NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Linzagolix choline for treating moderate to severe symptoms associated with uterine fibroids in adult women of reproductive age

Company/Developer	Theramex

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 23994	NICE ID: 10509	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Linzagolix choline is currently in clinical development for the treatment of moderate to severe symptoms of uterine fibroids (UFs) in adult women. UFs are the most common form of benign uterine tumours, causing heavy menstrual bleeding, pelvic pain, infertility, and pressure symptoms. They can also cause bleeding between periods, anaemia, abdominal pain and cramping, painful sex, difficult, frequent, or urgent urination or bowel movements, increased abdominal size and miscarriage. However, there is a lack of safe treatment options available for this condition. Current therapy with progestins is often unsatisfactory, with many women treated by surgical intervention.

Linzagolix choline is a gonadotropin-releasing hormone (GnRH) receptor antagonist. By attaching to GnRH receptors in the pituitary gland, it blocks the action of GnRH, leading to decreased blood concentrations of estrogen and progesterone, two hormones that promote the growth of UFs. Lower concentrations of estrogen and progesterone cause fibroid cells to stop dividing and to eventually die, which shrinks the fibroids and reduces the symptoms they cause (e.g. bleeding from the womb during or outside the menstrual period; abdominal pain such as period pain). Linzagolix choline has been shown to be safe and effective in treating symptoms of UFs. If licensed, oral linzagolix choline will offer an additional treatment option for adult women with moderate to severe symptoms of UFs who currently have few well-tolerated therapies available.

Proposed Indication

Linzagolix choline is indicated for the treatment of moderate to severe symptoms of uterine fibroids (UFs) in adult women (over 18 years of age) of reproductive age.[1]

Technology

Description

Linzagolix choline (Yselty, OBE2109, KLH-2109) is a gonadotropin-releasing hormone (GnRH) receptor antagonist. By attaching to GnRH receptors (targets) in the pituitary gland, it blocks the action of GnRH, leading to decreased blood concentrations of estrogen and progesterone, two hormones that promote the growth of UFs. Lower concentrations of estrogen and progesterone cause fibroid cells to stop dividing and to eventually die, which shrinks the fibroids and reduces the symptoms they cause (such as bleeding from the womb during or outside the menstrual period and abdominal pain such as period pain).[2]

In the phase III (NCT03070899) clinical trial, two dosing regimens (100 mg and 200 mg once daily) of oral linzagolix choline were administered in different trial arms, alone or in combination with hormonal add-back therapy (ABT).[1,3]

Key Innovation

Linzagolix choline has been proven to dose-dependently lower estradiol levels hence maintaining such levels within an optimal range to mitigate bone mineral density loss and other adverse effects typically associated with currently approved treatments for endometriosis (a similar disease to UFs as they both are benign hormone-dependent diseases typically affecting women of reproductive age), removing the need for ABT. Unlike marketed GnRH agonists, linzagolix choline has the potential to be administered orally once a day, with symptoms relieved within days, which may allow patients to receive the relief needed to live normal lives again and enhance their quality of life with fewer side effects and complications requiring doctor's visits or surgery.[4,5]

Linzagolix choline is supported by data from two high quality, phase III, randomised, double-blind, placebo-controlled trials (PRIMROSE 1 and 2) that demonstrated significant reductions in mean blood loss (MBL), days of uterine bleeding and fibroid/uterine volume. Response rates were maintained across the doses and up to 52 weeks with a significant improvement in pain and improved QoL compared to placebo. Linzagolix choline was well tolerated with very low rates of linzagolix-related serious adverse events and low rates of treatment-emergent adverse events leading to discontinuation.[6,7,a] If licensed, linzagolix choline will offer an additional treatment option for adult women of reproductive age with moderate to severe symptoms of UFs who currently have few well-tolerated therapies available.

Regulatory & Development Status

Linzagolix choline was granted marketing authorisation by the EMA for the treatment of UFs on the 14th June 2022.[1]

Linzagolix choline is already licensed in the EU for the treatment of moderate to severe symptoms of UF in adult women of reproductive age.[2]

Linzagolix choline is currently in phase III/II clinical development for endometriosis.[8]

[a] Information provided by Theramex

Patient Group

Disease Area and Clinical Need

UFs are the most common form of benign uterine tumours, causing heavy menstrual bleeding (HMB), pelvic pain, infertility and pressure symptoms.[9] They can also cause bleeding between periods, anaemia, abdominal pain and cramping, painful sex, difficult, frequent, or urgent urination or bowel movements, increased abdominal size and miscarriage.[10] Several studies have shown that women with fibroids, as a result of their associated symptomatology, have a higher risk of developing emotional distress, depression, and anxiety, which can strongly impact their quality of life. There are notable racial differences in the prevalence and presentation of fibroids. Fibroids are more common, tend to present at a younger age, are greater in number, and larger in size in women of African ancestry versus white or Asian women. Other risk factors include obesity, nulliparity, hypertension, late menopause, early menarche, family history of fibroids, and older age. The impact of diet, exercise, smoking, alcohol, stress, and other environmental factors on the pathogenesis of UFs remains less clear.[11]

UFs are the most common benign pelvic tumours in women, although prevalence may be underestimated due to asymptomatic women.[12] The incidence of fibroids increases with age until the menopause. Fibroids do not occur in pre-pubescent girls. 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 a crude incidence of 22.5 per 1000 women-years. The prevalence of fibroids is higher in black women than white women. Nearly 70% of white women and more than 80% of black women have had at least one fibroid by the age of 50 years. Approximately 40% of white women and 60% of black women have had fibroids by the age of 35 years.[13] The overall incidence of UFs in the UK between 2000 and 2009 was 5.8 per 1000 woman-years among women aged 15 – 54 years.[14]

Recommended Treatment Options

NICE recommends the following treatment options for women with HMB with no identified pathology, fibroids less than 3cm in diameter, or suspected or diagnosed adenomyosis:[15]

- Levonorgestrel-releasing intrauterine system (LNG-IUS)
- If a woman with HMB declines an LNG-IUS or it is not suitable, consider the following pharmacological treatments:
    - non-hormonal: tranexamic acid or non-steroidal anti-inflammatory drugs (NSAIDs)
    - hormonal: combined hormonal contraception or cyclical oral progestogens

NICE recommends the following treatment options for women with fibroids of 3 cm or more in diameter:[15]

- Pharmacological:
    - non-hormonal: tranexamic acid and NSAIDs
    - Hormonal: LNG-IUS, combined hormonal contraception, cyclical oral progestogens or ulipristal acetate (this is only indicated for some premenopausal women)
- Uterine artery embolisation for fibroids
- Surgical:
    - myomectomy
    - hysterectomy

NICE recommends the following treatment options for adult women with moderate to severe symptoms of uterine fibroids of reproductive age:[16]

- Pharmacological:

○ Relugolix with estradiol and norethisterone acetate

Clinical Trial Information	
Trial	**PRIMROSE 1; NCT03070899;** A Phase 3, Multicentre, Randomized, Double-blind, Placebo-controlled Study Investigating the Efficacy and Safety of Daily Oral Administration of OBE2109 Alone and in Combination With Add-back Therapy for the Management of Heavy Menstrual Bleeding Associated With Uterine Fibroids in Premenopausal Women **Phase III –** Completed **Location(s):** USA **Study completion date:** April 2021
Trial Design	Randomised, parallel-assignment, quadruple-blinded, placebo-controlled
Population	N=526 (actual); premenopausal female adult women (18 years and older) with presence of UF
Intervention(s)	• 100mg linzagolix choline and placebo add-back • 100mg linzagolix choline and add-back E2 1 mg / NETA 0.5 mg • 200mg linzagolix choline and placebo add-back • 200mg linzagolix choline and add-back E2 1 mg / NETA 0.5 mg
Comparator(s)	100mg linzagolix, placebo to match 100mg linzagolix, placebo add-back and add-back (E2 1 mg / NETA 0.5 mg)
Outcome(s)	Primary outcome measure: percentage of responders based on menstrual blood loss (MBL) volume reduction at week 24 (time frame: from baseline to week 24) See trial record for full list of other outcomes
Results (efficacy)	"In PRIMROSE 1, the responder rate of the 24-week primary endpoint was 56.4% (P=0.003) and 75.5% (P<0.001) for 100mg without ABT and 200mg with ABT respectively. Each showed statistically significant improvement in comparison to placebo, and each showed improvement in clinically important secondary endpoints such as reduction in pain, improvement of anemia and QOL."[7] "The pooled data of the 2 phase 3 study results showed responder rate of 56.4% in the group who received 100mg [linzagolix choline] alone and 89.3% in the group receiving 200mg [linzagolix choline] with ABT. In the arm where linzagolix choline 200mg alone was administered for 24 weeks, then added combination use of ABT, the volume of the uterine and fibroid decreased substantially during the linzagolix choline single use period. These results supports the high dose regimen of linzagolix choline without ABT to be an option for patients who are in need of rapid shrinkage of the uterine and fibroid volume."[6]
Results (safety)	"Safety results from week 24 to 52 of PRIMROSE 1 study showed low occurrence of hot flushes, headaches, and anemia, which were the most frequently observed adverse events up to week 24 (incidence rate > 5%). For

	subjects who continued treatment beyond 24 weeks, safety results showed similar incidence rate of adverse events between placebo and active treatment. With regards to BMD, the incremental decrease in lumbar spine was similar to placebo in the 100mg treatment arm at week 52 compared to week 24, with less change seen in the 200mg with ABT."[6]

Clinical Trial Information	
Trial	**PRIMROSE 2; NCT03070951;** A Phase 3, Multicentre, Randomized, Double-blind, Placebo-controlled Study Investigating the Efficacy and Safety of Daily Oral Administration of OBE2109 Alone and in Combination With Add-back Therapy for the Management of Heavy Menstrual Bleeding Associated With Uterine Fibroids in Premenopausal Women **Phase III –** Completed **Location(s):** 7 EU countries, USA and Ukraine **Study completion date:** October 2020
Trial Design	Randomised, parallel-assignment, quadruple-blinded, placebo-controlled
Population	N=511 (actual); premenopausal female adult women (18 years and older) with presence of UF
Intervention(s)	• 100mg linzagolix choline and placebo add-back • 100mg linzagolix choline and add-back E2 1 mg / NETA 0.5 mg • 200mg linzagolix choline and placebo add-back • 200mg linzagolix choline and add-back E2 1 mg / NETA 0.5 mg
Comparator(s)	100mg linzagolix choline, placebo to match 100mg linzagolix choline, placebo add-back and add-back (E2 1 mg / NETA 0.5 mg)
Outcome(s)	Primary outcome measure: percentage of responders based on menstrual blood loss (MBL) volume reduction at week 24 (time frame: from baseline to week 24) See trial record for full list of other outcomes
Results (efficacy)	"The effect of the responder rate of PRIMROSE 2 at week-52 long-term treatment was 53.2% and 91.6% for 100mg without ABT and 200mg with ABT respectively. The efficacy of linzagolix has been sustained from the 24-week results."[7] "The pooled data of the 2 phase 3 study results showed responder rate of 56.4% in the 100mg alone and 89.3% in the 200mg with ABT. In the arm where linzagolix choline 200mg alone was administered for 24 weeks, then added combination use of ABT, the volume of the uterine and fibroid decreased substantially during the linzagolix choline single use period. These results supports the high dose regimen of linzagolix choline without ABT to be an option for patients who are in need of rapid shrinkage of the uterine and fibroid volume."[6]

Results (safety)	"In the PRIMROSE 2 study at week 76 (week 24 of the post-administration observational period), both 100mg alone and 200mg with ABT treatment arm showed recovery in BMD."[6]

Clinical Trial Information

Trial	EudraCT 2021-000452-19; A long-term follow-up study to assess bone mineral density in subjects with uterine fibroids completing the Phase 3 studies of linzagolix choline, PRIMROSE 1 or PRIMROSE 2 **Phase III –** HU, PL, LV, RO – ongoing; BG - completed **Location(s):** 6 EU countries, USA and Ukraine **Study completion date:** unclear
Trial Design	Long-term follow-up study
Population	N=400; premenopausal female adult women (18 years and older) with presence of UF
Intervention(s)	• 100mg linzagolix choline and placebo add-back • 100mg linzagolix choline and add-back E2 1 mg / NETA 0.5 mg • 200mg linzagolix choline and placebo add-back • 200mg linzagolix choline and add-back E2 1 mg / NETA 0.5 mg
Comparator(s)	100mg linzagolix, placebo to match 100mg linzagolix, placebo add-back and add-back (E2 1 mg / NETA 0.5 mg)
Outcome(s)	Primary end point: the change in lumbar spine (L1-L4), femoral neck, and total hip BMD at 12, 18 and 24 months from the end of treatment in PRIMROSE 1 and PRIMROSE 2 study participants See trial record for full list of other outcomes
Results (efficacy)	"The pooled data of the 2 phase 3 study results showed responder rate of 56.4% in the 100mg alone and 89.3% in the 200mg with ABT. In the arm where linzagolix choline 200mg alone was administered for 24 weeks, then added combination use of ABT, the volume of the uterine and fibroid decreased substantially during the linzagolix choline single use period. These results supports the high dose regimen of linzagolix choline without ABT to be an option for patients who are in need of rapid shrinkage of the uterine and fibroid volume."[6]
Results (safety)	"In the PRIMROSE 2 study at week 76 (week 24 of the post-administration observational period), both 100mg alone and 200mg with ABT treatment arm showed recovery in BMD."[6]

Estimated Cost

The cost of linzagolix choline is not yet known.

Relevant Guidance

NICE Guidance

- NICE quality standard. Heavy menstrual bleeding (QS47). March 2018.
- NICE interventional procedure guidance. Ultrasound-guided high-intensity transcutaneous focused ultrasound for symptomatic uterine fibroids (IPG657). July 2019.
- NICE interventional procedure guidance. Laparoscopic techniques for hysterectomy (IPG239). November 2007.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- NICE Clinical Knowledge Summary. Fibroids. December 2022.[17]

Additional Information

Theramex did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

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