-45)	White: 73% Black: NA Asian: 27% Other: 0%	NR	NR	NR
	Placebo (N=88)	33.5 (18-45)	White: 73% Black: NA Asian: 27% Other: 0%	NR	NR	NR
Osuga 2021 (8)	Leuprorelin acetate (3.75 mg) (N=82)	36.1 (6.1)	NR	NR	NR	NR
	Placebo (N=99)	35.7 (6.1)	NR	NR	NR	NR

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2.2.3. Comparison of baseline pain outcomes

Baseline pain outcomes are reported in Table 14.

Dysmenorrhea at baseline, measured using the NRS, showed the higher score in SPIRIT 1 & 2 (9) (NRS ~ 7), compared to D'Hooghe 2019 (82) (NRS ~ 6). Osuga 2021 (8) measured baseline Dysmenorrhea using the mB&B and VAS. Mean mB&B score was 1.2 (for both leuprorelin acetate and placebo arms) and the mean VAS score was ~28 overall.

The SPIRIT 1 & 2 study (9) reported baseline dyspareunia using the NRS. The score reported in SPIRIT 1 (9) was 5.7 (in both arms) and the score reported in SPIRIT 2 (9) was 5.4 (Relugolix CT NRS:5.5 vs placebo NRS: 5.3). Osuga 2021 (8) measured this outcome using VAS, with a more varied score ranging from 9.5 (leuprorelin acetate arm) to 11 (placebo arm). D'Hooghe, 2019 (82) did not report dyspareunia at baseline.

Non-menstrual pelvic pain at baseline was measured using NRS, in SPIRIT 1 & 2 (9) and D'Hooghe 2019 (82) studies. The mean score reported in SPIRIT 1 & 2 was ~ 5.9 compared to a lower score reported in the D'Hooghe 2019 (82) study of ~ 4. This outcome was not reported in Osuga 2021 (8).

Pelvic pain at baseline was only reported in the Osuga 2021 (8) study using VAS (28.2 in both the leuprorelin acetate and placebo arms) and mB&B (1.2 in both the leuprorelin acetate and placebo arms).

Overall pelvic pain at baseline was measured using NRS in SPIRIT 1 & 2 (9) and D'Hooghe 2019 (82) studies. The mean score reported in SPIRIT 1 & 2 (9) was ~ 6 compared to a lower score in D'Hooghe 2019 (82) of ~ 4.1/4.2. This outcome was not reported in the Osuga 2021 (8) study.

Pain at baseline, reported using the EHP-30 pain domain (self-reported subscale of the HRQoL Endometriosis Health Profile), between studies was higher in Giudice 2022 (9) (SPIRIT 1 & 2 mean ~ 55 to 58) compared to Osuga 2021 (8) (mean ~ 24.8 to 26.5). This outcome was not reported in D'Hooghe 2019 (82). Although pain at baseline was not similar across studies, it was between arms within studies.

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Table 14 Comparison of baseline pain outcomes

Reference	Intervention	OPP Mean (SD)	Dysmenorrhea Mean (SD)	Dyspareunia Mean (SD)	NMPP Mean (SD)	Pelvic pain Mean (SD)	EHP-30, pain domain Mean (SD)
Giudice, 2022; SPIRIT 1 (9)	Relugolix CT (N=212)	NR	NRS: 7.2 (1.7)	NRS: 5.7 (2.3)	NRS: 5.9 (2)	NR	58.3 (16.7)
	Placebo (N=212)	NR	NRS: 7.1 (1.7)	NRS: 5.7 (2.3)	NRS: 5.8 (1.8)	NR	55.5 (16)
Giudice, 2022; SPIRIT 2 (9)	Relugolix CT (N=206)	NR	NRS: 7.1 (1.6)	NRS: 5.5 (2.3)	NRS:5.8 (1.9)	NR	56.2 (17.1)
	Placebo (N=204)	NR	NRS: 7 (1.6)	NRS: 5.3 (2.3)	NRS: 5.5 (1.9)	NR	55 (16.2)
Giudice, 2022; Pooled mITT SPIRIT 1 & 2 (144)	Relugolix CT (N=418)	NRS: 6.1 (1.82)	NR	NR	NR	NR	NR
	Placebo (N=416)	NRS: 6 (1.75)	NR	NR	NR	NR	NR
D'Hooghe, 2019 (82)	Leuprorelin acetate (3.75 mg) (N=89)	NRS: 4.2 (1.8)	NRS: 5.74 (1.59); M-B&B score: 1.2 (0.5)	NR	NRS: 3.78 (2.09)	NA	NR
	Placebo (N=88)	NRS: 4.12 (1.84)	NRS: 5.93 (1.56); M-B&B score: 1.2 (0.4)	NR	NRS: 3.7 (2.13)	NR	NR
Osuga 2021 (8)	Leuprorelin acetate (3.75 mg) (N=82)	NR	VAS: 27.1 (19.8)	VAS: 9.5 (10.7)	NR	M-B&B: 1.2 (0.5); VAS: 28.2 (17.6)	26.5 (19.6)
	Placebo (N=99)	NR	VAS: 28.4 (16.6)	VAS: 11 (14.2)	NR	M-B&B: 1.2 (0.5); VAS: 28.2 (17.6)	24.8 (20)

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2.2.4. Comparison of outcomes

Two outcomes were considered in the ITC: OPP and TPP.

The OPP outcome was reported in SPIRIT 1, SPIRIT 2 (9) and D'Hooghe 2019 (82) as change from baseline to 12-weeks using the numeric rating scale (NRS) (Table 12).

TPP was a composite outcome generated from the individual outcomes of non-menstrual pelvic pain (NMPP) or pelvic pain (PP), dyspareunia, and dysmenorrhea using change-from-baseline to 12-weeks, reported either using the modified Biberoglu and Behrman (mB&B) or Biberoglu and Behrman scale (B&B). These scales were reported for SPIRIT 1, SPIRIT 2 (9), D'Hooghe 2019 (82) and Osuga 2021 (8) trials (Table 12).

The pain scales used for TPP and OPP are described in detail in Appendix 4.1.

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2.2.4.1. Overall Pelvic Pain outcomes

Table 15 Results of individual studies – Overall pelvic pain (OPP)

Reference ID	Treatment	Outcome	Timepoint	Sample size (number analysed)	Instrument used	Outcome type	Mean	SD	SE
Giudice, 2022 (SPIRIT 1) (9)	Relugolix CT (once daily) for 24-weeks	OPP	12 weeks	193	Numerical Rating Scale (NRS)	Change from baseline	-2.6	2.54	NA
	Placebo (once-daily oral	OPP	12 weeks	189	Numerical Rating Scale (NRS)	Change from baseline	-1.6	1.85	NA
Giudice, 2022 (SPIRIT 2) (9)	Relugolix CT (once daily) for 24-weeks	OPP	12 weeks	186	Numerical Rating Scale (NRS)	Change from baseline	-2.7	2.18	NA
	Placebo (once-daily oral	OPP	12 weeks	188	Numerical Rating Scale (NRS)	Change from baseline	-1.9	2.08	NA
D'Hooghe, 2019 (82)	Leuprorelin acetate 3.75 mg (injection for 24 weeks)	OPP	12 weeks	83	Numerical Rating Scale (NRS)	Change from baseline	-2.58	2.11	NA
	Placebo (12 weeks)	OPP	12 weeks	81	Numerical Rating Scale (NRS)	Change from baseline	-1.71	1.8	NA

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2.2.4.2. Individual outcomes for total pelvic pain (TPP)

Individual outcomes :dysmenorrhea (Table 16), dyspareunia (Table 17), non-menstrual pelvic pain (NMPP) and pelvic pain (Table 18).

Table 16 Results of individual studies – Individual outcomes for total pelvic pain (TPP): dysmenorrhea (B&B scale)

Reference ID	Treatment	Outcome	Timepoint	Sample size (number analysed)	Instrument used	Outcome type	Mean	SD	95% CI (Lower bound)	95% CI (Upper bound)
Giudice, 2022 (pooled mITT population SPIRIT) (144)	Relugolix CT (once daily) for 24-weeks	Dysmenorrhoea	12 weeks	379	mB&B	Change from baseline	-1.2	0.8	NR	NR
	Placebo (once-daily oral	Dysmenorrhoea	12 weeks	377	mB&B	Change from baseline	-0.4	0.68	NR	NR
D'Hooghe, 2019 (82)	Leuprorelin acetate 3.75 mg (injection for 24 weeks)	Dysmenorrhoea	12 weeks	83	mB&B	Change from baseline	-2.08	NR	-2.26	-1.91
	Placebo (12 weeks)	Dysmenorrhoea	12 weeks	81	mB&B	Change from baseline	-0.66	NR	-0.85	-0.47
Osuga, 2021 (8)	Leuprorelin acetate (3.75 mg injection every 4-weeks for 12- weeks)	Dysmenorrhoea	12 weeks	75	B&B scale	Change from baseline	−2.1	0.5	NR	NR
	Placebo (for 12 weeks)	Dysmenorrhoea	12 weeks	93	B&B scale	Change from baseline	−0.4	0.8	NR	NR

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Table 17 Results of individual studies – Individual outcomes for total pelvic pain (TPP): dyspareunia (B&B scale)

Reference ID	Treatment	Outcome	Timepoint	Sample size (number analysed)	Instrument used	Outcome type	Mean	SD	95% CI (Lower bound)	95% CI (Upper bound)
Giudice, 2022 (SPIRIT 1) (9)	Relugolix CT (once daily) for 24-weeks	Dyspareunia	12 weeks	154	mB&B scale	Change from baseline	-0.6	0.85	NR	NR
	Placebo (once-daily oral	Dyspareunia	12 weeks	150	mB&B scale	Change from baseline	-0.5	0.77	NR	NR
Giudice, 2022 (SPIRIT 2) (9)	Relugolix CT(once daily) for 24-weeks	Dyspareunia	12 weeks	155	mB&B scale	Change from baseline	-0.7	0.76	NR	NR
	Placebo (once-daily oral	Dyspareunia	12 weeks	151	mB&B scale	Change from baseline	-0.5	0.78	NR	NR
D'Hooghe, 2019 (82)	Leuprorelin acetate 3.75 mg (injection for 24 weeks)	Dyspareunia	12 weeks	83	mB&B scale	Change from baseline	-0.92	NR	-1.14	-0.7
	Placebo	Dyspareunia	12 weeks	81	mB&B scale	Change from baseline	-0.54	NR	-0.76	-0.32
Osuga, 2021 (8)	Leuprorelin acetate (3.75 mg injection every 4-weeks for 12- weeks)	Dyspareunia	12 weeks	19	B&B scale	Change from baseline	−0.6	0.7	NR	NR
	Placebo (for 12 weeks)	Dyspareunia	12 weeks	31	B&B scale	Change from baseline	−0.2	0.7	NR	NR

Table 18 Results of individual studies – Individual outcomes for total pelvic pain (TPP): non menstrual pelvic pain and pelvic pain (B&B scale)

Reference ID	Treatment	Outcome	Timepoint	Sample size (number analysed)	Instrument used	Outcome type	Mean	SD	95% CI (Lower bound)	95% CI (Upper bound)
Giudice, 2022_Myovant Sciences (Pooled mITT population _SPIRIT) (144)	Relugolix CT (once daily) for 24-weeks	NMPP	12 weeks	379	mB&B scale	Change from baseline	-0.7	0.71	NR	NR
	Placebo (once-daily oral	NMPP	12 weeks	377	mB&B scale	Change from baseline	-0.5	0.63	NR	NR

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D'Hooghe, 2019 (82)	Leuprorelin acetate 3.75 mg (injection for 24 weeks)	NMPP	12 weeks	83	mB&B scale	Change from baseline	-1.26	NR	-1.42	-1.1
	Placebo (12 weeks)	NMPP	12 weeks	81	mB&B scale	Change from baseline	-0.72	NR	-0.88	-0.56
Osuga, 2021(8)	Leuprorelin acetate (3.75 mg injection every 4-weeks for 12- weeks)	Pelvic pain	12 weeks	75	B&B scale	Change from baseline	−1.1	0.7	NR	NR
	Placebo (for 12 weeks)	Pelvic pain	12 weeks	93	B&B scale	Change from baseline	−0.5	0.8	NR	NR

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The pooled dyspareunia outcome for SPIRIT 1 and SPIRIT 2 was estimated using the pooled mean and pooled variance (s_p^2) of the two individual means and individual variances (s_i^2) of the individual trial dyspareunia outcomes.

$$s_p^2 = \frac{\sum_{j=1}^{3}(\mathrm{n}_j - 1)s_i^2}{\sum_{j=1}^{3}(\mathrm{n}_j - 1)}$$

For the TPP composite outcome, each of the individual outcomes (non-menstrual pelvic pain (NMPP) or pelvic pain (PP), dyspareunia, dysmenorrhea) were combined into a pooled mean (summation of the three individual outcome means) and pooled standard error (se_p) using the individual standard errors of each outcome (se_i).

$$SE_p = \sqrt{\left(\sum_{i=1}^{3} {se_i}^2\right)}$$

As the three individual outcomes may be correlated, a sensitivity analysis was undertaken for the standard error (se_{corr}), adjusting for potential correlation of 0.5

$$SE_{corr} = \sqrt{\left(\sum_{i=1}^{3} {se_i}^2\right) + 2 * 0.5 * se_1 se_2 + 2 * 0.5 * se_2 se_3 + 2 * 0.5 * se_1 se_3}$$

2.3. Methods of analysis of studies included in the indirect treatment comparison

The continuous outcome was reported in each trial included as the mean and standard deviation of change-from-baseline (CFB) for each treatment arm. These were analysed as mean change-from-baseline, and also analysed as log odds ratios required for the economic model, estimated using standardised mean differences between treatment arms within a trial.

The standardised mean difference (SMD) is the difference in means (μ) between the intervention arm *k>1* of trial *i* (*i*=1,…,n; *k*=1,…,s) and reference treatment arms (k=1) in the trial divided by the pooled standard deviation (SD_p) of the two treatment arms:

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$$SMD = \frac{(\mu_{k>1} - \mu_{k=1})}{\sqrt{\frac{(n_{k=1}-1)SD_{k=1}^2 + (n_{k>1}-1)SD_{k>1}^2}{(n_{k=1}+n_{k>1}-2)}}}$$

In order for an odds ratio greater than one to represent a positive response, the SMD was multiplied by minus one, as reduction in pain was a desirable outcome (more negative).

The standard error of the SMD is

$$SE_{SMD} = \sqrt{\frac{1}{n_{k=1}} + \frac{1}{n_{k>1}} + \frac{SMD^2}{2(n_{k=1}+n_{k>1}-2)}}$$

For the composite outcome of TPP, the SMD for each individual outcome (dysp, NMPP/PP, dys) was calculated, and then combined to create the SMD for TPP, as the sum of the individual SMD, with corresponding standard error

$$SE_{pooled\ SMD} = \sqrt{\sum_{i=1}^{3} {SE_{SMD_i}}^2}$$

In a sensitivity analysis, the adjustment for the potential correlation between the three individual outcomes of 0.5 was

$$SE_{pooled\ SMD\ corr} = \sqrt{\sum_{i=1}^{3}({SE_{SMD_i}}^2) + 2 * 0.5 * SE_{SMD_1}SE_{SMD_2} + 2 * 0.5 * SE_{SMD_1}SE_{SMD_3} + 2 * 0.5 * SE_{SMD_2}SE_{SMD_3}}$$

The log-odds ratios are estimated using the formula (145):

$$ln(OR) = \frac{\pi}{\sqrt{3}}SMD$$

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The assumption required for this conversion is that the continuous outcomes are from a logistic distribution, and variation within each treatment arm within a trial is from the same distribution (146).

The formula for the SE of the log odds ratio is

$$SE\ ln(OR) = \frac{\pi}{\sqrt{3}} SE_{SMD}$$

The log odds ratio can be transformed to odds ratio using $e^{log\ OR}$ with corresponding 95% CI under the same transformation.

The network meta-analysis model for both the untransformed mean CFB and the log odds ratio wass a normal model with identity link function.

Given either the sample mean CFB y_{ik}^{Δ} of each arm *k* of trial *i* with corresponding standard change variance V_{ik}^{Δ} or the above log OR with corresponding variance, in which case the same notation of y_{ik}^{Δ} and V_{ik}^{Δ} are used, the distribution of these estimands are approximately normally distributed with likelihood:

$$y_{ik}^{\Delta} \sim N(\theta_{ik}, V_{ik}^{\Delta})$$

Using the identity link, the linear model can be written as:

$$\theta_{ik} = \mu_i + \ \delta_{i,k} I_{k \neq 1}.$$

If the change variance V_{ik}^{Δ} is not reported, the formula

$$V_{ik}^{\Delta} = V_{ik}^{b} + \ V_{ik}^{a} - 2\rho\sqrt{V_{ik}^{b} V_{ik}^{a}}$$

will be used with a within-patient correlation ρ of 0.5, unless reported, where V_{ik}^{b} is the follow-up variance and V_{ik}^{a} is the baseline variance.

Given y_{ik} as the continuous treatment effect of arm *k* relative to arm 1 (placebo) in trial *i,* with variance V_{ik} (*k*≥2):

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$$y_{ik} \sim N(\delta_{ik}, V_{ik})$$

Using the identity link, as before, the linear predictor is

$$\theta_{ik} = \delta_{ik}$$

For a random effects model, the trial-specific treatment effect comes from a common distribution:

$$\delta_{i,k} \sim N(d_{t_{i,k}} - d_{t_{i,1}}, \tau^2) \text{ (1)}$$

where $d_{t_{i,k}}$ is the treatment effect of the treatment $t_{i,k}$ in arm k compared with the network reference treatment and τ^2 is the across trials treatment effect heterogeneity variance, assumed the same for all treatment comparisons. As there are only three trials in the OPP and TPP analyses, random effects will not converge in Bayesian setting unless informative priors are used for the heterogeneity variance. We employed predictive distributions for the heterogeneity variance σ^2 as informative priors. For continuous outcomes we used those developed by Rhodes 2015 based on 6,492 meta-analyses (147).

For a fixed effect model, we set

$$\delta_{i,k} = d_{t_{i,k}} \text{ (2)}$$

which is equivalent to setting the between-trial heterogeneity τ^2 to zero thus assuming homogeneity of the underlying true treatment effects.

The preferred model was be chosen by looking at goodness of fit. This was measured using the posterior mean of the residual deviance, which is a measure of the magnitude of the difference between the observed data and the model predictions for those data. Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points. The deviance formula for a Binomial likelihood is provided in the NICE DSU TSD 2 (148). The total residual deviance is

$$\sum_i \sum_k 2\left(r_{ik}\, log\left(\frac{r_{ik}}{\hat{r}}\right) + (n_{ik} - r_{ik})\, log\left(\frac{n_{ik} - r_{ik}}{n_{ik} - \hat{r}_{ik}}\right)\right)$$

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and the fitted value (the model's prediction) for each individual is $\hat{r}_{ik} = n_{ik} p_{ik}$.

We also reported the Deviance Information Criterion (DIC) which penalises model fit with model complexity (149). This is defined as

$$DIC = D\left(\boldsymbol{x}\middle|\hat{\theta}\right) - 2p_D$$

Where $D\left(\boldsymbol{x}\middle|\hat{\theta}\right)$ is the deviance of the data $\boldsymbol{x}$ at the posterior mean $\hat{\theta}$ and $2p_D$

$$p_D = \overline{D(\boldsymbol{x}|\theta)} - D(\boldsymbol{x}|\hat{\theta})$$

having the interpretation of the effective number of parameters.

In comparing models, difference of ≥5 points for posterior mean residual deviance and DIC will be considered meaningful, with lower values being favoured.

Finally, we reported the between studies standard deviation (heterogeneity parameter) to assess the degree of statistical heterogeneity. To do this we used the Turner 2008 set of predictive distributions for the degree of heterogeneity expected in 80 settings depending on the outcomes assessed and comparisons made (150). However, as we used informative priors this did not give an assessment of the extent of heterogeneity in the network, only the assumed heterogeneity from the informative prior.

The relative treatment effects are themselves defined relative to the overall reference treatment

$$d_{t_{i1}t_{ik}} = d_{1t_{ik}} - d_{1t_{i1}}$$

where d_{1t_k} is the log odds ratio of the event or mean difference for treatment t_{ik} relative to the reference treatment. For mixed treatment comparisons, all treatment comparisons can be expressed in terms of effects relative to this reference treatment (labelled 1) via the "consistency equations" (151):

$$d_{23} = d_{13} - d_{12}$$

$$d_{24} = d_{14} - d_{12}$$

$$\vdots$$

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$$d_{(s-1),s} = d_{1s} - d_{1,(s-1)}$$

where s is the number of treatments being compared. Under both fixed effects and random effects, the model therefore only needs to estimate the basic parameters d_{1t_k}, the treatment effect of treatment t_{ik} relative to the reference treatment.

All trials in the network have only two arms so it was not necessary to adjust random effects models for correlation between treatment arm contrasts.

As we were working in the Bayesian framework, we used the following vague priors for our baseline and relative treatment effect parameters:

$$\mu_i \sim N(0, 100^2)$$

$$d_{1k} \sim N(0, 100^2)$$

and for the random effects between-trial standard deviation

$$\sigma \sim U(0,5)$$

NMA methods were be implemented using the R statistical programming language v4.0.0 or higher and the 'multinma' package.(152) The 'multinma' package conducts NMA by Bayesian Markov Chain Monte Carlo (MCMC) simulation through the software Stan (153, 154). We will use 4 chains each with 2000 iterations.

Convergence was assessed by visual inspection of the trace plots and the Brookes-Gelman-Rubin (BGR) Rhat statistic (155), which will be reported for model parameters.

The posterior distributions of relative treatment effects between interventions were summarized by their mean and 95% credible intervals (CrIs), which were constructed from the 2.5th and 97.5th percentiles of the MCMC samples. Results were presented on the natural scales (odds ratios rather than log odds ratios). Bayesian probabilities that treatments are superior were also estimated by taking the proportion of the MCMC samples for which a treatment comes has higher (or lower, if outcome is perceived negative, as for adverse events) treatment effect. Bayesian probabilities of superiority have a similar interpretation to frequentist one-sided p-values.

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The results of the NMA (Section 2.5) are presented in terms of triangle tables with relative treatment effect estimates between all interventions of interest and between interventions where direct evidence is available along with 95% CrI and Bayesian p-values for all outcomes presented (example in Table 19).

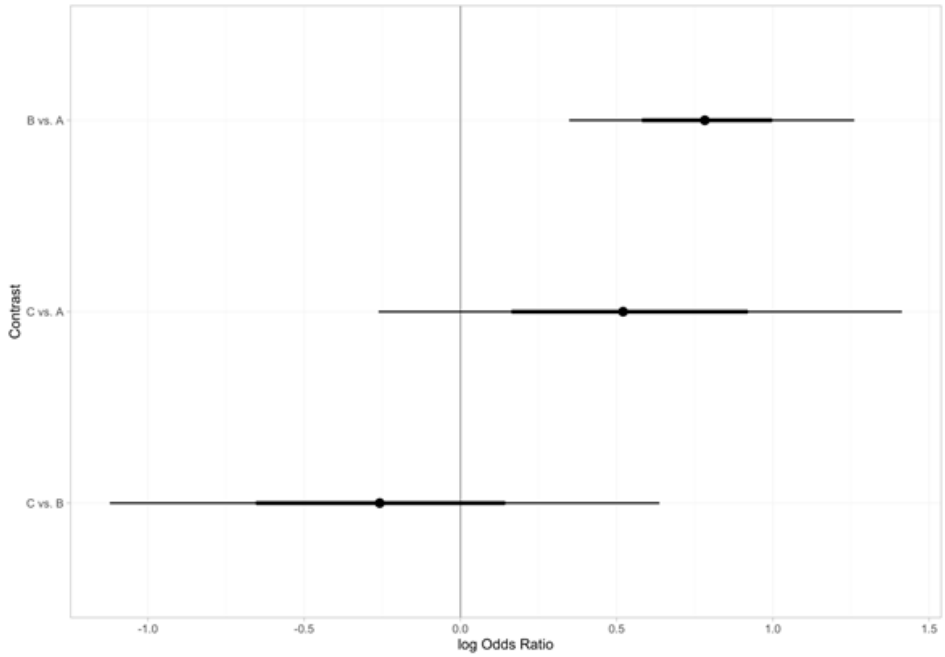
Table 19 Example of a odds ratio triangle table with results from the NMA in the bottom left-hand triangle.

Treatment 1	XX (XX; XX)	XX (XX; XX)
XX (XX; XX)	**Treatment 1**	XX (XX; XX)
XX (XX; XX)	XX (XX; XX)	**Treatment 3**

Results in each row and column are comparisons of the treatment row against the treatment column, so an OR above 1 in the second row and first column would indicate higher odds of event on treatment 1 than on treatment 2

The results of the analyses are also presented in forest plots. These plots present point estimates (median and 95% CrI) for the treatments and outcomes of interest. An example of what the forest plot might look like is shown in Figure 4.

Figure 4 Example forest plot



One of the advantages of NMA is that it allows for the ranking of interventions. Based on the results of the NMA, we can calculate the probability of each intervention taking a particular rank as well as the probability that treatment is best (Table 20). Surface under the cumulative ranking curve (SUCRA), with values close to 1.0 being favourable, was also calculated.

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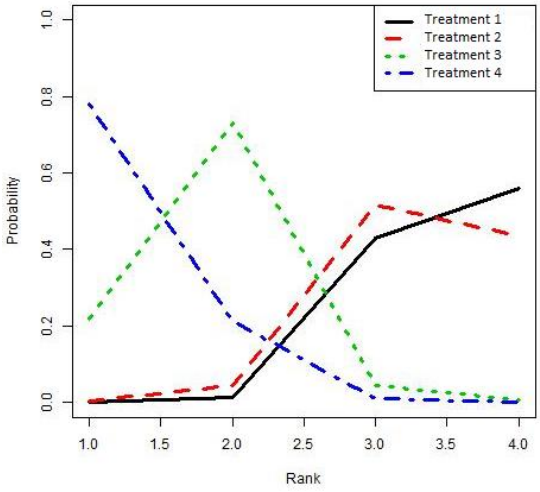
Table 20 Example of ranking table

Treatment	Probability Best	Mean Rank (95% CrI)	SUCRA
Treatment 1	0.01	4.0 (3.5, 4.0)	0.0
Treatment 2	0.32	1.9 (1.5, 2.3)	0.7
Treatment 3	0.39	1.3 (1.1, 1.5)	0.9

Results in each row and column are comparisons of the treatment row against the treatment column, so an OR above 1 in the second row and first column would indicate higher odds of event on treatment 1 than on treatment 2

Probabilities for each treatment taking each possible rank are also plotted in rankograms (example Figure 5). Ranking indicates the probability that each treatment is the best treatment, the second best, the third best, and so on for each outcome.

Figure 5 Example of a rankogram



2.4. Risk of bias of studies included in the indirect treatment comparison

A summary of the risk of bias assessment for each study included in the indirect treatment comparison are presented in Figure 6. All studies were judged as low risk for all domains.

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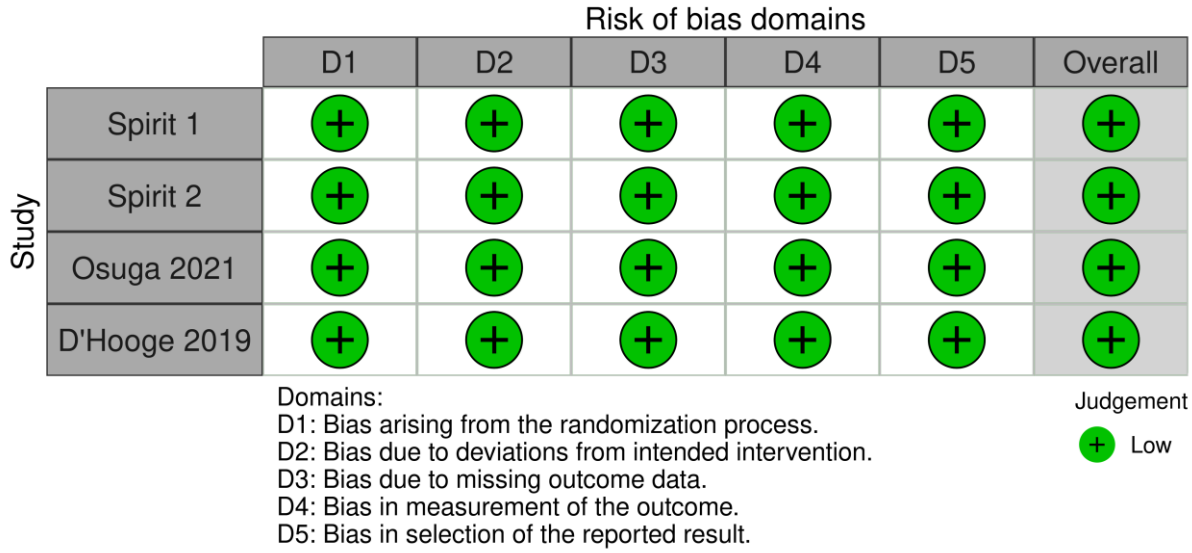
Figure 6 Cochrane risk of bias assessment of studies included in the ITC



2.5. Results of the indirect treatment comparison

2.5.1. Overall pelvic pain

For OPP, the total residual deviance was less than number of datapoints (n=6) for both models, suggesting good overall fit, and similar between fixed and random effect models. Both models converged, with Rhat close to 1.000. The fixed effects model was preferred due to limited heterogeneity (Table 21). Placebo has higher OPP than Relugolix CT, with 95% CrI excluding the null value. No benefit of leuprorelin acetate 3.75 mg compared with Relugolix CT, 95% CrI includes the null value of 0.

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Table 21 OPP mean difference, total residual deviance and DIC for fixed effects and random effects models

Treatment	Fixed effects, Mean difference (95% CrI)	Random effects, Mean difference (95% CrI)
Leuprorelin acetate 3.75 mg	0.0196 (-0.656, 0.717)	0.0383 (-0.72, 0.8)
Placebo	0.892 (0.589, 1.2)	0.902 (0.55, 1.26)
Relugolix CT	Comparison	Comparison
Total residual deviance	5.39	5.49
DIC	10.4	10.7

Results are presented as mean difference relative to Relugolix CT with 95% CrI. Mean difference <0 indicates reduced mean OPP relative to Relugolix CT.

Due to limited heterogeneity, results are presented for the fixed effect model only.

There is evidence that Relugolix CT and leuprorelin acetate 3.75 mg have greater reduction in OPP than placebo. There is no evidence of a difference between Relugolix CT and leuprorelin acetate 3.75 mg (Figure 7 and Table 22).

Figure 7 Fixed effects model - OPP mean difference - Forest plot

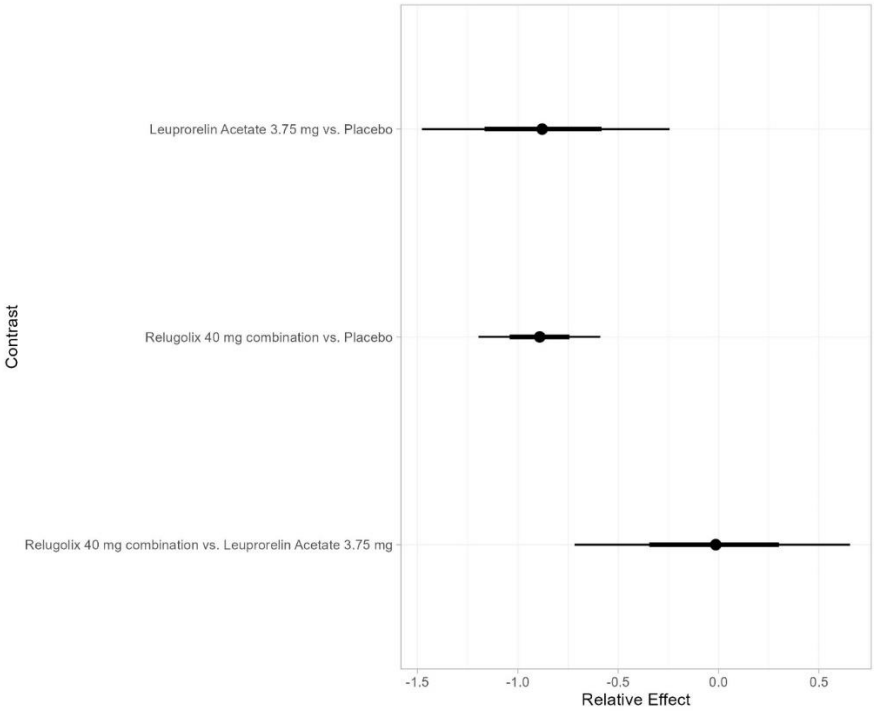

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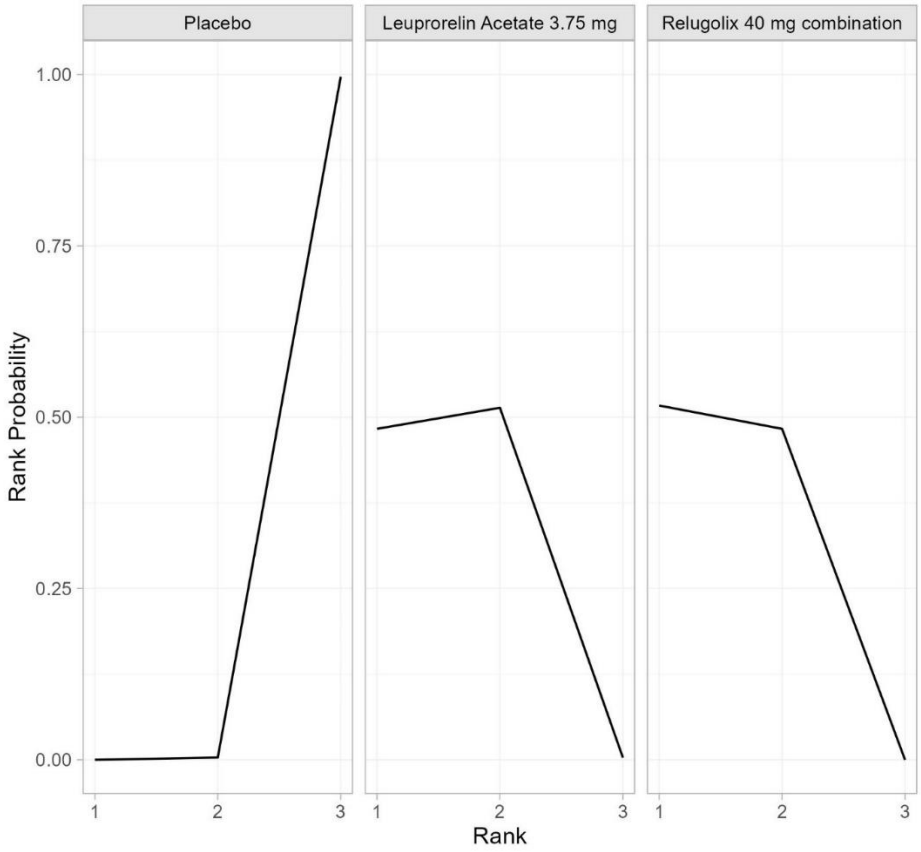
Table 22 Fixed effects model - OPP mean difference – treatment effects

Placebo	**0.87 (0.24, 1.48)**	**0.89 (0.59, 1.2)**
-0.87 (-1.48, -0.24), 0.997	**Leuprorelin Acetate 3.75 mg**	0.02 (-0.66, 0.72)
-0.89 (-1.2, -0.59), >0.999	-0.02 (-0.72, 0.66), 0.517	**Relugolix CT**

All mean differences with 95% CrI and Bayesian p-value. Values in bold indicate evidence of a difference. Mean difference < 0 favours row intervention over column intervention.

As shown in Figure 8, Relugolix CT has slightly highest probability (0.517) of having lowest (best) ranks compared with leuprorelin acetate 3.75 mg (0.483). Placebo has lowest probability of lower ranks and highest probability of highest (worst) ranks.

Figure 8 Fixed effects model - OPP mean difference – Rankograms



Placebo has the lowest SUCRA followed by leuprorelin acetate 3.75 mg and Relugolix CT in that order (Table 23). Very similar ranking of probabilities that leuprorelin acetate 3.75 mg or Relugolix CT is the most effective treatment.

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Table 23 Fixed effect model - OPP mean difference – Ranking probabilities

Treatment	Probability best	SUCRA	Mean rank (95%CrI)
Placebo	0	0.0016	3 (3, 3)
Leuprorelin acetate 3.75 mg	0.483	0.7399	1.52 (1, 2)
Relugolix CT	0.517	0.7585	1.48 (1, 2)

For OPP OR, the total residual deviance was less than number of datapoints (n=3) for both models, suggesting good overall fit, and similar between fixed and random effect models (Table 24). Both models converged, with Rhat close to 1.000. The fixed effects model was preferred due to limited heterogeneity. Placebo has lower chance of OPP response than Relugolix CT, with 95% CrI excluding the null value. No benefit of leuprorelin acetate 3.75 mg compared with Relugolix CT, 95% CrI includes the null value.

Table 24 OPP OR, total residual deviance and DIC for fixed effects and random effects models

Treatment	Fixed effects, OR (95% CrI)	Random effects, OR (95% CrI)
Leuprorelin Acetate 3.75 mg	1.11 (0.554, 1.94)	1.12 (0.522, 2.08)
Placebo	0.477 (0.367, 0.613)	0.479 (0.349, 0.65)
Relugolix CT	Comparison	Comparison
Total residual deviance	2.22	2.33
DIC	4.19	4.46

Results are OR of response relative to Relugolix 40 mg combination with 95% CrI. OR >1 indicating higher chance of OPP response relative to Relugolix 40 mg combination.

Due to limited heterogeneity, the following results are presented for the fixed effect model only.

As shown in Figure 9 and Table 25, there is evidence that Relugolix CT and leuprorelin acetate 3.75 mg have higher chance of OPP response than placebo.

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Figure 9 Fixed effects model - OPP OR - Forest plot

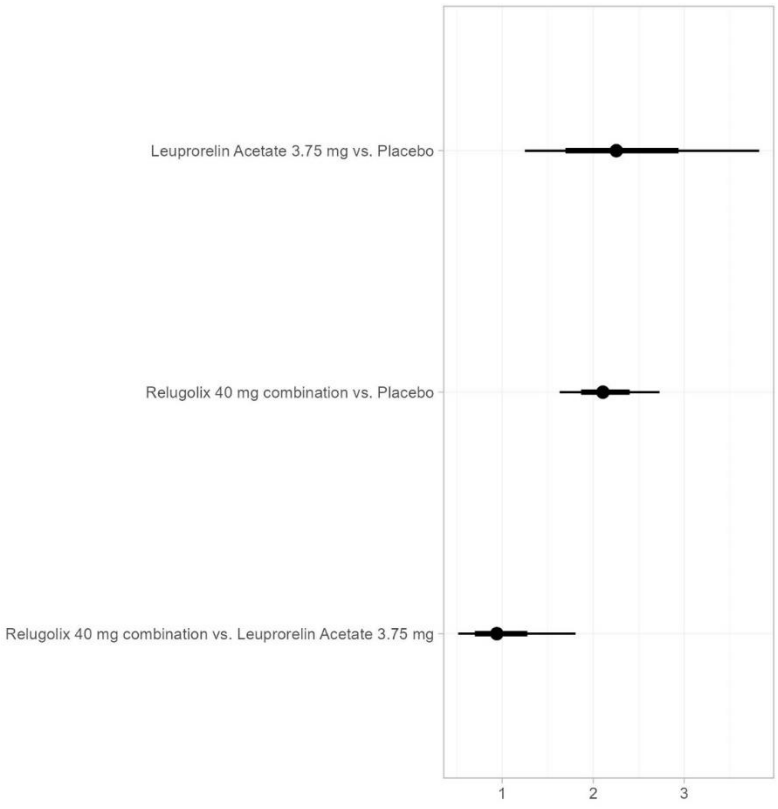

Table 25 Fixed effects model - OPP OR – treatment effects

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**

All OR with 95% CrI and Bayesian p-value. Values in bold indicate evidence of a difference. OR > 1 favours row intervention over column intervention.

Leuprorelin acetate 3.75 mg has slightly higher probability (0.58) of having lowest (best) ranks compared with Relugolix CT (0.42) (Figure 10). Placebo has lowest probability of lower ranks and highest probability of highest (worst) ranks.

Placebo has the lowest SUCRA followed by leuprorelin acetate 3.75 mg and Relugolix CT in that order (Table 26). Very similar ranking of probabilities that leuprorelin acetate 3.75 mg or Relugolix CT is the most effective treatment.

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Figure 10 Fixed effects model - OPP OR - Rankogram

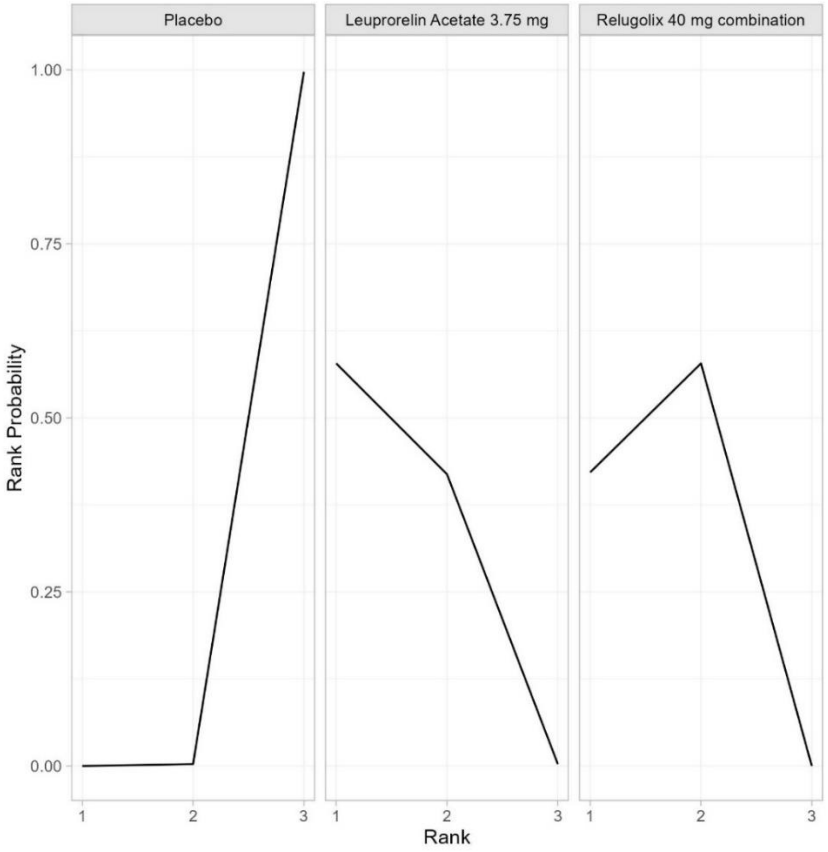

Table 26 Fixed effect model - OPP OR – Ranking probabilities

Treatment	Probability best	SUCRA	Mean rank (95%CrI)
Placebo	0	0.0013	3 (3, 3)
Leuprorelin acetate 3.75 mg	0.58	0.79	1.42 (1, 2)
Relugolix CT	0.42	0.71	1.58 (1, 2)

2.5.2. Total pelvic pain

For TPP, the total residual deviance was close to the number of datapoints (n=6) for both models, suggesting less appropriate overall fit, and similar between fixed and random effect models (Table 27). Both models converged, with Rhat close to 1.000. The fixed effects model was preferred due to limited heterogeneity.

There was evidence of a benefit of Relugolix CT compared with placebo, with 95% CrI excluding the null value. There was also evidence of benefit of leuprorelin acetate 3.75 mg compared with Relugolix CT, 95% CrI excludes the null value of 0.

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Table 27 TPP mean difference, total residual deviance and DIC for fixed effects and random effects models

Treatment	Fixed effects, Mean difference (95% CrI)	Random effects, Mean difference (95% CrI)
Leuprorelin acetate 3.75 mg	-1.35 (-1.74, -0.949)	-1.36 (-1.85, -0.864)
Placebo	1.15 (0.962, 1.34)	1.15 (0.857, 1.46)
Relugolix CT	Comparison	Comparison
Total residual deviance	6.19	6.01
DIC	11.3	11.2

Results are mean difference relative to Relugolix CT with 95% CrI. Mean difference <0 indicates reduced mean TPP relative to Relugolix CT.

Due to limited heterogeneity seen, the following results are presented for the fixed effect model only.

There is evidence that Relugolix CT and leuprorelin acetate 3.75 mg have greater reduction in TPP than placebo. There is evidence of greater reduction on leuprorelin acetate 3.75 mg compared with Relugolix CT combination on TPP (Figure 11 and Table 28).

Figure 11 Fixed effects model – TPP mean difference – forest plot

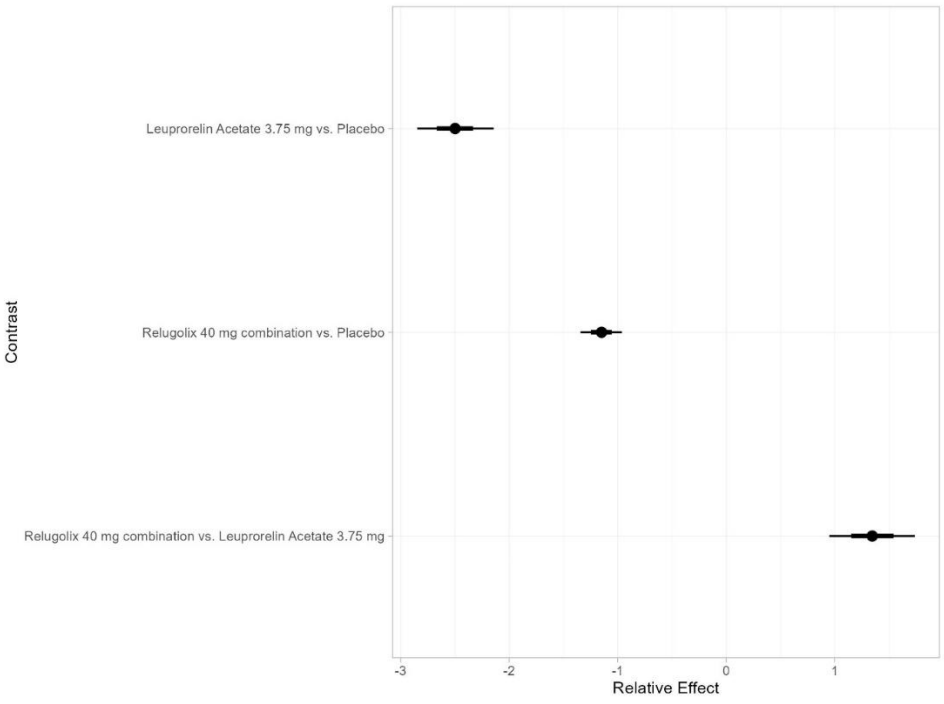

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Table 28 Fixed effects model – TPP mean difference – treatment effects

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**

All mean differences with 95% CrI and Bayesian p-value. Values in bold indicate evidence of a difference. Mean difference < 0 favours row intervention over column intervention.*

Leuprorelin acetate 3.75 mg has highest probability (>0.999) of having lowest (best) ranks compared with Relugolix CT (<0.001). Placebo has lowest probability of lower ranks and highest probability of highest (worst) ranks (Figure 12 and Table 29).

Placebo has the lowest SUCRA followed by Relugolix CT and leuprorelin acetate 3.75 mg in that order (Table 29). It is likely that leuprorelin acetate 3.75 mg is the most effective treatment based on ranking of probabilities.

Figure 12 Fixed effects model – TPP mean difference – Rankograms

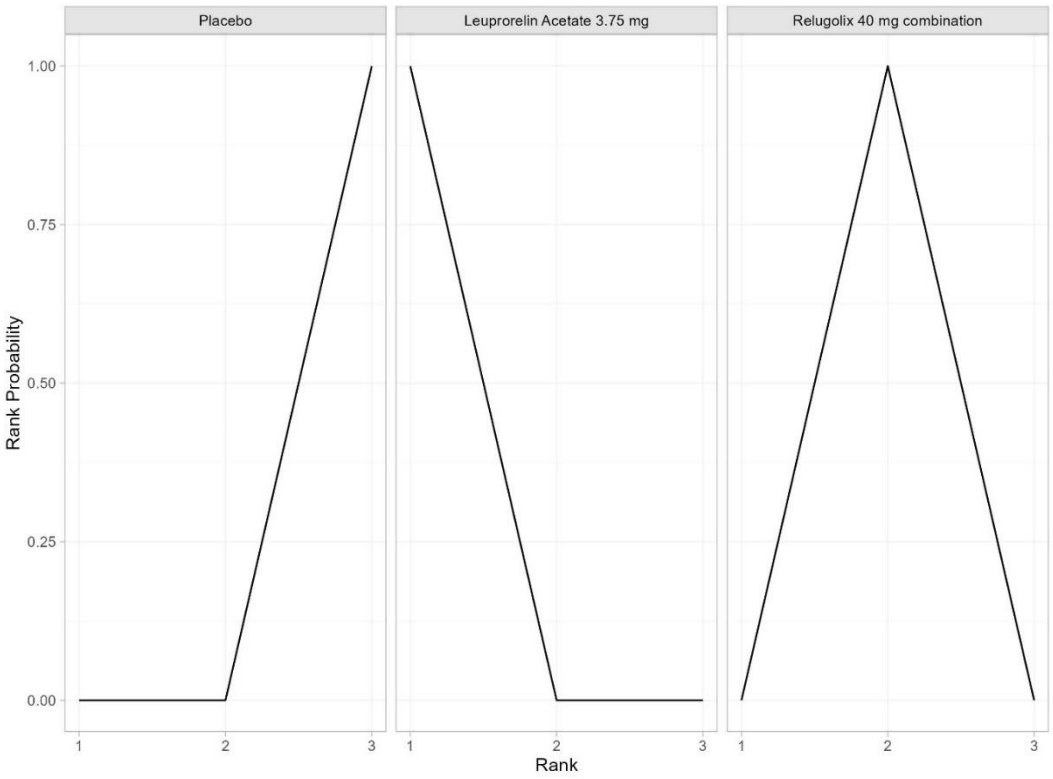

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Table 29 Fixed effects model - TPP mean difference – Ranking probabilities

Treatment	Probability best	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)

For TPP OR, total residual deviance is not less than number of datapoints (n=3) for both models, suggesting less appropriate overall fit, and similar between fixed and random effect model (Table 30). Models converged, with Rhat close to 1.000. Fixed effects preferred due to limited heterogeneity.

There is evidence of lower chance of TPP response on placebo than Relugolix CT, with 95% CrI excluding the null value. There is also evidence of higher chance of TPP response on leuprorelin acetate 3.75 mg than Relugolix CT, with 95% CrI excluding the null value.

Table 30 TPP OR, total residual deviance and DIC for fixed effects and random effects models

Treatment	Fixed effects, OR (95% CrI)	Random effects, OR (95% CrI)
Leuprorelin acetate 3.75 mg	21 (7.19, 48.8)	26.7 (3.22, 96.1)
Placebo	0.0602 (0.0365, 0.0943)	0.0657 (0.0127, 0.169)
Relugolix CT	Comparison	Comparison
Total residual deviance	6.46	5.58
DIC	8.41	8.12

Results are OR of response relative to Relugolix CT with 95% CrI. OR >1 indicates higher chance of TPP response relative to Relugolix CT.

Due to limited heterogeneity seen, the following results are presented for the fixed effect model only.

There is evidence that Relugolix CT and leuprorelin acetate 3.75 mg a have higher chance of TPP response than placebo (Figure 13 and Table 31). There is also

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evidence of higher chance of TPP response on leuprorelin acetate 3.75 mg compared with Relugolix CT.

Figure 13 Fixed effects model – TPP OR – forest plot

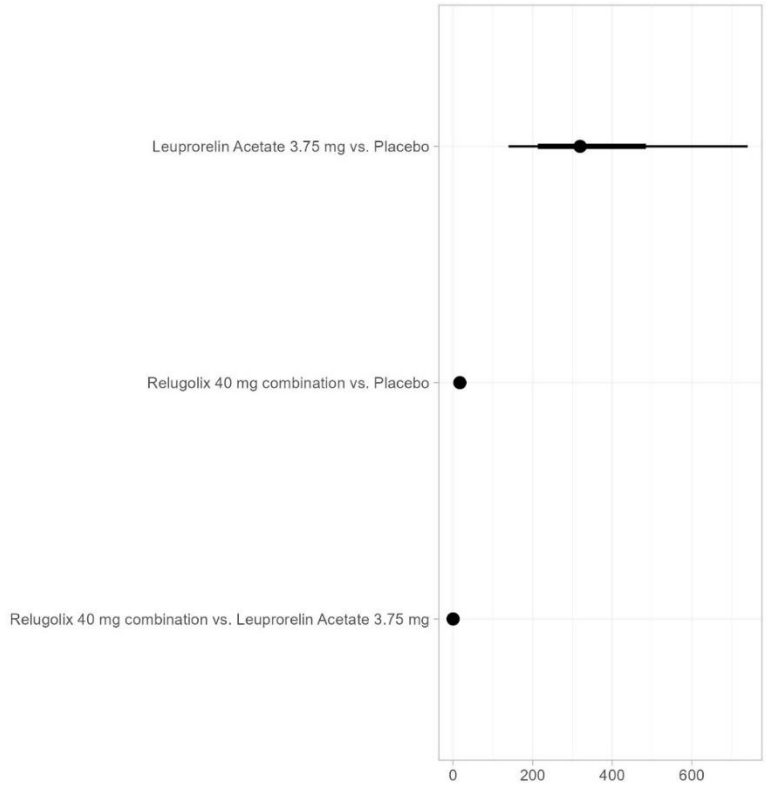

Table 31 Fixed effects model – TPP OR – treatment effects

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

All OR with 95% CrI and Bayesian p-value. Values in bold indicate evidence of a difference. OR > 1 favours row intervention over column intervention.

Leuprorelin acetate 3.75 mg has highest probability (>0.999) of having lowest (best) ranks compared with Relugolix CT (<0.001). Placebo has lowest probability of lower ranks and highest probability of highest (worst) ranks (Figure 14 and Table 32).

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Placebo has the lowest SUCRA followed by Relugolix CT, and leuprorelin acetate 3.75 mg in that order. Likely that leuprorelin acetate 3.75 mg is the most effective treatment based on ranking of probabilities.

Figure 14 Fixed effects model – TPP OR – Rankograms

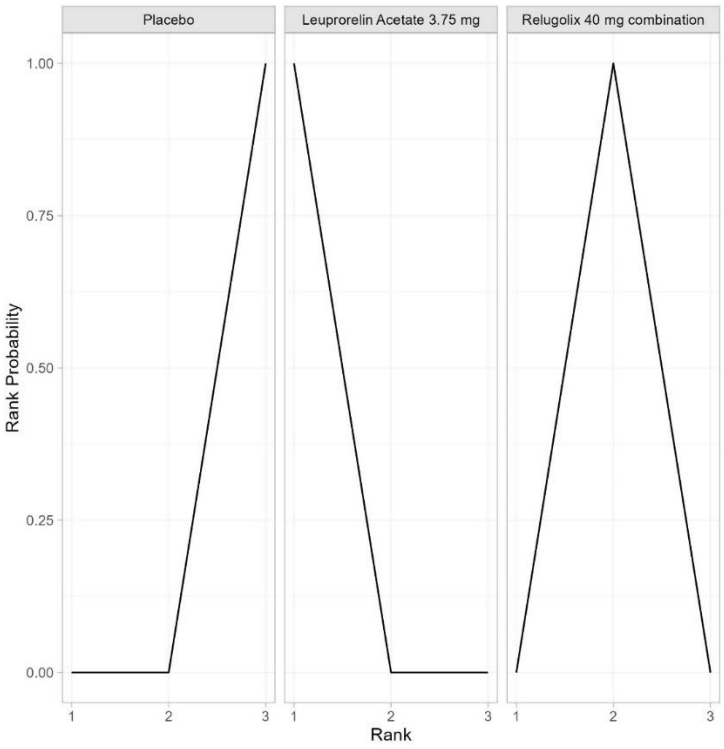

Table 32 Fixed effects model - TPP OR – Ranking probabilities

Treatment	Probability best	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)

2.5.2.1. Total pelvic pain sensitivity analysis

This analysis adjusted the standard error for potential correlation of 0.5 between the three individual outcomes which make up the TPP score.

The total residual deviance was less than number of datapoints (n=6) for both models, suggesting good overall fit, and similar between fixed and random effect

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models (Table 33). Both models converged, with Rhat close to 1.000. The fixed effects model was preferred due to limited heterogeneity.

There was evidence of a benefit of Relugolix CT compared with placebo, with 95% CrI excluding the null value. There was also evidence of benefit of leuprorelin acetate 3.75 mg compared with Relugolix CT, 95% CrI excludes the null value of 0.

Table 33 TPP mean difference, total residual deviance and DIC for fixed effects and random effects models sensitivity analysis

Treatment	Fixed effects, Mean difference (95% CrI)	Random effects, Mean difference (95% CrI)
Leuprorelin acetate 3.75 mg	-1.36 (-1.91, -0.835)	-1.35 (-1.97, -0.733)
Placebo	1.14 (0.871, 1.41)	1.15 (0.819, 1.52)
Relugolix CT	Comparison	Comparison
Total residual deviance	5.63	5.59
DIC	10.7	10.7

Results are mean difference relative to Relugolix 40 mg combination with 95% CrI. Mean difference <0 indicates reduced mean TPP relative to Relugolix 40 mg combination.

Due to limited heterogeneity, the following results are presented for the fixed effect model only.

There is evidence that Relugolix CT and leuprorelin acetate 3.75 mg have greater reduction in TPP than placebo. There is evidence of greater reduction on leuprorelin acetate 3.75 mg compared with Relugolix CT on TPP (Figure 15 and Table 34).

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Figure 15 Fixed effects model sensitivity analysis – TPP mean difference – forest plot

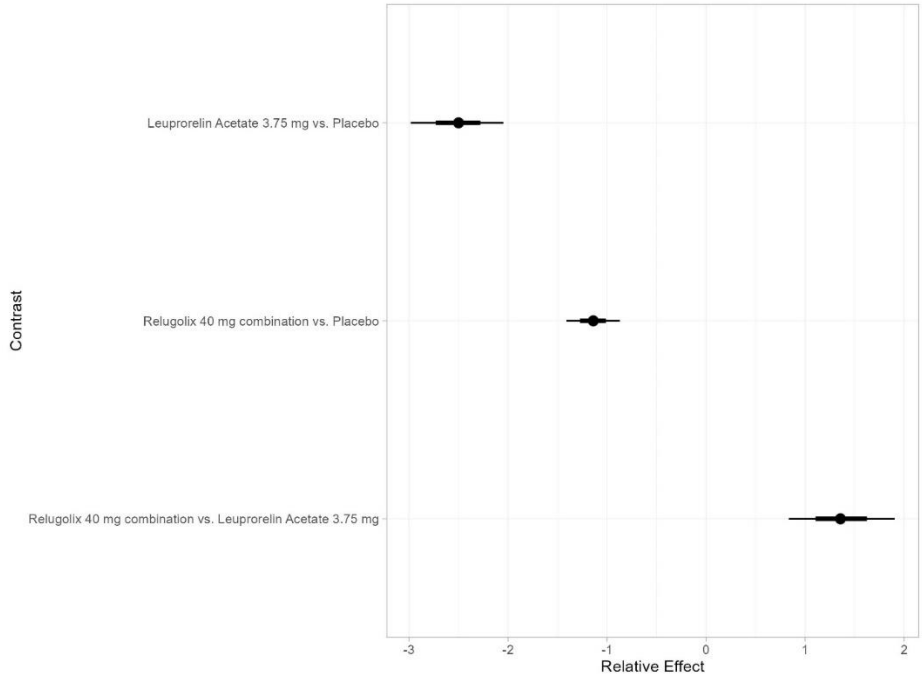

Table 34 Fixed effects model sensitivity analysis – TPP mean difference – treatment effects

Placebo	**2.5 (2.05, 2.98)**	**1.14 (0.87, 1.41)**
-2.5 (-2.98, -2.05), >0.999	Leuprorelin acetate 3.75 mg	**-1.36 (-1.91, -0.84)**
-1.14 (-1.41, -0.87), >0.999	**1.36 (0.84, 1.91), <0.001**	Relugolix CT

All mean differences with 95% CrI and Bayesian p-value. Values in bold indicate evidence of a difference. Mean difference < 0 favours row intervention over column intervention.*

Leuprorelin acetate 3.75 mg has highest probability (>0.999) of having lowest (best) ranks compared with Relugolix CT (<0.001). Placebo has lowest probability of lower ranks and highest probability of highest (worst) ranks (Figure 16 and Table 35).

Placebo has the lowest SUCRA followed by Relugolix CT and leuprorelin acetate 3.75 mg in that order (Table 35). It is likely that leuprorelin acetate 3.75 mg is the most effective treatment based on ranking of probabilities.

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Figure 16 Fixed effects model sensitivity analysis – TPP mean difference – Rankograms

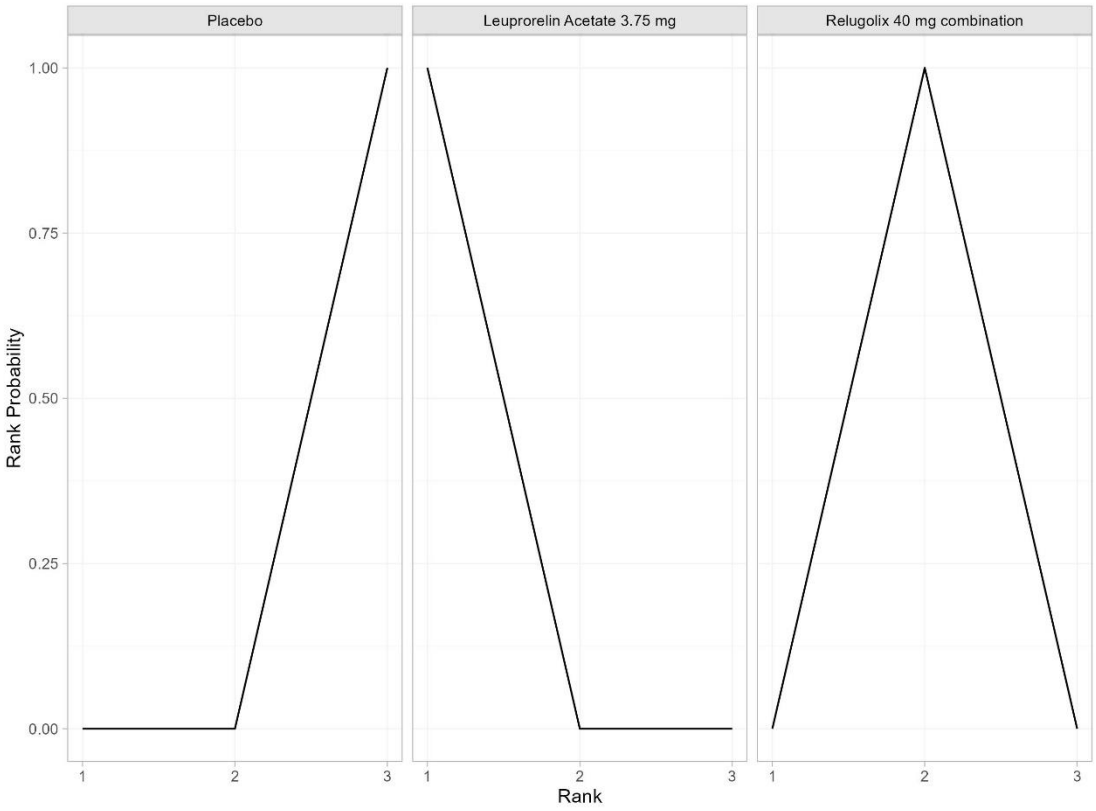

Table 35 Fixed effects model sensitivity analysis - TPP mean difference – Ranking probabilities

Treatment	Probability best	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)

For the analysis of OR of TPP response, total residual deviance is not less than number of datapoints (n=3) for both models, suggesting less appropriate overall fit, and similar between fixed and random effect models. Models converged, with Rhat close to 1.000. Fixed effects was preferred due to limited heterogeneity.

There is evidence of a lower chance of TPP response on placebo than Relugolix CT, with 95% CrI excluding the null value. There is also evidence of a higher chance of

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TPP response on leuprorelin acetate 3.75 mg than Relugolix CT, with 95% CrI excluding the null value.

Table 36 TPP OR, total residual deviance and DIC for fixed effects and random effects models sensitivity analysis

Treatment	Fixed effects, OR (95% CrI)	Random effects, OR (95% CrI)
Leuprorelin acetate 3.75 mg	**23.5 (4.66, 74.2)**	**27.7 (3.98, 92.9)**
Placebo	**0.0612 (0.0293, 0.113)**	**0.0673 (0.0242, 0.153)**
Relugolix CT	Comparison	Comparison
Total residual deviance	4.38	4.12
DIC	6.44	6.25

Results are OR of response relative to Relugolix CT with 95% CrI. OR >1 indicates higher chance of TPP response relative to Relugolix CT.

Due to limited heterogeneity seen, the following results are presented for the fixed effect model only.

There is evidence that Relugolix CT and leuprorelin acetate 3.75 mg have a higher chance of TPP response than placebo (Figure 17 and Table 37). There is evidence of a higher chance of TPP response greater reduction on leuprorelin acetate 3.75 mg compared with Relugolix CT.

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Figure 17 Fixed effects model – TPP OR – forest plot

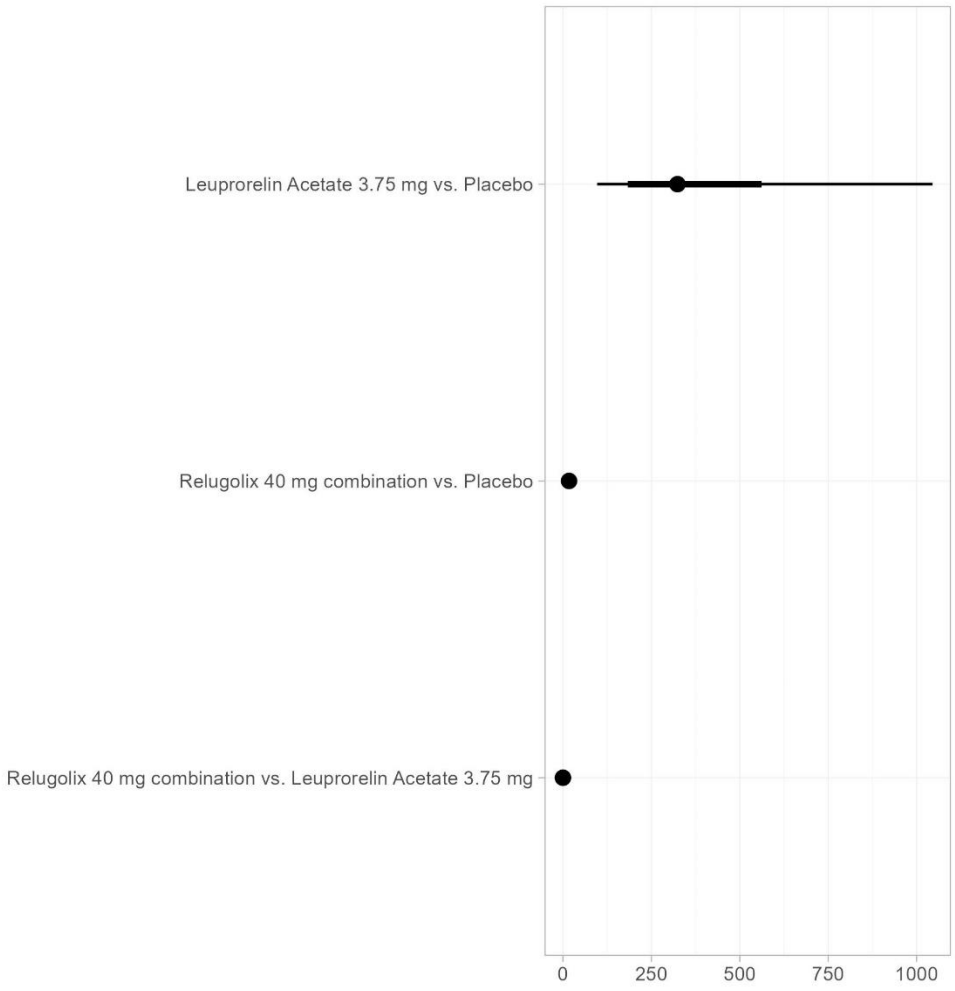

Table 37 Fixed effects model – TPP OR – treatment effects

Placebo	**0 (0, 0.01)**	**0.06 (0.03, 0.11)**
386.2 (96.71, 1044.86), >0.999	Leuprorelin acetate 3.75 mg	**23.52 (4.66, 74.24)**
18.46 (8.85, 34.1), >0.999	**0.07 (0.01, 0.21), <0.001**	Relugolix CT

All OR with 95% CrI and Bayesian p-value. Values in bold indicate evidence of a difference. OR > 1 favours row intervention over column intervention.

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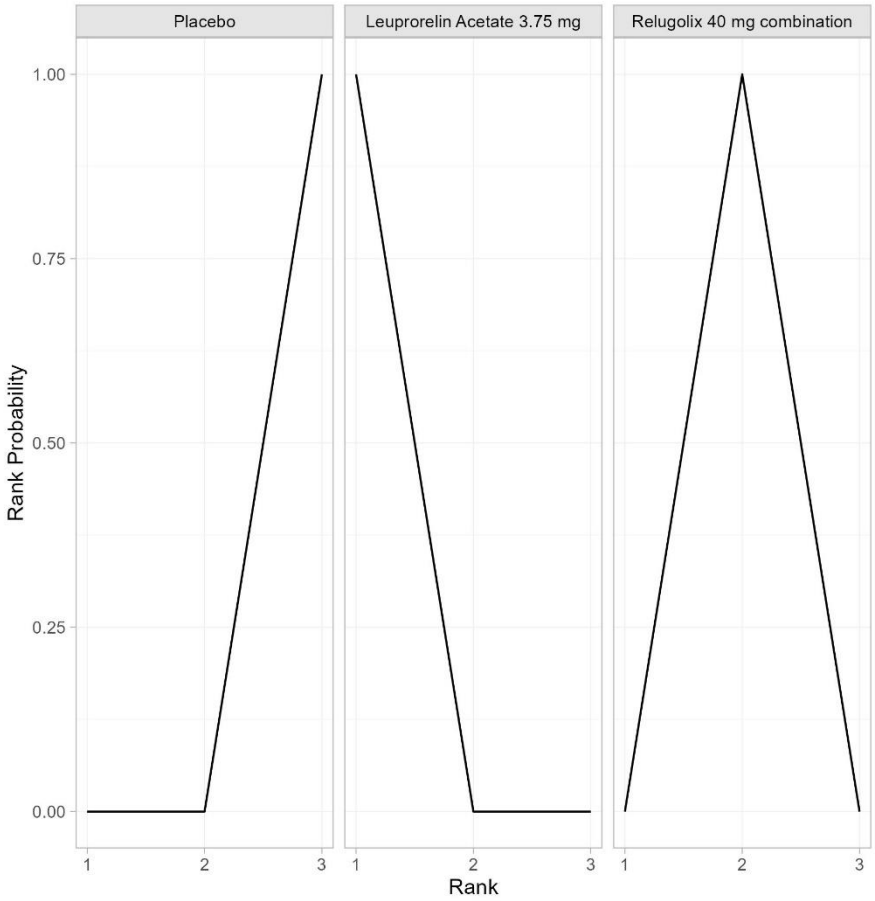
Figure 18 Fixed effects model – TPP OR – Rankograms



Leuprorelin acetate 3.75 mg has highest probability (>0.999) of having lowest (best) ranks compared with Relugolix CT (<0.001) (Table 38). Placebo has lowest probability of lower ranks and highest probability of highest (worst) ranks.

Placebo has the lowest SUCRA followed by Relugolix CT, and leuprorelin acetate 3.75 mg in that order (Table 38). Likely that leuprorelin acetate 3.75 mg is the most effective treatment based on ranking of probabilities.

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Table 38 Fixed effects model - TPP OR – Ranking probabilities

Treatment	Probability best	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)

2.6. Uncertainties in the indirect treatment comparison

A limitation of using TPP as an outcome was that it was estimated for all trials by combining the individual outcomes of non-menstrual pelvic pain or pelvic pain , dyspareunia and dysmenorrhea, with associated estimates of standard error. It was also necessary to estimate TPP for the pooled mITT population in SPIRIT 1 and 2, rather than the individual studies, as non-menstrual pelvic pain and dysmenorrhea were available in the pooled mITT population, but dyspareunia was not. Pelvic pain was used in Osuga 2021 (8) as non-menstrual pelvic pain was not reported (Table 12).

There was variation in the scales used for the individual outcomes of non-menstrual pelvic pain or pelvic pain , dyspareunia and dysmenorrhea (Table 12). The scales used included the modified Biberoglu and Behrman (mB&B) or the Biberoglu and Behrman scale (B&B). A short description of the scales is provided in Section 4.1. The dyspareunia outcome for mB&B in SPIRIT 1 and SPIRIT 2, and B&B in Osuga, 2021 (8) were only reported for patients who had sexual intercourse, with NRS>0 for SPIRIT 1 and SPIRIT 2. This was not reported in D'Hooghe 2019 (82).

Due to limited heterogeneity fixed effects models were chosen as base case for all analyses. For OPP mean difference and response, the total residual deviance was less than number of datapoints for both models, suggesting good overall fit (Table 21, Table 24). However, for the TPP mean difference and response (base case analysis) the total residual deviance was not less than number of datapoints for both models, suggesting less appropriate overall fit (Table 27, Table 30).

There were wide credible intervals for the TPP response analysis, representing uncertainty in the estimates (Table 31).

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2.7. Conclusions of the indirect treatment comparison

The fixed effects models were selected for all outcomes using DIC, residual deviance, and assessment of heterogeneity.

There is evidence that Relugolix CT and leuprorelin acetate 3.75 mg have greater reduction in OPP and higher chance of OPP response than placebo. There is no evidence of a difference between Relugolix CT and leuprorelin acetate 3.75 mg. The previous ITC analysis (included in Gedeon Richter's original evidence submission) found no evidence of difference between any treatments on OPP response.

TPP mean difference was calculated as the sum of NMPP or pelvic pain, dyspareunia and dysmenorrhea. Base case assumed no correlation between the three individual outcomes, and sensitivity assumed 0.5 correlation.

There is evidence that Relugolix CT and leuprorelin acetate 3.75 mg have greater reduction in TPP and higher chance of TPP response than placebo. There is also evidence of greater reduction on leuprorelin acetate 3.75 mg compared with Relugolix CT on TPP and a higher chance of TPP response. The previous ITC analyses of TPP response found no evidence of a difference between any treatments. The sensitivity analysis adjusting for potential correlation between three outcomes in TPP and TPP response gave the same conclusions.

Aside from the SPIRIT studies, data on baseline TPP scores were lacking in the included trials. This is a potentially important consideration as absolute reductions in TPP scores observed in the included trials will in part be a function of baseline scores. This may have introduced bias into the TPP analysis, but the direction of this bias is unknown.

Results of the ITC on the OPP outcome were consistent with previous analyses. However, results for the TPP outcome were not. It is unclear why TPP and OPP analyses would not be broadly consistent with each other. However, researchers have noted potentially important limitations with the B&B score. For example, modified versions of the B&B score combine the three pain symptoms into a 'pelvic symptoms score' or 'endometriosis symptom severity scale'. Combined scores can be misleading on account of the way in which they are estimated. For example, individuals reporting only moderate pain may record combined scores that are higher

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than those with severe dyspareunia combined with mild dysmenorrhea and no pelvic pain (156).

Thinking more broadly about the interpretation of results from the updated ITC, it is also worth noting that direct comparative effectiveness evidence is available from other therapeutic settings (e.g. uterine fibroids) suggesting comparable outcomes for relugolix and leuprorelin acetate (157). In this context, we suggest that the updated ITC on the TPP outcome should be treated with caution.

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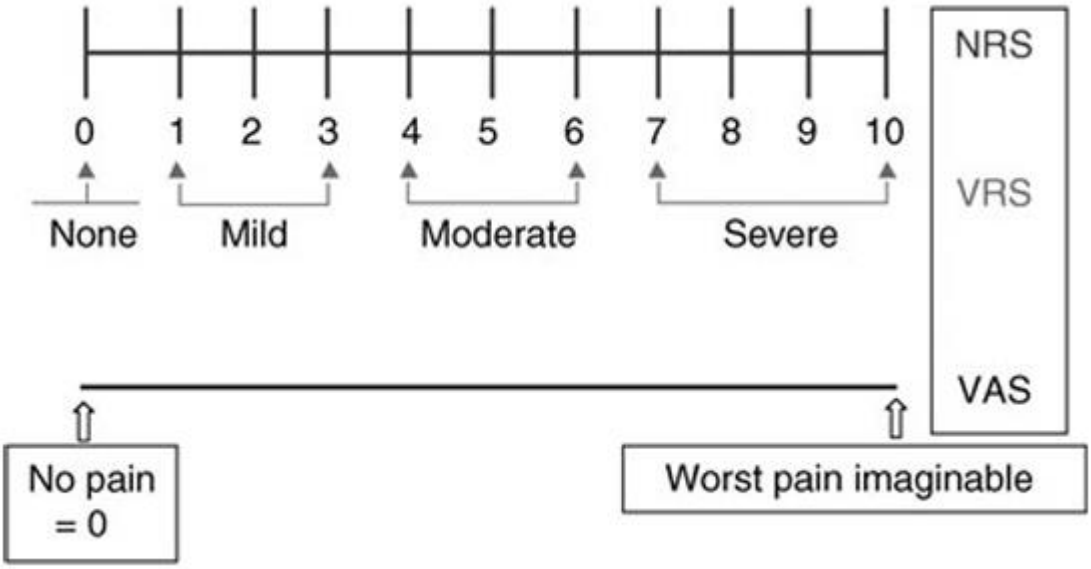
4. Appendices

4.1. Description of pain scales

4.1.1. Numeric rating scale (NRS)

The NRS is a segmented version of the visual analog scale (VAS) in which a respondent selects a whole number (0-10) that best reflects the intensity of pain. Like the VAS pain scale, the NRS is anchored by terms describing pain severity extremes (see figure below).



4.1.2. Biberoglu and Behrman (B&B) score.

The B&B scores consist of a rating based on the patient's assessment of three distinct pain symptoms (dysmenorrhea, pelvic pain and dyspareunia) and on two findings obtained during gynaecologic palpation (tenderness and induration). Each symptom is classified as absent, mild, moderate or severe. The original article only described a severity profile for symptoms and findings (for example severe dysmenorrhea is when the patient remains in bed for one or more days). Modified versions of the B&B score combine the three pain symptoms into the 'pelvic symptoms score' or 'endometriosis symptom severity scale' and the two 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' (Table 39).

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Table 39 Modified Biberoglu and Behrman Scales for Dysmenorrhea, Pelvic Pain, and Dyspareunia

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

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Relugolix–estradiol–norethisterone acetate for treating symptoms of endometriosis [ID3982]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 22 April 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Endometriosis UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Endometriosis UK are disappointed with NICE recently announcing that Relugolix–estradiol–norethisterone acetate has not been approved to treat those with endometriosis. We appreciated the opportunity to review the medicine being a new drug with potential to ease those suffering with endometriosis symptoms.

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	We feel, along with the wider community who were interviewed in relation to the drug, that Relugolix–estradiol–norethisterone acetate 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.
2	Due to the drug being taken daily, it allows those who may suffer with side effects which are deemed unmanageable by patients, to cease ingesting the drug immediately. This is much more effective than current available treatments such as a 3 monthly injection, where patients must wait out the side effects until the medicine has left their body. Due to the drug also having HRT included being included within the one tablet, this should mitigate the negative effects of menopause such as bone density. There was also positive feedback from our community who told us that 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.
3	Another benefit of the drug was that treatment could be used for a longer period when compared to currently available GnRH agonist treatments, where there is a licensing limit of 6-months. The drug can also be used as a contraceptive up until natural menopause which to some would be extremely useful and one less thing to worry about for those whose fertility is not a priority.
4	It is positive that new treatments are becoming available for endometriosis, and it is an optimistic step into the future of endometriosis care. We hope the drug company are able to address uncertainties in the clinical evidence and economic model within the consultation period to support approval of this treatment. Endometriosis UK welcomes future scopes into more potential new medicines with the hope that they will be approved for treatment to improve patient choice.
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Draft guidance company response – EAG critique

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Comment 1: Introduction to the company response to Draft Guidance (DG)

No External Assessment Group (EAG) critique required.

Comment 2: Request for a new systematic literature review (SLR)

In their response to the DG, the company updated the SLR as well as the study selection and the indirect treatment comparison (ITC).[1]

Clinical effectiveness searches

Revised searches were conducted on 29th April 2024 across a core selection of databases, comprising of MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (via the Cochrane Library), and the clinical trials registry the US National Institutes of Health Clinical Trial Registry (http://www.clinicaltrials.gov). The EAG queried the statement in Section 1.1.1 of the DG that the joint Embase/MEDLINE search was conducted using the Ovid platform as the strategy provided did not appear to contain Ovid syntax. The company confirmed that this was a typographical error and explained that the searches were originally designed in Ovid but were subsequently adapted to run in the Elsevier platform for Embase and the PubMed platform for MEDLINE, a revised document reporting all three database searches (including the individual Embase and MEDLINE searches) was provided.[2-4]

EAG comment: The new searches utilised a simplified structure containing facets for endometriosis AND named treatments AND RCTs (randomised controlled trials) and SRs (systematic reviews) filter. Strategies were clear and reproducible and the EAG noted that the key limitations identified in the original EAG report had been addressed and the revised searches were appropriate and fit for purpose.

An additional grey literature search for clinicaltrials.gov was reported but no strategy was provided, when queried the company clarified that *"a simple search was conducted on 8 May 2024 using the 'other terms' field without Boolean operators (e.g. endometriosis-related pain OR endometriosis, Filters: interventional studies/Adults (18-64 years))"*.[2] As with the original SLR, the revised searches may have benefitted from separate adverse events searches conducted to capture adverse events that are long-term, rare or unanticipated and therefore less likely to be retrieved by searches containing an RCT filter.[5] However, the inclusion of SRs in both the MEDLINE and Embase strategies may have mitigated against some loss of recall, but without rerunning the searches the EAG is unable to say what impact this may have had on the overall recall of results.

Overall, however, the EAG has no major concerns about the revised literature searches conducted.

Whilst the inclusion criteria for these revised searches included health-related quality of life (HRQoL) as an outcome of interest, the remaining economics searches from the original submission were not amended and updated, therefore the limitations for these sections outlined in the EAG report will still apply.[6]

Study selection

The original SLR identified 48 studies (58 publications), as per the PRISMA flowchart in Figure 43 of the company submission (CS) appendices.[7] The updated SLR identified 139 reports representing 111 unique studies, as per the PRISMA flowchart in Figure 1 of the DG response appendices.[3] According to the document, *"of the 139 reports, 114 were full-length journal publications, 23 were available as conference abstracts, and two were identified from a trial registry"*.[3]

The new SLR includes studies published through 2023, incorporates additional data sources such as conference abstracts and trial registries, and adds more studies from Asia. It also includes additional research on buserelin, goserelin, leuprorelin, and triptorelin, as well as long-term efficacy data from the

SPIRIT LTE study. While the new SLR adds more studies related to surgery, the company stated that *"no studies were identified that provide evidence for surgery as a comparator to Relugolix CT"*.[1]

EAG comment: The updated SLR mentions the inclusion of a wide array of studies, however, the company did not provide an overview what the references identified in the updated SLR added compared to the original SLR.

However, the identification of additional references confirms that it was important to revise the original SLR to ensure that all relevant references have been identified in order to inform the decision-making process.

Indirect treatment comparison (ITC)

Two ITCs were conducted, as in the original CS, one for overall pelvic pain (OPP) and the other for total pelvic pain (TPP). The ITC methods were reported in an addendum. Unlike in the original CS, where only odds ratios, calculated from standardised mean differences were reported, the mean changes from baseline, as provided in the request for clarification response, were included.

The studies included in the network for OPP were the same as those in the original CS[8] i.e. the company's trials SPIRIT 1 and 2, which compared relugolix CT (in combination with oestradiol and norethisterone acetate) to placebo, and D'Hooghe 2019 which compared leuprorelin to placebo.[9]

For TPP, the studies in the network were changed to include one trial of leuprorelin vs. placebo (Osuga 2021) but to exclude two trials.[10] The two excluded trials were one of dienogest vs. placebo (Lang 2018) and one of leuprorelin vs. dienogest (Strowitzki et al. 2010).[11, 12] The reason for exclusion was given as *"intervention not of interest"* for the latter, but the former was not mentioned at all in the addendum.[4]

There was also a difference in terms of how the study data from the two SPIRIT trials were pooled: in the CS, it was unclear, but in the company response to the DG, for TPP the data from each trial were considered separately, which is methodologically the more appropriate method, whereas for OPP the data were considered as a single trial. The explanation for this naïve pooling for TPP was as follows: *"It was also necessary to estimate TPP for the pooled mITT population in SPIRIT 1 and 2, rather than the individual studies, as non-menstrual pelvic pain and dysmenorrhea were available in the pooled mITT population, but dyspareunia was not"* (p. 156).[3]

Although the addendum shows that both fixed effect and random effects models were run, the company stated that they preferred the former because of lack of heterogeneity and only the results for the former were reported. These results are compared to those from the clarification response to the CS in Tables 1 and 2.

Table 1: OPP mean difference: Relugolix CT vs. comparators, fixed effect model

Comparator	Company response to DG	Clarification letter response
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)
CT = in combination with oestradiol and norethisterone acetate; OPP = overall pelvic pain		

Table 2: TPP mean difference: Relugolix CT vs. comparators, 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)
CT = in combination with oestradiol and norethisterone acetate; TPP = total pelvic pain		

The results for OPP are similar between the company response to the DG and to the clarification letter. However, those for TPP show much clearer advantage to leuprorelin, which the company acknowledges, but argues if less valid due to problems with the outcome measure.

EAG comment: The EAG considers that the scale of mean difference is appropriate and consistent with its request in the clarification letter. However, it is unclear why the two studies that were in the original network were excluded from the company response to DG.[11, 12] The explanation regarding naïve pooling of the SPIRIT 1 and 2 TPP data is also unclear.

Considering that the studies included in the OPP network were unchanged, it is unclear why the results differed between the company response to the DG and response to clarification letter, although there seems to be no change in the conclusion that there is little difference between relugolix CT and leuprorelin. However, there does seem to be a clearer advantage to leuprorelin in TPP with the company response to the DG. This is probably driven by the inclusion of Osuga 2021,[10] which has very similar values for mean change from baseline for leuprorelin and placebo as the originally included D'Hooghe 2019,[9] where the value for leuprorelin is about one point larger than for relugolix CT from the pooled SPIRIT trials. The company argument that the validity of TPP is questionable does depend partly on it combining scores. However, an examination of the individual outcomes shows the following:

- Dysmenorrhoea: clear advantage to leuprorelin (see Table 15, addendum)
- Dyspareunia: similarity between relugolix CT and leuprorelin (see Table 16, addendum)
- Non menstrual pelvic pain and pelvic pain: advantage to leuprorelin (see Table 17, addendum)

It therefore seems that, even according to two out of three of the individual outcomes, leuprorelin might produce greater pain relief than relugolix.

In conclusion, the lack of explanation for the change in OPP results and the exclusion of two of the studies from the TPP network continue to produce uncertainty in the results of the ITC.

Comment 3: Evidence on the efficacy of relugolix CT compared with surgery

As detailed in the response to DG, the company *"does not consider that surgery is a comparator to Relugolix CT"*.[1] Furthermore, the company noted that *"no studies were identified that provide evidence for surgery as a comparator to Relugolix CT"*.[1]

EAG comment: The company's economic model includes surgery as a comparator, further reinforcing its relevance to the appraisal. In the response to the DG, the company noted that *"the economic model submitted for this appraisal was designed at a global level with surgery as a comparator to Relugolix CT. This was done in the event that surgery may be considered a comparator in any of the markets in which Relugolix CT has been submitted for reimbursement"*.[1]It should be noted that Section 3.7 of the DG summarises the detailed discussion about comparators, resulting in the statement that *"the committee concluded that GnRH agonists and surgery were both relevant comparators in NHS clinical practice"*.[13]

To exclude surgery, the company must provide stronger evidence or more precisely redefine the target population.

In conditions such as endometriosis and uterine fibroids, surgery is typically integrated into the overall treatment pathway. While surgery has not always been included as a direct comparator in health technology assessments in other countries, the UK appraisal process should reflect local clinical practice, where surgery plays a significant role.

The company explained that, except in the first model cycles, surgery as a comparator is implemented in the same way as surgery as a follow-up treatment after relugolix CT or gonadotropin-releasing hormone (GnRH agonists). In the first model cycle, patients enter the model in the health state "Initial treatment" where they stay for only one cycle. After that, patients move to the health state "Waiting time before surgery". From there, the same transitions described in the original model (Figure 4.1 in EAG report) are possible.[6]

The company indicated that surgery costs, healthcare resource use, efficacy and health-related quality of life inputs are the same for first line surgery and follow-up surgery. described in the model technical report. The EAG is uncertain whether second line inputs could be generalised to first line. In theory, these should be obtained from a systematic review, as it was done for GnRH agonists as comparator. The impact of this is uncertain, although it is expected to be minor.

The EAG can confirm the results provided by the company when relugolix CT is compared to (first line) surgery, with an ICER of £2,130 per QALY gained in the North-Eastern quadrant of the CE-plane. These results are summarised in Table 3.

Table 3: Company cost-effectiveness results, relugolix CT vs. surgery

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Relugolix CT	£11,487	23.105	17.165				
Surgery	£9,741	23.095	16.345	£1,746	0.010	0.820	£2,130

Based on Table 3 in the company's response to Draft Guidance[1]
CT = in combination with oestradiol and norethisterone acetate; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Comment 4: Clarity on what constitutes best supportive care (BSC)

In response to the DG, the company responded to the committee's request to provide clarity regarding BSC. The text is reproduced below:

"Best supportive care after treatment with Relugolix CT is likely to be analgesics for pain management. Some patients may opt for surgery at this stage, and this is considered separately. Hormonal treatments are not considered best supportive care at this point in the treatment pathway as patients would have already failed these before moving on to Relugolix CT. Patients would therefore not be expected to restart treatment with hormonal treatments.

The original submitted model was developed at a global level and included hormonal treatments as best supportive care. However, these were subsequently removed as their inclusion was not reflective of best supportive care in England and Wales. An updated model that included only analgesics as best supportive care was submitted at clarification in November 2023".[13]

EAG comment: Key issues 1 (lack of clarity in the decision problem population), 2 (not all relevant comparators were included) and 7 (definition and role of BSC in the model), discussed in the EAG report, are still unresolved and the recommendations by the EAG have not been addressed.[6]

Comment 5: Model that more accurately reflects the treatment pathway

EAG comment: The company have reiterated that the current model structure reflects the treatment pathway and, therefore, the structure of the model has not been changed. Key issues 1, 2 and 6, as described in the EAG report remain thus unresolved.[6]

Comment 6: Scenarios using longer treatment durations for GnRH agonists

In response to the DG, the company provided cost effectiveness results of relugolix CT compared with gonadotropin-releasing hormone (GnRH) agonists.[1]

EAG comment: The EAG can confirm the results provided by the company when treatment durations for GnRH agonists are assumed to be 5, 7 or 10 years. In these three scenarios, relugolix CT dominated GnRH agonists. These results can be seen in Table 4. It should be noted however that, as the treatment duration for GnRH agonists increases, the incremental costs become more negative (relugolix CT less costly) but the incremental quality-adjusted life years (QALYs) decrease. The decrease in incremental QALYs is explained by the hazard ratio (HR) = 1.10 of GnRH agonists vs. relugolix CT, favouring GnRH agonists, and therefore, the longer GnRH agonists are taken the more effective they become compared to relugolix CT. With the base-case settings, it would take 15 years (60 treatment cycles) until GnRH agonists become more effective than relugolix CT. This would result in an ICER in the SW quadrant of the CE plane large enough to be considered above common cost effectiveness thresholds used by the National Institute for Health and Care Excellence (NICE). The results of this scenario can be seen in Table 8, where the results of the exploratory EAG scenarios are summarised.

Table 4: Company cost-effectiveness results, relugolix CT vs. GnRH agonists, scenarios where GnRH agonists treatment duration is capped

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Relugolix CT	£11,487	23.105	17.165				
GnRH agonists (capped at 5 years)	£11,651	23.101	16.766	-£164	0.004	0.398	Relugolix CT dominates
GnRH agonists (capped at 7 years)	£12,157	23.103	16.882	-£670	0.002	0.283	Relugolix CT dominates
GnRH agonists (capped at 10 years)	£12,724	23.104	17.020	-£1,237	0.001	0.145	Relugolix CT dominates

Based on Table 4, 5 and 6 in the company's response to Draft Guidance[1]
CT = in combination with oestradiol and norethisterone acetate; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Comment 7: Further validation and justification of the utilities used in the model and scenarios considering the impact of changing these values

The company did not submit additional evidence regarding the utility used in the model.

EAG comment: The concerns raised in the EAG report remain the same (summarised below) thus the EAG refers to Section 4.2.8 in the EAG report for additional details:[6]

- Concerns around the face validity of the utility values presented in Table 4.13 of the EAG report.
- Concerns around the company's approach to assume the same utility value for non-responders and the same utility value for responders irrespective of their treatment path and most importantly irrespective of the consecutive episodes of non-response.
- Concerns about using relatively old studies to inform disutility values due to AEs or surgical complications, e.g., long-term disutility value for patients undergoing hysterectomy.

The company presented the results of an additional scenario analysis where the utility of non-response was set equal to the baseline utility. These can be seen in Table 5. The EAG was unable to reproduce the results provided by the company. Since there is no guidance on how to replicate this scenario, the EAG changed the value of the utility for non-response in "Input sheet" – D320. By doing so, the model automatically changes the value in "Input sheet" – D322, D324, D326, D329, and D333. The ICER obtained was £1,566 per QALY gained in the North-Eastern quadrant of the CE-plane (whereas the company reported £1,683). As mentioned in the EAG comments in Sections 4.2.8.1 and 5.1, the total QALYs results are relatively insensitive to single changes in utilities. This was explained by the fact that in the results presented by the company, about 88% of the overall gain in QALYs from relugolix CT treatment as compared to GnRH agonists is obtained from a lower level of AEs and surgery-related complications for patients in the relugolix CT arm, and about 86% of the overall QALY gains from the lower level of the long-term surgery-related complications only (post-hysterectomy disutility).

Table 5: Company cost-effectiveness results, relugolix CT vs. GnRH agonists, scenario where utility of non-response was set equal to the baseline utility

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Relugolix CT	£11,487	23.105	17.112				
GnRH agonists	£10,280	23.098	16.395	£1,207	0.007	0.717	£1,683

Based on Table 3 in the company's response to Draft Guidance[1]
CT = in combination with oestradiol and norethisterone acetate; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Comment 8: Multiplicative approach to incorporating disutilities from adverse events

The company did not implement a multiplicative approach, given that it was understood that a multiplicative approach is typically used for an age-related decrement and an additive approach is used for other disutilities.

EAG comment: The EAG does not agree with this interpretation; however, it agrees with the company that a multiplicative approach is likely to have a minor impact on the model results.

Comment 9: Scenarios considering the EAG's approach to capturing disutility from infertility

The draft guidance stated that *'the EAG also noted that the model applied utility decrements to all people after hysterectomy, but it preferred that the decrement only be applied to people who were actively seeking to have become pregnant', was based on page 163 of the CS, where it is mentioned that a "disutility of 0.180 is applied to account for this (Table 66), representing the disutility linked to infertility and was derived from a global burden of disease report published by the World Health Organization"*.[1] The EAG interpretation, therefore, was based on what was written by the company in the CS.[8]

In response to the draft guidance, the company indicated now that they "*do not agree with this approach because it would assume that the disutility associated with a hysterectomy is only limited to infertility*", which means that the company disagrees with what the company indicated in the original submission and in some responses to the clarification letter such as:

- Following up on the operationalisation of fertility, the company assumed a long-term disutility value of -0.180 in all post-hysterectomy health states (i.e., "stable", "recurrence" and "reoperation"), to capture the disutility linked to infertility as women are not able to conceive post-hysterectomy. However, in response to clarification question B7, which asked whether other important and clinically and economically relevant outcomes may have been omitted from

the analysis, the company stated that "*disutility from infertility would only be expected to have an impact on the proportion of people actively trying to have a family*".[14] This particular issue has also been flagged by the EAG in the clarification question B22. The company in this response mentioned that "*they agree with the EAG that this parameter is uncertain, but it is difficult to determine what proportion of patients with a hysterectomy would be wishing to have children, particularly as this would change as the cohort ages. The intention was to capture QoL losses additional to those of infertility, which may include feelings of a loss of femininity associated with the loss of the uterus*".[14]

- Furthermore, in clarification question B22, the EAG asked if patients on relugolix CT treatment should also be assumed to experience a similar disutility value of -0.180, since patients on relugolix CT treatment are not able to conceive while on treatment. The company noted that "*both GnRH and relugolix are contraceptive, and the disutility of infertility related to this would already have been captured within the trial EQ-5D values given that the women participating in the trials would have been aware of this*".[14] The EAG does not agree with the company's answer, because, as also mentioned by the company above, childbearing wish may vary over age and this may not be captured in the EQ-5D trial data. In response to clarification question B7, the company went further in their response mentioning that "*a utility benefit for faster recovery of fertility following discontinuation of relugolix CT was considered too uncertain a parameter to include and would likely have little impact in results, given that the difference in time to regain in fertility between the two treatments is likely to be months rather than years*".[14] The EAG is unclear around this statement considering that GnRH agonists are only provided for a maximum duration of 1 year compared to relugolix CT which can be administered until women's menopause, which may have a totally different impact on the patient's 'regain of fertility'.

EAG comment: If, as the company state now, hysterectomy in fact can have a substantial impact on quality of life beyond infertility, and it is not plausible that only those who wish to have a child would experience a (long-term) disutility after having a hysterectomy (such as loss or sadness, loss of femininity or depression), it is still likely that the approach implemented (a single utility decrement for all women) is simplistic and the estimated value, which the company claims it is representing a disutility linked to infertility, is incorrect. Furthermore, as explained in the EAG report, the original source for this input being the Global Burden of Disease report published in 1990.[6] Therefore, the EAG is uncertain if this value is still representative.

The EAG could reproduce the results of the scenarios presented by the company, where the disutility of hysterectomy was assumed to be -0.01, -0.05 and -0.10. These are summarised in Table 6. Obviously, the lower the disutility the higher the ICER. In these scenarios, the ICER vs. GnRH agonists were still below the common thresholds used by NICE. The largest ICER compared to GnRH agonists was £9,383 for the scenario where the disutility of hysterectomy was assumed to be -0.01. For completeness, a scenario with no disutility for hysterectomy and the same scenarios considering surgery as comparator were explored by the EAG. The results of these scenarios can be seen in Table 8 and 9 of this report. All these scenarios however still assumed a single change in disutility, which was applied to *all* women. Results of exploratory scenarios where different utility decrements associated to hysterectomy/infertility are applied only to a proportion of women up to a certain age can also be found in Table 8 and 9 of this report.

Table 6: Company cost-effectiveness results, relugolix CT vs. GnRH agonists, scenarios with alternative disutility of hysterectomy

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Disutility of hysterectomy is 0.01							
Relugolix CT	£11,487	23.105	17.976				
GnRH agonists	£10,280	23.098	17.847	£1,207	0.007	0.129	£9,383
Disutility of hysterectomy is 0.05							
Relugolix CT	£11,487	23.105	17.785				
GnRH agonists	£10,280	23.098	17.521	£1,207	0.007	0.264	£4,573
Disutility of hysterectomy is 0.1							
Relugolix CT	£11,487	23.105	17.547	-	-	-	-
GnRH agonists	£10,280	23.098	17.113	£1,207	0.007	0.433	£2,787

Based on Table 8, 9 and 10 in the company's response to Draft Guidance[1]
CT = in combination with oestradiol and norethisterone acetate; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Therefore, the EAG still considers that issues associated to infertility are quite relevant for patients with endometriosis, as it may also lead to a different choice of subsequent treatments. This is currently not appropriately incorporated in the economic analysis.

Comment 10: Scenarios considering the impact of treatment waning

The company indicated that they do not anticipate any waning of treatment effect with relugolix CT and explored two scenarios where the discontinuation rates in the model were changed. The company first assumed the upper value of the discontinuation rate which was 0.033 and then a discontinuation rate of 0 was applied. The results of these scenarios had little impact on the model results as can be seen in Table 7.

Table 7: Company cost-effectiveness results, relugolix CT vs. GnRH agonists, scenarios with alternative relugolix CT discontinuation rates

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Maximum discontinuation rate							
Relugolix CT	£11,361	23.103	16.958				
GnRH agonists	£10,280	23.098	16.461	£1,082	0.005	0.497	£2,178
Minimum discontinuation rate							
Relugolix CT	11,446	23.107	17.367				
GnRH agonists	10,280	23.098	16.345	£1,166	0.009	0.906	£1,287

Based on Table 12, and 13 in the company's response to Draft Guidance[1]
CT = in combination with oestradiol and norethisterone acetate; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

EAG comment: The EAG is unclear whether changing relugolix CT discontinuation rates represent any kind of treatment effect waning. The EAG considers that the effect of waning could be captured by adjusting the response rates over time rather than treatment discontinuation. This would require non-trivial changes to the model, which at this stage, and given the lack of data to inform those response

rates over time, were not explored by the EAG. However, the impact on the model results is expected to be minor.

Comment 11: Full model validation and justification of counterintuitive results

In the response to the DG, the company provided further details on the model validation.[13]

EAG comment: The EAG would like to thank the company for the additional details regarding the validation efforts conducted on the model. Given the time constraints associated to this project, the EAG was unable to conduct the tests described by the company and therefore, could not confirm their results.

Regarding the counterintuitive results in the scenario where relugolix CT response rate is (arbitrarily) decreased to 1%, the EAG, again, would like to thank the company for the additional explanation. However, while understanding how the model works and how results are obtained is important, it does not imply that the results are valid. The EAG still considers that it would be reasonable to expect that the cost effectiveness of relugolix CT would increase with the proportion of patients achieving complete response (the more response, the better), but this is not the case.

Regarding the hypothetical scenario where 100% of people stopped relugolix CT at 9 or 12 months, the EAG would like to confirm that by changing the parameters in Input sheet – row 141, relugolix CT resulted in more QALYs (0.019 and 0.041, stopping at 9 and 12 months respectively) and fewer costs (-£145 and -£63, stopping at 9 and 12 months respectively) than GnRH agonists. These are the only changes the EAG made to the model. Therefore, it is unclear how the company observed that decreasing the duration of treatment on relugolix CT to 9- or 12-months resulted in both lower QALYs and lower costs vs. GnRH agonists, which in fact, would make sense.

Finally, regarding the probabilistic sensitivity analysis (PSA) parameters, the EAG would like to ask the company for the additional details. It appears as if the response to clarification question B31 is simply "*This has now been corrected*". In addition, the EAG would like to refer to Section 5.3.3 of the EAG report and where it was mentioned that the model implementation provided by the company contains some "legacy assumptions" from an original global model that includes certain functionalities that are not applicable to this NICE submission.[6] The model version received after clarification – thus, the one used to answer DG comments – still contained these "legacy" functionalities, but it was not mentioned which ones. As far as the EAG is concerned, this has not been clarified up to now. Furthermore, in the model version that the EAG is using to replicate the company's results (ID3982 relugolix GR UK adapted CEM clarification 191220240KM [CON]), it seems that a fixed 10% variation from the mean for all parameters in the PSA is still used, which is not in line with the response to clarification question B30.[14] Also, parameters such as the discount rates seem to be included in the PSA, whereas it is common practice to consider them as fixed and explore the impact of changing them in scenario analyses. In conclusion, it is unclear to the EAG whether this issue has been resolved or not.

EAG exploratory analyses and conclusions: The EAG would like to stress that no additional cost-effectiveness evidence have been presented by the company in response to the Draft Guidance. Therefore, the key issues and other concerns identified in the EAG report remain unresolved. In the absence of new evidence, the EAG considers that any changes made to the company base-case would have been arbitrary rather than evidence-based. For that reason, the EAG decided not to define a new preferred base-case. As mentioned in previous sections of this document, the EAG conducted a several exploratory analyses to assess the impact of changing certain assumptions and input parameters on the model results. The results of these exploratory analyses can be seen in Table 6, when the comparator is assumed to be GnRH agonists, and Table 7, where the comparator is assumed to be surgery. Since it is still unclear whether surgery is a relevant comparator for this appraisal, the EAG decided to present

these results separately instead of presenting them together with those including also GnRH agonists as comparator in a full incremental analysis. If the Appraisal Committee decides that surgery is indeed a relevant comparator, then cost-effectiveness results should be presented in a full incremental way.

It should be emphasised that the operationalisation of infertility, and the addition of comparators (if appropriate), can still have a substantial impact on the model results. This is shown in the scenarios where the long-term utility decrement associated to hysterectomy/infertility is applied to applied to 50% of the population following hysterectomy, in addition to 50% of the population in the relugolix CT and GnRH agonists arms while on treatment, and up to 45 years of age. In these scenarios the ICER compared to GnRH agonists exceeded £30,000 per QALY gained, when half of the original disutility value was assumed, and relugolix CT was dominated when the original disutility value was assumed. In both scenarios, relugolix CT was dominated by surgery. Despite being hypothetical, these scenarios illustrate the potential impact of modelling a more complex, and possibly more realistic, approach to infertility on the model results. It should also be noted that, in general, the ICER is insensitive to changes in all other input parameters. Therefore, it is crucial that the operationalisation of infertility in the model is done with caution, properly justified and exhaustively validated.

Table 8: EAG cost-effectiveness results, relugolix CT vs. GnRH agonists exploratory scenarios

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Company base-case							
Relugolix CT	£11,487	23.105	17.165				
GnRH agonists	£10,280	23.098	16.461	£1,207	0.007	0.704	£1,715
Scenarios GnRH agonists treatment duration capped at 15 years							
Relugolix CT	£11,487	23.105	17.165				
GnRH agonists	£13,144	23.105	17.167	-£1,656	0.000	-0.002	£746,754*
No disutility of hysterectomy							
Relugolix CT	£11,487	23.105	18.024				
GnRH agonists	£10,280	23.098	17.929	£1,207	0.007	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							
Relugolix CT	£11,487	23.105	17.704				
GnRH agonists	£10,280	23.098	17.665	£1,207	0.007	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							
Relugolix CT	£11,487	23.105	17.384				
GnRH agonists	£10,280	23.098	17.402	£1,207	0.007	-0.018	GnRH agonists dominate

* ICER in SW quadrant of CE plane.
CT = in combination with oestradiol and norethisterone acetate; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

Table 9: EAG cost-effectiveness results, relugolix CT vs. surgery exploratory scenarios

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Company base-case							
Relugolix CT	£11,487	23.105	17.165				

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. Costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Surgery	£9,741	23.095	16.345	£1,746	0.010	0.820	£2,130
Disutility of hysterectomy is 0.01							
Relugolix CT	£11,487	23.105	17.976				
Surgery	£9,741	23.095	17.900	£1,746	0.010	0.076	£23,010
Disutility of hysterectomy is 0.05							
Relugolix CT	£11,487	23.105	17.785				
Surgery	£9,741	23.095	17.534	£1,746	0.010	0.251	£6,959
Disutility of hysterectomy is 0.10							
Relugolix CT	£11,487	23.105	17.547				
Surgery	£9,741	23.095	17.077	£1,746	0.010	0.470	£3,717
No disutility of hysterectomy							
Relugolix CT	£11,487	23.105	18.024				
Surgery	£9,741	23.095	17.991	£1,746	0.010	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							
Relugolix CT	£11,487	23.105	17.704				
Surgery	£9,741	23.095	17.709	£1,746	0.010	-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							
Relugolix CT	£11,487	23.105	17.384				
Surgery	£9,741	23.095	17.426	£1,746	0.010	-0.042	Surgery dominates

CT = in combination with oestradiol and norethisterone acetate; ICER = incremental cost-effectiveness ratio; Inc. = incremental; LYG = life years gained; QALY = quality-adjusted life year

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