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ADISINSIGHT REPORT

Linzagolix: First Approval

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Abstract
Linzagolix (Yselty®) is an orally administered, selective, non-peptide small molecule gonadotrophin releasing hormone (GnRH) receptor antagonist that is being developed by Kissei Pharmaceutical for the treatment of uterine fibroids and endometriosis in women of reproductive age. Linzagolix binds to and blocks the GnRH receptor in the pituitary gland, modulating the hypothalamic pituitary-gonadal axis and dose-dependently reducing serum luteinising hormone and follicle-stimulating hormone production and serum estradiol levels. In June 2022, linzagolix was approved for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age in the EU. Linzagolix is under regulatory review the USA for this indication and is in phase 3 clinical development in the treatment of pain associated with endometriosis. This article summarizes the milestones in the development of linzagolix leading to this first approval for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

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Linzagolix (Yselty®): Key points

An oral, non-peptide small molecule gonadotrophin releasing hormone (GnRH) receptor antagonist being developed by Kissei Pharmaceutical for the treatment of uterine leiomyoma and endometriosis

Received its first approval on 17 June 2022 in the EU

Approved for use in the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age

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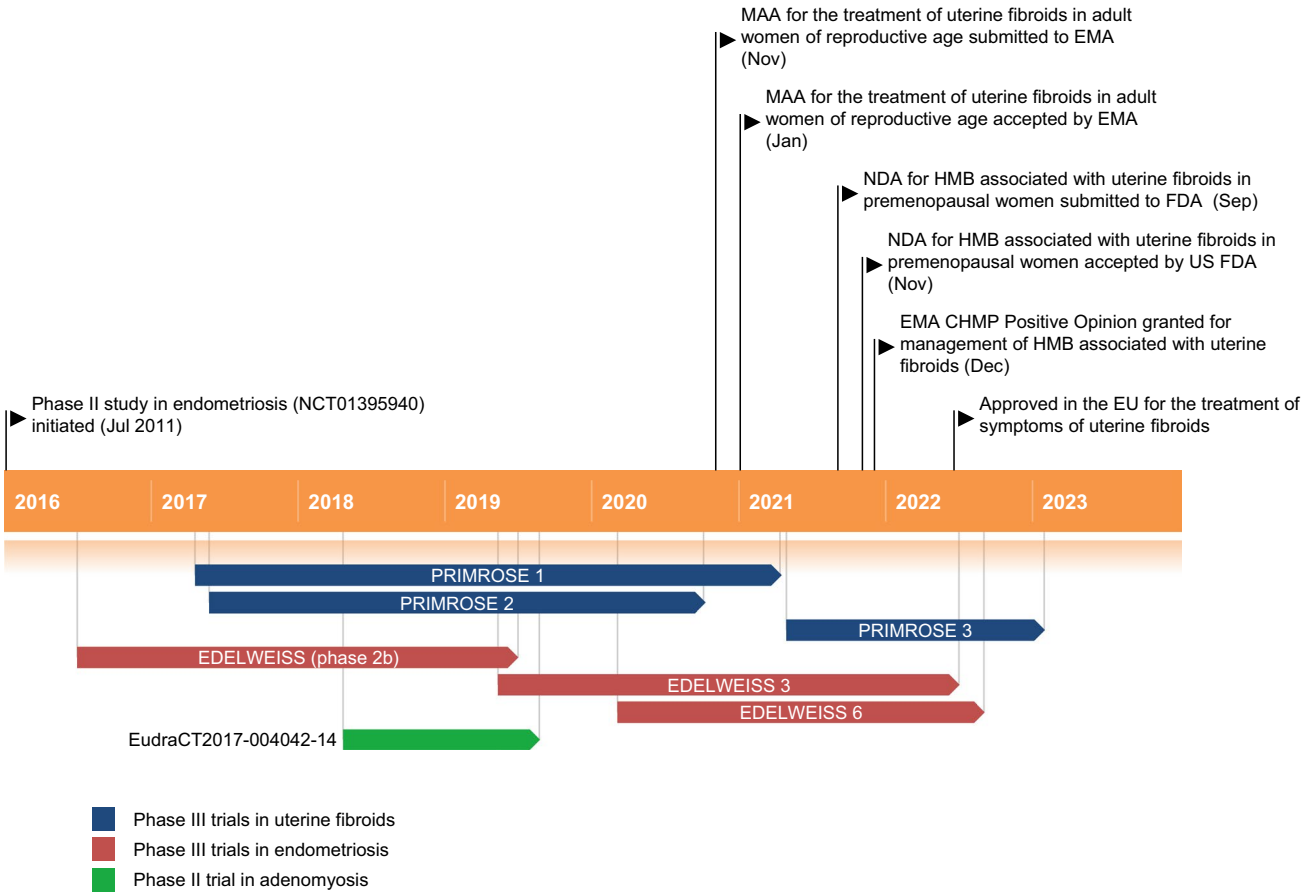
1 Introduction

Estrogen-related uterine disorders in women of reproductive age include fibroids (uterine leiomyomas), endometriosis (the presence of endometrium-like tissue outside the uterine cavity) and adenomyosis (a disorder where endometrial glands and stroma are found pathologically in uterine wall muscle) [1–3].

Uterine fibroids occur in > 70% of women of reproductive age [1, 4] and when symptomatic, are often accompanied by heavy menstrual bleeding, anaemia, abdominal pressure and pain, bloating, increased urinary frequency and reproductive dysfunction; they are also associated with an increased risk of pregnancy complications. Approximately 25% of women with fibroids experience symptoms severe enough to require treatment [4], which most often consists of surgery (myomectomy or hysterectomy). Pharmacological management provides an alternative for patients wishing to preserve fertility [1].

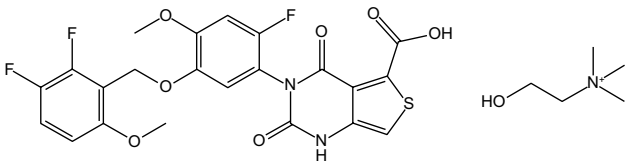
Endometriosis is an inflammatory disorder that is associated with chronic pain and infertility and affects 5–10% of women of reproductive age [2, 5, 6]. Estradiol, which is recognised to have proinflammatory and antiapoptotic effects on ectopic endometrial cells, is required for proliferation of endometriotic deposits [5]. Consequently, lowering levels



Key milestones in the development of linzagolix for the treatment of uterine fibroids and endometriosis in women of reproductive age. *HMB* heavy menstrual bleeding, *MAA* marketing authority application, *NDA* New Drug Application

of circulating estrogens is an effective medical approach [6, 7]. Although the pathogenesis of uterine adenomyosis is not fully understood [8], estrogens are thought to have an important role in its development. Adenomyosis has an estimated prevalence of 20-30% in women of reproductive age and can be associated with deep endometriosis. Women with the disorder often experience severe pelvic pain, abnormal uterine bleeding and infertility. As adenomyosis is estrogen-dependent, estrogen suppression may be of benefit in managing symptoms [8, 9].

The choice of pharmacological agents to manage these uterine disorders has been expanded more recently by the development of gonadotrophin releasing hormone (GnRH) antagonists, which can be administered with or without hormonal add-back therapy (ABT) [estradiol/norethisterone acetate] [1]. Linzagolix (as the choline salt) [Yselty®] is an orally administered, selective, non-peptide small molecule gonadotrophin releasing hormone (GnRH) receptor antagonist that is being developed by Kissei Pharmaceutical for the treatment of uterine fibroids and endometriosis in women of reproductive age [10, 11]. In June 2022, linzagolix was approved for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age in the EU [11, 12]. The recommended dosage is 100 mg or, if needed, 200 mg once daily with concomitant ABT (estradiol 1 mg and norethisterone acetate 0.5 mg tablet once daily) or 100 mg once daily without ABT for women in whom ABT is not recommended or who prefer to avoid hormonal therapy [12]. Linzagolix can be taken with or without food. Pregnancy must be ruled out prior to initiating treatment and treatment with linzagolix should preferably be started in the first week of a menstrual cycle. Short-term (< 6 months) use of linzagolix 200 mg once daily is indicated in clinical situations when reduction of uterine and fibroid volume is desired, although fibroid size may increase once treatment ceases. Linzagolix 200 mg once daily without ABT should not be prescribed for > 6 months because of the risk of bone mineral density (BMD) decrease with prolonged use. Treatment with linzagolix should be avoided in patients with moderate or severe kidney impairment or with end-stage kidney disease and in those with severe hepatic impairment because of increased unbound linzagolix mean exposures. Mood disorders including depression, alterations in mood, and emotional lability have been observed with treatment



Chemical structure of linzagolix choline

with GnRH antagonists including linzagolix; caution is required in patients with a history of depression and/or suicidal ideation. Linzagolix is contraindicated in pregnancy or breastfeeding and in patients with known osteoporosis or with genital bleeding of unknown aetiology [12]. Linzagolix is under regulatory review in the USA for uterine fibroids and is in phase 3 clinical development in the treatment of pain associated with endometriosis [13]; investigation of the potential role of linzagolix in the management of severe uterine adenomyosis is also underway [14].

1.1 Company Agreements and Patents

In July 2022, ObsEva terminated a license agreement with Kissei for linzagolix following notification from the FDA of review issues regarding deficiencies in the New Drug Application for linzagolix for uterine fibroids, which precluded discussion of labeling and post-marketing commitments at this time [15]. Termination of this license also caused ObsEva's licensing agreement with Theramex for linzagolix to be assigned to Kissei [15].

In February 2022, ObsEva entered into a licensing agreement with Theramex for the commercialization and market introduction of linzagolix worldwide excluding the USA, Canada and Asia [13]. In October 2021, ObsEva's exclusive license and supply agreement with Kissei for linzagolix was amended so that first commercial sales milestones for the EU and the US will be extended over a 5-year period [16]. In October 2021, ObsEva announced a strategic relationship with Syneos Health to commercialize linzagolix within the USA [16]. In November 2015, Kissei Pharmaceuticals had granted ObsEva worldwide rights, excluding Japan and other Asian countries, to develop and commercialise linzagolix for the treatment of endometriosis [17, 18]. In September 2021, Kissei Pharmaceutical entered into a licensing agreement with Bio Genuine for the development and commercialization rights of linzagolix in China. Under the terms of the agreement, Bio Genuine will develop and commercialize linzagolix in China [19].

As of December 2020, the linzagolix patent portfolio includes two US patent applications which, if granted, project to expire in 2038 (plus corresponding patent applications internationally, directed to uses of linzagolix for the treatment of sex hormone-dependent diseases) and four PCT applications, which, if granted in the US, project to expire between 2039 and 2040, directed to uses of linzagolix for the treatment of sex hormone-dependent diseases. The in-licensed patents include four US patents, projected to expire between 2030 and 2032, two US patent applications which, if granted, project to expire between 2031 and 2037 plus corresponding patents and patent applications internationally outside of specified Asian countries, directed to linzagolix as a composition of matter and uses of linzagolix for the treatment of sex hormone-dependent diseases [20].

1.2 Pharmacodynamics

Linzagolix binds to and blocks the GnRH receptor in the pituitary gland, modulating the hypothalamic pituitary-gonadal axis, resulting in a dose-dependent reduction of serum luteinising hormone (LH) and follicle-stimulating hormone (FSH) production and a subsequent dose-dependent reduction of serum estradiol and progesterone [12, 21]. Estradiol levels of 20–50 pg/mL (the low-normal range resulting from partial suppression) are the optimal range for improving symptoms associated with endometriosis or uterine fibroids; full suppression of the hypothalamic pituitary-gonadal axis results in estradiol levels < 20 pg/mL and is associated with an increased incidence of hot flushes [22].

GnRH receptors couple with Gαq/11, and their activation increases intracellular Ca^{2+} [23]. In vitro, linzagolix dose-dependently inhibited GnRH-stimulated Ca^{2+} flux (IC_{50} against human GnRH receptor of 36.7 nmol/L) and activity was comparable to that of the peptide GnRH antagonist cetrorelix (IC_{50} 19.9 nmol/L) [24]. In an ovariectomized cynomolgus monkey model, oral linzagolix suppressed serum LH levels dose-dependently over a 1–25 mg/kg dose range at 8 h after administration. After administration of linzagolix 25–100 mg/kg, a maximum reduction in LH levels of ≈ 80% from baseline was evident at 8 h, and suppression of LH persisted for ≥ 24 h (LH levels in animals receiving a < 10 mg/kg dose recovered after 24 h). In intact female cynomolgus monkeys, GnRH signalling (cyclic surges of serum estradiol and LH) was partially blocked with oral linzagolix 10 mg/kg twice daily and fully blocked with linzagolix 25 or 50 mg/kg twice daily compared with vehicle. On withdrawal of linzagolix administration, hormone secretion and regular menstrual cycles resumed within one cycle [24].

Linzagolix 100 or 200 mg once daily, with or without ABT, rapidly reduced estradiol levels in healthy premenopausal women ($n = 76$) in a 6-week phase 1 trial (EudraCT 2016-004732-38) in a dose-dependent manner [22]. Median estradiol levels after weeks 1 and 6 of treatment were 12.0

and 18.0 pg/mL in the linzagolix 100 mg/day group, 24.5 and 39.5 pg/mL in the linzagolix 100 mg/day + low ABT (estradiol/norethindrone acetate 0.5mg/0.1mg) group, 35.0 and 34.0 pg/mL in the linzagolix 100mg + standard ABT (estradiol/norethindrone acetate 1mg/0.5mg) group, 4.6 and 3.1 pg/mL in the linzagolix 200 mg group and 27.0 and 25.0 pg/mL in the linzagolix 200 mg + standard ABT group. In the final 4 weeks of treatment, amenorrhea was achieved in > 85% of women with linzagolix alone. The addition of ABT to a 200 mg/day dose of linzagolix increased serum estradiol levels to within the optimal range and reduced the incidence of hot flushes. Reductions in markers of bone metabolism were greatest in the linzagolix 200 mg/day group, but were mitigated by the coadministration of ABT. The effects of linzagolix are reversible following treatment withdrawal; 2 weeks after ceasing treatment, serum estradiol levels indicated that ovarian function has resumed [22].

Treatment with linzagolix 200 mg once daily resulted in full suppression of serum estradiol from 4 to 24 weeks in the phase 3 PRIMROSE 1 (NCT03070899) and PRIMROSE 2 (NCT03070951) trials in in premenopausal women with uterine fibroids [12]. Partial suppression was seen from 4 to 52 weeks in patients treated with once daily linzagolix 100 mg with or without ABT (ABT was estradiol 1 mg/norethisterone acetate 0.5 mg) and in those treated with linzagolix 200 mg with ABT (median serum estradiol levels 20–60 pg/mL). Progesterone levels were maintained at ≤ 3.1 ng/mL in the majority of patients in the linzagolix treatment arms in PRIMROSE 1 and PRIMROSE 2 (83% of those receiving linzagolix 200 mg for 24 weeks, 68% of those receiving linzagolix 100 mg for 52 weeks and ≈ 90% of those receiving linzagolix 100 mg or 200 mg with ABT for 52 weeks) [12]. At week 64 (i.e. 12 weeks after competing treatment) in patients who had amenorrhoea at week 52, the median time to first uterine bleeding was 30 days in PRIMROSE 1 and 31 days in PRIMROSE 2 [25].

In the phase 3 PRIMOROSE 1 and PRIMROSE 2 trials, increases in LDL cholesterol (mainly < 15% from baseline), HDL cholesterol, and triglycerides (< 20% from baseline) occurred in all linzagolix arms; increases in the linzagolix without ABT arms were generally higher than in the linzagolix with ABT arms [12]. Increases in lipid parameters were evident from week 12 and had generally stabilised after 52 weeks of treatment but were generally of no clinical relevance. At 12 weeks after stopping treatment, lipid levels had reduced but had not reached baseline levels [12].

Linzagolix had no clinically relevant effects on the QTc interval in a thorough-QTc study in healthy women; however caution is required in patients with known cardiovascular disease, a family history of QT prolongation or hypokalaemia, co-existing disorders leading to increased linzagolix plasma levels, and in concomitant use with medicinal products known to prolong the QT interval [12].

1.3 Pharmacokinetics

The pharmacokinetics of linzagolix are dose-linear and there is no relevant accumulation at steady state [12, 26]. After oral administration, linzagolix is rapidly absorbed, with peak plasma levels occurring ≈ 2 h after administration of a single 100 mg or 200 mg dose [12], has high (80%) bioavailability after oral administration and can be administered with or without food [12]. In a phase 1 trial in healthy premenopausal women (EudraCT 2016-004732-38), the median linzagolix trough levels were 3250–4750 ng/mL in the 100 mg/day group and 6700–11,700 ng/mL in the 200 mg/day group [22]. Linzagolix is highly bound to plasma proteins (> 99%; mainly to albumin) and the volume of distribution after 7 days' oral administration of linzagolix 100 mg or 200 mg is ≈ 11 L. Up to seven metabolites have been identified in plasma, urine and faeces; however, unchanged linzagolix is the predominant component in plasma and urine, and is one of the major components in faeces [12]. Linzagolix After administration of multiple doses of linzagolix 100 mg and 200 mg, the geometric mean apparent clearance is ≈ 0.5 L/h and the half-life is ≈ 15 h. Linzagolix is mainly excreted in urine, with approximately one-third excreted in faeces [12].

After administration of a single 200 mg dose of linzagolix in women with mild kidney impairment (eGFR 60-89 mL/min), unbound plasma linzagolix exposure was increased ≈ 1.3-fold; dosage adjustment is not required, but patients should be monitored for adverse reactions. In moderate (eGFR 30-59 mL/min), severe (eGFR < 30 mL/min) and end-stage kidney disease, ≈ 1.5-fold (in moderate) and 2-fold (in severe and end-stage kidney disease) higher unbound linzagolix mean exposures were seen after a single 200 mg dose of linzagolix [12]. Mild or moderate hepatic impairment (Child-Pugh A or B) had no clinically relevant effect on total plasma exposure after administration of a single 200 mg dose of linzagolix; however, in patients with severe hepatic impairment (Child-Pugh C), unbound linzagolix mean plasma exposures were increased 2- to 3-fold [12].

Linzagolix doses up to 200 mg neither induced nor inhibited CYP3A4 [27]. Linzagolix use should be avoided in patients using CYP2C8 sensitive substrate medicinal products with a narrow therapeutic index (e.g., paclitaxel, sorafenib and repaglinide) because of increased exposure to these products. Patients should be monitored for increases in adverse reactions associated with other CYP2C8 substrates when co-administered with linzagolix [12].

Features and properties of Linzagolix

Alternative names	KLH-2109; KLH-2109-choline; OBE-2109; OBE-2109-choline; Yselty
Class	2 ring heterocyclic compounds, Antihormones, Antineoplastics, Carboxylic acids, Fluorinated hydrocarbons, Ketones, Pyrimidines, Small molecules, Thiophenes
Mechanism of action	GnRH receptor antagonist
Route of administration	Oral
Pharmacodynamics	Binds to and blocks the GnRH receptor in the pituitary gland, modulating the hypothalamic pituitary-gonadal axis, which results in reduced LH and FSH production and a reduction in estrogen levels. Mild reduction in bone mineral density; no clinically relevant effects on serum lipids. Effects on hypothalamic pituitary-gonadal axis are reversible once treatment ceases.
Pharmacokinetics	Dose-linear; $T_{max} \approx 2$ h, > 99% plasma protein bound; $V_d \approx 11$ L, CL/F ≈ 0.5 L/h, $t_{1/2} \approx 15$ h, mainly excreted in urine as unchanged drug
Adverse events	
Most frequent	hot flushes, headache, BMD loss
Occasional	mood disorders, elevated liver enzymes, vaginal haemorrhage
ATC codes	
WHO ATC code	G02C (Other Gynecologicals)
EphMRA ATC code	G2X (Other Gynaecological products)
Chemical name	3-[5-[(2,3-difluoro-6-methoxyphenyl)methoxy]-2-fluoro-4-methoxyphenyl]-2,4-dioxo-1H-thieno[3,4-d]pyrimidine-5-carboxylate;2-hydroxyethyl(trimethyl)azanium

1.4 Therapeutic Trials

1.4.1 Heavy Menstrual Bleeding Due to Uterine Fibroids

Linzagolix was effective in reducing heavy menstrual bleeding in premenopausal women with uterine fibroids in two identically designed phase 3 trials [PRIMROSE 1 (NCT03070899) conducted in the USA ($n = 526$; mean age 42 years) and PRIMROSE 2 (NCT03070951) conducted in the USA and Europe ($n = 511$; mean age 43 years) [28–31]. Trial participants in both studies were randomized to receive once daily linzagolix 100 mg, linzagolix 100 mg + ABT, linzagolix 200 mg, linzagolix 200 mg + ABT or placebo for 52 weeks. At week 24 in PRIMROSE 1, the response rate (reduction in alkaline-hematin documented heavy menstrual bleeding to ≤ 80 mL menstrual blood loss and a reduction of ≥ 50% over the last 28 days at week 24; primary efficacy endpoint) was significantly higher in the linzagolix 100 mg, 100 mg + ABT, 200 mg and 200 mg + ABT groups than in the placebo group (56.4%, 66.4%, 71.4% and 75.5% vs 35.0%; $p \leq 0.003$). At week 24 in PRIMROSE 2 the response rate was also significantly higher with linzagolix (with or without ABT) than placebo (56.7%, 77.2%, 77.7% and 93.9% vs 29.4%; $p < 0.001$) [12, 30]. In both trials, a maximal effect was seen after 4 weeks of treatment in the linzagolix 100 mg arms (≈60% reduction in menstrual blood loss), and after 8 weeks in the linzagolix 100 mg + ABT, 200 mg and 200 mg + ABT arms (≈80–95% reduction) and was maintained at 52 weeks [12]. Response rates with linzagolix with or without ABT were maintained at 52 weeks in both trials [29, 30, 32]; at week 52, pooled data from PRIMROSE 1 and PRIMROSE 2 showed a response rate of 89.3% in women receiving linzagolix 200 mg with ABT and 56.4% in women receiving linzagolix 100 mg without ABT [32], which was consistent with response rates seen at week 24 (84.5% and 56.5%, respectively) [27].

At week 24, amenorrhea rates in PRIMROSE 1 and PRIMROSE 2 were significantly greater in the linzagolix treatment groups than in the placebo group and the time to reduced menstrual bleeding loss/amenorrhea and days of uterine bleeding were shorter. Mean haemoglobin levels were higher, mean uterine and fibroid volume was lower, and mean pain and mean health-related quality of life total scores were improved with linzagolix versus placebo [29–31]. The magnitude of improvements was greater with linzagolix 100 mg + ABT, 200 mg and 200 mg + ABT than with linzagolix 100 mg and improvements were maintained at week 52 [31].

In the PRIMROSE trials, eligible women had heavy menstrual bleeding (> 80 mL menstrual blood loss/cycle and had no significant risk of osteoporosis; at baseline mean menstrual blood loss/cycle was 199 mL in PRIMROSE 1 and 201 mL in PRIMROSE 2 [30].

1.4.2 Endometriosis-Associated Pain

Linzagolix improved dysmenorrhea and non-menstrual pelvic pain in the randomized, double-blind, placebo-controlled phase 3 EDELWEISS 3 trial (NCT03992846) conducted in Europe and the USA in women with

moderate-to-severe endometriosis-associated pain (n = 484) [33]. Patients were randomized to receive linzagolix 200 mg + ABT (estradiol 1 mg/norethisterone acetate 0.5 mg) linzagolix 75 mg or placebo once daily. Significantly more linzagolix 200 mg + ABT than placebo recipients reported reductions in dysmenorrhea (72.9% vs 23.5%; $p < 0.001$) and non-menstrual pelvic pain at 3 months (47.3% vs 30.9%; $p = 0.007$) [co-primary endpoints]. While significantly more linzagolix 75 mg than placebo recipients reported reductions in dysmenorrhea (44.0% vs 23.5%; $p < 0.001$), the between group difference for non-menstrual pelvic pain was not significant (38.9% vs 30.9%). At 6 months, improvements in the first five ranked secondary endpoints were significantly greater with linzagolix 200mg + ABT or linzagolix 75 mg than with placebo (changes in dysmenorrhea score [both $p < 0.001$ vs placebo]; changes in non-menstrual pelvic pain score [$p = 0.002$ and $p = 0.048$]; change in dyschezia score ($p = 0.012$ and 0.015]; change in overall pelvic pain [$p < 0.001$ and $p = 0.024$]; change in difficulty of doing daily activities [$p < 0.001$ and $p = 0.001$]) [33]. At 6 months, Mean Endometriosis Health Profile-30 scores were improved from baseline to a greater extent ($p < 0.05$) with linzagolix 200mg + ABT or linzagolix 75 mg than with placebo and a greater reduction in physician and patient intention for surgery in the linzagolix treatment arms was also reported ($p <$ 0.05 vs placebo) [34].

Linzagolix reduced endometriosis-associated pain and improved health-related quality of life in patients with endometriosis and moderate-to-severe endometriosis-associated pain in the dose-ranging, phase 2b EDELWEISS trial (NCT02778399) conducted in Europe and the USA [35]. EDELWEISS compared once daily oral doses of linzagolix 50 mg ($n = 49$), 75 mg ($n = 56$ fixed dose and $n = 58$ titrated dose), 100 mg ($n = 51$) and 200 mg ($n = 56$) with placebo ($n = 53$). Subjects randomized to placebo were crossed over to 100 mg after 12 weeks and those randomized to 200 mg were crossed over to 100 mg after 24 weeks; all trial participants could extend treatment to 52 weeks [28, 35, 36]. Significantly more linzagolix 75 mg, 100 mg and 200 mg recipients than placebo recipients were responders (≥ 30% reduction in overall pelvic pain) at 12 weeks (61.5%, 56.4%, and 56.3% vs 34.5%; $p = 0.003$, $p = 0.039$, $p = 0.034$ vs placebo, respectively) [primary endpoint]. The difference in response rates in the linzagolix 50 mg and placebo groups was not significant (49.4% vs 34.5%). At week 12, significantly more linzagolix 75 mg, 100 mg and 200 mg recipients than placebo recipients also experienced a ≥ 30% reduction in dysmenorrhea (68.2%, 68.6% and 78.9% vs 28.5%; all $p < 0.001$ vs placebo) and significantly more linzagolix 75 mg and 100 mg recipients than placebo recipients experienced a ≥ 30% reduction in non-menstrual pelvic pain (58.5% and 61.5% vs 37.1%; $p = 0.017$ and $p = 0.022$); the difference between the linzagolix 200 mg (47.7%) and placebo (37.1%) response rates was not significant. Significant improvements in the linzagolix ≥ 75 mg treatment arms compared to placebo ($p < 0.05$) in terms of health-related quality of life (HR-QOL; assessed using Patient Global Impression of Change and the 30-item Endometriosis Health Profile questionnaires) were evident at 12 weeks [35]. The proportion of responders for overall pelvic pain, dysmenorrhoea and non-menstrual pelvic pain and the improvements in HR-QOL seen with linzagolix doses ≥ 75 mg once daily at 12 weeks were maintained at 52 weeks [28, 36].

1.4.3 Uterine Adenomyosis

Treatment with high-dose linzagolix 200 mg once daily for 12 weeks followed by a 100 mg/day maintenance dosage for a further 12 weeks significantly reduced uterine volume and adenomyosis-related symptoms, including pelvic pain and dysmenorrhea, in an exploratory phase 2 trial in 8 premenopausal women with symptomatic uterine adenomyosis (EudraCT 2017-004042-14) [9]. At 24 weeks, mean uterine volume on MRI was significantly ($p = 0.0057$) reduced by 32% from baseline (from a mean 333 cm^3 to 204 cm^3; primary endpoint). The 55% reduction from baseline in mean uterine volume seen at the 12-week assessment was also significant ($p < 0.0001$; mean uterine volume reduced to 159 cm^3). Women eligible for this study were aged 37–45 years and had symptoms of heavy menstrual bleeding, pelvic pain and dysmenorrhea due to diffuse and disseminated uterine adenomyosis confirmed by MRI [9].

1.5 Adverse Events

Linzagolix was safe and well tolerated in the phase 3 PRIMROSE 1 and PRIMROSE 2 trials in patients with heavy menstrual bleeding associated with uterine fibroids [12, 30]. The most common adverse events in the linzagolix arms were hot flushes and headache, which were more common at higher linzagolix doses, and less frequently in the linzagolix + ABT arms [12]. At week 24, hot flushes occurred in 32-35% of those receiving linzagolix 200 mg without ABT and in < 15% of those receiving linzagolix 100 mg, linzagolix 100 mg + ABT or linzagolix 200 mg + ABT [30].

Key clinical trials of Linzagolix

Drug(s)	Indication	Phase	Status	Location(s)	Company	Identifier
Linzagolix, placebo, add-back therapy	HMB with uterine fibroids in premenopausal women	3	Ongoing	Europe, USA	ObsEva SA	PRIMROSE 3; EudraCT 2021-000452-19
Linzagolix, placebo, add-back therapy	HMB with uterine fibroids in premenopausal women	3	Completed	Europe	ObsEva SA	PRIMROSE 2; NCT03070951; EudraCT 2016-004059-53
Linzagolix, placebo, add-back therapy	HMB with uterine fibroids in premenopausal women	3	Completed	USA	ObsEva SA	PRIMROSE 1; NCT03070899
Linzagolix, placebo, add-back therapy	Endometriosis-associated pain	3	Ongoing	Europe, USA	ObsEva SA	EDELWEISS 6; NCT04335591; EudraCT 2019-002410-39
Linzagolix, placebo, add-back therapy	Endometriosis-associated pain	3	Terminated	USA, Canada, Puerto Rico	ObsEva SA	EDELWEISS 5; NCT04372121
Linzagolix, placebo, add-back therapy	Endometriosis-associated pain	3	Ongoing	Europe & USA	ObsEva SA	EDELWEISS 3; NCT03992846; EudraCT 2019-000283-26
Linzagolix, placebo, add-back therapy	Endometriosis-associated pain	3	Terminated	USA, Canada, Puerto Rico	ObsEva SA	EDELWEISS 2; NCT03986944
Linzagolix, placebo	Endometriosis-associated pain	2b	Completed	Poland, Russia, Ukraine, USA	ObsEva SA	EDELWEISS; NCT02778399
Linzagolix	Rectovaginal endometriosis	2	Terminated	France	ObsEva SA	EudraCT 2017-004043-21
Linzagolix, placebo, leuprorelin acetate (reference)	Endometriosis-associated pain	2	Completed	Japan	Kissei Pharmaceutical	NCT02778919
Linzagolix	Endometriosis-associated pain	2a	Completed	Japan	Kissei Pharmaceutical	NCT01629420
Linzagolix, placebo	Endometriosis-associated pain	2a	Completed	Japan	Kissei Pharmaceutical	NCT01533532
Linzagolix	Endometriosis-associated pain	2a	Completed	Japan	Kissei Pharmaceutical	NCT01395940
Linzagolix	Uterine adenomyosis	2	Completed	France	ObsEva SA	EudraCT 2017-004042-14

Add-back therapy was estradiol/ norethisterone acetate. The phase 3 EDELWEISS 2 and 5 trials terminated prematurely due to Covid-19 impact on enrollment. *HMB* heavy menstrual bleeding

Headaches were reported in 4.0% and 6.2% of linzagolix 100 mg and 200 mg recipients and 1.4% and 2.4% of linzagolix 100 mg + ABT and linzagolix + ABT 200 mg recipients [12]. Other adverse reactions (including mood disorders and elevated liver enzymes) occurred in < 3% of patients [12]. Vaginal haemorrhage was reported in 1.6% of linzagolix recipients, metrorrhagia on 1.3% and menorrhagia in 0.6%. Vaginal haemorrhage (but not metrorrhagia or menorrhagia) was more frequent in the linzagolix + ABT groups than in the linzagolix without ABT groups (up to 2.4% vs 1.0%) [12]

The most frequent adverse events reported with daily linzagolix 200 mg + ABT, linzagolix 75 mg or placebo during 6 months' treatment in women with moderate-to-severe endometriosis-associated pain in the phase 3 EDELWEISS 3 trial were headache (10.5%, 8.1%, and 8.0%, respectively), hot flushes (6.8%, 7.5%, and 2.5%), and fatigue (6.8%, 3.8%, and 2.5%) [33]. Hot flushes (14.3%, 19.3%, 26.9%, and 42.1% with linzagolix 50 mg, 75 mg, 100 mg or 200 mg vs 10.9% with placebo) and headache (20.4%, 20.2%, 23.1% and 29.8% vs 25.5%) were the most frequent adverse events reported at 12 weeks in the phase 2 dose-ranging EDELWEISS trial in women with moderate-to-severe endometriosis-associated pain [35].

In patients with uterine adenomyosis treated with linzagolix in a phase 2 study (EudraCT 2017-004042-14), mild and moderate hot flushes were the most common treatment-emergent adverse events related to the study drug. No serious adverse effects were reported. Hot flushes occurred

most frequently during the 12-week linzagolix 200 mg/day treatment period (in 6 of 8 women) and resolved during the 12-week 100 mg/day treatment period (reported in 1 of 8 women) [9].

1.5.1 Effects on Bone Mineral Density

In PRIMROSE 1 and PRIMROSE 2, the mean % loss in BMD at the lumbar spine at week 24 was 0-2% in the linzagolix 100 mg, linzagolix 100 mg + ABT or linzagolix 200 mg + ABT groups and 3-4% in the linzagolix 200 mg without ABT group [30]. At 24 weeks, mean decreases from baseline of > 3% and > 8% in lumbar spine BMD were seen in 36% and 3% of patients in the linzagolix 100 mg arm, 0% and 20% of those in the linzagolix 100 mg + ABT arm, 55% and 4% of those in the linzagolix 200 mg and 26% and 1% of those in the linzagolix 200 mg + ABT arm. The rate of BMD loss slowed during weeks 24–52 of treatment (linzagolix 200 mg without ABT was not studied during this time period [12]) [30]; after 12 months of treatment, mean decreases from baseline of > 3% and > 8% in lumbar spine BMD were seen in 38% and 7% of patients in the linzagolix 100 mg arm, 16% and 0% of those in the linzagolix 100 mg + ABT arm and 27% and 1% of those in the linzagolix 200 mg + ABT arm [12]. At the 24-week post-treatment evaluation (i.e. at 76 weeks) in PRIMROSE 1 and PRIMROSE 2, there was evidence of recovery of BMD from changes seen at 52 weeks in all treatment groups [12, 25].

At 6 months in the phase 3 EDELWEISS 3 trial in women with moderate-to-severe endometriosis-associated pain, the mean BMD decrease at the lumbar spine in linzagolix 200 mg + ABT recipients was 0.79% and that in linzagolix 75 mg recipients was 0.89% [33]. At 24 weeks in the phase 2, dose-ranging EDELWEISS trial in women with moderate-to-severe endometriosis-associated pain, mean BMD decreases in the lumbar spine at 24 weeks were < 1% in the linzagolix 50 mg and 75 mg treatment arms and 1.37% and 2.6% in the linzagolix 100 mg and 200 mg arms. Dose-related reductions in BMD of the femoral neck and total hip were also evident [35]. At 52 weeks, mean BMD decreases in the lumbar spine were ≤ 1.14% in the linzagolix 50 mg and 75 mg arms and 1.4% and 2.19% in the 100 mg and 200/100 mg arms [31].

In patients with uterine adenomyosis treated in the phase 2 trial of linzagolix 200 mg/day for 12 weeks the 100 mg/day for 12 weeks, the mean % BMD loss at 24 weeks was − 2.4% for the spine, − 1.3% for the femoral neck and − 4.1% for the total hip [9].

1.6 Ongoing Clinical Trials

Ongoing clinical trials of linzagolix are the 2-year phase 3 PRIMROSE 3 trial (EudraCT 2021-000452-19), which is enrolling women who participated in PRIMROSE 1 and PRIMROSE 2 and will evaluate long-term effects on BMD, and the EDELWEISS 3 and EDELWEISS 6 trials in women with endometriosis-related pain. The Kissei pipeline (as at February 2022) indicates that a clinical trial of linzagolix in endometriosis and uterine leiomyoma conducted by Bio Genuine in China is planned [37].

2 Current Status

Linzagolix received its first approval on 17 June 2022 for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age in the EU [11, 12].

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Declarations

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