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HEALTH TECHNOLOGY BRIEFING
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Relugolix in combination with estradiol/norethindrone acetate for moderate to severe symtpoms of uterine fibroids

NIHRIO ID	21727	**NICE ID**	10369
Developer/Company	Gedeon Richter UK Ltd.	**UKPS ID**	657345

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

SUMMARY

Relugolix in combination with estradiol/norethindrone acetate is in clinical development for the treatment of moderate to severe symptoms associated with uterine fibroids. Uterine fibroids are non-cancerous growths that develop in or around the womb. Many women with fibroids do not develop symptoms, however, symptoms can include heavy and/or painful periods, abdominal pain, lower back pain, a frequent need to urinate, constipation and pain or discomfort during sex. Current treatment options aim to reduce heavy periods, for example using contraception, however, treatments for fibroids remain limited.

Relugolix is a small molecule that binds to the gonadotropin-releasing hormone receptor in the pituitary gland, decreasing the release of hormones which control oestrogen and progesterone production by the ovaries. Results from clinical trials demonstrated that relugolix in combination with estradiol and norethisterone acetate reduced menstrual bleeding in women with uterine fibroids. Relugolix is administered orally, and if licensed would offer an additional treatment option for women moderate to severe symptoms associated with uterine fibroids.

PROPOSED INDICATION

Treatment of women with heavy menstrual bleeding associated with uterine fibroids[1]

TECHNOLOGY

DESCRIPTION

Relugolix is a small molecule, gonadotropin-releasing hormone (GnRH) receptor antagonist that binds to and blocks GnRH receptor in the anterior pituitary gland. Blocking GnRH decreases the release of gonadotropins – luteinizing hormone (LH) and follicle-stimulating hormone (FSH) – thereby decreasing the downstream production of oestrogen and progesterone by the ovaries.[2]

In a phase III clinical trial (NCT03751124), relugolix 40 mg once daily was co-administered with estradiol (1.0 mg) and norethindrone acetate (0.5 mg).[1]

INNOVATION AND/OR ADVANTAGES

Currently there are no GnRH antagonists recommended by NICE for the treatment of heavy menstrual bleeding.[3] 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 hormone levels and menstruation after discontinuation of treatment, leading to a more rapid recovery of fertility than injectable formulations of GnRH agonists.[4]

Myovant Sciences have posted positive top-line results from two phase III trials, LIBERTY 1 and LIBERTY 2, which evaluated the efficacy and safety of relugolix combination therapy in women with heavy menstrual bleeding associated with uterine fibroids. In both trials, on average, women had an 84.3% reduction in menstrual blood loss compared to baseline.[2]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Relugolix is not currently licensed in the UK/EU for any indication.

Estradiol with norethisterone is currently licensed for the following:[5]

- Menopausal symptoms
- Menopausal symptoms/osteoporosis prophylaxis in women with a uterus whose last menstrual period occurred over 12 months previously

Common or very common side effects associated with estradiol include: headaches, nausea and skin reactions. With oral use, common or very common side effects include: asthenia; gastrointestinal discomfort; gastrointestinal disorders; haemorrhage; menstrual cycle irregularities; muscle complaints; pelvic pain; weight changes.[6]

Common or very common side effects associated with norethisterone acetate include menstrual cycle irregularities. With oral use, common or very common side effects include: appetite change; depression; fatigue; gastrointestinal disorder; headaches; hypertension; libido disorder; nervousness; rash; weight change.[7]

Relugolix, in combination with estradiol/norethisterone is currently in clinical trials for the treatment of endometriosis-associated pain.[8,9]

PATIENT GROUP

DISEASE BACKGROUND

Uterine fibroids (uterine myomas or leiomyomas) are non-cancerous growths that develop in or around the womb (uterus). The growths are made up of muscle and fibrous tissue, and can vary in size. Many women do not experience symptoms, however, 1 in 3 women may experience heavy or painful periods, abdominal pain, lower back pain, a frequent need to urinate, constipation and dyspareunia (pain or discomfort during sex).[10]

Fibroids most often occur in women aged 30 years to 50 years. Fibroids are thought to develop more frequently in women of African-Caribbean origin and in overweight or obese women, because being overweight increases the level of oestrogen in the body. Women who have had children have a lower risk of developing fibroids, and the risk decreases further the more children you have.[10]

Fibroids can grow anywhere in the womb and can vary from the size of a pea to the size of a melon. The three main types are:[10]

- Intramural fibroids – in the muscle of the womb
- Subserosal fibroids – outside of the wall of the womb and in the pelvis
- Submucosal fibroids – in the muscle layer beneath the womb's inner lining, and in the cavity of the womb

CLINICAL NEED AND BURDEN OF DISEASE

Heavy menstrual bleeding is common in women with uterine fibrosis and diagnostic studies have detected uterine fibroids in approximately 30% of women with heavy menstrual bleeding.[11]

The prevalence of symptomatic fibroids is low in women younger than 30 years of age — fibroids occur in 20–50% of women older than 30 years. Peak incidence is in women in their 40s, with an estimated incidence in 2018, of 22.5 per 1000 women-years.[12]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Current treatments aim to reduce heavy periods. This can be achieved through non-contraceptive means, for example tranexamic acid and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and mefenamic acid. In addition, taking contraception, such as Levonorgestrel intrauterine system (LNG-IUS), the contraceptive pill, oral progesterone or injected progesterone, can reduce heavy periods.[13]

If symptoms persist despite treatment to reduce heavy periods, medication can be prescribed to shrink fibroids, such as gonadotropin releasing hormone analogues (GnRHas), however, these can cause menopause-like symptoms and osteoporosis. Women who have not experienced the menopause may be offered ulipristal acetate, however, in some cases, this can cause liver damage and is therefore being monitored for safety.[13]

Surgery may be considered if the symptoms are particularly severe and medication has been ineffective. Examples of surgeries include: hysterectomy (removal of the womb), myomectomy (removal of fibroids), hysteroscopic resection and hysteroscopic morcellation (telecscopic removal of fibroids). In addition to traditional surgical techniques to treat fibroids, non-surgical

treatments are now offered. These include uterine artery embolization (shrinking of blood vessels supplying the fibroids), endometrial ablation (removing the lining of the womb), MRI-guided percutaneous laser ablation and MRI-guided transcutaneous focused ultrasound (laser or ultrasound energy used to destroy fibroids). [13]

CURRENT TREATMENT OPTIONS

The following medicinal products are currently licensed in the UK for the treatment of heavy bleeding associated with uterine fibroids:[13]

- Tranexamic acid
- Non-steroidal anti-inflammatories (ibuprofen or mefanamic acid)
- The contraceptive pill
- Oral/injected progesterone
- GnRHas
- Ulipristal acetate

PLACE OF TECHNOLOGY

If licensed, relugolix in combination with estradiol and norethisterone acetate, would offer an additional treatment option for women with moderate to severe symptoms of uterine fibroids.[1]

CLINICAL TRIAL SUMMARY INFORMATION

Trial	NCT035751124, EudraCT 2018-001368-43 An International Phase 3 Double-Blind, Placebo-Controlled, Randomized Withdrawal Study of Relugolix With Estradiol and Norethindrone Acetate in Women With Heavy Menstrual Bleeding Associated With Uterine Fibroids **Phase III – Active, not recruiting** **Locations:** Europe (excluding the UK), USA and other countries **Primary completion date:** February 2021
Trial design	Randomised, parallel assignment
Population	- N = 229 - Heavy menstrual bleeding associated with uterine fibroids; completed the open-label extension study (MVT-601-3003) - Females aged 18 to 51 years
Intervention(s)	- Relugolix plus E2/NETA (Relugolix 40mg co-administered with estradiol (1.0mg) and norethindrone acetate (0.5mg) for up to 52 weeks)
Comparator(s)	- Placebo for relugolix plus placebo for E2/NETA (Placebo for relugolix administered with placebo for estradiol (1.0mg) and norethindrone acetate (0.5mg) for up to 52 weeks or until heavy menstrual bleeding occurs)
Outcome(s)	- Proportion of women who maintain a menstrual blood loss volume <80mL [time frame: at week 24 (week 72 relative to the parent study baseline)] For full list of outcomes, see trial record
Results (efficacy)	-

Results (safety)	-

Trial	**LIBERTY EXTENSION,** NCT03412890, EudraCT 2017-003310-74 LIBERTY EXTENSION: An International Phase 3 Open-Label, Single-Arm, Long-Term Efficacy and Safety Extension Study to Evaluate Relugolix Co-Administered With Low-Dose Estradiol and Norethindrone Acetate in Women With Heavy Menstrual Bleeding Associated With Uterine Fibroids **Phase III – Active, not recruiting** **Locations:** Europe (excluding the UK), USA and other countries **Primary completion date:** January 2020
Trial design	Single group assignment, open-label extension
Population	- N = 477 - Heavy menstrual bleeding associated with uterine fibroids, completed 24 weeks of study drug treatment and study participation in either MVT-601-3001 or MVT-601-3002 - Females aged 18 to 50 years
Intervention(s)	- Relugolix 40mg co-administered with estradiol (1.0mg) and norethindrone acetate (0.5mg) for up to 28 weeks
Comparator(s)	No comparator
Outcome(s)	- Responder rate based on reduction in menstrual blood loss volume [time frame: from parent study baseline up to last 35 days of treatment, anticipated to be up to 52 weeks] For full list of outcomes, see trial record
Results (efficacy)	-
Results (safety)	-

Trial	**LIBERTY 2**, NCT03103087, EudraCT 2016-005113-50 LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered With and Without Low-Dose Estradiol and Norethindrone Acetate in Women With Heavy Menstrual Bleeding Associated With Uterine Fibroids **Phase III – Active, not recruiting** **Locations:** Europe (excluding the UK), USA and other countries **Primary completion date:** July 2019
Trial design	Randomised, parallel assignment, triple masked
Population	- N = 382 - Heavy menstrual bleeding associated with uterine fibroids - Females aged 18 to 50 years
Intervention(s)	- Relugolix plus E2/NETA (relugolix 40mg co-administered with estradiol (1.0mg) and norethindrone acetate (0.5mg) for 24 weeks)

Comparator(s)	- Relugolix then relugolix plus E2/NETA (relugolix 40mg co-administered with placebo for E2/NETA for 12 weeks followed by Relugolix 40mg co-administered with estraiol/norethindrone acetate (1.0/0.5mg) for 12 weeks) - Placebo comparator (placebo for Relugolix co-administered with placebo E2/NETA for 24 weeks)
Outcome(s)	- Proportion of women who achieve a menstrual blood loss volume of < 80 mL and a ⩾ 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment [time frame: from baseline up to last 35 days of treatment anticipated to be up to 24 weeks] See trial record for full list of outcomes
Results (efficacy)	The reduction from baseline to week 24 in distress due to HMB, passing blood clots, and pelvic pressure, measured by the BPD scale, was significantly greater with Relugolix-CT (-45.0) than with placebo (-16.1) (difference -29.9; p< 0.0001). Percentages of treatment responders, defined as those with a clinically meaningful change from baseline to Week 24 of ≥ 20 points, were significantly greater with Relugolix-CT than placebo. On the BPD scale, 61.7% vs 27.6% on Relugolix-CT vs placebo were responders, with a significant difference of 34.2% (p<0.0001). Regarding the RA scale, 60.9% and 35.4% of patients on Relugolix-CT and placebo, respectively, were responders, with a statistically significant difference of 25.5% (p<0.0001)[14]
Results (safety)	The overall incidence of adverse events in the relugolix combination and placebo groups was comparable (60.3% vs. 58.9%). In the relugolix combination therapy group, 1.6% of women discontinued treatment early due to adverse events compared with 4.7% in the placebo group. There were no adverse events in the relugolix combination group reported by at least 10% of women and more frequently than in the placebo group. The incidence of hot flashes in the relugolix combination group was similar to placebo (5.6% versus 3.9%). There were no pregnancies in the relugolix combination group and one in the placebo group[15]

Trial	**LIBERTY 1,** NCT03049735, EudraCT 2016-003727-27 LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered With and Without Low-Dose Estradiol and Norethindrone Acetate in Women With Heavy Menstrual Bleeding Associated With Uterine Fibroids **Phase III – Active, not recruiting** **Locations:** Europe (including the UK), US and other countries **Primary completion date:** April 2019
Trial design	Randomised, parallel assignment, triple masked
Population	- N = 388 (planned) - Heavy menstrual bleeding associated with uterine fibroids - Females aged 18 to 50 years

Intervention(s)	- Relugolix plus E2/NETA (relugolix 40mg co-administered with estradiol (1.0mg) and norethindrone acetate (0.5mg) for 24 weeks)
Comparator(s)	- Relugolix then relugolix plus E2/NETA (relugolix 40mg co-administered with placebo for E2/NETA for 12 weeks followed by Relugolix 40mg co-administered with estraiol/norethindrone acetate (1.0/0.5mg) for 12 weeks) - Placebo comparator (placebo for Relugolix co-administered with placebo E2/NETA for 24 weeks)
Outcome(s)	- Proportion of women who achieve a menstrual blood loss volume of < 80 mL and a ⩾ 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment [time frame: from baseline up to last 35 days of treatment anticipated to be up to 24 weeks] See trial record for full list of outcomes
Results (efficacy)	The reduction from baseline to week 24 in distress due to HMB, passing blood clots, and pelvic pressure, measured by the BPD scale, was significantly greater with Relugolix-CT (-45.0) than with placebo (-16.1) (difference -29.9; p< 0.0001). Percentages of treatment responders, defined as those with a clinically meaningful change from baseline to Week 24 of ≥ 20 points, were significantly greater with Relugolix-CT than placebo. On the BPD scale, 61.7% vs 27.6% on Relugolix-CT vs placebo were responders, with a significant difference of 34.2% (p<0.0001). Regarding the RA scale, 60.9% and 35.4% of patients on Relugolix-CT and placebo, respectively, were responders, with a statistically significant difference of 25.5% (p<0.0001)[14]
Results (safety)	The overall incidence of adverse events in the relugolix combination and placebo groups was comparable (62% vs. 66%). In the relugolix combination therapy group 5% of women discontinued treatment early due to adverse events compared with 4% in the placebo group. The only adverse event in the relugolix combination arm occurring in at least 10% of women and more frequently than in the placebo arm was hot flush (11% versus 8%). There were no pregnancies in the relugolix combination group and one in the placebo group[16]

ESTIMATED COST

The cost of relugolix is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Guideline. Heavy menstrual bleeding: assessment and management. [NG88]. March 2018.
- NICE Interventional procedures guidance. Magnetic resonance image-guided transcutaneous focused ultrasound for uterine fibroids. [IPG413]. November 2011.

- NICE Interventional procedures guidance. Uterine artery embolisation for fibroids. [IPG367]. November 2010.
- NICE Interventional procedures guidance. Laparoscopic techniques for hysterectomy. [IPG239]. November 2007.
- NICE Interventional procedures guidance. Laparoscopic uterine nerve ablation (LUNA) for chronic pelvic pain. [IPG234] October 2007.
- NICE Interventional procedures guidance. Magnetic resonance (MR) image-guided percutaneous laser ablation of uterine fibroids. [IPG30]. December 2003.
- NICE Interventional procedures guidance. Laparoscopic laser myomectomy. [IPG23]. November 2003.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

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- European Menopause and Andropause Society. EMAS Position Statement: Management of Uterine Fibroids. 2014. [23]
- Royal College of Obstetricians and Gynaecologists. Clinical recommendations on the use of uterine artery embolization (UAE) in the management of fibroids. 2013.[24]

ADDITIONAL INFORMATION

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