NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Linzagolix for treating endometriosis-associated pain

Company/Developer	Theramex

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 27273	NICE TSID: N/A	UKPS ID: 668577

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Linzagolix is in clinical development for the treatment of endometriosis-associated pain. Endometriosis is when the endometrium (the tissue that lines the inside of the uterus or womb) starts to grow outside of the uterus, including in the ovaries and fallopian tubes. Each month, this misplaced tissue first builds up then breaks down, but since it cannot leave the body it remains in place and causes irritation and inflammation. Symptoms can include: excessively painful menstrual cramps that may be felt in the abdomen or lower back, abnormal or heavy menstrual flow, infertility and discomfort when going to the toilet. Current treatments are limited to painkillers, neuromodulators and neuropathic treatments. Hormonal treatments can also be recommended, but cannot improve fertility.

Linzagolix is a type of hormone receptor antagonist. These bind to receptors in the pituitary gland, inhibiting gonadotropin production, which reduces ovarian production of the hormone oestradiol. This in turn reduces growth of endometriosis tissue. If licensed, linzagolix would offer a new treatment option for patients with endometriosis-associated pain.

Proposed Indication

Treatment of endometriosis-associated pain.[1]

Technology

Description

Linzagolix (OBE2109, KLH-2109, Yselty) is a non-peptide, gonadotropin-releasing hormone (GnRH) receptor antagonist. These drugs competitively bind to GnRH receptors in the pituitary gland, resulting in the rapidly reversible dose-dependent inhibition of gonadotropin production. This reduces ovarian production of oestradiol, which in turn limits the growth of endometriosis tissue. [2,3]

Linzagolix is currently in clinical development for the treatment of endometriosis-associated pain.[a] In the phase III clinical trials NCT03992846 and NCT04335591, participants received linzagolix via orally-administered tablet, either 75 mg or 200 mg plus an add-back capsule (E2 1 mg / NETA 0.5 mg).[1,4]

Key Innovation

Although GnRH agonists are effective in relieving endometriosis-associated symptoms, they decrease bone mineral content, which means they can only be used temporarily without an add-back therapy. In addition, GnRH agonists induce a transient increase in the secretion of gonadotropins (flare), which results in a temporary worsening of symptoms, and they cannot be orally administered. An alternative approach is the use of GnRH receptor antagonists such as linzagolix, which do not induce an initial clinical flare and typically have fewer side effects than GnRH agonists.[5,6] The advantages of linzagolix include rapid onset of action, dose-dependent suppression of oestradiol production and reversibility of its effects.[7]

If licenced, linzagolix will provide a new treatment option for patients with endometriosis-associated pain.

Regulatory & Development Status

Linzagolix currently has Marketing Authorisation in the EU and UK for the management of moderate to severe symptoms of uterine fibroids in adult women.[8]

Patient Group

Disease Area and Clinical Need

Endometriosis is a common, oestrogen-dependent, chronic gynaecological disorder in which the endometrium starts to grow outside of the uterus, including in the ovaries and fallopian tubes.[9-11] Each month, this misplaced endometrial tissue responds to the hormonal changes of the menstrual cycle by building up and breaking down. 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. This tissue can irritate surrounding tissue, eventually developing scar tissue and adhesions (bands of fibrous tissue) that can cause pelvic tissues and organs to stick to each other.[12,13] This inflammation and irritation can contribute to the painful symptoms associated with endometriosis. 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; discomfort when going to the toilet; and other gastrointestinal problems such as diarrhoea, constipation and/or nausea. The pathogenesis of endometriosis is unknown but common risk factors for the disease include having a first-degree relative with the disease, an abnormal uterus or immune system dysfunction.[9,12]

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%.[14] In England in 2021-22, there were 21,113 finished consultant episodes (FCEs) and 20,416 admissions for endometriosis (ICD-10 code N80) which resulted in 18,428 FCE bed days and 9,738 day cases.[15]

Recommended Treatment Options

Currently there are no pharmacological treatment options recommended by the National Institute for Health and Care Excellence (NICE) specifically for the treatment of endometriosis associated pain. NICE guidelines currently recommend a short trial (3 months) of paracetamol or a nonsteroidal anti-inflammatory alone or in combination for the first-line treatment of endometriosis-associated pain. Neuromodulators and neuropathic treatments are also considered as a pain treatment.[6] 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.[16]

Clinical Trial Information

Trial	**EDELWEISS 3,** NCT03992846; A Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled, Clinical Study to Assess the Efficacy and Safety of Linzagolix in Subjects With Moderate to Severe Endometriosis-associated Pain. **Phase III:** Completed **Location:** Eight EU countries, Ukraine and USA **Primary completion date:** October 2021
Trial Design	Randomised, parallel assignment, quadruple-blinded
Population	N = 486 (actual); females aged 18-49 years; with the most recent surgical and - if available - histological diagnosis of pelvic endometriosis up to 10 years before screening; moderate to severe endometriosis-associated pain during screening duration; regular menstrual cycles; BMI ≥ 18 kg/m^2 at visit.

Intervention(s)	Linzagolix 75 mg or linzagolix 200 mg + add-back (E2 1 mg / NETA 0.5 mg) administered orally once daily.
Comparator(s)	Placebo to match 75 mg linzagolix tablet, placebo to match 200 mg linzagolix tablet or placebo to match add-back capsule
Outcome(s)	• Dysmenorrhea [Time frame: baseline to month 3] • Non-menstrual pelvic pain [Time frame: baseline to month 3] See trial record for full list of other outcomes
Results (efficacy)	Both dysmenorrhea and non-menstrual pelvic pain showed rapid reductions compared to placebo (after 1 and 2 months of treatment, respectively), with continued reduction up to 6 months of treatment and with higher reductions with linzagolix 200 mg + add-back therapy compared to linzagolix 75 mg. A similar pattern was seen for the secondary endpoints of dyschezia (painful bowel movements) and worst pelvic pain (defined as the 5 days with worst pain during a 28-day period).[17]
Results (safety)	Both linzagolix doses were generally well-tolerated with minimal bone mineral density decrease and few adverse events occurring in more than 5% of patients up to 6 months.[18]

Clinical Trial Information	
Trial	**EDELWEISS 6**, NCT04335591; A Double-blind Randomized Extension Study to Assess the Long-term Efficacy and Safety of Linzagolix in Subjects With Endometriosis-associated Pain **Phase III:** Ongoing **Location:** Seven EU countries, Ukraine and USA **Primary completion date:** April 2022
Trial Design	Randomised, parallel assignment, quadruple-blinded
Population	N = 288 (estimated); females aged 18-50 years; must have completed the 6-month treatment in the main study; must agree to continue to use only the analgesic rescue medication permitted by the protocol during the Treatment and Follow-up Periods
Intervention(s)	Linzagolix 75 mg or linzagolix 200 mg + add-back (E2 1 mg / NETA 0.5 mg) administered orally once daily.
Comparator(s)	Placebo to match 75 mg linzagolix tablet, placebo to match 200 mg linzagolix tablet or placebo to match add-back capsule
Outcome(s)	• Dysmenorrhea [Time frame: baseline to month 12] • Non-menstrual pelvic pain [Time frame: baseline to month 12] See trial record for full list of other outcomes

Results (efficacy)	-
Results (safety)	-

Estimated Cost

The estimated cost of linzagolix is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Relugolix–estradiol–norethisterone acetate for treating pain associated with endometriosis (ID3982). Expected date of issue to be confirmed.
- NICE guidance in development. Endometriosis: diagnosis and management - surgical management - pain management post-surgery (GID-NG10385). Expected date of issue to be confirmed.
- NICE guidance in development. Endometriosis: diagnosis and management - diagnosing endometriosis (GID-NG10392). Expected date of issue to be confirmed.
- NICE guidance in development. Endometriosis: diagnosis and management - surgical management if fertility is a priority GID-NG10393). Expected date of issue to be confirmed.
- NICE clinical guideline. Heavy menstrual bleeding: assessment and management (NG88). May 2021.
- NICE clinical guideline. Endometriosis: diagnosis and management (NG73). September 2017.
- NICE quality standard. Endometriosis (QS172). August 2018.

NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- European Society of Human Reproduction and Embryology (ESHRE). Guideline on the management of women with endometriosis. 2022.[19]
- NICE clinical knowledge summary. Endometriosis. 2020.[20]

Additional Information

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