

Changes have been made to this item. Details of the corrigendum are at the end of this document.

**5.18 RELUGOLIX WITH ESTRADIOL AND WITH
NORETHISTERONE ACETATE,
Tablet containing relugolix 40 mg with estradiol (as
hemihydrate) 1 mg and with norethisterone acetate
0.5 mg,
Ryeqo[®],
Gedeon Richter Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested Section 85 Authority Required listing of Ryeqo[®] (herein Ryeqo), a fixed dose combination (FDC) therapy containing relugolix (a gonadotropin hormone-releasing hormone [GnRH] antagonist), with estradiol (E2, an estrogen steroid hormone) and norethisterone acetate (NETA, a progesterone steroid hormone) as add-back hormone therapy, to manage moderate to severe pain associated with endometriosis in women who have failed to gain adequate pain relief from existing treatments.
- 1.2 GnRH therapy (or analogues) includes GnRH agonists and antagonists. Currently, there are two GnRH agonists available on the PBS for the treatment of endometriosis, including goserelin 3.6 mg implant and nafarelin 200 mcg nasal spray. Add-back therapy is used to manage the hypoestrogenic effects of GnRH analogues, including loss in bone mineral content. For patients requiring add-back therapy, the submission identified several estrogen and progesterone treatments prescribed in Australia from a clinician survey (N=12). Treatments identified included some that are TGA approved and PBS listed for endometriosis, treatments that are not TGA approved for endometriosis but have unrestricted listing on the PBS, and other treatments that are only PBS listed for non-endometriosis indications or treatments that are not PBS listed for any indication. Ryeqo will be the first GnRH antagonist FDC with add-back hormone replacement therapy (E2 and NETA) available on the PBS for endometriosis.
- 1.3 The basis of the requested listing as presented in the submission was cost-utility analysis versus goserelin (GnRH agonist) and best supportive care (BSC) i.e. contraceptive therapy.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Moderate to severe endometriosis-associated pain for women of reproductive age who are not receiving adequate relief from current therapy
Intervention	Ryeqo is a once daily oral fixed dose combination (FDC) containing 40 mg relugolix, 1 mg estradiol (E2) and 0.5 mg norethisterone acetate (NETA) (i.e., E2 and NETA as add-back therapy)
Comparator	Main comparator: Goserelin (Zoladex®) 3.6 mg implant every 28 days, plus add-back therapy (estrogen and progesterone treatments). Comparator (ongoing use) ^a : best supportive care (BSC) defined as contraceptive therapies (hormone treatment with oral contraceptive, combined oral contraceptive pills, progestogen and levonorgestrel-releasing intra-uterine devices).
Outcomes	Primary outcome measures: Dysmenorrhea; non-menstrual pelvic pain. Secondary outcome measures: Pelvic pain, dyspareunia, analgesic and opioid use, adverse effects, quality of life.
Clinical claim	- Ryeqo in women with moderate to severe endometriosis-associated pain, is non-inferior in terms of efficacy and safety to goserelin plus add-back therapy; - Ryeqo is superior to goserelin monotherapy in terms of safety; - Ryeqo is superior to BSC in terms of efficacy and non-inferior in terms of safety.

Source: Table 1.1.1, pp. 4-5 of the submission.

GnRH=gonadotropin hormone-releasing hormone;

^a due to the proposed continuous use of Ryeqo and limitations on duration of use of GnRH agonists (goserelin and nafarelin).

2 Background

Registration status

2.1 The sponsor sought assessment of Ryeqo for endometriosis under the parallel Therapeutic Goods Administration (TGA) and PBAC process. Ryeqo was TGA registered for this indication on 31 January 2024. The indication in the approved product information (PI) was:

“Ryeqo is indicated in adult women of reproductive age for:

Symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis”

2.2 The approved PI also includes the following advice regarding bone mineral density (BMD) loss:

“Assessment of BMD by dual-energy X-ray absorptiometry (DXA) is recommended at baseline and after one year of treatment.

Use is recommended to be limited to 24 months, with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician.

Annual DXA is recommended while taking Ryeqo”

2.3 The TGA Delegate also sought advice from the Advisory Committee on Medicines (ACM) regarding the lack of clinical data for adolescent patients (aged 12-18 years). The ACM was of the view that the indication be limited to women aged 18 years and older. In providing this view, the ACM noted that adolescence is a critical time for bone accrual and the absence of data creates significant uncertainty that results in an

unfavourable risk benefit profile at this time. The ACM also noted that a diagnosis of endometriosis is difficult to make at a younger age (see also paragraph 3.5).

- 2.4 In August 2022, the FDA approved Ryego as Myfembree® for the management of moderate to severe pain associated with endometriosis in premenopausal women, with treatment duration up to 24 months. In Japan, Ryego is approved as Relumina® for treatment of endometriosis. At the time of PBAC consideration, the National Institute of Health and Care Excellence (NICE) health technology assessment (HTA) of Ryego for treating pain associated with endometriosis was in development¹.
- 2.5 Ryego was TGA approved in September 2022 for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Previous PBAC consideration

- 2.6 The PBAC has not previously considered Ryego for the treatment of endometriosis-associated pain. Currently, PBS-listed treatments for endometriosis include goserelin (listed on December 1994), nafarelin (listed for initial treatment on October 1994 and subsequent treatment on May 2000) and medroxyprogesterone 10 mg. Goserelin and nafarelin are both GnRH agonists. Additional hormonal therapies such as contraceptives are available on the PBS with general/unrestricted benefit (e.g. norethisterone, levonorgestrel and etonogestrel).

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RELUGOLIX + OESTRADIOL (AS HEMIHYDRATE) + NORETHISTERONE					
relugolix 40 mg + oestradiol (as hemihydrate) 1 mg + norethisterone 0.5 mg tablet, 28	NEW	1	28	5	Ryego
Restriction Summary [new 1] / Treatment of Concept: [new 2]					
	Category / Program: GENERAL – General Schedule				
	Prescriber type: ☒ Medical Practitioners ☒ Nurse practitioners				
	Restriction type: ☒ Authority Required (Streamlined)				

¹ NICE. Relugolix–estradiol–norethisterone acetate for treating pain associated with endometriosis [ID3982]. Available from: <https://www.nice.org.uk/guidance/indevelopment/gid-ta10873/documents>. Accessed on 30/11/2023.

Public Summary Document - March 2024 PBAC Meeting

	Administrative Advice: Continuing Therapy Only: <i>For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</i>
	Indication: Endometriosis
	Treatment Phase: ongoing Initial treatment
	Clinical criteria:
	Experiencing moderate to severe pain associated with endometriosis. <i>Patient must have experienced moderate to severe pain associated with endometriosis.</i>
	Clinical criteria
	The condition must be endometriosis visually proven or laparoscopic confirmed by a specialist <i>The condition must be visually proven</i>
	AND
	Clinical criteria:
	Patient must have has received inadequate response or is unsuitable for previous therapies. <i>Patient must have received an inadequate response to, or be intolerant to, previous first line therapies for this condition, including at least one of the following: (i) hormonal contraceptives, (ii) analgesics</i>
	Clinical criteria:
	If patient had surgery for their endometriosis, treatment must not commence until 3 months after the surgical procedure. <i>Patient must not have undergone surgery for this condition in the last 3 months; OR</i>
	<i>Patient must not commence this treatment until 3 months post-surgery</i>
	AND
	Clinical criteria:
	Patient does not have a history of, nor currently has, osteoporosis, or at risk of other metabolic bone disease <i>Patient must not have a history of, nor currently have any of the following: (i) osteoporosis, (ii) risk of other metabolic bone disease.</i>
	Treatment criteria:
	<i>Must be treated by a gynaecologist</i>
	Population criteria:
	<i>Patient must be pre-menopausal</i>
	Caution: <i>Ryego should not be used interchangeably with other GnRH agonists and/or hormonal contraceptives brands due to differences in dose and schedule of treatment</i>
	Administrative Advice: The first tablet must be taken within 5 days of the onset of menstrual bleeding (If treatment is initiated on another day of the menstrual cycle, irregular and/or heavy bleeding may initially occur).
	Caution: <i>Pregnancy must be ruled out prior to initiating treatment.</i>
	Caution: Non-hormonal methods of contraception must be used for at least 1 month after initiation of treatment.
	Indication: Endometriosis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	<i>Patient must have received prior PBS-subsidised treatment with this drug for this condition</i>

- 3.2 At the recommended dose of one tablet per day, the requested maximum quantity and number of repeats would provide for six months of treatment. The submission

stated allowing the standard 6 months of treatment would align with the frequency of specialist visits.

- 3.3 The submission requested a price for 28-day supply of Ryego (DPMQ \$[REDACTED]) which is approximately equivalent to the price for a 28-day supply of goserelin 3.6 mg implant (DPMQ \$212.70). The submission stated there was a small premium (i.e. \$[REDACTED]) to account for the addition of the add-back treatment. The submission did not propose a special pricing arrangement. The submission did not discuss pricing for nafarelin, which is also a GnRH agonist listed on the PBS for endometriosis. See also Table 8 and Table 9 below, under Economic analysis for further discussion.
- 3.4 The submission stated that the Authority Required (STREAMLINED) listing was appropriate given Ryego is a new medication and noted that other GnRH analogues were first listed as Authority Required items (currently restricted benefit items).
- 3.5 The requested restriction was broad, given:
- There were no response criteria for continued use.
 - There was no maximum duration of treatment. The approved PI includes wording for dosage “Use is recommended to be limited to 24 months, with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician”. The pre-PBAC response proposed adding a prescriber instruction that describes the recommended duration of treatment.
 - The restriction was silent on age. The proposed and final TGA approved indication was limited to adult women of reproductive age (given the lack of clinical evidence in women less than 18 years) and the submission assumed only women aged 30-55 years would access treatment in the financial estimates. The ESC noted that this would exclude some patients under 18 who have severe pain associated with endometriosis and could potentially benefit from treatment; but it was also noted the lack of clinical evidence in patients under 18 years and ACM’s advice that that adolescence is a critical time for bone accrual. The pre-PBAC response proposed an additional population criterion which requires patients to be aged 18 years or older to be eligible for treatment with Ryego and revised the financial estimates to include women aged 18-55 years.
 - The prescriber type specifies all medical practitioners. The submission noted throughout that second-line hormonal treatment of endometriosis usually involves specialist care by a gynaecologist. The Pre-Sub Committee Response (PSCR) noted that the sponsor would prefer wording that captures all specialists with experience in diagnosis and treatment of endometriosis. The ESC considered that this was reasonable and considered that wording should include general practitioners specialising in diagnosis and treatment of endometriosis.
- 3.6 The ESC noted that there was no requirement for BMD testing in the proposed restriction. The approved PI recommends that clinicians perform a DXA scan before

commencing treatment, and then annually. The ACM had also advised that attainment of lumbar spine peak bone mass occurs at ages 33 to 40 years and total hip peak bone mass (PBM) occurred at aged 16 to 19 years in women, and that BMD data needs to be interpreted in this context.

- 3.7 The submission stated that clinical judgement may be used to determine whether a patient will be given an annual DXA scan and was unlikely to cause a significant equity of access issue. The PSCR argued that “while the PI recommends a pre-treatment DXA scan, it is not mandated” and that BMD testing would be implemented at clinician discretion. The pre-PBAC response proposed that to ensure awareness of the risk of BMD loss among prescribers, the PBAC could consider including prescribing instructions to the restriction: ‘A DXA scan is recommended at baseline, after the first 52 weeks of treatment, and annually thereafter’.
- 3.8 The PSCR stated that current MBS item numbers for DXA scans could suffice for ongoing treatment, however there are no applicable item numbers for baseline testing. The ESC agreed with the PSCR that there are no applicable item numbers for baseline testing, but noted that for ongoing testing, although some patients may be eligible for a DXA scan every 12 or 24 months under the existing items, not all patients would meet the criteria. The ESC noted that access to a DXA scan on the private market is available for \$50-\$90².
- 3.9 The PBAC noted that MBS Item 12312 might be applicable for use following initial treatment with Ryego if condition (d) is met (see below).
- 12312: Bone densitometry, using dual energy X-ray absorptiometry, involving the measurement of 2 or more sites (including interpretation and reporting) for diagnosis and monitoring of bone loss associated with one or more of the following:... (d) female hypogonadism lasting more than 6 months before the age of 45;
- 3.10 For ongoing monitoring of bone density MBS Item 12306 may be applicable for 24 monthly repeats if condition (b) is met:
- 12306: Bone densitometry, using dual energy X-ray absorptiometry, involving the measurement of 2 or more sites (including interpretation and reporting), for: (b) monitoring of low bone mineral density proven by bone densitometry at least 12 months previously.
- 3.11 Item 12321 may be applicable for 12 monthly repeats if condition (a) is met:
- 12321: Bone densitometry, using dual energy X-ray absorptiometry, involving the measurement of 2 or more sites at least 12 months after a significant change in therapy (including interpretation and reporting), for: (a) established low bone mineral density.

² [The Bone Bus – By Measure Up](#)

- 3.12 The ESC noted that for GnRH analogues included on the PBS the Australian PIs recommend BMD measurement for retreatment (nafarelin) or for 'longer treatment' (goserelin). In addition, the PBS restriction for subsequent treatment (6-12 months) with nafarelin includes the criteria "Patient must have had a recent bone density assessment". The PBS restriction for goserelin does not allow treatment beyond 6 months.
- 3.13 The sponsor requested grandfathered patients be allowed access to therapy, without requiring a specific grandfathered clause. The sponsor is currently providing treatment with Ryeqo to some women with endometriosis pain and the submission estimated that approximately < 500 patients will be receiving Ryeqo for this indication. The PBAC noted that the proposed initial treatment listing would not exclude these patients and considered that a separate grandfather restriction was not required.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Endometriosis is a chronic disease that occurs when tissue similar to the lining of the uterus (endometrium tissue) grows outside the uterine cavity. Women with endometriosis typically experience pelvic pain and heavy bleeding during menstruation, while abdominal pain, bloating and fatigue can occur throughout the menstrual cycle. Women with endometriosis are also more likely to have co-existing conditions and chronic diseases, such as uterine fibroids, fibromyalgia, migraine, ovarian cancer, thyroid cancer, cardiovascular diseases and immune disorders.
- 4.2 Diagnostic work-up includes a review of medical history, clinical abdominal and pelvic examination, and imaging (ultrasound, Computer Tomography (CT) or Magnetic Resonance Imaging (MRI)). However, diagnosis may be difficult due to variation in symptom presentation and treatment patterns; symptoms may be attributed to multiple conditions, endometriosis-associated pain is not easily measured and there are no clinically relevant biomarkers. The delay between symptom onset and diagnosis is on average 7-12 years.
- 4.3 There is no known cure for endometriosis. Treatment targets the management of symptoms and is usually iterative over time. Endometriosis pain is highly individualised and can be managed with medical and/or surgical treatments, which include analgesics, hormonal contraceptives or other hormonal treatments, removal of lesions via laparoscopy or laparotomy (abdominal surgery)³, and hysterectomy (removal of the uterus). Despite medical and surgical treatment options, symptoms often recur (50% of patients typically have recurrence of symptoms over 5 years).⁴ In

³ Dunselman GA, Vermeulen N, Becker C et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod* 2014; 29(3): 400-412.

⁴ Zondervan KT, Becker CM and Missmer SA. Endometriosis. *N Engl J Med* 2020; 382: 1244-1256.

most cases, symptoms of endometriosis subside after menopause, which in Australia occurs at an average age of 51 years.^{5,6}

- 4.4 A patient round table and follow up survey was conducted by the sponsor to understand the patients' experiences with moderate to severe pain associated with endometriosis. Three of the six patients were currently being prescribed Ryego. The endometriosis pain was described as stabbing by the patients, as well as debilitating, draining, mentally exhausting, and resulting in them 'having to take time off work'. Patients reported switching or adding treatments, sometimes one or more times a year, mainly because previous treatments 'stopped working' or were costly. Treatments used included analgesics (e.g. Panadol® and Nurofen®), hormonal contraceptives (e.g. Mirena®), GnRH agonists (goserelin, nafarelin), aromatase inhibitor (letrozole) and others (e.g. cannabidiol oil, laparoscopy, physiotherapy).
- 4.5 Australian guidelines include the RANZCOG (2021) endometriosis clinical practice guideline and the Therapeutic Guidelines (2020) for endometriosis, which recommend first-line treatment of analgesia with or without hormone therapies. Guidelines recommend a 3-month trial of a nonsteroidal anti-inflammatory drug (NSAID) or paracetamol (or a combination of both). Hormone treatment for endometriosis includes combined hormonal contraceptives and progestogens, with specialist treatment of GnRH agonist and antagonist or aromatase inhibitors.
- 4.6 The Australian Therapeutic Guidelines 2020 recommend GnRH agonists (goserelin implant and nafarelin nasal spray) as second-line treatment and GnRH must be used concurrently with contraception. Use of GnRH agonists is limited to 6 months duration due to the hypoestrogenic adverse effect (e.g. decreased BMD, hot flushes). However, estrogen and progestogen replacement (add-back) therapy allow use of GnRH agonists for up to 2 years. The PBAC noted that PBS listings for goserelin and nafarelin reflect the clinical algorithm at the time they were listed, prior to recommendations that they should be used in combination with add-back therapy. The PBAC considered that changes to these restrictions to align with clinical practice may be required and would welcome a submission.
- 4.7 In the King Edward Memorial Hospital (KEMH) Western Australia – Gynaecology clinical practice guideline (2023)⁷, the goserelin prescribing protocol recommends treatment with goserelin if patients have inadequate response to first-line therapy (analgesics and hormone therapy). Goserelin 3.6 mg is PBS-listed for treatment of endometriosis for up to 6 months, however beyond 6 months, both strengths of goserelin (3.6 and 10.8 mg) are available on the State-wide medicines formulary funded by Health Department of Western Australia for endometriosis (as with the PBS

⁵ Jean Hailes for Women's Health. Endometriosis complications, 2017. Melbourne: Jean Hailes for Women's Health.

⁶ Australian Menopause Society. Fact Sheets. <https://www.menopause.org.au/health-info/fact-sheets>

⁷ King Edward Memorial Hospital Clinical Practice Guideline Gynaecology (non-oncological), available from <https://www.kemh.health.wa.gov.au/~media/HSPs/NMHS/Hospitals/WNHS/Documents/Clinical-guidelines/Obs-Gyn-Guidelines/Gynaecology-Non-Oncological.pdf?thn=0>, accessed 20/12/2023.

indication). While the prescribing protocol recommended maximum duration of goserelin is 24 months, add-back therapy is usually commenced to minimise adverse effects and regular BMD scans are recommended before and during treatment with goserelin. The KEMH 2023 goserelin prescribing protocol noted a medicine usage review in 2017, which found that goserelin is often prescribed before other, less costly, medications have been trialled and before standard surgery. Duration of goserelin therapy is often limited due to the cost to hospital and patients and adverse effects (notably reduction in BMD).

- 4.8 The Australian guidelines are generally consistent with international guidelines for endometriosis. The European Society of Human Reproduction and Embryology (EHSRE 2022) guidance for treatment options for endometriosis-associated pain include analgesics/NSAIDs, hormone treatment and surgery, with decision making taking into consideration patient preferences, side effects, individual efficacy, costs and availability. The first-line treatment options are NSAIDs and low-dose combined oral contraceptive pills or progestins. Second-line treatment includes GnRH agonists and antagonists (for example if hormonal contraceptives or progestogens have been ineffective) due to their safety profile, however evidence is limited regarding the dosage and duration of treatment. GnRH antagonists include elagolix, relugolix and linzagolix. GnRH agonist or antagonist treatment is recommended for use with combined hormonal add-back therapy to prevent bone loss and hypoestrogenic symptoms. Based on evidence to date, no specific GnRH can be recommended over another in managing endometriosis-associated pain. Aromatase inhibitors should be considered as the second/third-line therapeutic option if patients do not achieve adequate response or are intolerant to earlier treatments. Aromatase inhibitors may be used in combination with oral contraceptives, progestogens, GnRH agonists or antagonists.
- 4.9 Ryeqo is a once daily oral FDC containing 40 mg relugolix, 1 mg E2 (hemihydrate), and 0.5 mg NETA. It provides hormone therapy to treat endometriosis-associated pain while minimising the risk associated with the therapy. Ryeqo also provides contraception when taken for at least one month. While Ryeqo inhibits ovulation and may cause amenorrhoea, ovulation and menstrual bleeding will return after discontinuing treatment.
- 4.10 Relugolix is a non-peptide GnRH receptor antagonist that binds to and inhibits GnRH receptors in the anterior pituitary gland. Inhibition of GnRH receptor results in a dose dependent decrease in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are reduced. The reduction in FSH concentrations prevents follicular growth and development, thereby reducing the production of estrogen. Prevention of an LH surge inhibits ovulation and development of the corpus luteum, which precludes the production of progesterone. The hypoestrogenic state is the main cause of adverse effects, including decreased BMD and vasomotor

symptoms (e.g. hot flushes, vaginal dryness and headache). Add-back therapy, usually with E2 and NETA can reduce the adverse effects.

- 4.11 E2 is a synthetic form of the endogenously produced hormone which is a potent agonist of the nuclear estrogen receptor subtypes. Exogenously administered estradiol alleviates symptoms associated with a hypoestrogenic state such as vasomotor symptoms and BMD loss. NETA is a synthetic progestogen. The addition of a progestogen reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated goserelin + add-back therapy as the main comparator. The submission also nominated BSC after GnRH + add-back treatment, defined as contraceptive therapies, as a relevant comparator given PBS restrictions limit the duration of use with GnRH analogues. Currently, patients are eligible for up to 6 months treatment with goserelin on the PBS (one course per lifetime) as well as up to 6 months treatment with nafarelin on the PBS (subsequent courses permitted after a two-year break). As the requested restriction for Ryego does not include a maximum duration of treatment, the submission contended that Ryego would mostly replace oral contraceptives following up to 12 months of treatment with GnRH agonists on the PBS.
- 5.2 The ESC agreed with the Commentary that nomination of goserelin with add-back therapy as the main comparator was appropriate. Both a DUSC (2019)⁸ report and a sponsor commissioned report (Prospection report 2023)⁹ of the 10% PBS sample found goserelin was the most frequently used GnRH analogue for endometriosis in Australia, and as a fixed-dose combination product the comparison to the components consisting of a GnRH analogue + add-back hormones, given concomitantly, was appropriate. The submission noted that the sponsor will not be marketing a monotherapy formulation of relugolix in Australia, but argued that the clinical efficacy and safety of all GnRH analogues was similar when dosed consistently (i.e. full suppression). The submission also assumed that the clinical efficacy and safety of various add-back regimens were similar.
- 5.3 Although the main body of the submission nominated GnRH + add-back as the appropriate main comparator, the submission presented a modelled economic evaluation comparing Ryego (GnRH + add-back) versus GnRH (with or without add-back). Notwithstanding this inconsistency, GnRH monotherapy (i.e. without add-back)

⁸ DUSC 2019, GnRH Agonists: utilisation analysis, available from: <https://www.pbs.gov.au/pbs/industry/listing/participants/public-release-docs/2019-06/gnrh-agonists-utilisation-analysis>, accessed 20/12/2023.

⁹ Prospection. Summary of Endometriosis PBS market. Produced for Gedeon Richter – October 2023. (Attachment 'Prospection Gedeon Richter – Endometriosis Market Review 10% PBS data.pdf' of the submission).

is a potentially relevant comparator to establish the additional benefit associated with add-back treatment in the context of a fixed dose combination product. However, the ESC agreed with the Commentary that it is unlikely that Ryego would replace GnRH monotherapy in practice (i.e. increase the propensity of prescribers to initiate add-back treatment) and hence the comparison between Ryego versus GnRH $\pm$ (with and without) add-back was not informative.

- 5.4 Whether BSC (after GnRH + add-back treatment), defined as contraceptive therapies, was also a relevant comparator depends on the expected duration of treatment with different GnRH + add-back regimens. For Ryego, the proposed PBS restriction does not include a maximum duration of treatment and the submission assumed up to 5 years of treatment in the modelled economic evaluation, but the approved PI recommends treatment be limited to 24 months with extension of treatment conditional on the risk of continued bone loss. For current treatment options, the Australian and international guidelines generally recommend up to 12–24 months of treatment with a GnRH analogue + add-back regimen. The maximum of 6 months of goserelin and nafarelin allowed on the PBS aligns with the recommendations for GnRH monotherapy rather than GnRH + add-back treatments. The submission estimated that approximately 37% of Australian patients are prescribed concomitant add-back therapy when they receive treatment with GnRH agonist (based on an international clinician survey (N=200, Research Partnership Inizio Advisory 2023)¹⁰ given concomitant use cannot be reliably estimated from PBS data), and a similar proportion of patients remain on a GnRH analogue for greater than 6 months including sequential use of both GnRH analogues (goserelin and nafarelin) on the PBS (DUSC report 2019, Prospection report 2023). Although use of GnRH treatment beyond 12 months is not permitted on the PBS, patients may still access treatment privately (non-PBS) with or without rebate via private health insurance, or through state-based formularies for example with up to 24 months of GnRH treatment funded in Western Australia¹¹. Hence in practice, Ryego would likely replace various GnRH + add-back regimens, where the first 12 months of GnRH treatment would be provided through the PBS and subsequent GnRH treatment would be non-PBS use.
- 5.5 Despite nominating BSC (after GnRH + add-back) as a relevant comparator, the submission presented a modelled economic evaluation comparing Ryego (GnRH + add-back FDC) versus BSC in the absence of GnRH treatment. The ESC agreed with the Commentary that this modelled comparison was also not informative given it was unlikely that Ryego would replace BSC in patients who would otherwise not initiate GnRH therapy (i.e. increase the propensity of prescriber to initiate a GnRH analogue).

¹⁰ Research Partnership Inizio Advisory. Endometriosis Market Understanding: Quantitative Phase 2. May 2023. PowerPoint Presentation. (Attachment '20231023_Endometriosis Report QUANT data_incl 30 Aust GYN_Summary.pdf' of the submission).

¹¹ King Edward Memorial Hospital Clinical Practice Guideline Gynaecology (non-oncological), available from <https://www.kemh.health.wa.gov.au/~media/HSPs/NMHS/Hospitals/WNHS/Documents/Clinical-guidelines/Obs-Gyn-Guidelines/Gynaecology-Non-Oncological.pdf?thn=0>, accessed 20/12/2023.

The PSCR argued that based on the results of an international survey of gynaecologists Ryeqo may replace contraceptives (BSC) in 20% of cases. The ESC noted that the same survey showed that contraceptives are almost always used in the first line setting and considered that as Ryeqo was positioned as second or later line treatment after previous medical or surgical interventions, it was unlikely to replace contraceptives in patients who would not otherwise receive a GnRH therapy.

- 5.6 The Commentary noted that a more informative comparison to reflect the proposed longer use of GnRH + add-back treatment on the PBS would be to estimate the costs and benefits associated with the current treatment algorithm on the PBS (GnRH + add-back treatment for up to 12 months, followed by BSC thereafter) versus the proposed treatment algorithm on the PBS with Ryeqo (GnRH + add-back FDC for up to 24 months followed by BSC). The ESC noted that the PBAC may also wish to consider a comparison of daily or yearly costs for Ryeqo treatment compared with GnRH + add-back, given that treatment guidelines include up to 24 months of treatment with GnRH when used in combination with add-back (to reduce the impact of treatment on BMD).
- 5.7 The submission did not nominate any near market comparators. However, other treatment options in endometriosis with GnRH antagonists include elagolix (Orilissa®) and linzagolix (Yselty®). Elagolix is an oral, non-peptide, short-acting GnRH, which was approved by the FDA in July 2018 for the management of moderate to severe pain associated with endometriosis. Elagolix has not been evaluated by TGA. Linzagolix is also an orally active GnRH antagonist, but it is not yet approved by the FDA. Linzagolix is under evaluation by the TGA for the treatment of moderate to severe symptoms of uterine fibroids.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor provided a recorded hearing for this item. The clinician described who would likely be prescribed Ryeqo. It was noted that Ryeqo provides an alternative to other GnRH therapies but with less dramatic impact on the production of estrogen, so it would likely be targeted to women where profound suppression is not required (i.e. those who have failed surgery and medical management; potentially have other symptoms such as heavy menstrual bleeding; or are in their late 40s and looking into management of menopausal symptoms). Ryeqo will suit women who are a bit older, in order to bring forward menopause. It is expected that women with persistent significant pain can stay on treatment with Ryeqo for longer than current therapies. The clinician suggested that BMD testing would not be routinely required, unless other factors suggested it was necessary, such as continuous cortisone, or immunosuppression, or previous test showing osteopenia/osteoporosis, or if prescribing longer term treatment. The clinician also considered the need to monitor BMD loss is not as significant given add-back therapy is included.

- 6.2 The hearing included additional comments from the CEO of Endometriosis Australia highlighting the impact on women in the workplace and the often-unpaid time off work required which may result in losing employment.
- 6.3 The PBAC considered that the hearing was informative as it provided a clinical perspective on who would likely be prescribed Ryego.

Consumer comments

- 6.4 The PBAC noted and welcomed the input from individuals with the health condition (7), other interested individuals (3), health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with Ryego including that it is well tolerated and able to suppress the condition, with fewer side effects than current GnRH therapies. Other comments describe the impacts of endometriosis on quality of life, including severe pain, an inability to complete daily tasks, reduced social life, and the need for multiple surgeries. Individuals expressed hope that Ryego will reduce pain and allow those with endometriosis to regain a sense of normalcy. Other comments noted the difficulties in accessing current therapies especially for those in rural or remote areas and described the advantages of Ryego being in tablet form.
- 6.5 The PBAC noted the advice received from Pelvic Pain Foundation of Australia. The comments noted that there are insufficient clinical management options available for the management of pain in women. The comments noted that Ryego may not be suitable for all women, but considered that based on clinical experience, it may be better tolerated and more convenient than goserelin. The PBAC noted that this advice supported the moderate clinical need for alternative GnRH therapies with add-back.

Clinical trials

- 6.6 There were no head-to-head trials of Ryego vs goserelin + add-back (main comparator) or BSC (after GnRH + add-back treatment) for endometriosis-associated pain. The submission stated that a linked evidence approach was used to support the clinical claim, which was based on randomised controlled trials (RCTs) and systematic reviews. The main trial evidence and relevant detail of the supportive evidence are presented to provide context for the clinical claim. The main trial evidence presented in the submission was the comparison of relugolix (concomitant and delayed add-back) vs placebo and relugolix vs leuprorelin (a GnRH agonist). The submission also included an indirect comparison of Ryego to BSC (contraceptive) and as supportive evidence a trial comparing GnRH (with or without add-back) to contraceptive and a number of systematic reviews of GnRH and contraceptive treatments for endometriosis.

Ryego (relugolix + E2/NETA FDC) vs placebo

- 6.7 The submission was based on two RCTs comparing Ryego FDC versus relugolix + delayed add-back (E2/NETA) therapy versus placebo (SPIRIT 1 and SPIRIT 2) and an open-label, single-arm, long-term study (SPIRIT Extension) of Ryego. The submission

described SPIRIT 1 and SPRIT 2 as pivotal trial evidence of Ryeqo. An additional observational BMD study, conducted contemporaneously with the SPIRIT trials was included as supportive evidence to characterise longitudinal bone density over 52 weeks without any medication other than background calcium and vitamin D preparations to treat bone loss.

Relugolix monotherapy vs leuporelin (GnRH agonist)

- 6.8 The submission was based on one RCT comparing relugolix monotherapy versus leuporelin (GnRH agonist) (Harada et al 2022) and a dose-finding study comparing relugolix versus leuporelin or placebo with an open-label, parallel-group extension (Osuga et al 2021 and Osuga et al 2021 Extension). The submission assumed leuporelin as proxy for goserelin for treatment of endometriosis, noting that different agents from the same GnRH agonist class are comparable in terms of efficacy and safety based on reporting by FDA¹², EMA¹³ and the included systematic reviews, and that the PBAC considered dose relativities for goserelin and leuporelin are seen as equivalent when used in the treatment of men with prostate cancer (e.g. 10.8 mg goserelin = 22.5 mg leuporelin)¹⁴. However, leuporelin is not PBS-listed nor TGA registered for endometriosis.
- 6.9 The submission also included three published systematic reviews/meta-analyses comparing the efficacy and safety of GnRH agonists +/- (with or without) add-back for endometriosis (Veth et al 2023 and Wu et al 2014) and BMD loss (Farmer et al 2003) in women with endometriosis.

Ryeqo (relugolix + E2/NETA FDC) vs BSC

- 6.10 The submission presented indirect comparison between Ryeqo (SPIRIT 1 and SPRIT 2) versus oral contraceptives (Roghaei et al 2010 and Harada et al 2008) using placebo as the common reference. The submission assumed that all contraceptive therapies have comparable efficacy and safety when used for endometriosis, noting the PBAC dose relativities of oral contraceptives: "Despite different active ingredients, strengths and formulations of combinations, all oral contraceptives have been considered of similar utility and thus equivalent for pricing purposes"¹⁵. Based on the above rationale that different agents of GnRH agonist are comparable, the submission also

¹²US Food and Drug Administration (FDA). FDA Drug Safety Communication: Ongoing Safety Review of GnRH Agonists and possible increased risk of diabetes and certain cardiovascular diseases. Available from: <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-ongoing-safety-review-gnrh-agonists-and-possible-increased-risk>

¹³ European Medicines Agency (EMA). Assessment report leuporelin-containing depot medicinal products, 14 May 2020. Available from: https://www.ema.europa.eu/en/documents/referral/leuporelin-containing-depot-medicines-article-31-referral-public-assessment-report-prac_en.pdf

¹⁴ Australian Government PBS Therapeutic Relativity Sheets. ATC L02 – Endocrine Therapy. Effective Date: 12/16, #4. Available from: <https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets>

¹⁵ Australian Government PBS Therapeutic Relativity Sheets. ATC G03 – Sex Hormones and Modulators of the Genital System. Effective Date: 10/19, #1. Available: <https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets>

included a trial by Zupi et al 2004, comparing leuprorelin (GnRH agonist) + add-back (E2/NETA) therapy versus leuprorelin alone or combination oral contraceptive in patients with recurrence of endometriosis-associated pain after surgery. Two additional trials (Osuga et al 2019 and Osuga et al 2020) were identified comparing contraceptive (dienogest) and placebo in the treatment of dysmenorrhea, which were included in the sensitivity analysis of the indirect comparison.

6.11 The submission identified six systematic reviews (Gibbons et al 2021, Grandi et al 2019, Brown et al 2018, Jensen et al 2018, Fu et al 2017, Brown et al 2012) as additional evidence comparing contraceptive therapies versus placebo or no treatment or other interventions for treatment of symptomatic endometriosis.

6.12 Details of the trials presented in the submission are provided in Table 2 below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Relugolix (concomitant and delayed add-back) vs PBO		
SPIRIT 1, MVT-601-3101 (NCT03204318)	Myovant Sciences GmbH. Study MVT-601-3101. SPIRIT 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered with and without Low-Dose Estradiol and Norethisterone Acetate in Women with Endometriosis-Associated Pain.	11 Feb 2021
SPIRIT 2, MVT-601-3102 (NCT03204331)	Myovant Sciences GmbH. Study MVT-601-3102. SPIRIT 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered with and without Low-Dose Estradiol and Norethisterone Acetate in Women with Endometriosis-Associated Pain. As-Saine S, Becker CM, Johnson N, Warsi QA, Wagman RB, et al. Efficacy and Safety of Relugolix Combination Therapy in Women with Endometriosis-Associated Pain: Phase 3 Randomized, Double-Blind Placebo Controlled Study (SPIRIT 2). Abstract. (As-Saine 2020)	04 Feb 2021 (addendum 15 June 2021) Fertil Steril 2020; 114(3):Suppl. E77. ASRM Conference Sept 2020
SPIRIT 1 and SPIRIT 2	Giudice LC, As-Sanie S, Arjona JC, Becker CM, Abrao MS, et al. Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3, randomised, double-blind, studies (SPIRIT 1 and 2).	The Lancet 2022; 399(10343):2267-2279
SPIRIT Extension, MVT-601-3103 (NCT03654274)	Myovant Sciences GmbH. Study MVT-601-3103. SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethisterone Acetate in Women with Endometriosis-Associated Pain. Clinical Study Report 52-week Clinical Study Report 104-week Clinical Study Report Post Treatment Follow-up (PTFU). Addendum to 104-week Clinical Study Report	23 Jun 2021 21 Jul 2022 22 May 2023
BMD Study, MVT-601-034 (NCT03744507)	Myovant Sciences GmbH. Study MVT-601-034. A Prospective Observational Study of Bone Mineral Density in Women With Uterine Fibroids or Endometriosis. Clinical Study Report Endometriosis Cohort.	01 Mar 2021
Relugolix vs leuprorelin (GnRHs)		
Relugolix Monotherapy Phase 3 Study, TAK-385/3-A (NCT03931915)	Harada T, Osuga Y, Suzuki Y, Fujisawa M, Fukui M, Kitawaki J. Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain compared with leuprorelin in Japanese women: a phase 3, randomized, double-blind, noninferiority study.	Fertil Steril 2022; 117:583–92.

Public Summary Document - March 2024 PBAC Meeting

Trial ID	Protocol title/ Publication title	Publication citation
Relugolix Monotherapy Phase 2 Study, TAK-385/CCT-101 (NCT01458301)	Osuga Y, Seki Y, Tanimoto M, Kusumoto T, Kudou K, Terakawa N. Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain in a dose-response manner: a randomized, double-blind, placebo-controlled study. Doi: 10.1016/j.fertnstert.2020.07.055.	Fertil Steril. 2021 Feb; 115(2):397-405
Relugolix Monotherapy Phase 2 Extension Study, TAK-385/OCT-101 (NCT01452685)	Osuga Y, Seki Y, Tanimoto M, Kusumoto T, Kudou K, Terakawa N. Relugolix, an oral gonadotropin-releasing hormone (GnRH) receptor antagonist, in women with endometriosis-associated pain: phase 2 safety and efficacy 24-week results. Doi: 10.1186/s12905-021-01393-3.	BMC Womens Health. 2021 Jun 21; 21(1):250
BSC (contraceptives)		
Zupi 2004	Zupi E, Sbracia M, Marconi D, et al. Add-back therapy in the treatment of endometriosis-associated pain.	Fertil Steril. 2004; 82(5):1303-1308
Harada 2008	Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial.	Fertil Steril. 2008 Nov; 90(5):1583-1588
Roghaei 2010 (IRCT138812043414N1)	Roghaei MA, Tehrani HG, Taherian A, Koleini N. Effects of Letrozole Compared with Danazol on Patients with Confirmed Endometriosis: A Randomized Clinical Trial.	Int J Fertil Steril 2010; 4(2):67-72
Systematic reviews		
Veth 2023	Veth VB, van de Kar MM, Duffy JM, van Wely M, Mijatovic V, Maas JW. Gonadotropin-releasing hormone analogues for endometriosis. Doi: 10.1002/14651858.CD014788.	Cochrane Database Syst Rev. 2023 Jun 21; (6):CD014788
Wu 2014	Wu D, Hu M, Hong L, et al. Clinical efficacy of add back therapy in treatment of endometriosis: a meta analysis. DOI 10.1007/s00404-014-3230-8.	Arch Gynecol Obstet 2014; 290:513-523
Farmer 2003	Farmer JE, Prentice A, Breeze A, Ahmad G, Duffy JMN, Watson A, Pick A. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. DOI: 10.1002/14651858.CD001297.	Cochrane Database Syst Rev. 2003 Oct 20; (4):CD001297.
Gibbons 2021	Gibbons T, Georgiou EX, Cheong YC, Wise MR. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery. Doi: 10.1002/14651858.CD005072.	Cochrane Database Syst Rev. 2021 Dec 20; 12(12):CD005072
Grandi 2019	Grandi G, Barra F, Ferrero S, et al. Hormonal contraception in women with endometriosis: a systematic review.	Eur J Contracept Reprod Health Care. 2019 Feb; 24(1):61-70
Brown 2018	Brown J, Crawford TJ, Datta S, Prentice A. Oral contraceptives for pain associated with endometriosis. Doi: 10.1002/14651858.CD001019.	Cochrane Database Syst Rev. 2018 May 22; 5(5):CD001019
Jensen 2018	Jensen JT, Schlaff W and Gordon K. Use of combined hormonal contraceptives for the treatment of endometriosis-related pain: a systematic review of the evidence.	Fertil Steril 2018; 110(1):137-152
Fu 2017	Fu, J; Song, H; Zhou, M; Zhu, H; Wang, Y; Chen, H; Huang, W. Progesterone receptor modulators for endometriosis. Doi: 10.1002/14651858.CD009881.	Cochrane Database Syst Rev. 2017 Jul 25; 7(7):CD009881
Brown 2012	Brown, J; Kives, S; Akhtar, M. Progestagens and anti-progestagens for pain associated with endometriosis.	Cochrane Database Syst Rev. 2012 Mar 14; 2012(3):CD002122

Source: Table 2.2.2, pp40-44 of the submission.

ASRM=American Society for Reproductive Medicine; COC=combined oral contraceptive; GnRHa=gonadotropin hormone-releasing hormone analogue; IUD=intra-uterine device; PBO=placebo;

6.13 The key features of the included trials are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Bias	Treatment arms	Population	Outcome(s)	S3
Relugolix (concomitant and delayed add-back) vs PBO							
SPIRIT 1	638	P3, MC R, DB, PC, 24w (+35d run-in ^a)	Low	Relugolix + E2/NETA (Ryego) Relugolix + delayed E2/NETA ⁱ PBO	moderate-severe EAP	1°: dysmenorrhea, NMPP 2°: dyspareunia, BMD	✓
SPIRIT 2	623	P3, MC R, DB, PC, 24w (+35d run-in ^a)	Low	Relugolix + E2/NETA (Ryego) Relugolix + delayed E2/NETA ⁱ PBO	moderate-severe EAP	1°: dysmenorrhea, NMPP 2°: dyspareunia, BMD	✓
SPIRIT Extension	802 ^b	P3, MC, NC, OL, 80w ^c	High	Relugolix + E2/NETA (Ryego)	From SPIRIT 1 and SPIRIT 2	1°: dysmenorrhea, NMPP 2°: dyspareunia, BMD	✓
BMD study	452 ^d	Prospective, MC, 52w	-	No treatment ^e	with endometriosis	1°: BMD 2°: EQ-5D-5L, Aes	-
Relugolix vs leuporelin (GnRHa)							
Harada 2022	335	P3, MC, R, DB, DD 24w (+6w pre-study ^f)	Low	Relugolix 40 mg Leuporelin 3.75 or 1.88 mg	moderate EAP	1°: pelvic pain 2°: dysmenorrhea, NMPP, dyspareunia	-
Osuga 2021	457	P2, MC, R, DB, PC 12w (+12w pre-study ^g)	Low	Relugolix 10, 20 or 40 mg Leuporelin 3.75 mg PBO	at least moderate EAP	1°: pelvic pain 2°: dyspareunia, BMD	-
Osuga 2021 Extension	397	P2, R, OL parallel 12w ^h	High	Continued from Osuga 2021	From Osuga 2021	1°: safety (BMD) 2°: pelvic pain, dysmenorrhea, dyspareunia	-
BSC (contraceptives)							
Zupi 2004	133	R, 52w (+6m post-treatment)	High	Leuporelin Leuporelin + E2/NETA Estroprogestin	EAP after surgery	pelvic pain, dysmenorrhea, dyspareunia, BMD	-
Harada 2008	100	P2, R, MC, DB, PC 4m	Low	E2/NETA ^q PBO	moderate-severe EAP	1°: dysmenorrhea, 2°: NMPP	-
Roghaei 2010	105	R, PC, 10m	High	Letrozoler Danazol PBO ^r	symptomatic endometriosis	pelvic pain, dysmenorrhea, dyspareunia	-
Systematic reviews							
Veth 2023 (MA)	7355	72 included ⁱ	Unclear [^]	GnRHa ^k , GnRHa ^k + add-back, hormonal treatment, PBO	symptomatic endometriosis	1°: pain ^m , BMD 2°: QoL, Aes	-
Wu 2014 (MA)	945	13 studies	Unclear [^]	GnRHa (goserelin or leuporelin) GnRHa + add-back (hormonal or non-hormonal)	symptomatic endometriosis	1°: BMD, pelvic pain	-
Farmer 2003 (MA)	2391	30 studies ⁿ	Unclear [^]	GnRHa ^k , GnRHa ^k + add-back, PBO, no treatment, and/or other treatments	symptomatic endometriosis	BMD	-
Gibbons 2021(MA)	157	4 studies	High [^]	LNG-IUD, GnRHa	symptomatic endometriosis (post-surgery)	1°: overall pain 2°: pelvic pain, dysmenorrhea	-
Grandi 2019	3377	28 studies	High [^]	Hormonal contraceptives ^s	EAP	dysmenorrhea, pelvic pain, dyspareunia	-

Trial	N	Design/ duration	Bias	Treatment arms	Population	Outcome(s)	S3
Brown 2018(MA)	612	5 included ^l	High ^a	Hormonal contraceptives, other drug (GnRHa), PBO	symptomatic endometriosis	dysmenorrhea	-
Jensen 2018	1762	18 studies	High ^a	Combined hormonal contraceptive, other drug (GnRHa), PBO	EAP	dysmenorrhea, NMPP, pelvic pain, dyspareunia	-
Fu 2017 (MA)	960	10 studies	Unclear ^a	PRMs, other drug (GnRHa), PBO	symptomatic endometriosis	1°: pain, Aes 2°: QoL	-
Brown 2012 (MA)	1551	13 studies	Unclear ^a	Progestogens, anti-progestogens, other drug ^t , PBO	EAP	1°: Pain 2°: Aes	-

Source: compiled during the evaluation.

AE=adverse event; BMD=bone mineral density; DB=double-blind; DD=double-dummy; EAP=endometriosis associated pain; E2=estradiol; GnRHa=gonadotropin hormone-releasing hormone analogue; LNG-IUD=levonorgestrel intrauterine device; MC=multi-centre; N=number; NC=non-comparative single arm study; NETA=norethindrone acetate; NMPP=non-menstrual pelvic pain; OL=open label; PBO=placebo; PC=placebo-controlled; PRM=progesterone receptor modulator; P3=Phase 3; R=randomised; d=day; w=week; y=year; S3=Section 3 of the submission;

^a assessment based on publication

- a Screening period was 1-15 days. Single-blind run-in period (35 days) in which only the patients were blinded to study treatment. Patients had one placebo tablet and one placebo capsule each day and report their pain and analgesic medication use. If needed, the run-in period may be extended for logistical reasons (e.g. repeat endometrial biopsy) up to Day R70 with sponsor approval. The run-in period (through the day prior to first dose of randomized study drug) serve as baseline pain assessment period for the study.
- b Patients who completed 24 weeks of study drug treatment in SPIRIT 1 or SPIRIT 2 (including placebo) and consented were enrolled in extension study. 799 out of 802 patients enrolled were included in the efficacy and safety analyses (3 excluded due to noncompliance).
- c Baseline for extension study was conducted at the same time as Week 24 visit for the pivotal study ("Week 24/Baseline visit"). Prespecified interim analysis in accordance to protocol was conducted for all safety and efficacy endpoints through the Week 52 visit.
- d N enrolled in endometriosis cohort. The study recruited 2 cohorts of premenopausal women: i) with uterine fibroids or ii) endometriosis.
- e BMD study was conducted contemporaneously with the relugolix interventional studies for uterine fibroids and endometriosis (SPIRIT 1 and SPIRIT 2) in a subset of the same study sites.
- f Screening period was 1-6 weeks, and the pretreatment period was 3-6 weeks before randomization. Patients were given 1 placebo injection and a daily placebo tablet during the pretreatment period that started between days 1 and 5 of menstruation cycle under single-blind conditions, which corresponds to days -42 to -21 and is defined as baseline of the study.
- g Pretreatment period was 4-12 weeks, during which patients underwent a single-blind double-dummy (relugolix and leuporelin) placebo run-in period initiated on days 1 to 5 of the first menstruation before randomization.
- h Patients who completed 12-week treatment period (Osuga 2021) could enter a 12-week extension study (total treatment period of 24 weeks) and had the 4-week follow-up period after completion of the extension.
- i relugolix + delayed E2/NETA dosed with relugolix 40 mg daily for 12 weeks followed by relugolix 40 mg plus E2/NETA daily for 12 weeks.
- j 17 studies compared GnRHa v GnRHa + add-back, however, none had low bias for the primary meta-analysis (pain). Sensitivity analysis was performed on all studies.
- k Most common GnRHa included goserelin, leuporelin, nafarelin, triptorelin, buserelin.
- l Only 3 studies (n=404) were included in the meta-analysis.
- m Both overall pain and other sub-forms of pain, i.e. dysmenorrhoea, dyspareunia and pelvic pain.
- n Only 15 studies (n=910) were included in the meta-analysis, as other studies did not provide enough data.
- p Treatment began on the third day (± 2 days) of the menstrual cycle and continued for four cycles (28 ± 2 days)
- q Patients received monophasic oral contraceptive pill (ethinylestradiol 0.035 mg + norethisterone 1 mg) for 21 days plus 7 days of placebo.
- r all patients received calcium and vitamin D.
- s included combined hormonal contraceptives, combined oral contraceptives, progestin-only pills and progestin-only contraceptives.
- t danazol, oral or subdermal contraceptive, oral contraceptive pill and danazol, GnRHa.

6.14 The SPIRIT 1 and SPIRIT 2 trials had the same design; multicentre (SPIRIT 2 included 5 sites in Australia), randomised, double-blind, placebo-controlled trials where patients received either Ryego, relugolix + delayed add-back therapy or placebo for 24 weeks. SPIRIT Extension was an open-label extension of SPIRIT 1 and SPIRIT 2 where all patients received Ryego for 80 weeks. SPIRIT Extension included an addendum of the 1-year post-treatment follow-up (PTFU) on BMD and resumption of menstruation. SPIRIT Extension PTFU included 324 (40.6%) patients, which were a mix of patients who have and have not met the pre-defined protocol-specified bone loss (decline in BMD >3% at the lumbar spine or hip).

- 6.15 Harada et al 2022 and Osuga et al 2021 were multicentre, randomised double-blind trials conducted in Japan. Harada 2022 randomised eligible patients to relugolix 40 mg or leuprorelin 3.75mg or 1.88mg (dependent on weight) for 24 weeks. Osuga et al 2021 was a dose-response study in which patients were randomised to three dose levels of relugolix (10, 20, and 40 mg) compared to placebo and leuprorelin as an active comparator for 12 weeks. Patients who completed 12 weeks of treatment could continue to receive the same treatment in an open-label extension (Osuga et al 2021 Extension) for another 12 weeks (total 24 weeks). Patients in the included studies were all premenopausal women aged 18 years and above, and there was no clinical evidence presented for women of reproductive age less than 18 years.
- 6.16 Across the SPIRIT trials, the dosing regimen of Ryego was generally consistent with the approved PI. SPIRIT 1 and SPIRIT 2 also included a treatment arm dosed with relugolix monotherapy 40 mg daily for 12 weeks followed relugolix 40 mg co-administered with E2/NETA daily for another 12 weeks. Patients in Harada et al 2022 and Osuga et al 2021 were dosed with relugolix monotherapy. However, the sponsor is neither seeking TGA registration nor PBS listing for relugolix monotherapy dose regimen. All relugolix trials presented patient reported outcome measures for endometriosis-associated pain using either 0-10 numerical rating scale (NRS) or 0-100 mm visual analogue scale (VAS) as the primary or secondary outcome after 12/24 weeks.
- 6.17 Zupi et al 2004 and Roghaei et al 2010 were randomised single centre studies conducted in Italy and Iran, respectively. In Zupi et al 2004 patients received either leuprorelin + add-back (transdermal E2 25 mcg and oral NETA 5 mg) therapy, leuprorelin or oral contraceptive (oral E2 30 mcg and gestodene 0.75 mg) alone for 12 months. In Roghaei et al 2010, patients received either letrozole, danazol or placebo, concurrently with calcium and vitamin for 6 months. Harada et al 2008 was a double-blind placebo-controlled trial conducted in Japan in which patients with moderate or severe dysmenorrhea received oral contraceptive (E2 35 mcg and NETA 1 mg) for 21 days plus placebo for 7 days or identical placebo for 28 days; treatment continued for 4 menstrual cycles. Pelvic pain and dysmenorrhea were assessed in all trials.
- 6.18 The risk of bias in SPIRIT 1, SPIRIT 2, Harada et al 2022, Harada et al 2008 and Osuga et al 2021 was considered low. The other studies were considered to be high risk bias due to the nature of their study design being open-label (extension studies, Zupi et al 2004), non-comparative single arm (SPIRIT Extension), or blinding was not reported (Roghaei et al 2010). Across the systematic reviews, overall, the review authors assessed the quality of data as low to moderate, and considered the risk of bias of the included trials as high or unclear.
- 6.19 Patient characteristics at baseline were generally balanced across the treatment arms within the trials. However, there were differences across the trials owing in part to differences in the eligibility criteria:

- Duration of disease: Patients in Harada et al 2022 (relugolix versus leuprorelin) had shorter mean disease duration (1.3–1.4 years) compared to other included trials (3.7–4.7 years).
 - Pain severity: Patients in SPIRIT 1 and SPIRIT 2 trials had more severe pain including dysmenorrhea, NMPP and dyspareunia.
 - Dysmenorrhea score: Patients in SPIRIT 1 and SPIRIT 2 had worse mean score (NRS: 6.9-7.2) compared to Harada et al 2022 (VAS: 33.1-34.2) and Osuga et al 2021 (VAS: 27.1-30.4)
 - NMPP score: Patients in SPIRIT 1 and SPIRIT 2 had worse mean score (NRS: 5.5-5.9) compared to Harada et al 2022 (VAS: 11.3-11.8) and not reported in Osuga et al 2021.
 - Dyspareunia score: Patients in SPIRIT 1 and SPIRIT 2 had worse mean score (NRS: 5.3-5.7) compared to Harada et al 2022 (VAS: 27.7-28.7) and Osuga et al 2021 (VAS: 8.8-12.5)
 - Endometriosis Health Profile-30 (EHP-30) pain domain: Patients in SPIRIT 1 and SPIRIT 2 had worse mean pain score (55.0-58.3) compared to Harada et al 2022 (32.4-34.1) and Osuga et al 2021 (24.8-28.9).
 - Concomitant analgesics: A high proportion of patients in SPIRIT 1 and SPIRIT 2 trials had concomitant analgesics (86.3-90.3%), whereas this was not reported in Harada et al 2022 and Osuga et al 2021.
- 6.20 A comparison of baseline characteristics across the extension studies showed that patients enrolled in SPIRIT Extension and SPIRIT Extension PTFU were generally similar to baseline characteristics at the start of the double-blind SPIRIT 1/SPIRIT 2 trials. Patients enrolled in the open label Osuga et al 2021 Extension study were also generally comparable to Osuga et al 2021.
- 6.21 The submission did not provide sufficient information on the baseline characteristics of patients enrolled in the BSC studies and trials included in the systematic reviews. Based on available data, there were differences in the patient characteristics across the main trials (described above), the supportive BSC studies and the trials in the systematic reviews, including the type and severity of endometriosis-associated pain (such as dysmenorrhea, pelvic pain and dyspareunia) and use of prior and concomitant interventions (e.g. hormonal or non-hormonal contraceptive, GnRH or surgical therapy). The implications of these differences in the baseline characteristics on treatment efficacy were not addressed in the submission.

Comparative effectiveness

- 6.22 Clinical guidelines indicate that the main goal of treatment for endometriosis-associated pain was a reduction in pain, of which there are three main types: dysmenorrhea (painful menstruation), NMPP and dyspareunia (painful intercourse).

- 6.23 In the SPIRIT trials, patients rated their worst pelvic pain in the past 24 hours on a 11-point NRS scale from 0-10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. The co-primary outcomes were proportion of responders on dysmenorrhea and NMPP NRS at the end of treatment (Week 24) in the Ryeqo group compared to placebo. The proportion of responders in the relugolix + delayed add-back group compared with placebo was analysed as a secondary endpoint. Response on dysmenorrhea and NMPP NRS were defined as:
- Dysmenorrhea response — a reduction from baseline in dysmenorrhea NRS score by ≥ 2.8 points at Week 24 or score ≤ 0.1 if baseline dysmenorrhea score was < 2.8 , and patient did not have increased use of study-specified analgesics for pelvic pain at Week 24 relative to baseline.
 - NMPP response — a reduction from baseline in NMPP NRS score by ≥ 2.1 points at Week 24 or score ≤ 0.1 if baseline NMPP NRS score was < 2.1 , and patient did not have increased use of study-specified analgesics for pelvic pain at Week 24 relative to baseline.
- 6.24 The relugolix monotherapy trials used the VAS to measure pain, which is similar to the NRS but consists of a 100 mm line and patients mark a point between 0 mm (meaning no pain) and 100 mm (unbearable pain). Other pain measures included the change in Biberoglu and Behrman (B&B), modified B&B (mB&B) and EHP-30 score. B&B score consists of a rating based on the patient's assessment of three distinct pain symptoms (dysmenorrhea, pelvic pain and dyspareunia) and on two signs obtained during gynaecologic palpation (pelvic tenderness and induration). Each symptom is classified as absent, mild, moderate or severe. EHP-30 is an endometriosis-specific health-related quality of life (HrQoL) instrument with 30 questions and five scales: pain, feeling of control and powerlessness, emotional well-being, social support and self-image, with high scores indicating worse health state.
- 6.25 The submission nominated a non-inferiority margin as the upper limit of the 95% confidence interval (CI) < 10 on the VAS score. This was assumed from the test of non-inferiority between relugolix vs leuprorelin in Harada et al 2022, where the acceptable range of difference was the maximum VAS score of 10.0 (2-sided 95% CI).

Trial results

- 6.26 Table 4 presents the change from baseline in pain outcome (NRS or VAS) for dysmenorrhea (painful menstruation), NMPP and dyspareunia (painful intercourse) at Week 12/24 and Week 104 in the relugolix studies. Results for Zupi et al 2004 are also discussed to provide context of the results for GnRH antagonist (leuprorelin) with and without add-back versus BSC. Figure 1 below presents results of dysmenorrhea and non-menstrual pelvic pain from SPIRIT 1 and SPIRIT 2.

Table 4: Change from baseline in pain (NRS, VAS and EHP-30) for dysmenorrhea, NMPP and dyspareunia at Week 12/24 and Week 104 in SPIRIT (Ryego) and relugolix monotherapy trials.

Outcome	Drug n/N (%)	PBO n/N (%)	Active control n/N (%)	RD (95%CI)
1°: % Dysmenorrhea responders (reduction from baseline in dysmenorrhea NRS score ≥ 2.8 and no increase in analgesics use)^a				
	Ryego	PBO	REL+dAB	
SPIRIT 1, Ryego v PBO, Wk 24	158/212 (74.5)	57/212 (26.9)	-	47.6 (39.3, 56.0)
SPIRIT 1, REL+dAB v PBO, Wk 24	-	57/212 (26.9)	151/211 (71.6)	44.7 (36.2, 53.2)
SPIRIT 2, Ryego v PBO, Wk 24	155/206 (75.2)	62/204 (30.4)	-	44.9 (36.2, 53.5)
SPIRIT 2, REL+dAB v PBO, Wk 24	-	62/204 (30.4)	150/206 (72.8)	42.4 (33.7, 51.2)
SPIRIT 1/2 pooled, Ryego v PBO, Wk 24	312/418 (74.8)	118/416 (28.6)	-	46.2 (40.2, 52.2)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 24	-	118/416 (28.6)	300/417 (72.1)	43.5 (37.3, 49.6)
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, Wk 52	235/277 (84.8)	208/275 (75.6)	203/247 (82.2)	..#
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, Wk 104	235/277 (84.8)	205/275 (83.0)	221/247 (80.4)	..#
1°: % NMPP responder (reduction from baseline in NMPP NRS score ≥ 2.1 and no increase in analgesics use)^c				
	Ryego	PBO	REL+dAB	
SPIRIT 1, Ryego v PBO, Wk 24	124/212 (58.5)	84/212 (39.6)	-	18.9 (9.5, 28.2)
SPIRIT 1, REL+dAB v PBO, Wk 24	-	84/212 (39.6)	122/211 (57.8)	18.2 (8.8, 27.6)
SPIRIT 2, Ryego v PBO, Wk 24	136/206 (66.0)	87/204 (42.6)	-	23.4 (14.0, 32.8)
SPIRIT 2, REL+dAB v PBO, Wk 24	-	87/204 (42.6)	109/206 (52.9)	10.3 (0.7, 19.9)
SPIRIT 1/2 pooled, Ryego v PBO, Wk 24	259/418 (62.1)	169/416 (41.0)	-	21.1 (14.4, 27.7)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 24	-	169/416 (41.0)	230/417 (55.3)	14.3 (7.5, 21.0)
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, Wk 52	204/277 (73.6)	187/247 (68.0)	174/247 (70.4)	..#
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, Wk 104	210/277 (75.8)	201/247 (73.1)	177/247 (71.7)	..#
LS mean (SE) change from baseline in dysmenorrhea NRS/VAS score				
	Ryego	PBO	REL+dAB	
SPIRIT 1, Ryego v PBO, NRS Wk 24	-5.1 (0.2)	-1.8 (0.2)	-	-3.3 (-3.8, -2.8)
SPIRIT 1, REL+dAB v PBO, NRS Wk 24	-	-1.8 (0.2)	-4.9 (0.2)	<0.05
SPIRIT 2, Ryego v PBO, NRS Wk 24	-5.1 (0.2)	-2.0 (0.2)	-	-3.2 (-3.7, -2.7)
SPIRIT 2, REL+dAB v PBO, NRS Wk 24	-	-2.0 (0.2)	-4.6 (0.2)	<0.05
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, NRS Wk 52	-5.9 (0.15)	-5.3 (0.15)	-5.7 (0.16)	..#
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, NRS Wk 104	-5.9 (0.17)	-5.6 (0.17)	-5.7 (0.18)	..#
	REL	PBO	LEU	
Harada 2022, REL v LEU, VAS Wk 24	-32.6 (0.3)	-	-33.7 (0.3)	1.1 (0.2, 1.9)
Osuga 2021, REL v PBO, VAS Wk 12	-29.7 (17.4)	-5.2 (17.1)	-	<0.0001
Osuga 2021, REL v LEU, VAS Wk 12	-29.7 (17.4)	-	-26.9 (19.9)	NS
Osuga 2021 Ext, REL v PBO, VAS Wk 24	-29.5 (17.5)	-5.8 (17.1)	-	<0.05
Osuga 2021 Ext, REL v LEU, VAS Wk 24	-29.5 (17.5)	-	-27.2 (19.9)	NS
LS mean (SE) change from baseline in NMPP NRS/VAS score				
	Ryego	PBO	REL+dAB	
SPIRIT 1, Ryego v PBO, NRS Wk 24	-2.9 (0.2)	-2.0 (0.2)	-	-0.9 (-1.4, -0.4)
SPIRIT 1, REL+dAB v PBO, NRS Wk 24	-	-2.0 (0.2)	-2.8 (0.2)	<0.05
SPIRIT 2, Ryego v PBO, NRS Wk 24	-2.7 (0.2)	-2.0 (0.2)	-	-0.7 (-1.2, -0.3)
SPIRIT 2, REL+dAB v PBO, NRS Wk 24	-	-2.0 (0.2)	-2.5 (0.2)	<0.05

Outcome	Drug n/N (%)	PBO n/N (%)	Active control n/N (%)	RD (95%CI)
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, NRS Wk 52	-3.6 (0.15)	-3.4 (0.16)	-3.4 (0.15)	..#
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, NRS Wk 104	-4.0 (0.16)	-3.5 (0.17)	-3.8 (0.16)	..#
	REL	PBO	LEU	
Harada 2022, REL v LEU, VAS Wk 24	-6.7 (0.7)	-	-8.0 (0.7)	1.4 (-0.5, 3.2)
LS mean (SE) change from baseline in overall pelvic pain NRS/VAS score				
	Ryego	PBO	REL+dAB	
SPIRIT 1, Ryego v PBO, NRS Wk 24	-3.1 (0.2)	-1.9 (0.17)	-	-1.1 (-1.6, -0.7)
SPIRIT 1, REL+dAB v PBO, NRS Wk 24	-	-1.9 (0.17)	-2.9 (0.2)	<0.05
SPIRIT 2, Ryego v PBO, NRS Wk 24	-2.9 (0.2)	-2.0 (0.2)	-	-0.9 (-1.4, -0.5)
SPIRIT 2, REL+dAB v PBO, NRS Wk 24	-	-2.0 (0.2)	-2.7 (0.2)	<0.05
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, NRS Wk 52	-3.9 (0.15)	-3.6 (0.15)	-3.6 (0.16)	..#
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, NRS Wk 104	-4.2 (0.16)	-4.0 (0.16)	-3.9 (0.17)	..#
	REL	PBO	LEU	
Harada 2022, REL v LEU, VAS Wk 24	-11.8 (0.7)	-	-13.4 (0.7)	1.6 (-0.3, 3.5)
Osuga 2021, REL v PBO, VAS Wk 12	-10.4 (1.1)	-3.8 (1.1)	-	-6.8 (-9.2, -4.4)
Osuga 2021, REL v LEU, VAS Wk 12	-10.4 (1.1)	-	-10.6 (1.7)	NS
Osuga 2021 Ext, REL v PBO, VAS Wk 24	-11.9 (11.3)	-3.2 (12.2)	-	<0.05
Osuga 2021 Ext, REL v LEU, VAS Wk 24	-11.9 (11.3)	-	-12.7 (12.6)	NS
LS mean (SE) change from baseline in dyspareunia NRS/VAS score				
	Ryego	PBO	REL+dAB	
SPIRIT 1, Ryego v PBO, NRS Wk 24	-2.4 (0.2)	-1.7 (0.2)	-	-0.7 (-1.3, -0.1)
SPIRIT 1, REL+dAB v PBO, NRS Wk 24	-	-1.7 (0.2)	-2.2 (0.2)	<0.05
SPIRIT 2, Ryego v PBO, NRS Wk 24	-2.4 (0.2)	-1.9 (0.2)	-	-0.5 (-1.0, 0.0)
SPIRIT 2, REL+dAB v PBO, NRS Wk 24	-	-1.9 (0.2)	-2.3 (0.2)	<0.05
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, NRS Wk 52	-3.3 (0.18)	-3.0 (0.18)	-3.0 (0.19)	..#
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, NRS Wk 104	-3.5 (0.21)	-3.4 (0.21)	-2.9 (0.22)	..#
	REL	PBO	LEU	
Harada 2022, REL v LEU, VAS Wk 24	-13.2 (3.3)	-	-15.4 (3.7)	2.2 (-7.7, 12.1)
Osuga 2021, REL v PBO, VAS Wk 12	5.0 (8.9) ^d	11.1 (15.2) ^d	-	NS
Osuga 2021, REL v LEU, VAS Wk 12	5.0 (8.9) ^d	-	3.8 (8.9) ^d	NS
Osuga 2021 Ext, REL v PBO, VAS Wk 24	-0.9 (12.0)	-1.1 (12.7)	-	NS
Osuga 2021 Ext, REL v LEU, VAS Wk 24	-0.9 (12.0)	-	-4.6 (15.1)	NS
LS mean (SE) change from baseline in EHP-30 pain domain				
	Ryego	PBO	REL+dAB	
SPIRIT 1, Ryego v PBO, Wk 24	-33.8 (1.83)	-18.7 (1.8)	-	-15.1 (-19.7, -10.5)
SPIRIT 1, REL+dAB v PBO, Wk 24	-	-18.7 (1.8)	-32.1 (1.76)	<0.05
SPIRIT 2, Ryego v PBO, Wk 24	-32.2 (1.7)	-19.9 (1.7)	-	-12.3 (-16.7, -7.9)
SPIRIT 2, REL+dAB v PBO, Wk 24	-	-19.9 (1.7)	-30.8 (1.7)	<0.05
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, Wk 52	-37.7 (1.34)	-35.1 (1.32)	-36.1 (1.37)	..#
SPIRIT Ext ^b , Ryego v PBO v REL+dAB, Wk 104	-41.3 (1.33)	-37.7 (1.29)	-38.9 (1.36)	..#
	REL	PBO	LEU	
Harada 2022, REL v LEU, Wk 24	-28.61 (1.40)	-	-32.01 (1.42)	3.4 (-0.5, 7.3)
Osuga 2021, REL v PBO, Wk 12	-25.3 (2.1)	-5.6 (2.0)	-	<0.05
Osuga 2021, REL v LEU, Wk 12	-25.3 (2.1)	-	-23.3 (2.4)	NS

Outcome	Drug n/N (%)	PBO n/N (%)	Active control n/N (%)	RD (95%CI)
Osuga 2021 Ext, REL v PBO, Wk 24	-25.9 (2.1)	-5.4 (2.2)		<0.05
Osuga 2021 Ext, REL v LEU, Wk 24	-25.9 (2.1)		-26.4 (2.6)	NS

Source: Tables 2.5.2 and 2.5.3, pp113-115, Tables 2.5.5 and 2.5.6, pp121-123, Table 2.5.12, pp131-132, Table 2.5.16, p142, Tables 2.5.20-2.5.22, pp148-150 of the submission.

dAB=delayed add-back (E2/NETA) therapy; EHP-30=Endometriosis Health Profile-30; EOT=end of treatment; E2=estradiol (exogenously applied); HrQoL=health-related quality of life; ITT=intention to treat; LEU=leuporelin; LS=least squares; mITT=modified intention-to-treat; NETA=norethindrone acetate; NMPP=non-menstrual pelvic pain; NRS=numerical rating scale; NS=not significant; PBO=placebo; REL=relugolix 40mg; SE=standard error; VAS=visual analogue scale; wk=week;

No treatment comparisons were performed for the extension study

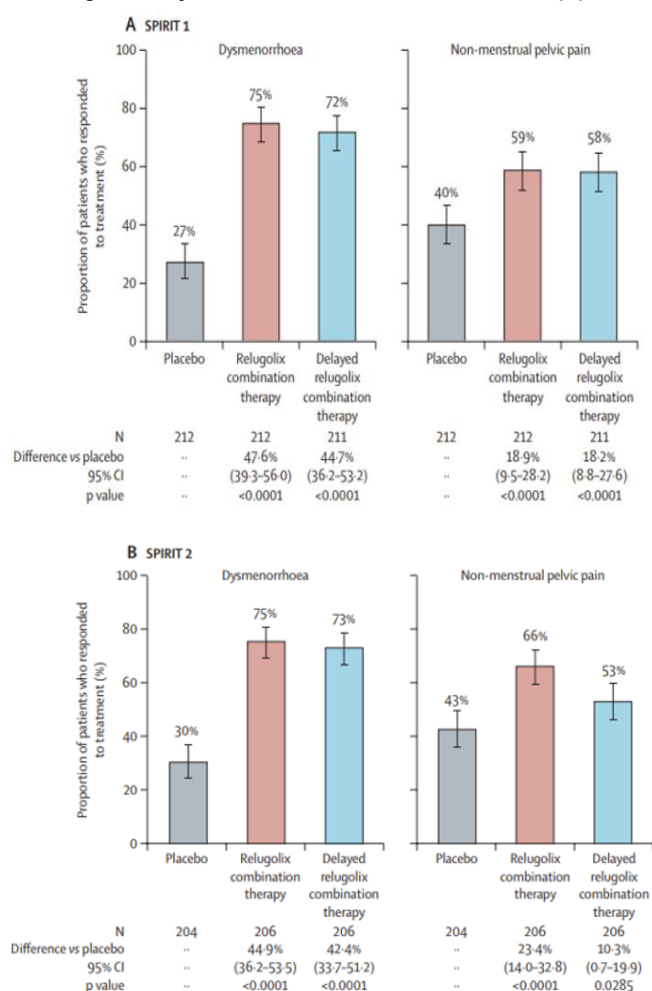
a Responders had dysmenorrhea NRS score declined from baseline to Week 24/EOT by ≥ 2.8 points or Week 24/EOT score ≤ 0.1 if baseline dysmenorrhea pain score was < 2.8 , and did not have increased use of study-specified analgesics for pelvic pain at Week 24/EOT relative to baseline.

b In SPIRIT Extension all patients received open-label Ryego.

c Responders had NMPP NRS score declined from baseline to Week 24/EOT by ≥ 2.1 points or Week 24/EOT score ≤ 0.1 if baseline NMPP score was < 2.1 , and did not have increased use of study-specified analgesics for pelvic pain at Week 24/EOT relative to baseline.

d Results presented in the submission was inconsistent with Osuga 2021. Mean change from baseline in dyspareunia estimated from Figure 2, Osuga 2021 was -0.9 for REL, -4.6 for PBO and -6.5 for LEU.

Figure 1: Dysmenorrhea and NMPP in SPIRIT 1 (A) & SPIRIT 2 (B).



Error bars represent 95% CI (Primary endpoint analysis)

Source: Ryego submission executive summary, p4; Giudice LC, As-Sanie S, Arjona JC, Becker CM, Abrao MS, et al. Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3, randomised, double-blind, studies (SPIRIT 1 and 2). The Lancet 2022;399(10343):2267-2279. (Giudice 2022) [https://doi.org/10.1016/S0140-6736\(22\)00622-5](https://doi.org/10.1016/S0140-6736(22)00622-5)

Ryeqo vs placebo

- 6.27 Across SPIRIT 1 and SPIRIT 2, the proportion of dysmenorrhea responders (reduction from baseline in dysmenorrhea NRS score ≥ 2.8) and NMPP responders (reduction from baseline in NMPP NRS ≥ 2.1), was significantly higher in the Ryeqo group compared to placebo at Week 24. In the pooled SPIRIT 1/SPIRIT 2 analyses at Week 24, risk difference (RD) between Ryeqo vs placebo treated patients for dysmenorrhea response was 74.8% vs 28.6%, RD = 46.2, 95%CI: 40.2, 52.2 and NMPP response was 62.1% vs 41.0%, RD = 21.1, 95%CI: 14.4, 27.7. The proportion of dysmenorrhea and NMPP responders was maintained in the Ryeqo group and increased in the group initially treated with PBO during long-term treatment in SPIRIT Extension to Week 104.
- 6.28 The changes (reductions) from baseline in NRS score (dysmenorrhea, NMPP, overall pelvic pain and dyspareunia) and EHP-30 pain domain were also significantly greater in the Ryeqo group compared to placebo at Week 24. The results for relugolix + delayed add-back therapy group were consistent with Ryeqo group. In the relugolix + delayed add-back group, from baseline to Week 12 when patients received relugolix monotherapy there was a higher proportion of dysmenorrhea and NMPP responders than in Ryeqo group, however, following the addition of add-back therapy at Week 12 there was a small decline in response rates before increasing over time similar to Ryeqo group.
- 6.29 Across SPIRIT 1 and SPIRIT 2, there was greater mean (SD) improvement from baseline in overall health status on the EQ-5D-5L VAS at Week 24 in the Ryeqo group compared to placebo (SPIRIT 1: 22.8 (21.3) vs 14.0 (23.5), and SPIRIT 2: 20.2 (23.7) vs 12.7 (24.8)).

Relugolix monotherapy vs leuprorelin (GnRH agonist)

- 6.30 In Harada et al 2022, the (least squares mean (SE)) change from baseline in VAS (maximum) score for pelvic pain was significantly greater in the leuprorelin group compared to relugolix group at Week 24 (-57.4 (1.4) vs -52.6 (1.3), RD = 4.9, 95%CI: 1.2, 8.7). Given that the upper bound of the 95% CI of the mean change in the maximum VAS score for pelvic pain between groups was 8.7, which was below the nominated non-inferiority margin of 10.0, the submission claimed that non-inferiority was supported, assuming that all GnRH agonists are comparable (e.g. leuprorelin, goserelin and nafarelin). There was no difference between groups in the mean change from baseline in VAS (mean) score for pelvic pain, NMPP and dyspareunia, EHP-30 pain domain and B&B score at Week 24.
- 6.31 In Osuga et al 2021 and Osuga et al 2021 Extension, there was no difference between groups in the mean change (reduction) from baseline in VAS (mean) score for dysmenorrhea, pelvic pain and dyspareunia, EHP-30 domain scores, B&B and mB&B score at Week 12 and Week 24. The results suggested that treatment with leuprorelin was similar in the reduction of dysmenorrhea, overall pelvic pain and dyspareunia compared to relugolix at Week 24.

GnRH agonist (leuprorelin) + add-back therapy vs BSC (oral contraceptive)

- 6.32 In Zupi et al 2004, the mean change (reduction) from baseline in VAS for dysmenorrhea and pelvic pain was significantly greater in the leuprorelin + add-back group compared to oral contraceptive (estrogen/progestin) after 6 months ($p < 0.05$), 12 months ($p < 0.01$) of treatment and 6 months post discontinuation of treatment ($p < 0.01$). The results for leuprorelin alone group were consistent with leuprorelin + add-back group. However, there were no differences between groups for change in VAS for dyspareunia at 6 months or 12 months. In addition, Zupi et al 2024 showed there was improvement in quality of life SF-36 pain domain for patients treated with GnRH analogue + add-back similar to GnRH analogue alone, compared to oral contraceptive group. However, the scores for other domains (general health, vitality and physical function) was similar between GnRH analogue alone and oral contraceptive.

Systematic reviews / meta-analysis

- 6.33 The submission identified 9 published systematic reviews/meta-analyses for endometriosis-associated pain. Three reviews (Veth et al 2023, Wu et al 2014 and Farmer et al 2003) compared GnRH analogues + add-back therapy to GnRH analogue alone (such as buserelin, goserelin, leuprorelin, nafarelin and triptorelin). Six reviews (Gibbons et al 2021, Grandi et al 2019, Brown et al 2018, Jensen et al 2018, Fu et al 2017 and Brown et al 2012) compared different contraceptives to placebo, no treatment or other interventions (including GnRH). None of the reviews included Ryego or relugolix treatment (i.e. the SPIRIT trials, Harada et al 2022, Osuga et al 2021 and Osuga et al 2021 Extension).
- 6.34 Broadly, the reviews suggest GnRH analogues + add-back was no different to GnRH alone in improving endometriosis pain, but GnRH analogues with or without add-back therapy was superior to hormonal contraceptives or placebo in improving pelvic pain. There was generally no difference between the various contraceptives in the treatment of endometriosis pain symptoms. Three reviews (Veth et al 2023, Wu et al 2014 and Farmer et al 2003) reported the safety outcome of change in BMD, with results indicating that patients treated with GnRH analogue + add-back tend to have a reduction in BMD loss (lumber spine) compared to GnRH alone or hormonal contraceptive. Overall, the results from the reviews should be interpreted with caution due to poor quality of evidence (majority of studies graded as high risk of bias) and very low to low certainty of results due to heterogeneity across the studies (variation in outcomes, measurement instruments, treatment follow-up, baseline characteristics, types and doses of GnRH and contraceptives).

Indirect treatment comparisons (ITCs)

- 6.35 The indirect comparison was conducted using Bayesian approach using the GeMTC package-based R Shiny app. The main analysis used fixed effects models, as the precise variance between studies could not be estimated due to low number of studies

included. The submission presented results for two outcomes – change from baseline in dysmenorrhea and NMPP scores (NRS or VAS). VAS (0-100) scores were transformed to NRS (0-10) scores by applying a conversion factor (e.g. 0.1) calculated by dividing the upper limit of the NRS (e.g., 10) by the upper limit of the VAS (e.g., 100). The outcomes were reported at Week 24 for Ryeqo (SPIRIT 1 and SPIRIT 2), and danazol (Harada et al 2008), Week 16 for oral contraceptive (Roghaei et al 2010) and Week 12 for dienogest (Osuga et al 2019 and Osuga et al 2020). The submission described the base case as the indirect comparisons of Ryeqo vs oral contraceptive and danazol treatment (Harada et al 2008 and Roghaei et al 2010) for dysmenorrhea and Ryeqo vs oral contraceptive (Harada et al 2008) for NMPP at Week 16-24. In the sensitivity analysis, the submission included additional BSC treatment with dienogest 0.5 mg (Osuga et al 2019) and dienogest 1 mg (Osuga et al 2020). Osuga et al 2019 and Osuga et al 2020 were excluded from the base case ITC as the studies reported dysmenorrhea outcomes after 12 weeks of treatment and the enrolled patients were not required to have confirmed endometriosis. The rationale for using the dienogest 0.5 mg dose arms was unclear, particularly as Osuga et al 2019 was a dose finding study that included dienogest 0.5, 1 and 2 mg, whereas Osuga et al 2020 only used dienogest 1 mg.

- 6.36 The inclusion of danazol (Harada et al 2008) in the indirect comparison makes the results less relevant to clinical practice, given danazol (synthetic steroid) is not currently approved by TGA or listed on the PBS. The Australian Therapeutic Guidelines indicate that danazol is used by specialists when other treatments are not tolerated and treatment must be used concurrently with nonhormonal contraceptive for a limited duration of 6 to 9 months. Danazol is associated with significant AEs (e.g., hirsutism, acne, voice change, liver toxicity, dyslipidaemia and potential increased risk of ovarian cancer). For this reason, danazol is no longer described in international EHSRE 2022 guidelines as a treatment for endometriosis-associated pain.
- 6.37 Table 5 presents the study results for the change in dysmenorrhea and NMPP score, and the indirect comparisons between Ryeqo and contraceptive.

Table 5: Indirect comparison of Ryeqo versus contraceptive for endometriosis pain (dysmenorrhea and NMPP)

Outcome	Drug LS mean (SE)	Control LS mean (SE)	RD (95%CI)
Change from baseline in dysmenorrhea NRS/VAS score			
<u>Ryeqo</u>			
SPIRIT 1, Ryeqo v PBO, NRS Wk 24	-5.1 (0.2)	-1.8 (0.2)	-3.3 (-3.8, -2.8)
SPIRIT 2, Ryeqo v PBO, NRS Wk 24	-5.1 (0.2)	-2.0 (0.2)	-3.2 (-3.7, -2.7)
<u>BSC</u>			
Harada 2008, OCP v PBO, VAS Wk 16	-31.1	-9.6	NR
Roghaei 2010, DAN v PBO, 11-item Wk 24	-0.77	0.54	NR
Osuga 2019, DNG 0.5 v PBO, VAS Wk 12	-35.8 (4.9)	-21.0 (3.9)	-14.2 (-23.6, -4.7)
Osuga 2019, DNG 1 v PBO, VAS Wk 12 ^a	-44.3 (4.0)	-21.0 (3.9)	-25.2 (-34.6, -15.8)
Osuga 2020, DNG 1 v PBO, VAS Wk 12 ^b	-44.9	-7.4	-34.3 (-44.3, -24.4)
Change from baseline in NMPP NRS/VAS score			
<u>Ryeqo</u>			
SPIRIT 1, Ryeqo v PBO, NRS Wk 24	-2.9 (0.2)	-2.0 (0.2)	-0.9 (-1.4, -0.4)
SPIRIT 2, Ryeqo v PBO, NRS Wk 24	-2.7 (0.2)	-2.0 (0.2)	-0.7 (-1.2, -0.3)
<u>BSC</u>			
Harada 2008, OCP v PBO, VAS Wk 16	-8.4	-1.8	-
Indirect comparisons (Bayesian) – change from baseline in dysmenorrhea			
Ryeqo v OCP/DAN, Wk 16-24			-1.09 (-1.3, -0.88)
Ryeqo v OCP, Wk 16-24			NR
Ryeqo v OCP/DAN/DNG 0.5-0.1, Wk 12-24 [^]			-0.75 (-0.91, -0.59)
Ryeqo v OCP/DAN/DNG 0.1, Wk 12-24 [^]			-
Ryeqo v PBO, Wk 24			-3.2 (-3.23, -3.17)
OCP/DAN v PBO, Wk 16-24			-2.11 (-2.32, -1.9)
OCP/DAN/DNG 0.5-0.1, Wk12-24 [^]			-2.45 (-2.61, -2.3)
Indirect comparisons (Bayesian) – change from baseline in NMPP			
Ryeqo v OCP, Wk 16-24			-0.14 (-0.22, -0.06)
Ryeqo v PBO, Wk 24			-0.8 (-0.83, -0.77)
OCP v PBO, Wk 16-24			-0.66 (-0.74, -0.59)

Difference in response was calculated using Review Manager (version 5.3).

Source: Tables 2.6.3-2.6.8, pp190-194, Tables A3.1-A3.2, pp306-307 of the submission.

DAN=danazol; DNG=dienogest; LS=least squares; NMPP=nonmenstrual pelvic pain; NR=not reported; NRS=numerical rating scale; OCP=oral contraceptive pill; PBO=placebo; SD=standard deviation; SE=standard error; VAS=visual analogue scale; wk=week;

[^] Sensitivity analysis including Osuga 2019 and Osuga 2020, which reported outcomes after 12 weeks of treatment.

A Data for DNG 1 group extracted from Osuga 2019.

B Data could not be verified. Osuga 2020 reported mean (SD) change in dysmenorrhea: -45 (28.3) in DNG group and -7.3 (26.7) in PBO.

6.38 The results showed that treatment with Ryeqo or contraceptive (oral contraceptive pill, danazol and dienogest) were more effective than placebo in the reduction from baseline in dysmenorrhea and NMPP score (NRS/VAS) at Week 12, 16 or 24. The indirect comparisons found that results favoured Ryeqo over all contraceptive treatment for reduction in dysmenorrhea and NMPP.

Comparative harms

6.39 Table 6 summarises the key safety outcomes in the SPIRIT trials and relugolix monotherapy trials (Harada et al 2022, Osuga et al 2021 and Osuga et al 2021 Extension).

Table 6: Overall summary of adverse events in SPIRIT (Ryego) and relugolix monotherapy trials.

Trial ID	Drug n/N (%)	PBO n/N (%)	Active control n/N (%)	RR (95% CI)	RD (95% CI)
Any adverse event (AE)					
	Ryego	PBO	REL+dAB		
SPIRIT 1, Ryego v PBO, 24w	151/212 (71.2)	140/212 (66.0)	-	1.08 (0.95, 1.23)	0.05 (-0.04, 0.14)
SPIRIT 1, REL+dAB v PBO, Wk 24	-	140/212 (66.0)	163/211 (77.3)	1.17 (1.04, 1.32)	0.11 (0.03, 0.20)
SPIRIT 2, Ryego v PBO, 24w	166/206 (80.6)	153/204 (75.0)	-	1.07 (0.97, 1.19)	0.06 (-0.02, 0.14)
SPIRIT 2, REL+dAB v PBO, Wk 24	-	153/204 (75.0)	168/206 (81.6)	1.09 (0.98, 1.20)	0.07 (-0.01, 0.15)
SPIRIT 1/2 pooled, Ryego v PBO, Wk 24	317/418 (75.8)	293/416 (70.4)	-	1.08 (0.99, 1.17)	0.05 (-0.01, 0.11)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 24	-	293/416 (70.4)	331/417 (79.4)	1.12 (1.04, 1.21)	0.09 (0.03, 0.15)
SPIRIT Ext ^A , Ryego v PBO v REL+dAB, Wk 104	204/277 (73.6)	215/275 (78.2)	177/247 (71.7)	- ^a	- ^a
	REL	PBO	LEU		
Harada 2022, REL v LEU, 24w	154/171 (90.1)	-	157/164 (95.7)	0.94 (0.89, 1.00)	-0.06 (-0.11, 0.00)
Osuga 2021 [#] , REL v PBO, 12w	97/103 (94.2)	69/97 (71.1)	-	1.32 (1.16, 1.52)	0.23 (0.13, 0.33)
Osuga 2021 [#] , REL v LEU, 12w	97/103 (94.2)	-	73/80 (91.3)	1.03 (0.95, 1.12)	0.03 (-0.05, 0.11)
Osuga 2021 ext [#] , REL v PBO, 24w	98/103 (95.1)	79/97 (81.4)	-	1.17 (1.05, 1.30)	0.14 (0.05, 0.22)
Osuga 2021 ext [#] , REL v LEU, 24w	98/103 (95.1)	-	78/80 (97.5)	0.98 (0.92, 1.03)	-0.02 (-0.08, 0.03)
Any AE related to study drug					
	Ryego	PBO	REL+dAB		
SPIRIT 1, Ryego v PBO, 24w	86/212 (40.6)	73/212 (34.4)	-	1.18 (0.92, 1.51)	0.06 (-0.03, 0.15)
SPIRIT 1, REL+dAB v PBO, Wk 24	-	73/212 (34.4)	125/211 (59.2)	1.72 (1.39, 2.14)	0.25 (0.16, 0.34)
SPIRIT 2, Ryego v PBO, 24w	112/206 (54.4)	83/204 (40.7)	-	1.34 (1.09, 1.54)	0.14 (0.04, 0.23)
SPIRIT 2, REL+dAB v PBO, Wk 24	-	83/204 (40.7)	117/206 (56.8)	1.40 (1.14, 1.71)	0.16 (0.07, 0.26)
SPIRIT 1/2 pooled, Ryego v PBO, Wk 24	198/418 (47.4)	156/416 (37.5)	-	1.27 (1.08, 1.49)	0.10 (0.02, 0.17)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 24	-	156/416 (37.5)	156/416 (58.0)	1.54 (1.26, 1.90)	0.21 (0.12, 0.29)
SPIRIT Ext ^A , Ryego v PBO v REL+dAB, Wk 104	94/277 (33.9)	135/275 (49.1)	93/247 (37.7)	- ^a	- ^a
	REL	PBO	LEU		
Harada 2022, REL v LEU, 24w	136/171 (79.5)	-	149/164 (90.9)	0.88 (0.80, 0.96)	-0.11 (-0.19, -0.04)
Osuga 2021 [#] , REL v PBO, 12w	88/103 (85.4)	36/97 (37.1)	-	2.30 (1.76, 3.02)	0.48 (0.37, 0.60)
Osuga 2021 [#] , REL v LEU, 12w	88/103 (85.4)	-	67/80 (83.8)	1.02 (0.90, 1.16)	0.02 (-0.09, 0.12)
Osuga 2021 Ext [#] , REL v PBO, 24w	91/103 (88.3)	38/97 (39.2)	-	2.26 (1.74, 2.92)	0.49 (0.38, 0.61)
Osuga 2021 Ext [#] , REL v LEU, 24w	91/103 (88.3)	-	72/80 (90.1)	0.98 (0.89, 1.09)	-0.02 (-0.11, 0.07)
Grade 3 or higher AE					
	Ryego	PBO	REL+dAB		
SPIRIT 1, Ryego v PBO, 24w	10/212 (4.7)	12/212 (5.7)	-	0.83 (0.37, 1.89)	-0.01 (-0.05, 0.03)
SPIRIT 1, REL+dAB v PBO, Wk 24	-	12/212 (5.7)	9/211 (4.3)	0.75 (0.32, 1.75)	-0.01 (-0.06, 0.03)
SPIRIT 2, Ryego v PBO, 24w	14/206 (6.8)	7/204 (3.4)	-	1.98 (0.82, 4.81)	0.03 (-0.01, 0.08)
SPIRIT 2, REL+dAB v PBO, Wk 24	-	7/204 (3.4)	12/206 (5.8)	1.70 (0.68, 4.23)	0.02 (-0.02, 0.06)
SPIRIT 1/2 pooled, Ryego v PBO, Wk 24	24/418 (5.7)	19/416 (4.6)	-	1.26 (0.54, 2.95)	0.01 (-0.03, 0.05)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 24	-	19/416 (4.6)	21/417 (5.0)	1.11 (0.50, 2.46)	0.01 (-0.03, 0.04)
SPIRIT Ext ^A , Ryego v PBO v REL+dAB, Wk 104	15/277 (5.4)	30/275 (10.9)	23/247 (9.3)	- ^a	- ^a
Serious AE					
	Ryego	PBO	REL+dAB		

Trial ID	Drug n/N (%)	PBO n/N (%)	Active control n/N (%)	RR (95% CI)	RD (95% CI)
SPIRIT 1, Ryego v PBO, 24w	3/212 (1.4)	5/212 (2.4)	-	0.60 (0.15, 2.48)	-0.01 (-0.04, 0.02)
SPIRIT 1, REL+dAB v PBO, Wk 24	-	5/212 (2.4)	3/211 (1.4)	0.60 (0.15, 2.49)	-0.01 (-0.04, 0.02)
SPIRIT 2, Ryego v PBO, 24w	9/206 (4.4)	4/204 (2.0)	-	2.23 (0.70, 7.12)	0.02 (-0.01, 0.06)
SPIRIT 2, REL+dAB v PBO, Wk 24	-	4/204 (2.0)	6/206 (2.9)	1.49 (0.43, 5.19)	0.01 (-0.02, 0.04)
SPIRIT 1/2 pooled, Ryego v PBO, Wk 24	12/418 (2.9)	9/416 (2.2)	-	1.23 (0.34, 4.44)	0.01 (-0.03, 0.04)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 24	-	9/416 (2.2)	9/417 (2.2)	1.00 (0.39, 2.56)	-0.00 (-0.02, 0.02)
SPIRIT Ext ^a , Ryego v PBO v REL+dAB, Wk 104	7/277 (2.5)	18/275 (6.5)	19/247 (7.7)	- ^a	- ^a
	REL	PBO	LEU		
Harada 2022, REL v LEU, 24w	1/171 (0.6)	-	1/164 (0.6)	0.96 (0.06, 15.21)	0.00 (-0.02, 0.02)
Osuga 2021 [#] , REL v PBO, 12w	0	3/97 (3.1)	-	0.13 (0.01, 2.57)	-0.03 (-0.07, 0.01)
Osuga 2021 [#] , REL v LEU, 12w	-	3/97 (3.1)	0	-	-
Osuga 2021 Ext [#] , REL v PBO, 24w	0	5/97 (5.2)	-	0.09 (0.00, 1.53)	-0.05 (-0.10, 0.00)
Osuga 2021 Ext [#] , REL v LEU, 24w	-	5/97 (5.2)	0	-	-
Discontinuation due to AE					
	Ryego	PBO	REL+dAB		
SPIRIT 1, Ryego v PBO, 24w	8/212 (3.8)	4/212 (1.9)	-	2.00 (0.61, 6.54)	0.02 (-0.01, 0.05)
SPIRIT 1, REL+dAB v PBO, Wk 24	-	4/212 (1.9)	9/211 (4.3)	2.26 (0.71, 7.23)	0.02 (-0.01, 0.06)
SPIRIT 2, Ryego v PBO, 24w	11/206 (5.3)	8/204 (3.9)	-	1.36 (0.56, 3.32)	0.01 (-0.03, 0.05)
SPIRIT 2, REL+dAB v PBO, Wk 24	-	8/204 (3.9)	15/206 (7.3)	1.86 (0.80, 4.28)	0.03 (-0.01, 0.08)
SPIRIT 1/2 pooled, Ryego v PBO, Wk 24	19/418 (4.5)	12/416 (2.9)	-	1.56 (0.77, 3.19)	0.02 (-0.01, 0.04)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 24	-	12/416 (2.9)	24/417 (5.8)	1.99 (1.01, 3.91)	0.03 (0.00, 0.05)
SPIRIT Ext ^a , Ryego v PBO v REL+dAB, Wk 104	15/277 (5.4)	22/275 (8.0)	17/247 (6.9)	- ^a	- ^a
	REL	PBO	LEU		
Harada 2022, REL v LEU, 24w	5/171 (2.9)	-	7/164 (4.3)	0.69 (0.22, 2.12)	-0.01 (-0.05, 0.03)
Osuga 2021 [#] , REL v PBO, 12w	1/103 (1.0)	1/97 (1.0)	-	0.94 (0.06, 14.85)	0.00 (-0.03, 0.03)
Osuga 2021 [#] , REL v LEU, 12w	1/103 (1.0)	-	3/80 (3.8)	0.26 (0.03, 2.44)	-0.03 (-0.07, 0.02)
Osuga 2021 Ext [#] , REL v PBO, 24w	-	6/97 (6.2)	-	0.31 (0.06, 1.52)	-0.04 (-0.10, 0.01)
Osuga 2021 Ext [#] , REL v LEU, 24w	2/103 (1.9)	-	9/80 (11.3)	0.17 (0.04, 0.78)	-0.09 (-0.17, -0.02)

Bold text=statistically significant.

Source: Table 2.5.27, p156 of the submission; pp168-169 of the submission, Table 3 of Harada 2022, Table 2 of Osuga 2021, Table 1 of Osuga 2021 extension.

AE=adverse event; dAB=delayed add-back (E2/NETA) therapy; E2=estradiol; LEU=leuporelin; NETA=norethisterone acetate; n=number of participants with event; N=total participants in group, NE=not estimable, PBO=placebo; RD=risk difference, RR=risk ratio, REL=relugolix; wk=week;

^a Cumulative experience (pivotal SPIRIT trials and SPIRIT Extension study). All patients received Ryego during the extension study.

[#] In Osuga 2021, the relugolix treatment group refers to the relugolix 40 mg group.

a No treatment comparisons were performed for the extension study

6.40 The incidence of any AEs, serious AEs and discontinuations due to AEs was similar between Ryego and placebo at Week 24 in SPIRIT 1 and SPIRIT 2. Patients treated with Ryego and relugolix + delayed add-back had significantly more drug-related AEs, with numerically higher incidence in the delayed add-back group (58%) compared to Ryego (47.4%). There were also significantly more AEs and discontinuations due to AEs in the relugolix + delayed add-back group compared to placebo at Week 24. Commonly

reported AEs included headaches, hot flushes and nasopharyngitis. Patients treated with relugolix + delayed add-back reported significantly more decrease in bone density compared to placebo.

- 6.41 Across the relugolix monotherapy trials, the incidence of any AEs, serious AEs and discontinuation was similar between relugolix and leuprorelin (GnRH agonist). However, patients treated with relugolix had significantly more drug-related AEs compared leuprorelin and placebo at Weeks 12 and 24. The most commonly reported AEs were generally consistent with the mechanism of action of relugolix i.e. vasomotor symptoms.
- 6.42 Safety outcomes in the long-term SPIRIT Extension where all patients received open label Ryeqo showed fewer AEs for patients who had received Ryeqo and relugolix + delayed add-back in the RCTs compared to those originally randomised to placebo at Week 104, likely due to differences in the duration of exposure to Ryeqo (i.e. up to 80 weeks in placebo, 92 weeks in relugolix + delayed add-back and 104 weeks for Ryeqo). There were no fatal AEs reported to Week 24 and Week 104 across the SPIRIT trials and relugolix monotherapy trials. Cumulatively (across the double-blind treatment and extension study) AEs of special interest reported with increasing frequency included bone health events, vasomotor symptoms and mood disorders.
- 6.43 In addition, menstruation status was assessed 30-day PTFU after patients discontinued or completed study treatment in SPIRIT Extension. All patients with menstruation follow-up data reported return of menses unless there was a reason for non-recovery (e.g. pregnancy, medication or surgery). The median time to resumption of menses was 33.0 days, 32.0 days, and 32.0 days in Ryeqo group, relugolix + delayed add-back group and placebo, respectively.

Bone mineral density (BMD)

- 6.44 Table 7 and Figure 2 present the percent change from baseline in BMD at the lumbar spine (L1-L4) and total hip in the pooled SPIRIT 1/SPIRIT 2 trials to Week 24 and SPIRIT Extension to Week 104, respectively.

Table 7: Change from baseline in BMD at the lumbar spine and total hip in SPIRIT 1/SPIRIT 2 to Week 24.

Trial ID	Ryeqo	PBO	REL + dAB	RD (95%CI)#
LS mean (SE) change from baseline in BMD at lumbar Spine (L1-L4)				
SPIRIT 1/2 pooled, Ryeqo v PBO, Wk 12	-0.49 (0.16)	0.09 (0.16)	-	-0.57 (-0.89, -0.26)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 12	-	0.09 (0.16)	-1.76 (0.17)	-1.85 (-2.16, -1.54)
SPIRIT 1/2 pooled, Ryeqo v REL+dAB, Wk 12	-0.49 (0.16)	-	-1.76 (0.17)	1.28 (0.97, 1.59)^
SPIRIT 1/2 pooled, Ryeqo v PBO, Wk 24	-0.72 (0.17)	0.12 (0.18)	-	-0.84 (-1.20, -0.49)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 24	-	0.12 (0.18)	-1.94 (0.18)	-2.07 (-2.42, -1.71)
SPIRIT 1/2 pooled, Ryeqo v REL+dAB, Wk 24	-0.72 (0.17)	-	-1.94 (0.18)	1.22 (0.87, 1.68)
LS mean (SE) change from baseline in BMD at total hip				
SPIRIT 1/2 pooled, Ryeqo v PBO, Wk 12	-0.15 (0.14)	0.11 (0.14)	-	-0.26 (-0.53, 0.01)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 12	-	0.11 (0.14)	-0.74 (0.14)	-0.85 (-1.12, -0.58)
SPIRIT 1/2 pooled, Ryeqo v REL+dAB, Wk 12	-0.15 (0.14)	-	-0.74 (0.14)	0.59 (0.32, 0.86)^
SPIRIT 1/2 pooled, Ryeqo v PBO, Wk 24	-0.34 (0.15)	0.03 (0.15)	-	-0.37 (-0.67, -0.07)
SPIRIT 1/2 pooled, REL+dAB v PBO, Wk 24	-	0.03 (0.15)	-0.83 (0.15)	-0.87 (-1.17, -0.57)
SPIRIT 1/2 pooled, Ryeqo v REL+dAB, Wk 24	-0.34 (0.15)	-	-0.83 (0.15)	0.49 (0.20, 0.79)

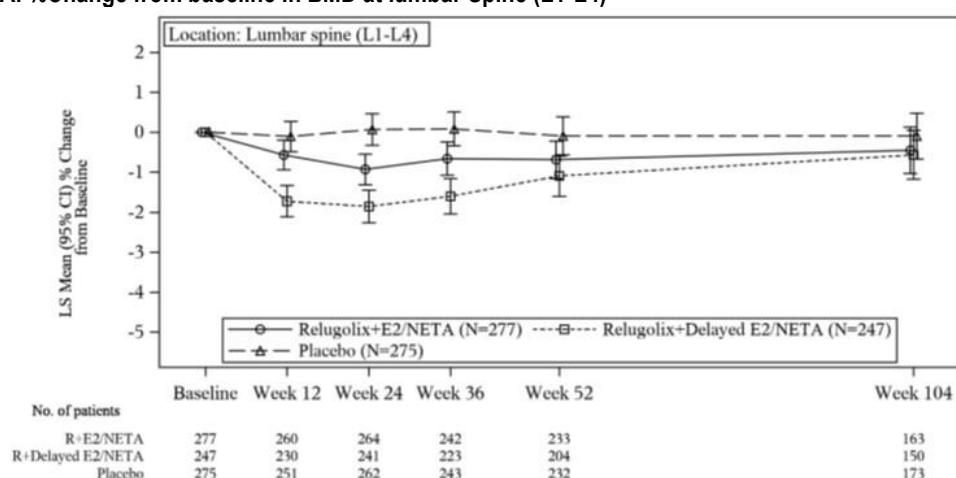
Source: Tables 2.5.30-31, pp.160-163 of the submission;

AE=adverse event; BMD=bone mineral density; dAB=delayed add-back (E2/NETA) therapy; E2=estradiol; LEU=leuporelin; LS=least squares; NETA=norethisterone acetate; PBO=placebo; RD=risk difference, REL=relugolix; SE=standard error; wk=week;

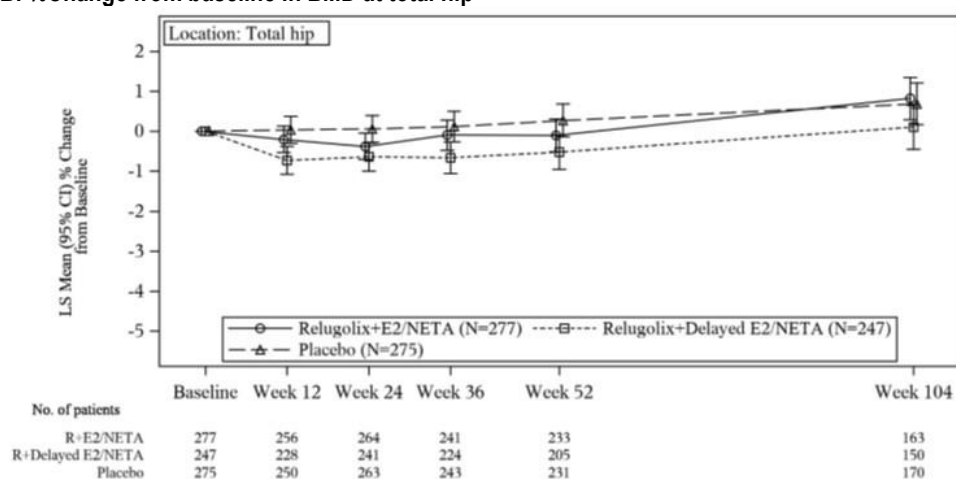
The between-group differences were not formally tested except for Ryeqo vs REL+dAB at week 12..

^ p-value <0.0001 based on comparison of LS means difference between Ryeqo group and relugolix 40 mg + delayed add-back group. The LS means and 95%CI are based on mixed-effect model with treatment group, age at baseline, visit, baseline BMD value, stratification factors (geographic region and time since initial endometriosis diagnosis), race group, body mass index at baseline and treatment-by-visit interaction as fixed effects using unstructured variance-covariance matrix. Visit is considered as a categorical variable.

Figure 2: %Change from baseline in BMD at the lumbar spine and total hip in SPIRIT Extension to Week 104
A. %Change from baseline in BMD at lumbar Spine (L1-L4)



B. %Change from baseline in BMD at total hip



Source: Figure 2.5.19, p164 of the submission.

CI=confidence interval; E2 = estradiol; LS=least squares; N=number of patients (SPIRIT Extension) in the pivotal study (SPIRIT 1, SPIRIT 2) treatment group; NETA=norethisterone acetate; R=relugolix.

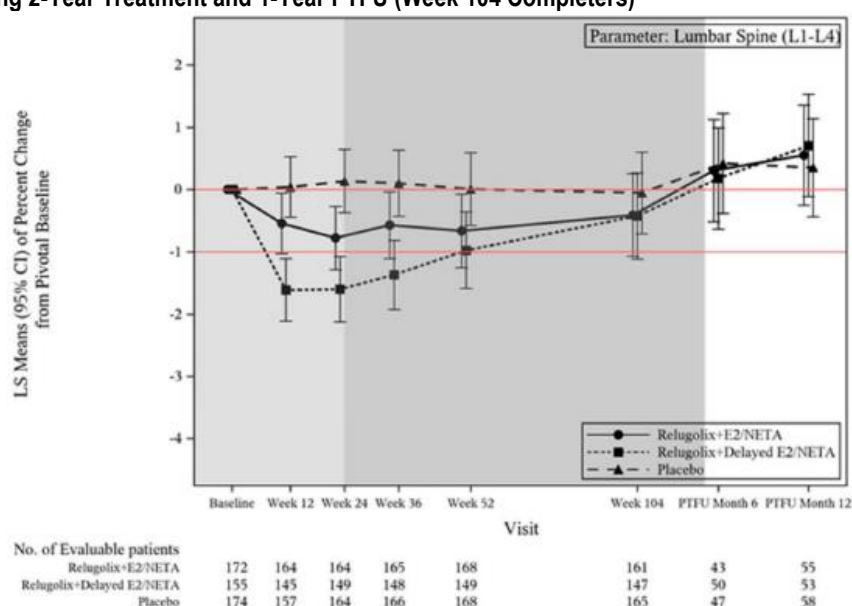
Note: LS means and 95% CI are generated based on mixed-effects model with BMD at baseline, age at baseline, geographic region (North American vs Rest of World), time since initial surgical diagnosis (< 5 years vs ≥ 5 years), body mass index at baseline, race (African American vs Other), visit, pivotal study (SPIRIT 1, SPIRIT 2) treatment group, and treatment-by-visit interaction as fixed effects using an unstructured matrix. The multiple visits for each patient are considered as random effect within each patient. Error bars represent 95% CI.

6.45 The pooled SPIRIT 1/SPIRIT 2 and SPIRIT Extension data showed a significantly greater mean change (reduction) from baseline in BMD at lumbar spine and total hip for the Ryego group and relugolix + delayed add-back group at Week 12 and Week 24 compared to placebo. The change in BMD for the Ryego group was maintained from Week 24 to Week 52, with a small trend towards BMD recovery at Week 104. Whereas, patients in relugolix + delayed add-back group who initially received relugolix monotherapy had significantly greater BMD loss earlier at Week 12, however, BMD loss appeared to stabilise with a trend towards BMD recovery at Week 104, potentially reflecting the effect of the addition of hormonal add-back to

relugolix at Week 12. The placebo group had minimal change in BMD over time to Week 104, although there was a small increase in BMD at the hip.

- 6.46 The SPIRIT Extension PTFU BMD data at 6- and 12-month post-treatment showed that across the treatment groups, in patients who met the prespecified BMD loss criteria (reduction in BMD >3% at the lumbar spine or hip), there was recovery of BMD (defined as >0% change) from last-on treatment DXA to 6 months or 12 months PTFU DXA. A higher proportion of patients in Ryego, relugolix + add-back and placebo group had BMD recovery at the lumbar spine (48.2%, 51.6% and 52.8%) than at total hip (16.1%, 35.5% and 28.3%). Across the 3 groups there were 23 (13.5%) patients who did not show BMD recovery post-treatment (defined as change $\leq 0\%$ from last on-treatment DXA to last PTFU visit) at the lumbar spine or total hip.
- 6.47 The pre-PBAC response included the follow up data from the SPIRIT 1 and SPIRIT 2 studies provided to ACM which showed improvements to above baseline BMD after discontinuing 104 weeks of treatment, see figure below.

Figure 3: By-Visit Least Squares Mean Percent Change from Pivotal Baseline in Bone Mineral Density at the Lumbar Spine During 2-Year Treatment and 1-Year PTFU (Week 104 Completers)



Source: Pre-ACM response (Attachment 1); pre-PBAC response.

- 6.48 The ESC noted the special warning included in the approved PI, regarding risk of bone loss: "In some women treated with Ryego, who had normal BMD at start of treatment, a bone loss varying from >3-8% was reported. Following an initial non-clinically relevant decrease in BMD, it stabilised after 12-24 weeks of treatment and thereafter remained stable (as measured up to 2 years). The mean decrease in BMD during the first year of treatment with Ryego was 0.69%. However, decreases of >3% were seen in 21% of patients."
- 6.49 Across the relugolix monotherapy trials (Harada et al 2022, Osuga et al 2021 and Osuga et al 2021 Extension) there was similar mean reduction from baseline in BMD

between relugolix (4.8-4.9%) and leuporelin (4.4-4.84%) at Week 24. Results from Osuga et al 2021 also indicate that the reduction in BMD was time and dose dependent. While change from baseline in BMD was reported in the relugolix monotherapy trials, the results may not be comparable to the SPIRIT trials. For example, it was unclear from Harada et al 2022 the site of assessment of BMD loss and Osuga et al 2021 reported the mean percent change in BMD for lumbar spine (L1-L5).

- 6.50 Evidence from Zupi et al 2004 comparing leuporelin (GnRH agonist) + add-back to leuporelin and placebo showed that there was smaller reduction in BMD in leuporelin + add-back group compared to leuporelin alone ($p < 0.05$). Compared to patients treated with oral contraceptive, both GnRH agonist groups (with and without add-back) showed significant reduction from baseline in BMD after 12 months of treatment ($p < 0.05$ and $p < 0.01$, respectively). At 6 months after treatment discontinuation, there was no difference in BMD between the leuporelin + add-back and oral contraceptive groups but there was significantly lower BMD in leuporelin alone group compared to oral contraceptive ($p < 0.03$).
- 6.51 An independent search conducted during the evaluation to identify longer term (beyond 6 months) use of GnRH + add-back found 6 studies (Taskin et al 1996, Pierce et al 2000, Surrey et al 2002, Fernandez et al 2004, Bedaiwy and Casper 2006 and Alshehre et al 2020) with treatment duration ranging from 10 months to 10 years. Of these, two small studies (Pierce et al 2000 (N=49) and Bedaiwy and Casper 2006 (N=5)) included treatment duration 2 years and beyond. Pierce et al 2000 investigated the use of GnRH agonist (goserelin) with and without add-back therapy for 6-24 months and the effect on BMD up to 6 years post-treatment. The results indicate similar BMD loss with long-term use of goserelin with and without add-back, although there was a numerically smaller reduction in BMD in the add-back group. Further, BMD was not fully recovered at 6 years after treatment discontinuation. Bedaiwy and Casper 2006 reported a pilot case study in patients with advanced endometriosis associated with severe pelvic pain treated with GnRH + add-back up to 10 years. The results showed no clinically significant loss of BMD (i.e. $> 3\%$) and the average BMD in the lumbar spine, total hip and femoral neck was generally maintained over the follow-up period for all five patients over 10 years.

Benefits/harms

- 6.52 The submission did not present comparative efficacy or safety data to allow for a quantitative comparison of the benefits and harms of treatment between Ryego and the appropriate comparator goserelin + add-back therapy in the treatment of women with endometriosis-associated pain. Accordingly, a benefits/harms table was not presented.

Clinical claim

- 6.53 In patients with endometriosis associated pain who have inadequate symptom control with first-line treatment or following surgery, the submission described Ryego as non-inferior to goserelin + add-back therapy and goserelin monotherapy and superior to BSC (contraceptive) in terms of effectiveness. In terms of safety, the submission described Ryego as non-inferior to goserelin + add-back and BSC but superior to goserelin monotherapy.

Comparison with GnRH (goserelin or nafarelin)

- 6.54 Overall, the ESC considered the clinical claim of non-inferior effectiveness and safety compared with goserelin with and without add-back may be reasonably supported by the indirect evidence presented in the submission. The ESC noted that this includes caveats that different agents from the same GnRH agonist class are assumed to be comparable in terms of efficacy and safety in the treatment of endometriosis pain and all contraceptive therapies are also assumed to be comparable when used for endometriosis. The ESC considered that this added uncertainty to the clinical claim but was likely to be reasonable. There were similar incidences of AEs and reduction in BMD at Week 24 between relugolix and leuprorelin, supporting the claim of non-inferior safety to goserelin + add-back therapy.
- 6.55 The ESC considered the comparison between Ryego and GnRH + add-back was the most relevant comparison, whereas the comparison between Ryego and GnRH analogue monotherapy (no add-back) was not informative as it was unlikely that Ryego would replace GnRH monotherapy in practice.
- 6.56 The ESC noted the while the use of nafarelin is small relative to goserelin (DUSC report 2019, Prospection report 2023), the non-inferior efficacy of Ryego to GnRH + add-back applied to this comparison also.

Comparison with BSC

- 6.57 Overall, the ESC considered the clinical claim of superior effectiveness of BSC (contraceptive) may be reasonably supported by the indirect evidence presented in the submission. This was based on indirect comparisons that favoured Ryego over contraceptive treatment for reduction in dysmenorrhea and NMPP at Week 16-24, and supportive evidence that indicates GnRH analogues with or without add-back was superior to hormonal contraceptives in improving pelvic pain.
- 6.58 However, the ESC considered the claim of non-inferior safety vs BSC was not adequately supported, given patients treated with GnRH therapy (with or without add-back) experienced significant reductions in BMD from baseline after 12 months of treatment and evidence comparing longer-term treatment was limited. The PSCR argued that the TGA Clinical Evaluation noted that “there was a significant decrease in BMD at the lumbar spine over the first 24 weeks of treatment with Ryego compared to placebo, but by two years of treatment the loss of BMD in the relugolix groups in

the pivotal studies appears to have stabilised, and to some extent reversed”. The PSCR stated that this was also echoed in the ACM advice. The ESC noted that ACM advice also questioned the long-term impact on bone health and was of the view that accrual of PBM has the potential to be impacted. The ACM also discussed the low dose of estradiol (1 mg) in the fixed dose combination and noted that this dose is unlikely to be adequate to prevent the full extent of bone loss. The ESC noted the ACM advice, and the final PI, recommending assessment of BMD at baseline and then annually.

- 6.59 The ESC considered the comparison between Ryego BSC was not informative as it was unlikely that Ryego would replace BSC in practice.
- 6.60 The PBAC considered that the claim of non-inferior comparative effectiveness compared with GnRH + add-back was reasonable.
- 6.61 The PBAC considered that the claim of non-inferior comparative safety compared with GnRH + add-back was reasonable.

Economic analysis

- 6.62 The submission presented two modelled economic evaluations comparing Ryego versus:
 - (i) GnRH agonists (assuming sequential use of goserelin and nafarelin) over a one-year time horizon), and
 - (ii) BSC (assuming only contraceptive therapies) over a five-year time horizon.
- 6.63 The Commentary noted that neither comparison was wholly informative for PBAC decision making given they do not compare Ryego to a GnRH analogue plus add-back therapy. The evaluation considered a more informative comparison would be to estimate the costs and benefits associated with the current treatment algorithm on the PBS (GnRH plus add-back treatment for up to 12 months followed by BSC thereafter) versus the proposed treatment algorithm on the PBS with Ryego (GnRH plus add-back for up to 24 months followed by BSC). An indicative sensitivity analysis using the model was conducted during the evaluation comparing two years of Ryego followed by BSC vs one year of Ryego followed by BSC over a five-year time horizon. One-year of Ryego followed by subsequent treatments was proxy for the current treatment algorithm on PBS of GnRH plus add-back treatment for up to 12 months followed by BSC thereafter. The PBAC noted that many computational errors, inappropriate sources for resource use and inputs that could not be verified from the cited sources were identified during the evaluation in the included models, making the results unreliable. The PBAC considered that the modelled economic evaluations presented were not informative for decision-making.
- 6.64 The requested price for Ryego (\$██████) was less than the average 28-day cost of goserelin + add-back treatment (\$217.46), but more than the average 28-day cost of nafarelin + add-back treatment assuming nafarelin 400 mcg per day (\$120.33). The cost of nafarelin would double if the dose increases to 800 mcg per day for when

symptoms persist, which may be a relevant comparison for the clinical setting being proposed for Ryego. The ESC noted that inclusion of costs for BMD monitoring would result in the average daily cost for Ryego being higher than goserelin + add-back treatment. However, costs for administration of goserelin may offset the additional cost of BMD monitoring. The ESC noted that the submission and PSCR did not address the lower cost of nafarelin + add-back therapy.

- 6.65 The ESC noted that given the clinical claim for the most relevant comparator (GnRH + add-back) was non-inferior efficacy and safety, the PBAC may wish to consider a cost-minimisation approach. The ESC noted that consideration would need to be given to the following factors for a cost-minimisation approach:
- The time period for comparison (e.g. average daily cost, cost over 1-2 years).
 - The inclusion of MBS or private costs for BMD testing
 - The inclusion of appropriate administration MBS costs where applicable (goserelin).
 - The inclusion of nafarelin + add-back as a relevant comparator for a proportion of patients.
- 6.66 The pre-PBAC response accepted the approach suggested by ESC and provided the following comparison table.

Table 8: Pre-PBAC response — Updated comparison of DPMQs for Ryego vs goserelin and nafarelin (plus add-back therapy)

Component	Ryego FDC	Goserelin	Nafarelin (400 mcg)	Nafarelin (800 mcg)	Add-back therapy (Assuming 50/50 split of the below)	
					Levonorgestrel 100 mcg + ethinylestradiol 20 mcg ^a	Norethisterone 350 mcg ^b
PBS item code	-	1454M	2962X	5815C	2416E	1967M
PBS item (max qty)	Tablets (28)	Implant (1)	Nasal spray 200 mcg (60 actuations)	Nasal spray 200 mcg (120 actuations)	Tablets (4x28)	Tablets (4x28)
Treatment duration per max qty	28 days	28 days	30 days	30 days	112 days	112 days
DPMQ	\$█	\$212.70	\$123.83	\$221.77	\$19.10	\$18.97
Cost per 28 days	\$█	\$212.70	\$115.57	\$206.99	\$4.78	\$4.74
					Average: \$4.76	
Cost per year	\$█	\$2,774.60	\$1,507.57	\$2,700.05	\$62.35	\$61.83
Cost of BMD testing yr 1 (MBS item 12321 Fee: \$112.70; 75% benefit: \$84.55)	\$0.00	\$0.00	\$84.55	\$84.55		
Cost of implant administration yr 1 (MBS item 14206 \$39.20 + MBS item 23 \$41.40)	\$0.00	\$1,051.40	\$0.00	\$0.00		
Total cost over 2 years (incl BMD testing and add-back)	\$█	\$5,673.38	\$3,223.87	\$5,608.83	Average \$62.09	
Total cost over 2 years (incl BMD testing, add-back and implantation)	\$█	\$7,776.18	\$3,223.87	\$5,608.83		
Distribution of use	100%	88%	6.8%	5.2%		
Total cost over 2 years	\$█	\$7,352.97				
Difference in cost over 2 years	-\$█					

Source: Ryego - CMA - Pre PBAC.xlsx

Note: the PBS item code 5815C included in this table applies to assisted reproductive technology and is not applicable to this indication. Italics indicate additional analyses provided in the Pre-PBAC response.

- 6.67 The pre-PBAC response proposed that nafarelin represents a █% market share and that it may be reasonable to include nafarelin 400 mcg (57%) and 800 mcg per day (43%) as the dose split. The response also proposed the 2-year calculation exclude the cost of BMD testing for Ryego but include it for nafarelin.
- 6.68 The Secretariat noted the pre-PBAC response used the 75% benefit for the MBS item for BMD testing whereas the 100% benefit is typically used for MBS items in economic analyses. In addition, the dosage split for nafarelin proposed in the pre-PBAC appeared to be based on use of item 2962X (for endometriosis) and item 5815C (for assisted reproductive technology). This may overestimate use of the higher dose, however the assumption of 57% use of the higher dose was conservative.
- 6.69 The PBAC requested recalculation of the comparison table using a 12-month comparison of Ryego with sequential use of 6 months goserelin + add-back and

6 months nafarelin + add-back, as a frame of reference. The PBAC considered it would be reasonable for the nafarelin dose to be split between 57% at 200 mcg twice daily and 43% at 400 mcg twice daily using PBS item code 2962X (nafarelin for endometriosis) with increased maximum quantity of 2 packs. There should be one BMD scan for the comparators as patients would require it after treatment with goserelin and before nafarelin (or vice versa). The revised PBAC cost comparison is presented below.

Table 9: Updated comparison of DPMQs for Ryego vs goserelin and nafarelin (plus add-back therapy)

Component	Ryego FDC	Goserelin	Nafarelin (400 mcg)	Nafarelin (800 mcg)	Add-back therapy (Assuming 50/50 split of the below)	
					Levonorgestrel 100 mcg + ethinylestradiol 20 mcg ^a	Norethisterone 350 mcg ^b
PBS item code	-	1454M	2962X	2962X	2416E	1967M
PBS item (max qty)	tablets (28)	implant (1)	Nasal spray 200 mcg (60 actuations)	Nasal spray 200 mcg (120 actuations)	Tablets (4x28)	Tables (4x28)
Treatment duration per max qty	28 days	28 days	30 days	30 days	112 days	112 days
DPMQ	\$█	\$212.70	\$123.83	\$221.77	\$19.10	\$18.97
Cost per 28 days	\$█	\$212.70	\$115.57	\$206.99	\$4.78	\$4.74
					Average: \$4.76	
Cost per 6 months (inc. add-back)	\$█	\$1,418.34	\$784.86	\$1,381.07		
Cost of BMD testing yr 1 (MBS item 12321 Fee: \$112.70)	\$112.70	\$0.00	\$112.70	\$112.70		
Cost of implant administration over 6 months (MBS item 14206 \$39.20 + MBS item 23 \$41.40)	\$0.00	\$525.70	\$0.00	\$0.00		
12 months medicine costs: 12 months Ryego vs 6 months goserelin + 6 months nafarelin ^a incl add-back	\$█ (\$█ x 2)	\$2,459.57 (\$1,418.34 + 0.57 x \$784.86 + 0.43 x \$1381.07)				
As above, incl BMD testing and implantation	\$█ (\$█ + \$112.70)	\$3,097.97 (\$2459.57 + \$525.70 + \$112.70)				
Difference in cost over 1 year	-\$█					

Source: calculated by the secretariat

^a Nafarelin cost assumes 57% at 200 mcg twice daily and 43% at 400 mcg twice daily

Drug cost/patient/year

- 6.70 The submission estimated that the drug cost for Ryego would be \$ [REDACTED] per year assuming 100% compliance for the economic analysis (see Table 9). The financial estimates assumed compliance of 80% for Ryego and 95% for goserelin and nafarelin.

Estimated PBS usage & financial implications

- 6.71 This submission was considered by DUSC.
- 6.72 The submission estimated the financial implications of the proposed listing using an epidemiological approach for a cohort of women aged 30-55 years with cumulative prevalence of endometriosis based on the Australian Longitudinal Study of Women's Health (ALSWH) 2020. There was no age limit in the requested restriction (although the approved TGA indication is limited to adult women of reproductive age, given lack of clinical evidence in patients aged <18 years). DUSC considered limiting the eligible population to those aged between 30 to 55 years in the financial estimates was not appropriate as it would substantially underestimate the patient population and advised that the eligible population should be revised to those aged 18 years or over. The revised financial estimates provided in the pre-PBAC response revised the eligible population to patients aged 18-55 years.
- 6.73 All Ryego patients were assumed to receive Ryego treatment for one year. The evaluation and DUSC considered this is likely to underestimate use of Ryego in practice, as patients may receive treatment for longer than 12 months. The requested restriction did not include a maximum duration of treatment and the approved PI recommends use is limited to 24 months, "with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician". The revised estimates provided in the pre-PBAC response revised the duration of therapy to 2 years.
- 6.74 The submission assumed patients who failed or had inadequate response to prior first-line treatments would receive Ryego and Ryego would substitute for hormonal treatments and pain relievers currently available on the PBS, namely: goserelin, progesterone, norethisterone, medroxyprogesterone acetate, levonorgestrel-releasing IUD, ibuprofen, codeine with paracetamol, tramadol.
- 6.75 In the context of a fixed dose combination product, Ryego would likely replace various GnRH treatments with concomitant add-back (E2/NETA) therapy. The submission's financial estimates only considered use of goserelin in 5% of patients, and there were errors in the estimates that underestimated the number of scripts per patient for goserelin. The Commentary considered that in practice, it is unlikely that Ryego would replace GnRH treatment alone or BSC (contraceptive) alone in patients who would otherwise not initiate GnRH therapy. An additional sensitivity analysis was conducted during the evaluation to estimate the financial implications of the current treatment on the PBS with GnRH + add-back therapy for 12 months (goserelin + ABT for 6 months then switch to nafarelin + ABT for 6 months) versus the proposed use on the PBS with

Ryeqo for 24 months. This approach was also adopted in the revised estimates provided in the pre-PBAC response.

6.76 The key inputs in the financial analysis are summarised in Table 10.

Table 10: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible population		
Australian women aged 30-55 years	Yr 1 (2025): 4,887,999 Yr 2: 4,954,018 Yr 3: 5,009,034 Yr 4: 5,067,391 Yr 5: 5,132,250 Yr 6: 5,201,938 ABS, Population Projections, Australia, 2017 (projecting population growth from 2025)	Underestimated, as the submission assumed only women aged 30-55 years would be eligible for treatment. The proposed TGA indication is for adult women of reproductive age. The SPIRIT trials of Ryeqo enrolled premenopausal women aged ≥18 years. The submission used an older ABS population projection (2017), which is slightly higher than the updated ABS projections (November 2023).
Proportion diagnosed with endometriosis	14% (diagnosed by age 44-49 years) ALSWH (Rowlands 2021 and AIHW Endometriosis web report 2023)	Uncertain. ALSWH data showed that the incidence and prevalence of endometriosis varies with age. Cumulative prevalence of clinically confirmed and suspected endometriosis in women born between 1973-78 was shown to increase from 0.92% in patients aged 20-24 years, 4.04% in 25-29 years, 6.95% in 30-34 years, 9.60% in 35-39 years and 11.44% in 40-44 years. Further, a higher proportion of women in a younger cohort (born 1989-95) were estimated to be diagnosed with endometriosis by age 31 (i.e. 9.2% vs 6.9% born in 1973-78), due to increased awareness and diagnosis. DUSC considered the data source to be reasonable, however due to increase in societal awareness and differences in clinical practice of endometriosis compared to the past, this parameter is likely underestimated. DUSC also noted the risk of overdiagnosis as the pain experienced by patients may not be due to endometriosis.
Proportion with moderate to severe pain	30% Survey of Australian gynaecologists (N=12; Attachment 'E01 Australian clinician survey results')	The survey estimated 50% (from 7 clinicians) and 30% (3 clinicians) of patients with endometriosis had moderate to severe pain. The submission assumed that gynaecologists' perceptions would be skewed towards estimating a higher proportion and used 30% in the base case. DUSC considered this parameter to be underestimated given pain is one of the main symptoms of endometriosis. The revised estimates provided with the pre-PBAC response revised this input to 50%.
Proportion failed or have inadequate first line treatment	Yr 1: █% Yr 2: █% Yr 3: █% Yr 4: █% Yr 5: █% Yr 6: █% Assumption	The submission assumed annual █% proportional increase on the prevalent patients who failed or have inadequate response to first-line treatment and would be eligible for Ryeqo. The submission did not provide a rationale for the annual increase in patients failing prior treatments. DUSC considered this assumption was underestimated given endometriosis treatment is characterised by multiple options, each with short effectiveness duration. DUSC noted the wide range of diagnostic variability and surgical skills in clinical practice and commented that patients treated by non-specialists may be more likely to fail or have inadequate first-line treatment.

Public Summary Document - March 2024 PBAC Meeting

Parameter	Value applied and source		Comment
Treatment utilisation			
Uptake rate of Ryeqo	Yr 1: █ % Yr 2: █ % Yr 3: █ % Yr 4: █ % Yr 5: █ % Yr 6: █ % Assumed from a survey of Australian gynaecologists (N=30; Research Partnership Inizio Advisory, 2023)		The uptake rate was assumed from the proportion (█ %) of patients expected to use Ryeqo from the share of other treatment modalities currently prescribed including hormonal combined contraceptives and GnRH analogues. However, the same survey also reported that the majority (█ %) of Australian gynaecologists were highly likely to prescribe Ryeqo. DUSC noted this assumption was aligned with international uptake rates. However, DUSC considered uptake rates were underestimated given the short effectiveness duration for treatments for endometriosis. The PBAC considered these uptake rates too high for a prevalent pool of patients noting that the cumulative uptake exceeds █ %.
Ryeqo compliance	80% Assumption		Underestimated. Overall compliance in the SPIRIT trials was high 97.4-99% for Ryeqo group to Week 24 and cumulative compliance >98% in all treatment groups to Week 104 in SPIRIT Extension. This assumption was also inconsistent with the modelled economic evaluation, which assumed 100% compliance for Ryeqo. DUSC considered compliance could be high due to the ease of administration and a highly motivated eligible population. However, DUSC considered compliance could also be lower in clinical practice where patients are non-responsive to treatment because the cause of pain is not endometriosis.
Ryeqo scripts per year per patient	10.43 Calculated, taking into account assumed compliance, assuming one year of treatment		The assumption of one year of Ryeqo treatment may not be reasonable given that the requested restriction did not include a response criteria for continued use and a maximum duration of treatment. DUSC agreed with the commentary and considered this parameter to be underestimated.
Scripts per year per patient (PBS drugs)	Drug	Scripts/yr	The scripts per year for goserelin were underestimated and therefore cost offsets in the model were underestimated. The PBAC noted that this was revised in the revised estimated provided with the pre-PBAC response. Other errors due to data input, were identified in the calculation of scripts per patient per year for progesterone, levonorgestrel IUD and ibuprofen. DUSC noted the included medicines are used for a variety of indications and commented on the uncertainty regarding the proposed market for Ryeqo and the drugs to be displaced.
	Goserelin	0.03	
	Progesterone	19.47	
	Norethisterone	2.61	
	Medroxyprogesterone acetate	29.20	
	Levonorgestrel IUD	0.0005	
	Ibuprofen	9.73	
	Codeine	58.4	
	Codeine with paracetamol	58.4	
	Tramadol	58.4	
Calculated, taking into account assumed compliance.			

Parameter	Value applied and source		Comment
Substituted PBS drugs: % of comparator market	Drug	Market share	Inappropriately, the assumed drugs did not include an estrogen component, to account for combination contraceptives, similarly to the economic evaluation. These market shares are inconsistent with the economic model which assumed equal distribution of BSC patients amongst progesterone, norethisterone, medroxyprogesterone acetate and levonorgestrel-releasing IUD. The submission also inappropriately excluded nafarelin from the financial model. DUSC agreed with the commentary that this parameter would require revision to be consistent with the economic model. The financial model estimated that more than half of the endometriosis market was on codeine with paracetamol, and only 5% on goserelin. It was unclear whether the estimated market reflects patients with moderate to severe pain, and whether such a large estimated proportion of patients would be on codeine with paracetamol. The PBAC noted that this was revised in the estimated provided with the pre-PBAC response.
	Goserelin	%	
	Progesterone	%	
	Norethisterone	%	
	Medroxyprogesterone acetate	%	
	Levonorgestrel IUD	%	
	Ibuprofen	%	
	Codeine	%	
	Codeine with paracetamol	%	
	Tramadol	%	

Source: compiled during the evaluation.

AIHW=Australian Institute of Health and Welfare; ALSWH=Australian Longitudinal Study on Women's Health; DPMQ=dispensed price for maximum quantity; Endo=endometriosis; GnRH=gonadotropin hormone-releasing hormone; IUD=intra-uterine device; MBS=Medicare Benefits Schedule; PBS=Pharmaceutical Benefits Scheme; RPBS=Repatriation Pharmaceutical Benefits Scheme, Yr=year

6.77 The predicted use of Ryego and financial implications associated with the proposed listing as presented in the submission are summarised in Table 11.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	2	2	2	3	3
Number of scripts dispensed ^a	4	4	4	5	5	5
Estimated financial implications of Ryego						
Cost to PBS/RPBS less copayments	\$6	\$7	\$8	\$8	\$9	\$9
Estimated financial implications for other PBS drugs^b						
Impact to PBS/RPBS less copayments	-\$11	-\$11	-\$11	-\$11	-\$11	-\$11
Net financial implications						
Net cost to PBS/RPBS	\$10	\$6	\$7	\$7	\$7	\$8

Source: Tables 4.2.1-4.4.1, pp.257-261 of the submission.

^a Assuming 10.43 scripts per year as estimated by the submission.

^b Assumed goserelin, progesterone, norethisterone, medroxyprogesterone, levonorgestrel IUD, ibuprofen, codeine, codeine with paracetamol, tramadol.

The redacted values correspond to the following ranges:

¹ 10,000 to < 20,000

² 20,000 to < 30,000

³ 30,000 to < 40,000

⁴ 200,000 to < 300,000

⁵ 300,000 to < 400,000

⁶ \$30 million to < \$40 million

⁷ \$40 million to < \$50 million

⁸ \$50 million to < \$60 million

⁹ \$60 million to < \$70 million

¹⁰ \$20 million to < \$30 million

¹¹ net cost saving

6.78 The pre-PBAC response revised predicted use of Ryego and financial implications associated with the proposed listing are summarised in Table 12. The revisions to these estimates are:

- including all patients aged 18-55
- assuming 50% of patients have moderate-severe pain
- assuming patients are treated with Ryego for 2 years (with the cost of 2 years of treatment applied in the initial year of treatment)
- assuming offsets for 100% of patients treated with goserelin + add-back for 6 months, followed by nafarelin + add-back for a further 6 months.
- corrections to errors identified in add-back therapy and scripts per patient per year for goserelin.

Table 12: Estimated use and financial implications – pre-PBAC response

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	I ¹	I ²	I ³	I ⁴	I ⁴	I ⁵
Number of scripts dispensed ^a	I ⁶	I ⁷	I ⁷	I ⁷	I ⁷	I ⁷
Estimated financial implications of Ryego						
Cost to PBS/RPBS less copayments	\$I ⁸	\$I ⁹	\$I ⁹	\$I ⁹	\$I ¹⁰	\$I ¹⁰
Estimated financial implications for other PBS drugs						
Impact to PBS/RPBS less copayments	-\$I ¹¹	-\$I ¹¹	-\$I ¹¹	-\$I ¹¹	-\$I ¹¹	-\$I ¹¹
Net financial implications						
Net cost to PBS/RPBS	\$I ⁸	\$I ⁸	\$I ⁸	\$I ⁸	\$I ⁸	\$I ⁸

Source: Pre-PBAC response

The redacted values correspond to the following ranges:

¹ 40,000 to < 50,000

² 50,000 to < 60,000

³ 60,000 to < 70,000

⁴ 70,000 to < 80,000

⁵ 80,000 to < 90,000

⁶ 900,000 to < 1,000,000

⁷ 1,000,000 to < 2,000,000

⁸ \$100 million to < \$200 million

⁹ \$200 million to < \$300 million

¹⁰ \$300 million to < \$400 million

¹¹ net cost saving

6.79 The pre-PBAC revised total net cost to the PBS/RPBS of listing Ryego was estimated to be \$100 million to < \$200 million in Year 6, and a total of \$800 million to < \$900 million in the first 6 years of listing.

6.80 The PBAC considered the financial estimates as provided in the pre-PBAC response were substantially overestimated. At PBAC's request, additional revisions to the pre-PBAC response were made to adjust for the following:

- The assumption that 50% of patients have moderate-severe pain, was revised back to 30% as per the original submission. The PBAC considered this estimate was uncertain and the increase was not well-justified. The PBAC agreed with the submission that gynaecologists' perceptions would be skewed towards estimating a higher proportion.
 - The PBAC requested a revised prevalence of 12% to better reflect prevalence in the broader age group as there is evidence that the prevalence rate is lower in younger patients and the assumption of 14% was based on the 44-49 age group. AIHW cites the results of a US online survey (Fuldeore & Soliman 2017) reporting a prevalence of diagnosed endometriosis of 6.1% in patients aged 18-49.
 - The uptake assumptions in the submission were based on the global market research survey based on patients aged 30-55. Prescribing of Ryeqo would be expected to be lower in younger patients, which would reduce the overall treatment uptake. In addition, the PBAC noted that the uptake rates were applied to the prevalent population such that the cumulative uptake by year 6 was greater than 100%. The PBAC considered that the cumulative uptake over 6 years would be no higher than 100% of eligible patients. The PBAC considered uptake assumptions should be revised as shown in the table below.
 - The estimates applied a treatment duration of 2 years to all patients, including in the first year of treatment. This would overestimate the utilisation in year 1 and should be corrected.
- 6.81 Revised estimates using the PBAC requested revisions resulted in the forward estimates as shown in Table 13. The revised total cost to the PBS/RPBS of listing Ryeqo (without offsets or BMD testing costs) was estimated to be \$20 million to < \$30 million in Year 6, and a total of \$100 million to < \$200 million in the first 6 years of listing.

Table 13: Estimated use and financial implications – PBAC requested revisions

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Uptake estimates						
Submission	%	%	%	%	%	%
PBAC revised	%	%	%	%	%	%
PBAC cumulative uptake	%	%	%	%	%	%
Estimated extent of use						
Number of patients initiating treatment	1	1	1	1	1	1
Total patients treated	1	2	2	2	2	2
Number of scripts dispensed	3	3	3	3	3	3
Estimated financial implications of Ryego						
Cost to PBS/RPBS less copayments	\$4	\$5	\$5	\$5	\$5	\$6
Estimated financial implications for other PBS drugs						
Impact to PBS/RPBS less copayments (indicative)	-\$3	-\$3	-\$3	-\$3	-\$3	-\$3
Net financial implications						
Net cost to PBS/RPBS (indicative)	\$7	\$6	\$6	\$6	\$4	\$4

Source: Pre-PBAC response, with revised assumptions as noted above.

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 10,000 to < 20,000

³ 100,000 to < 200,000

⁴ \$10 million to < \$20 million

⁵ \$30 million to < \$40 million

⁶ \$20 million to < \$30 million

⁷ \$0 to < \$10 million

⁸ net cost saving

- 6.82 The PBAC noted that the cost offsets for nafarelin and goserelin in the pre-PBAC revised estimates appear substantially overestimated and implausible based on the current PBS utilisation of these medicines, although corrections to the utilisation, as noted above, substantially reduced the cost offsets. Although the Commentary considered that it is unlikely that Ryego would replace GnRH treatment alone or BSC (contraceptive) alone in patients who would otherwise not initiate GnRH therapy, the PBAC considered as an FDC with add-back therapy, available in an oral form, it is expected Ryego may be more widely used than currently available therapies. The PBAC considered the offsets should be reduced to be consistent with the current PBS usage of GnRH therapy for endometriosis and hence to account for additional patients accessing treatment.
- 6.83 The PI recommends that clinicians perform a dual X-ray absorptiometry (DXA) scan before commencing treatment and one year after commencing treatment in at risk patients. DUSC considered the financial implications associated with ongoing BMD monitoring to be uncertain. The submission did not include any assessment of costs to the MBS in the financial estimates.

- 6.84 The PBAC noted that there remain substantial uncertainties, specifically:
- The duration of Ryeqo treatment (treatment was assumed to be 2 years in the revised estimates).
 - A high level of uncertainty in the prevalence of moderate-severe pain associated with endometriosis and in the uptake rates for Ryeqo.
 - Multiple errors were identified in the inputs for scripts per year, DPMQs and pack sizes for substituted PBS drugs. Some errors were fixed by the evaluators, however errors in some substituted treatments may remain. The PBAC considered these errors should be corrected, however noted the errors were unlikely to substantially impact the overall estimates as they were a small proportion of the total cost.
- 6.85 Overall, the estimated costs to the PBS/RPBS were uncertain. The DUSC considered that the submission underestimated the financial impact of listing Ryeqo, however the in the revised estimates provided in the pre-PBAC response the total cost was more than 1 times that in the submission estimates. The PBAC considered that the revised estimates as shown in Table 13 provided the best estimate of the costs for listing for Ryeqo, but noted that offsets and the cost of BMD monitoring would need to be revised and corrected to give a more accurate estimate of the net financial impact of listing Ryeqo.

Quality Use of Medicines

- 6.86 No quality use of medicines issues were identified in the submission and no QUM activities were proposed in the submission. DUSC commented that patients should understand the implications of BMD loss before initiating Ryeqo treatment.
- 6.87 DUSC also noted the submission did not propose a treatment pathway for patients following 24 months of Ryeqo treatment, given Ryeqo only manages the symptoms of pain.

Financial Management – Risk Sharing Arrangements

- 6.88 The Sponsor indicated willingness to work with the Department of Health and Aged Care on finalising annual financial thresholds.

Options to present additional relevant information

- 6.89 The submission discussed out-of-pocket expenses in endometriosis. A 2017 survey of 407 women with endometriosis or chronic pelvic pain without a diagnosis of endometriosis, found that around 30% of the total health costs incurred, were out-of-pocket expenses (Armour et al. 2019).
- 6.90 The submission also discussed the potential for opioid dependency. Opioid based pain medication may have abuse liability and could lead to opioid dependencies. The submission summarised health impacts (health problems, opioid overdoses and

mortality) and social impacts of opioid dependency. Hence, an opioid sparing regimen in pain management is therefore desirable.

- 6.91 The submission showed that in SPIRIT 1, the proportion of Ryego and REL with delayed ABT patients not using opioids increased from 70% and 69%, respectively, at baseline to 86% and 83%, respectively, at 24 weeks, whilst in SPIRIT 2, the proportion of Ryego patients not using opioids decreased slightly from baseline to 24 weeks. In SPIRIT 2, the proportion of placebo patients not using opioids decreased from 76% at baseline to 66% at 24 weeks, whilst in SPIRIT 1, the proportion of placebo patients not using opioids increased slightly from baseline to 24 weeks.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of relugolix with estradiol and with norethisterone acetate (Ryego), on the basis that it should be available as a General Schedule Authority Required (STREAMLINED) listing for the treatment of moderate to severe pain associated with endometriosis in women who have failed to gain adequate pain relief from hormonal treatments and analgesics. The PBAC's recommendation for listing was based on its assessment that the cost-effectiveness of Ryego would be acceptable if it were no more costly over a 12-month period than 12 months of GnRH therapy (plus add-back therapy) as currently supplied through the PBS. The PBAC noted based on current PBS restrictions that GnRH therapy is available as 6 months of goserelin and 6 months of nafarelin. The PBAC acknowledged that Ryego would be used on average for more than 12 months and considered the cost calculated for the first 12 months of therapy provides an appropriate frame of reference for the cost of therapy beyond 12 months. The PBAC noted that based on the proposed price, the cost of Ryego, including BMD monitoring and goserelin implantation costs, was lower over 12 months than the comparator costs and was therefore considered cost-effective (see Table 9).
- 7.2 The PBAC considered that the listing of Ryego, as a fixed dose combination (FDC), with the potential for ongoing treatment for 2 years or longer, is likely to result in a substantial net cost to the PBS as it would be used for longer than the existing therapies. The PBAC considered that the financial estimates had a high level of uncertainty due to uncertain prevalence and uptake estimates but considered that the revised estimates presented in the pre-PBAC response were substantially overestimated. The PBAC advised that additional revisions to prevalence and uptake were required as well as a risk sharing arrangement (RSA) with % caps to manage the uncertainties in the financial estimates.
- 7.3 The PBAC considered there was a moderate clinical need for an additional GnRH therapy in this treatment space, and considering it is a FDC with add-back therapy, available in an oral form, it is expected Ryego may be more widely used than currently available therapies. Consumers noted that Ryego may be better tolerated than

alternative GnRH treatments and can be used for longer. The PBAC noted the support from consumers and clinicians for subsidised access to this treatment option (see paragraphs 6.1 and 6.2).

- 7.4 The PBAC noted that there were significant safety concerns regarding bone mineral density (BMD) loss, particularly for younger women, and where patients receive ongoing treatment with GnRH therapy, including Ryeqo, for more than 1–2 years. The PBAC noted this could be monitored for at-risk patients using dual energy X-ray absorptiometry (DXA) scans for BMD testing. The PBAC noted and was reassured by the additional follow up data provided in the pre-PBAC response which showed BMD recovery of the lumbar spine after discontinuing 104 weeks of treatment (see paragraph 6.47). The PBAC noted the sponsor hearing proposed older patients nearing menopause would be most suited for treatment with Ryeqo. However, the PBAC remained concerned about potential BMD loss in the younger cohort of patients who had not reached peak bone mass (patients up to 40 years of age) and it was considered appropriate to include a criterion in the restriction for access to Ryeqo requiring a BMD scan for patients up to 40 years of age following the first course of treatment. It was noted these patients would be covered by MBS Item 12312 under condition (d) (see paragraph 3.9). The PBAC advised that female hypogonadism after 6 months treatment would be met and that only patients up to the age of 40 would require this level of monitoring, if no other risk factors were present. The PBAC also considered the additional proposed prescriber instruction in the pre-PBAC response would be appropriate to ensure prescribers are aware of the risk of BMD loss: “A DXA scan is recommended at baseline, after the first 52 weeks of treatment, and annually thereafter”.
- 7.5 The PBAC confirmed that an Authority Required (STREAMLINED) listing was appropriate. The PBAC also advised the following additional amendments to the proposed restriction:
- A prescriber instruction that describes the recommended duration of treatment: “Use is recommended to be limited to 24 months, with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician”.
 - A population criterion specifying that “Patient must be aged 18 years or older”.
 - The prescriber type be specified as “Must be treated by a specialist medical practitioner with experience in the diagnosis and management of endometriosis” rather than “Must be treated by a gynaecologist”.
- 7.6 The PBAC noted that for current treatment options, the Australian and international guidelines generally recommend up to 12–24 months of treatment with a GnRH analogue + add-back regimen (see paragraph 5.4). The PBAC considered the nominated main comparator of goserelin + add-back therapy was appropriate, noting that all GnRH analogues can be considered equally effective, as could all add-back

therapies (see paragraph 6.54). The PBAC did not consider GnRH monotherapy to be a relevant comparator. The PBAC also did not consider BSC (after GnRH + add-back treatment), defined as contraceptive therapies, was a relevant comparator given the expected duration of use of a GnRH analogue + add-back was up to 24 months. It was considered current PBS limitations on duration of use of goserelin and nafarelin did not exclude private use up to 24 months with the addition of add-back therapy, and thus GnRH + add-back was the appropriate main comparator for the expected duration of Ryeqo use. The PBAC noted that PBS listings for goserelin and nafarelin reflect the clinical algorithm at the time they were listed, prior to recommendations that they should be used in combination with add-back therapy (see also Section 4). The PBAC considered that changes to these restrictions to align with clinical practice may be required, and would welcome a submission.

- 7.7 The PBAC noted there were no head-to-head trial data for the main comparator (goserelin + add back) and that the main evidence presented in the submission used a linked approach based on the comparison of relugolix (concomitant and delayed add-back) vs placebo from SPIRIT 1 and SPIRIT 2 and relugolix vs leuprorelin (a GnRH agonist) from TAK-385/3-A (Harada et al 2022). The PBAC also noted the open-label extension study (SPIRIT Extension) of Ryeqo included an addendum of the 1-year post-treatment follow-up (PTFU) on BMD outcomes.
- 7.8 The PBAC noted across SPIRIT 1 and SPIRIT 2, the proportion of dysmenorrhoea responders (reduction from baseline in dysmenorrhoea NRS score ≥ 2.8) and NMPP responders (reduction from baseline in NMPP NRS ≥ 2.1), was significantly higher in the Ryeqo group compared to placebo at Week 24 (see Table 4 and Figure 1). In the pooled SPIRIT 1/SPIRIT 2 analyses at Week 24, the risk difference (RD) between Ryeqo vs placebo treated patients for dysmenorrhoea response was 74.8% vs 28.6%, RD = 46.2, 95%CI: 40.2, 52.2 and NMPP response was 62.1% vs 41.0%, RD = 21.1, 95%CI: 14.4, 27.7.
- 7.9 The PBAC noted the comparison of relugolix vs leuprorelin (Harada 2022) supported overall non-inferiority based on the non-inferiority margins for the VAS score for pelvic pain (see paragraph 6.30).
- 7.10 The PBAC noted the comparative safety data from Spirit 1 and 2 showed adverse events with Ryeqo were generally similar to placebo (see Table 6). The PBAC noted that the loss of BMD over 24 weeks treatment was generally greater with delayed add-back than Ryeqo FDC (see Table 7). As noted above in paragraph 7.4, the PBAC was reassured that data from the PTFU from the SPIRIT Extension study suggested stabilisation with some recovery of bone mineral loss following 104 weeks treatment.
- 7.11 The PBAC considered that overall, for the comparison of Ryeqo with GnRH + add-back, the clinical claim of non-inferior comparative effectiveness and safety was reasonably supported by the indirect evidence presented in the submission. The PBAC acknowledged that this relies on the assumptions that all GnRH therapies are comparable in terms of efficacy and safety in the treatment of endometriosis pain and

all contraceptive therapies are comparable when used for endometriosis, but considered that this conclusion was reasonable.

- 7.12 The PBAC agreed with the ESC that the economic model presented was not informative for decision-making. The PBAC proposed that the comparison of costs as updated in the pre-PBAC response, in Table 8, presented a way forward using the cost of current GnRH therapies + add-back as a frame of reference. The PBAC noted the revised comparison table presented in Table 9 represented a basis on which PBAC could be confident that the cost of therapy with Ryeqo over the first 12 months of treatment would be no more costly than current GnRH + add-back therapies used sequentially. The PBAC acknowledged that Ryeqo would likely be used on average for more than 12 months and considered the cost calculated for the first 12 months of therapy provides an appropriate frame of reference for the cost of therapy beyond 12 months.
- 7.13 The PBAC noted the DUSC advice that the financial implications were uncertain and underestimated due to the assumptions of age, diagnosis rate, the proportion of patients with moderate to severe pain and duration of use. The PBAC noted the pre-PBAC response addressed the issues raised by DUSC and substantially increased the estimated financial implications over 6 years (see Table 12). However, the PBAC considered that prevalence would be lower in the age group from 18-30 years of age and should be reduced from 14% to 12%. The PBAC noted that the uptake rates were applied to the prevalent population such that the cumulative uptake by year 6 was greater than 100%. The PBAC considered that the cumulative uptake over 6 years would be no higher than 100% of eligible patients. In addition, the PBAC considered that the assumption that 50% of patients have moderate-severe pain, should be revised back to 30% as per the original submission. The PBAC also noted that a treatment duration of 2 years was applied to all patients in the first year of listing and considered that this should be corrected. The PBAC noted these revisions would reduce the revised estimates (see Table 13 – PBAC requested revisions).
- 7.14 The PBAC considered that there were further revisions to the estimates required to estimate the net cost associated with listing Ryeqo. The PBAC noted that the cost offsets for nafarelin and goserelin, assuming 100% of patients receive 6 months of treatment with each, appear substantially overestimated and implausible based on the current PBS utilisation of these medicines. Although the Commentary considered that it is unlikely that Ryeqo would replace GnRH treatment alone or BSC (contraceptive) alone in patients who would otherwise not initiate GnRH therapy, the PBAC considered as an FDC with add-back therapy, available in an oral form, it is expected Ryeqo may be more widely used than currently available therapies. The PBAC considered the offsets should be reduced to be consistent with the current PBS usage of GnRH therapy for endometriosis and hence to account for additional patients accessing treatment. The PBAC also noted that BMD costs were excluded from the estimates, and advised that costs for annual testing of patients up to 40 years of age, while on treatment, should be included.

- 7.15 The PBAC noted that there was a considerable degree of uncertainty regarding the estimated uptake and treatment duration for Ryeqo. The PBAC considered there was also uncertainty regarding the safety and cost-effectiveness for ongoing treatment with Ryeqo as the clinical data were limited to 2 years of treatment. The PBAC considered that to address these uncertainties a risk sharing arrangement is required with 10% rebate for use over the caps, based on revised estimates in Table 13.
- 7.16 The PBAC considered Ryeqo is not suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements, consistent with other GnRH agonists.
- 7.17 Ryeqo should not be exempt from the Early Supply Rule as it currently applies to GnRH agonists such as goserelin.
- 7.18 The PBAC recommended that Ryeqo should not be treated as interchangeable on an individual patient basis with any other drugs, according to s101(3BA) of the National Health Act.
- 7.19 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for Ryeqo:
- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over alternative therapies;
 - b) The treatment is not expected to address a high and urgent unmet clinical need due to availability of other treatments;
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.20 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RELUGOLIX + OESTRADIOL (AS HEMIHYDRATE) + NORETHISTERONE					
relugolix 40 mg + oestradiol (as hemihydrate) 1 mg + norethisterone 0.5 mg tablet, 28	NEW	1	28	5	Ryeqo
Restriction Summary [new 1] / Treatment of Concept: [new 2]					
	Category / Program: GENERAL – General Schedule				
	Prescriber type: ☒ Medical Practitioners				
	Restriction type: ☒ Authority Required (Streamlined)				
	Indication: Endometriosis				
	Treatment Phase: Initial treatment				
	Clinical criteria:				
	Patient must have experienced moderate to severe pain associated with endometriosis.				
	Clinical criteria				
	The condition must be visually proven				
	AND				
	Clinical criteria:				
	Patient must have received an inadequate response to, or be intolerant to, previous first line therapies for this condition, including at least one of the following: (i) hormonal contraceptives, (ii) analgesics				
	Clinical criteria:				
	Patient must not have undergone surgery for this condition in the last 3 months; OR				
	Patient must not commence this treatment until 3 months post-surgery				
	AND				
	Clinical criteria:				
	Patient must not have a history of, nor currently have any of the following: (i) osteoporosis, (ii) risk of other metabolic bone disease.				
	Treatment criteria:				
	Must be treated by a specialist medical practitioner with experience in the diagnosis and management of endometriosis				
	Population criteria:				
	Patient must be pre-menopausal				
	AND				
	Population criteria:				
	Patient must be at least 18 years of age				
	Caution: Ryeqo should not be used interchangeably with other GnRH agonists and/or hormonal contraceptives brands due to differences in dose and schedule of treatment				
	Prescribing instructions: Assessment of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) is recommended at baseline, after the first 52 weeks of treatment, and annually thereafter. Depending on the degree of change in BMD, the benefit and risks of Ryeqo may need to be reconsidered. Use is recommended to be limited to 24 months, with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician.				

Restriction Summary [new 1] / Treatment of Concept: [new 2]	
	Category / Program: GENERAL – General Schedule
	Prescriber type: ☒ Medical Practitioners
	Restriction type: ☒ Authority Required (Streamlined)
	Indication: Endometriosis
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not have undergone surgery for this condition in the last 3 months
	AND
	Clinical criteria:
	Patient must not have a history of, nor currently have any of the following: (i) osteoporosis, (ii) risk of other metabolic bone disease.
	Treatment criteria
	Must be treated by a specialist medical practitioner with experience in the diagnosis and management of endometriosis
	Population criteria:
	Patient must be pre-menopausal
	Caution: Ryego should not be used interchangeably with other GnRH agonists and/or hormonal contraceptives brands due to differences in dose and schedule of treatment
	Prescribing instructions: The prescriber must only request for this treatment phase for the patient if ongoing treatment with this drug is likely to result in an adequate response.
	Prescribing instructions: Details of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) for continuing treatment beyond 6 months if under 41 years of age must be documented in the patient's medical record.
	Prescribing instructions: Assessment of bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) is recommended at baseline, after the first 52 weeks of treatment, and annually thereafter. Depending on the degree of change in BMD, the benefit and risks of Ryego may need to be reconsidered. Use is recommended to be limited to 24 months, with extension of therapy conditional on stability of DXA and reassessment of risk/benefit in the individual patient by the treating physician.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.

11 Corrigendum

The following changes were made:

Change made	Date of revision
Paragraph 7.16: change to recommendation regarding nurse practitioner prescribing.	31/7/2024
Paragraph 8.1: change to prescriber type to remove nurse practitioners and related administrative advice.	31/7/2024