NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
JUNE 2021

Relugolix combination therapy for treating endometriosis-associated pain

NIHRIO ID	20496	**NICE ID**	10597
Developer/Company	Gideon Richer UK Ltd	**UKPS ID**	658466

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Relugolix in combination with estradiol and norethindrone is currently in clinical development for the treatment of endometriosis-associated pain. Endometriosis is a common, long-term gynaecological disorder where the tissue that normally lines the womb (endometrium) grows in other places. When this tissue breaks down as part of the normal menstrual cycle it becomes trapped in a woman's pelvis. This can negatively impact the quality of life for women with the disease, as it results in painful periods (dysmenorrhea) and other endometriosis-associated pain. Currently there are no medicinal products approved specifically to cure endometriosis with most treatments directed at reducing the pain and reducing the severity of other associated symptoms.

Relugolix is co-administered with estradiol and norethindrone in the form of an oral tablet. Relugolix works by selectively binding to the gonadotrophin-releasing hormone (GnRH) receptor to block luteinizing hormone (LH) and follicle stimulating hormone (FSH) from binding to this receptor. This results in less production and release of oestrogen and progesterone by the ovaries so that menstruation is reduced. If licenced, relugolix combination therapy would be the first GnRH antagonist approved for the treatment of endometriosis-associated pain.

PROPOSED INDICATION

Treatment of adult women with endometriosis-associated pain.[1,2]

TECHNOLOGY

DESCRIPTION

Relugolix combination tablet consists of relugolix (TAK-385) and estradiol/norethindrone acetate.[3] Relugolix is an orally available, non-peptide gonadotropin-releasing hormone (GnRH) antagonist, with potential antineoplastic activity. Relugolix competitively binds to and blocks the GnRH binding to the GnRH receptor.[4] This inhibits the secretion and release of both luteinizing hormone (LH) and follicle stimulating hormone (FSH), thereby decreasing the downstream production of oestrogen and progesterone by the ovaries.[3,4] As a result, relugolix decreases blood concentrations of oestrogen and progesterone within days and induces amenorrhoea.[5]

In the phase III clinical trials SPIRIT 1 (NCT03204318) and SPIRIT 2 (NCT03204331) participants receive relugolix 40mg tablet by oral administration, once daily, co-administered with estradiol (1.0mg) and norethindrone acetate (0.5mg) for 24 weeks.[1,2] In the SPIRIT extension clinical trial (NCT03654274) participants receive the same intervention for up to 104 weeks.[6]

INNOVATION AND/OR ADVANTAGES

Currently there are no GnRH antagonists recommended by NICE for the treatment of endometriosis-associated pain.[7] GnRH antagonists do not cause clinical flares and have a faster onset of action than GnRH agonists. Furthermore, because of its oral formulation and half-life, relugolix allows a faster recovery of normal hormonal levels and menstruation after discontinuation of treatment, leading to a more rapid recovery of fertility than the injectable depot formulations of GnRH agonists.[5,8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Relugolix does not currently have a Marketing Authorisation in the EU/UK for any indication.

Relugolix is also in phase II and/or III clinical development for contraception against pregnancy, uterine fibroids, heavy menstrual bleeding, prostate cancer, and uterine leiomyoma.[9]

PATIENT GROUP

DISEASE BACKGROUND

Endometriosis is a common, oestrogen-dependent, chronic gynaecological disorder in which the endometrium (the tissue that lines the inside of the uterus or womb) starts to grow in other places, such as the ovaries, fallopian tubes, bowels bladder, diaphragm, or in caesarean section scars.[10-12] Each month, this misplaced endometrium tissue responds to the hormonal changes of the menstrual cycle by building up and breaking down.[13] However, unlike the endometrium tissue lining of the womb, which leaves the body as a period, the tissue has no way of leaving the body and results in small bleeding inside of the pelvis. This leads to inflammation, swelling and scarring of the normal tissue surrounding the endometriosis

implants.[11,13] This inflammation, irritation and scar tissue can contribute to the painful symptoms associated with endometriosis.[10]

Symptoms of endometriosis can vary significantly from person to person but the most common symptoms include: excessively painful menstrual cramps that may be felt in the abdomen or lower back; abnormal or heavy menstrual flow; infertility; pain during and after sex; difficulty getting pregnant; discomfort when going to the toilet; and other gastrointestinal problems such as diarrhoea, constipation and/or nausea.[11,13]

The pathogenesis of endometriosis is unknown but common risk factors for the disease include: women who have a first-degree relative with the disease; women who are giving birth for the first time after age 30; and women with an abnormal uterus.[13] Consistent evidence from family and twin based studies supports a heritable component to endometriosis. Results of a recent genome-wide association studies are consistent with a heritable component in endometriosis, but no genetic specific gene has been identified.[14]

CLINICAL NEED AND BURDEN OF DISEASE

Endometriosis is one of the most common gynaecological disorders in women of reproductive age. The prevalence is difficult to determine because of variability in clinical presentation but is thought to affect 1.5 million women in the UK. It is estimated that 10% of women of reproductive age have endometriosis and this prevalence rises in women with infertility to about 30-50%.[15]

Endometriosis is reported to have a negative effect on health-related quality of life for women suffering with the disease. In addition to the painful symptoms associated with endometriosis, women with the disease can also experience a range of non-clinical symptoms including depression, feelings of isolation, fatigue and a lack of energy.[16]

According to the hospital episodes statistics for England in 2019/20, there were 22,530 finished consultant episodes (FCE) for endometriosis which resulted in 21,888 admissions, 10,623 day cases and 19,973 FCE bed days.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Currently, there is no cure for endometriosis. The different treatments available for endometriosis aim to relieve pain and reduce the severity of symptoms, improve patient quality of life, and slow the growth of endometriosis tissue.[18,19]

The type of treatment that a patient receives is dependent on several factors such as: age; what the main symptoms are; or if the patient wants to become pregnant.[19] The main treatment options include analgesic medications, neuromodulators and neuropathic pain management, hormonal treatments, and surgical management. [7]

CURRENT TREATMENT OPTIONS

Currently there are no pharmacological treatment options recommended by NICE specifically for the treatment of endometriosis associated pain.

NICE guidelines currently recommend a short trial (3 months) of paracetamol or a non-steroidal anti-inflammatory (NSAIDs) alone or in combination for the first-line treatment of endometriosis-associated pain. Neuromodulators and neuropathic treatments are also considered as a pain treatment.[7]

Hormonal treatments such as the combined oral contraceptive pill, progestogen-only pill, progestogen injection (Depot-provera or Sayana Press), progestogen implant (Nexoplanon), or levonorgestrel intrauterine system (Mirena) can also be recommended.[20]

PLACE OF TECHNOLOGY

If licensed relugolix will be the first GnRH antagonist approved for the treatment of endometriosis-associated pain and will be an additional treatment option for women with this disease.[7]

CLINICAL TRIAL INFORMATION

Trial	**SPIRIT 1,** NCT03204318**,** 2017-001588-19**;** An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered With and Without Low-Dose Estradiol and Norethindrone Acetate in Women With Endometriosis-Associated Pain
Trial design	Randomized, parallel assignment, triple masked, placebo-controlled
Population	N=638; females; adults aged 18 years to 50 years; premenopausal; diagnosis of endometriosis; surgical or direct visualisation and/or histopathologic confirmation of endometriosis
Intervention(s)	Relugolix (oral administration); co-formulated estradiol (1.0mg) and acetate (0.5mg) (oral administration)
Comparator(s)	Placebo (oral administration)
Outcome(s)	Primary outcome measures: • Percentage of participants who meet the dysmenorrhoea responder criteria at week 24 or end of treatment (EOT) [Time Frame: Week 24 or EOT] • Percentage of participants who meet the non-menstrual pelvic pain (NMPP) responder criteria at week 24 or EOT [Time Frame: Week 24 or EOT] See trial record for full list of outcome measures.
Results (efficacy)	Relugolix combination therapy achieved both co-primary endpoints by demonstrating clinically-meaningful pain reductions for 74.5% of women with dysmenorrhoea (menstrual pain) and 58.5% of women with non-menstrual pelvic pain, compared to 26.9% and 39.6% of women in the placebo group respectively. On average, women receiving relugolix combination therapy had a 73.3% reduction on the 11-point (0-10) Numerical Rating Scale for dysmenorrhoea

	from 7.3 (severe pain) to 1.8 (mild pain). All seven key secondary endpoints measured at Week 24 and compared to placebo achieved statistical significance.[21]
Results (safety)	The only reported adverse events in at least 10% of women in the relugolix combination group were headache and hot flashes.[21]

Trial	**SPIRIT 2,** NCT03204331**,** 2017-001632-19**;** An International Phase III Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered With and Without Low-Dose Estradiol and Norethindrone Acetate in Women With Endometriosis-Associated Pain **Phase III** – Active, not recruiting **Locations:** 5 EU countries (not incl UK), USA, and other countries **Actual Primary Completion Date:** 01 April 2020
Trial design	Randomised, parallel assignment, triple masked, placebo controlled
Population	N=623; females; adults aged 18 years to 50 years; premenopausal; diagnosis of endometriosis; surgical or direct visualisation and/or histopathologic confirmation of endometriosis
Intervention(s)	Relugolix (oral administration); co-formulated estradiol (1.0mg) and acetate (0.5mg) (oral administration)
Comparator(s)	Placebo (oral administration)
Outcome(s)	Primary outcome measures: • Percentage of participants who meet the dysmenorrhoea responder criteria at week 24 or EOT [Time Frame: Week 24 or EOT] • Percentage of participants who meet the NMPP responder criteria at week 24 or EOT [Time Frame: Week 24 or EOT] See trial record for full list of outcome measures.
Results (efficacy)	In the co-primary endpoint analysis of SPIRIT 2, 75.2% of women receiving once-daily relugolix combination therapy achieved a clinically-meaningful reduction in dysmenorrhea versus 30.4% of women in the placebo group ($p < 0.0001$). For non-menstrual pelvic pain, relugolix combination therapy achieved a clinically-meaningful reduction in 66.0% of women versus 42.6% women in the placebo group ($p < 0.0001$). On average, women receiving relugolix combination therapy had a 75.1% reduction on the 11-point (0 to 10) Numerical Rating Scale for dysmenorrhea from 7.2 (severe pain) to 1.7 (mild pain).[22]
Results (safety)	Relugolix combination therapy was generally well-tolerated with minimal bone mineral density loss over 24 weeks. The overall incidence of adverse events in the relugolix

	combination and placebo groups was similar (80.6% vs 75.0%) In the relugolix combination therapy group, 5.3% of women discontinued treatment early due to adverse events versus 3.9% in the placebo group. The most frequently reported adverse events, reported in at least 10% of women in the relugolix combination group, were headache, nasopharyngitis, and hot flushes.[22]

Trial	**SPIRIT EXTENSION,** NCT03654274**,** 2017-004066-10**;** An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women With Endometriosis-Associated Pain **Phase III** – Active, not recruiting **Locations:** 10 EU countries (not incl UK), USA, Canada and other countries **Estimated primary completion date:** 30 December 2021
Trial design	Single group assignment, open-label, extension study
Population	N=803; females; adults aged 18 to 51 years; previously completed 24 weeks of study drug treatment and study participation in either parent study, NCT03204331 or NCT03654274; is not expected to undergo gynaecological surgery or other surgical procedures for treatment of endometriosis during the study or study follow-up period; has agreed to continue to use only study-specified analgesic medications during the study
Intervention(s)	Relugolix (oral administration); co-formulated estradiol (1.0mg) and acetate (0.5mg) (oral administration)
Comparator(s)	None
Outcome(s)	Primary outcome measures: • Proportion of women who respond or maintain response based on assessment of dysmenorrhoea at week 52 and week 104 [Time Frame: Week 52 and Week 104] • Proportion of women who respond or maintain response based on NMPP at week 52 and week 104 [Time Frame: Week 52 and Week 104] See trial record for full list of outcome measures.
Results (efficacy)	84.8% and 73.3% of women receiving relugolix combination therapy over one year achieve clinically meaningful pain reductions in dysmenorrhoea and NMPP, respectively. On average, women reported an 82.8% reduction on the 11-point numerical rating scale (0-10) for dysmenorrhoea from 7.4 (severe pain) to 1.3 (mild pain) over one year.[23]
Results (safety)	The most commonly reported adverse events were headache, nasopharyngitis, and hot flashes.[23]

ESTIMATED COST

The estimated cost of relugolix is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Heavy menstrual bleeding: assessment and management (NG88). March 2020.
- NICE clinical guideline. Endometriosis: diagnosis and management (NG73). September 2017.
- NICE quality standard. Endometriosis (QS172). August 2018.
- NICE interventional procedure guidance. Laparoscopic uterine nerve ablation (LUNA) for chronic pelvic pain (PIG234). October 2007.
- NICE interventional procedure guidance. Laparoscopic helium plasma coagulation for the treatment of endometriosis (IPG171). March 2006.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Complex Gynaecology (Severe Endometriosis). E10/S/a.

OTHER GUIDANCE

- NICE clinical knowledge Summary. Endometriosis. 2020.[24]
- European Society of Human Reproduction and Embryology (ESHRE). Guideline on the management of women with endometriosis. 2013.[25]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. *An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered With and Without Low-Dose Estradiol and Norethindrone Acetate in Women With Endometriosis-Associated Pain*. *Trial ID: NCT03204318*. 2017. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03204318 [Accessed 29 May 2021].

2 Clinicaltrials.gov. *An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered With and Without Low-Dose Estradiol and Norethindrone Acetate in Women With Endometriosis-Associated Pain*. *Trial ID: NCT03204331*. 2017. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03204331 [Accessed 29 May 2021].

3 Myovant Sciences. *Relugolix Combination Tablet.* 2021. Available from: https://www.myovant.com/our-science/relugolix-combination-tablet/ [Accessed 31 May 2021].

4 National Library of Medicine. *PubChem Compound Summary for Relugolix.* 2021. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Relugolix [Accessed 31 May 2021].
5 Osuga Y, Enya K, Kudou K, Hoshiai H. Relugolix, a novel oral gonadotropin-releasing hormone antagonist, in the treatment of pain symptoms associated with uterine fibroids: a randomized, placebo-controlled, phase 3 study in Japanese women. *Fertil Steril*. 2019 Nov;112(5):922-9.e2. Available from: https://doi.org/10.1016/j.fertnstert.2019.07.013.
6 Clinicaltrials.gov. *SPIRIT EXTENSION: Efficacy and Safety Extension Study of Relugolix in Women With Endometriosis-Associated Pain*. *Trial ID: NCT03654274*. 2018. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03654274 [Accessed 31 May 2021].
7 National Institute for Health and Care Excellence (NICE). *Endometriosis: Diagnosis and management* (*NG73)*. Last Update Date: Available from: https://www.nice.org.uk/guidance/ng73/resources/endometriosis-diagnosis-and-management-pdf-1837632548293 [Accessed 29 May 2021].
8 Osuga Y, Enya K, Kudou K, Tanimoto M, Hoshiai H. Oral Gonadotropin-Releasing Hormone Antagonist Relugolix Compared With Leuprorelin Injections for Uterine Leiomyomas: A Randomized Controlled Trial. *Obstetrics & Gynecology*. 2019;133(3). Available from: https://journals.lww.com/greenjournal/Fulltext/2019/03000/Oral_Gonadotropin_Releasing_Hormone_Antagonist.3.aspx.
9 Clinicaltrials.gov. *Search for relugolix clinical studies: Phase II and III.* 2021. Available from: https://clinicaltrials.gov/ct2/results?cond=&term=&type=&rslt=&age_v=&gndr=&intr=relugolix&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 30 May 2021].
10 UCLA Health. *Endometriosis: Symptoms, Treatment, Diagnosis.* 2021. Available from: https://www.uclahealth.org/obgyn/endometriosis [Accessed 29 May 2021].
11 NHS Inform. *Endometriosis.* 2021. Available from: https://www.nhsinform.scot/illnesses-and-conditions/sexual-and-reproductive/endometriosis#about-endometriosis [Accessed 29 March 2021].
12 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. *Fertil Steril*. 2021 Feb;115(2):397-405. Available from: https://doi.org/10.1016/j.fertnstert.2020.07.055.
13 Johns Hopkins Medicine. *Endometriosis.* 2021. Available from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/endometriosis [Accessed 29 May 2021].
14 Hickey M, Ballard K, Farquhar C. Endometriosis. *BMJ*. 2014;348(mar19 5):g1752-g. Available from: https://doi.org/10.1136/bmj.g1752.
15 National Institute for Health and Care Excellence (NICE). *Endometriosis: How common is it?* 2020. Available from: https://cks.nice.org.uk/topics/endometriosis/background-information/prevalence/ [Accessed 30 May 2021].
16 Bourdel N, Chauvet P, Billone V, Douridas G, Fauconnier A, Gerbaud L, et al. Systematic review of quality of life measures in patients with endometriosis. *PLOS ONE*. 2019;14(1):e0208464. Available from: https://doi.org/10.1371/journal.pone.0208464.
17 NHS Digital. *Hospital Admitted Patient Care Activity 2019-20*. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Downloaded 17 September 2020].
18 Endometriosis UK. *Endometriosis Treatment.* 2021. Available from: https://www.endometriosis-uk.org/endometriosis-treatment [Accessed 29 May 2021].
19 National Health Service (NHS). *Endometriosis: Treatment.* 2019. Available from: https://www.nhs.uk/conditions/endometriosis/treatment/ [Accessed 29 March 2021].
20 National Institute for Health and Care Excellence (NICE). *Scenario: Management of endometriosis.* 2020. Available from:

https://cks.nice.org.uk/topics/endometriosis/management/management-of-endometriosis/ [Accessed 01 June 2021].

21 Trial Site News. *Myovant Reports Data from SPIRIT 1, the Second Phase III Trial of Once-Daily Relugolix Combination Therapy in Women with Endometrial Pain.* 2020. Available from: https://trialsitenews.com/myovant-reports-data-from-spirit-1-the-second-phase-iii-trial-of-once-daily-relugolix-combination-therapy-in-women-with-endometrial-pain/ [Accessed 30 May 2021].

22 Myovant Sciences. *Myovant Sciences Announces Positive Results from Phase 3 SPIRIT 2 Study Evaluating Once-Daily Relugolix Combination Therapy in Women with Endometriosis and from Ovulation Inhibition Study.* 2020. Available from: https://www.globenewswire.com/news-release/2020/04/22/2019886/0/en/Myovant-Sciences-Announces-Positive-Results-from-Phase-3-SPIRIT-2-Study-Evaluating-Once-Daily-Relugolix-Combination-Therapy-in-Women-with-Endometriosis-and-from-Ovulation-Inhibitio.html [Accessed 20 May 2021].

23 Trial Site News. *Myovant and Pfizer Announce One-Year Data from Phase 3 SPIRIT Extension Study of Once-Daily Relugolix Combination Therapy in Women with Endometriosis.* 2021. Available from: https://trialsitenews.com/myovant-and-pfizer-announce-one-year-data-from-phase-3-spirit-extension-study-of-once-daily-relugolix-combination-therapy-in-women-with-endometriosis/ [Accessed 31 May 2021].

24 National Institute for Health and Care Excellence (NICE). *Endometriosis.* 2020. Available from: https://cks.nice.org.uk/topics/endometriosis/ [Accessed 31 May 2021].

25 European Society of Human Reproduction and Embryology (ESHRE). *Guideline on the management of women with endometriosis.* 2013. Available from: https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Endometriosis-guideline.aspx [Accessed 31 May 2021].

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.