17 October 2024
EMA/CHMP/73456/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Yselty

International non-proprietary name: Linzagolix choline

Procedure No. EMEA/H/C/005442/II/0013

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABT	Add-back therapy
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time zero to infinity
BMD	Bone Mineral Density
BMI	Body Mass Index
CDF	Cumulative distribution function
CI	Confidence interval
C_{max}	Maximum plasma concentration
COC	Combined oral contraceptive
CDF	Cumulative distribution function
CYP450	Cytochrome P450
DXA	Dual-energy X-ray absorptiometry
E2	Estradiol/Estradiol
EAP	Endometriosis-associated pain
ECG	Electrocardiography
EQ-5D-5L	Health outcomes questionnaire from the EuroQoL Group
ESHRE	European Society of Human Reproduction and Embryology
FAS	Full analysis set
FBG	Fluid bed granulation
FSH	Follicle-stimulating hormone
FuEAS	Follow-up Extension Analysis Set
GGT	Gamma-glutamyltransferase
GnRH	Gonadotropin-releasing hormone
Hb	Haemoglobin
HMB	Heavy menstrual bleeding
HPRA	Health Products Regulatory Authority
HRQL	Health Related Quality of Life
HSG	High shear granulation
IUD	Intra-Uterine Device
INR	International normalized ratio

J-Tpeakc	Heart-rate corrected J-Tpeak interval
LFT	Liver function test
LH	Luteinizing hormone
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MCT	Meaningful change threshold
MHRA	Medicines and Healthcare products Regulatory Agency
MPA	Swedish Medical Products Agency
mPGIS	Monthly Patient Global Impression of Severity
NETA	Norethisterone acetate
NMPP	Non-menstrual pelvic pain
NRS	Numeric Rating Scale
OPP	Overall pelvic pain
PD	Pharmacodynamics
PDF	Probability distribution function
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PPGIC	Post-treatment Patient Global Impression of Change
PRO	Patient-reported outcome
PSIQ	Physician Surgery Intention Question
PT	Preferred term
PTFU	Post-treatment follow-up
ROC	Receiver operating characteristic
QoL	Quality of Life
QTcF	QT interval corrected for heart rate (QTc) using Fridericia’s correction formula
SAE	Serious adverse event
SD	Standard deviation
SSIQ	Subject Surgery Intention Question
TEAS	Treatment Extension Analysis Set
TQT	Thorough QT (study)
ULN	Upper Limit Normal
VRS	Verbal Rating Scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Theramex Ireland Limited submitted to the European Medicines Agency on 15 February 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of endometriosis-associated pain in adult women of reproductive age for YSELTY, based on final results from studies Edelweiss 3 (18-OBE2109-003) and Edelweiss 6 (19-OBE2109-006) as well as additional supporting studies. Edelweiss 3 is a pivotal phase 3, randomised, double-blind, placebo-controlled, safety and efficacy study to evaluate linzagolix with add-back therapy as a therapy for pain associated with endometriosis, while Edelweiss 6 is an open-label extension study including patients who completed Edelweiss 3 pivotal study regardless of their previous treatment assignment and met the eligibility criteria. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted. As part of the application, the MAH is requesting a 1-year extension of the market protection.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) EMEA-002039-PIP01-16 on the granting of a (product-specific) waiver for both indications, i.e. leiomyoma of uterus (uterine fibroids) and endometriosis.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. This request was withdrawn by the MAH during the assessment.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.1.1. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Finbarr Leacy Co-Rapporteur: Margareta Bego

Timetable	Actual dates
Submission date	15 February 2024
Start of procedure:	2 March 2024
CHMP Rapporteur Assessment Report	29 April 2024
PRAC Rapporteur Assessment Report	2 May 2024
CHMP Co-Rapporteur Assessment	7 May 2024
PRAC Outcome	16 May 2024
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 May 2024
Request for supplementary information (RSI)	30 May 2024
CHMP Rapporteur Assessment Report	21 August 2024
PRAC Rapporteur Assessment Report	23 August 2024
PRAC members comments	28 August 2024
PRAC Outcome	5 September 2024
CHMP members comments	9 September 2024
Updated CHMP Rapporteur Assessment Report	12 September 2024
Request for supplementary information (RSI)	19 September 2024
PRAC Rapporteur Assessment Report	1 October 2024
CHMP Rapporteur Assessment Report	1 October 2024
CHMP members comments	3 October 2024
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	9 October 2024
Updated CHMP Rapporteur Assessment Report	9 October 2024
Opinion	17 October 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Endometriosis is an estrogen-dependent gynaecological condition, defined as the presence of endometrium-like tissue outside the uterus. It is one of the most common gynaecological diseases (Eskenazi 1997). Establishment and growth of such endometriotic tissue is estrogen-dependent, thus the condition is predominantly found in women in their reproductive years and disappears spontaneously after menopause (Kitawaki 2002). A chronic, inflammatory reaction, induced by the ectopic endometrial cells, results in a variety of symptoms including dysmenorrhea (DYS), dyspareunia, chronic non-menstrual pelvic pain, dysuria and dyschezia, and infertility (Fauconnier 2005; Dunselman 2014).

Symptoms of endometriosis have an impact on the woman's quality of life (QoL), her physical and psychosocial functioning, including social life, absenteeism from school or work, intimacy and intimate partnerships, as well as mental health and emotional wellbeing (Culley 2013). Traditionally, a definitive diagnosis was made based on surgical visualization and histologic confirmation. More recently, a paradigm shift has been observed and a ''clinically suspected endometriosis'' in patients who have undergone a thorough medical assessment is leading to the initiation of treatment without prior surgery (Taylor 2018).

State the claimed the therapeutic indication

The initially claimed indication was: *Yselty in indicated in adult women of reproductive age for the treatment of endometriosis-associated pain.* During the course of the procedure, per CHMP request, the indication was updated to:

Yselty is indicated in adult women of reproductive age for:

- *[…]*

symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis (see section 5.1).

Epidemiology

Although the exact prevalence of endometriosis is unknown, the World Health Organization estimates that endometriosis affects approximately 10% of women of reproductive age while some other estimates in the literature cite the prevalence as high as 17% (WHO fact sheet, Giudice 2010, Missmer 2004, Culley 2013) and, as such, is among the most common gynaecologic conditions.

A serious clinical consequence of endometriosis includes infertility and the prevalence of endometriosis among women with infertility is estimated at 50% (Meuleman 2009). The economic impact of endometriosis is substantial, leading some countries, for example France, to identify endometriosis as a national health priority. The condition incurs direct costs which include healthcare expenditures for diagnosis and endometriosis treatment (i.e., expenses associated with consultations, surgeries and hormonal therapies) as well as indirect costs encompassing reduced work performance and lost productivity. Taken together, these costs contribute to the overall financial strain on healthcare systems, and its direct and indirect healthcare costs are comparable to other common diseases such as type 2 diabetes, rheumatoid arthritis, and Crohn's disease (Zondervan 2018).

Management

Current Treatment

The principal objective in treating endometriosis is symptom-relief management. Treatment options for women with endometriosis-associated pain are diverse and consist of analgesic therapies, hormonal therapies, conservative or minimal invasive surgery, or a combination of these (Dunselman 2014). Approximately 30% of women with endometriosis develop chronic pelvic pain that is unresponsive to conventional treatments, including surgery (Horne 2022). Thus, despite these available treatment modalities, there is still a major need for better options for the treatment of endometriosis.

According to the 2022 Endometriosis guideline published by the European Society of Human Reproduction and Embryology (ESHRE), there is scarce evidence to support the use of simple analgesics, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), for management of pain symptoms related to endometriosis (ESHRE 2022).

First-line hormonal therapies such as combined oral contraceptives (COC) and progestins are effective in two-thirds of women suffering from endometriosis associated pain. These hormonal therapies aim at inhibiting ovulation, preventing cyclic endometrium growth, and suppressing menstruation by achieving a stable steroid hormone milieu, based on the concept that the response of the eutopic and ectopic endometrium is substantially similar (Vercellini 2008; Vercellini 2009).

The administration of COCs, although not approved for the treatment of EAP, results in anovulation, reduction of menstrual bleeding, decidualization of endometriotic lesions, downregulation of cell proliferation and enhanced apoptosis in the endometrium (Meresman, 2002).

However, over time many women on COCs no longer have adequate pain relief and require additional medical therapy (Practice Committee of the American Society for Reproductive Medicine 2014). Only one randomized placebo-controlled clinical trial of combined hormonal contraceptives has been published demonstrating a statistically significant, though modest, 50% reduction in dysmenorrhea, but no beneficial effect on non-menstrual pelvic pain or dyspareunia (Harada 2008).

Progestin monotherapy can be efficacious for the reduction of endometriosis-associated pain as it induces anovulation and a hypoestrogenic state by suppressing the release of pituitary gonadotropin. Progestins also have direct effects on the endometrium, causing decidualization of ectopic and ectopic endometrium leading to atrophy of the endometriotic implants (Schweppe 2001). However, progestin monotherapy is often associated with breakthrough bleeding, alterations in mood, weight gain, and breast tenderness (Vercellini 2003). In addition, progestins are not always effective and progestin resistance occurs in 30%–50% of women using progestin-based therapies for endometriosis (Flores 2018; Donnez 2021).

Other hormonal therapies with proven efficacy for the treatment of endometriosis-associated pain are often limited due to undesirable side effects. For example, depot GnRH agonists – available only as

intramuscular or subcuteneous injections – stimulate the receptor leading to a flare in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which results in an increase in estradiol (E2) secretion. However, eventually they lead – through a constant stimulation of the GnRH receptor at the pituitary level – to its desensitization, to reduced LH and FSH output and ultimately to suppression of ovulation and a significant reduction in serum estrogen; thus, their use is associated with hypoestrogenic side-effects. Short-term side effects include menopausal symptoms such as hot flushes, vaginal dryness, loss of libido and emotional lability, and their long-term use is limited by substantial bone mineral density (BMD) reduction (Olive 2008). For example, leuprorelin has a negative impact on bone mineralization, with an estimated loss of 3% in lumbar spine BMD after 3 months of treatment, which increases to approximately 6% after 12 months of continuous use (Hornstein 1998; LUPRON DEPOT US label). To minimize or prevent the hypoestrogenic side effects of GnRH agonists, add-back hormone replacement therapy (estrogen or progestin or combination of both) is frequently used and is known to improve quality of life, BMD and adherence rates to treatment.

As a result, if treatment fails due the inability to tolerate the aforementioned medications or in case of progesterone resistance, additional medical interventions become necessary. This highlights the ongoing necessity for a reliable and durable oral treatment option that can effectively manage symptoms associated with endometriosis, while simultaneously minimizing the adverse effects it may induce. GnRH antagonists are a promising new oral treatment option that allows dose-dependent control of E2 levels, reducing endometriosis implants and endometriosis-associated pain without or with limited hypo-estrogenic side-effects including hot flushes and BMD loss (Ezzati 2015).

A new class of GnRH analogue was developed more recently, the oral GnRH receptor antagonists. These have the ability to bind competitively to the receptor and thus dose-dependently reduce serum E2. Based on Barbieri's hypothesis, there are two ways to achieve optimal E2 levels with a GnRH antagonist: i.e, (i) to administer a high dose of GnRH antagonist associated with hormonal ABT, or (ii) to administer a low dose of GnRH antagonist which partially suppress E2 hence will maintain sufficient endogenous E2 to prevent long term adverse impacts of hypoestrogenism.

Hormonal ABT is used to minimize or prevent the hypoestrogenic side effects of full estrogen suppression with GnRH analogues, and in addition to bone protection, is known to improve QoL and adherence to treatment. The use of an exogenous source of estrogen ensures systemic E2 concentrations remain in a range that effectively manages endometriosis-associated pain while minimizing the risk of BMD loss and avoiding bothersome vasomotor symptoms. A progesterone such as norethisterone acetate (NETA) is added to prevent the potentially negative effects of unopposed estrogen on the uterine endometrium, in particular endometrial hyperplasia and cancer.

Orally active, non-peptide GnRH receptor antagonists have been developed for the treatment of endometriosis and uterine fibroids.

For example, Relugolix/E2/NETA has been approved in Europe for the treatment of symptoms of uterine fibroids and symptomatic treatment of endometriosis in adult women of reproductive age (Ryeqo SmPC). The relugolix regimen requires and is co-formulated with hormonal ABT (E2 1 mg + NETA 0.5 mg) for prevention of BMD loss and vasomotor symptoms.

The ABT combination of E2 1 mg/NETA 0.5 mg was approved in the EU in 1998 as Activelle and is indicated as hormone replacement therapy for estrogen deficiency symptoms in postmenopausal women with more than one year since last menses, and for the prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of or contraindicated for other medicinal products approved for the prevention of osteoporosis. This ABT was used in the development programs of elagolix, relugolix and linzagolix. To address the needs of women with EAP,

linzagolix 200 mg dose with ABT emerges as a new therapeutic option to adequately control endometriosis symptoms.

2.1.2. About the product

To date, more than 2800 subjects have been exposed to different doses (25, 50, 75, 100, 200, 400 and 700 mg) of linzagolix in clinical trials. Linzagolix was well tolerated in single doses up to 700 mg and in multiple doses up to 400 mg for 7 days. The dose of 200 mg with ABT once daily has been administered for up to 52 weeks and 200 mg without ABT once daily for up to 24 weeks of treatment.

Uterine fibroid indication

Marketing authorisation has been granted in the EU for linzagolix in the indication of UF in 2022, based on two Phase 3 trials, PRIMROSE 1 (16-OBE2109-008) and PRIMROSE 2 (16-OBE2109-009). The approved doses include 100 mg with and without hormonal ABT (1 mg E2/0.5 mg NETA) and 200 mg with hormonal ABT for long-term treatment, and 200 mg linzagolix alone for up to 6 months. In total, 951 subjects were treated in these trials with linzagolix; of these, 541 subjects received the 200 mg dose of linzagolix either with or without ABT.

Endometriosis-associated pain indication

Four Phase 2 clinical trials have been performed in subjects with EAP: KLH1201, KLH1202, KLH1203 and KLH1204. These studies influenced the selection of doses utilised in later studies, particularly study KLH1202 which tested the 50 mg, 100 mg, and 200 mg doses for 12 weeks.

Notably, in trial KLH1204, which tested linzagolix doses of 25 mg, 50 mg, 75 mg, and 100 mg, the average numeric rating scale (NRS) score of pelvic pain was decreased (i.e., improved) with linzagolix 100 mg to a level comparable with that of leuprorelin acetate as the reference drug.

Regarding safety, the occurrence of adverse reactions at each linzagolix dose was observed at a lower rate and at a less severe extent than that of leuprorelin acetate. A decrease in the bone mineral density for linzagolix was also less than that for leuprorelin acetate.

. The results of another Phase 2b study (15-OBE2109-001; EDELWEISS 1) in subjects with EAP indicated that the minimal effective dose to reduce pelvic pain in subjects with moderate to severe endometriosis was 75 mg linzagolix. In this trial, both the 75 mg and 200 mg doses showed statistically significant improvements in the dysmenorrhea (DYS), non-menstrual pelvic pain (NMPP), and overall pelvic pain after 12 weeks of treatment in terms of a change from baseline on the 0-3 verbal rating scale (VRS) scores. Notably, the highest response rate for DYS at Week 12 compared to placebo was achieved by subjects treated with the 200 mg dose, with an estimated proportion of 78.9% (95% confidence interval [CI]: 65.49, 88.08) and OR of 9.41 (95% CI: 3.707, 23.885, $p<0.001$). This high response rate, defined as a 30% or greater reduction from baseline in DYS (VRS scores), was maintained until Week 24 (84.1%) in the 200 mg dose; thus the 200 mg was considered the highly effective dose. With the linzagolix 75 mg dose, bone mineral density loss (BMD) after 24 weeks of treatment was -0.80% for lumbar spine (the bone site most sensitive to BMD changes) with the lower boundary of the 95% confidence interval at -1.57%. In the linzagolix 200 mg group, the decrease in BMD was more relevant with -2.60% of BMD loss after 24 weeks of treatment (with the lower bound of the CI at -3.56%) which indicated the need for combining this dose with a low dose estrogen/progestin add-back therapy (1 mg E2/0.5 mg NETA) to mitigate BMD loss during long-term treatment. The dosing regimens selected to be tested in the Phase 3 program in EAP were driven by the results of this EDELWEISS 1 study: 75 mg dose as the minimally effective dose and the 200 mg – combined with ABT to ameliorate BMD loss – as the maximally effective dose tested.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did not request scientific advice from the CHMP/EMA.

They did get National Scientific Advice from the Swedish Agency.

The efficacy of linzagolix to reduce dysmenorrhoea (DYS) and non-menstrual pelvic pain (NMPP) due to moderate-to-severe EAP was assessed in a Phase 3 double-blind, placebo-controlled clinical trial (18-OBE2109-003; EDELWEISS 3). Eligibility was confirmed based on data collected during the screening period. Two dosing regimens were evaluated in the EDELWEISS 3 study: (i) 75 mg without ABT and (ii) 200 mg linzagolix with ABT (estradiol 1 mg/norethisterone acetate 0.5mg, E2/NETA), administered once daily for 6 months. The LGX 200 mg dose administered with ABT met the co-primary efficacy objectives, demonstrating clinically meaningful reductions in DYS and NMPP at 3 months with a stable or decreased use of analgesics for endometriosis-associated pain.

After 6 months of treatment, subjects were to either enter a 6-month drug-free post-treatment follow-up (PTFU) or – if eligible – were offered an opportunity to continue treatment for an additional 6 months as part of a separate extension trial (19-OBE2109-006; EDELWEISS 6) followed by a 6-month drug-free post-extension-treatment follow-up (ExFU). An assessment of efficacy after stopping treatment is based on the 6-month post-treatment follow-up period in the EDELWEISS 6 study.

Dose-ranging studies included five Phase 2 studies in subjects with endometriosis, four of which were performed by Kissei in Japan, and one study (15-OBE2109-001; EDELWEISS 1) was conducted by ObsEva in Europe and US. The final dosing regimen proposed in the current application was confirmed in the Phase 3 double-blind, randomized, placebo-controlled EDELWEISS 3 study conducted in Europe and US.

Note that the previous MAH, ObsEva, initiated a second Phase 3 confirmatory study in subjects with endometriosis to be conducted in the US and Canada (18-OBE2109-002; EDELWEISS 2) with its extension (19-OBE2100-005; EDELWEISS 5). The studies followed the same design as that employed in the EDELWEISS 3 and EDELWEISS 6 studies, respectively. However, the EDELWEISS 2 study and its extension EDELWEISS 5 were prematurely terminated due to recruitment issues and thus were not evaluable for efficacy. Nonetheless, data from both of these studies have been incorporated in the safety assessment.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

A scientific statement on environmental impact of the new indication for Yselty, in addition to the approved indication (treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age) has been provided.

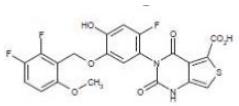
A phase II risk assessment has been completed in the initial assessment and showed that the active substance, linzagolix, does not present a risk to the environment. No further studies are warranted for this extension of indication application.

This extension of indication is considered to result in a negligible increase in the exposure of the environment to the active substance. Therefore, it is considered that linzagolix presents the same risk for the environment as it was anticipated in previous procedures.

For completeness, an updated ERA table with the results of the study on aerobic transformation in aquatic sediment systems (OECD 308) and on Medaka Extended One Generation Reproduction Fish Test (OECD 204) that were submitted in 2022 (EU procedure number: EMEA/H/C/005442/IB/0001) is provided below.

Table 1 Summary of main study results

Substance (INN/Invented Name): Linzagolix			
CAS-number (if available): 935283-04-8 (free acid, active moiety) 1321816-57-2 (choline salt)			
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log Kow @ PH5	1.8 (highest between pH 5-9)	Potentially not B
	BCF	-	
Persistence	DT50, 12°C	DT50 water, (12 °C) = 76.8 d TP KPO17 is also vP in water and sediment	vP
Toxicity	NOEC Extended One Generation Reproduction Test fish test	0.1 mg/L	not T
PBT-statement:	The compound is neither considered as PBT nor as vPvB.		
Phase II Physical-chemical properties and fate			
Study type	Test protocol	Results	Remarks
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50, water = 14.9/ 35.0 d DT50, sediment = 48.7/ 65.2 d DT50, whole system =19.5/ 55.9 d	at 20°C W/S systems: (1) Calwich Abbey Lake (UK), Corg= 4.8% (2) Middle Pond Lamsdale (UK),

		Mineralisation = 1.6/ 2.8% at test end NERmax = 88.2/ 54.8% at test end NERtype 1 (strongly sorbed and physically entrapped) = 12.8/ 21.2% at test end % shifting to sediment (day 14) = 33%/ 48% Transformation products >10% = yes in (1) KPO17 = 24.7% at d 28 DT50 water, TP = 54 d DT50 sediment, TP = 105 d DT50 total system, TP = 74.2 d	Corg= 1.4% TP KPO17: 3-{5-[(2,3-difluoro-6-methoxyphenyl) methoxy]-2-fluoro-4-hydroxyphenyl}-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,4-d]pyrimidine-5-carboxylic acid  Molecular Weight: 494.4 g/mol	
Phase IIa Effect studies					
Study type	Test protocol	Endpoint	Value	Unit	Remarks
Medaka (Oryzias latipes) Extended One Generation Reproduction Test	OECD 240	NOEC	0.1	mg/L	F1-Hatch and Juvenile Survival

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of linzagolix.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2 Tabular overview of clinical studies

Study Identifier	Study Title	Third countries involved	Ethical standards
17-OBE2109-001	A Phase 1, 2-Part, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of a Single Supratherapeutic Dose of OBE2109 and to Evaluate the Effects of Therapeutic and Supratherapeutic Doses of OBE2109 on the QTc Interval in Healthy Adult Female Subjects	USA	GCP
18-OBE2109-009	Evaluation of the Safety and Pharmacokinetics of a Single Dose of Linzagolix in Female Subjects with Normal and Impaired Hepatic Function	USA	GCP
18-OBE2109-010	Evaluation of the Safety and Pharmacokinetics of a Single Dose of Linzagolix in Female Subjects with Normal and Impaired Renal Function	USA	GCP
KLH1201	Early phase II clinical study of KLH-2109 in endometriosis patients (1)	Japan	GCP
KLH1202	Early phase II clinical study of KLH-2109 in endometriosis patients (2)	Japan	GCP
KLH1203	Early phase II clinical study of KLH-2109 in endometriosis patients (3)	Japan	GCP
KLH1204	Late phase II clinical study of KLH-2109 in endometriosis patients.	Japan	GCP
15-OBE2109-001	A Randomized, Double-Blind, Placebo-Controlled, Phase 2b Dose-Ranging Study to Assess the Efficacy and Safety of OBE2109 in Subjects with Endometriosis Associated Pain	Russia, Ukraine, USA	GCP
16-OBE2109-008	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.	USA	GCP

16-OBE2109-009	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 addback therapy for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.	Ukraine, USA	GCP
20-OBE2109-007	A long-term follow-up study to assess bone mineral density in subjects with uterine fibroids completing the Phase 3 studies of linzagolix, PRIMROSE 1 or PRIMROSE 2	Ukraine, USA	GCP
18-OBE2109-002	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	USA and Canada	GCP
19-OBE2109-005	A double-blind randomized extension study to assess the long-term efficacy and safety of linzagolix in subjects with endometriosis-associated pain	USA and Canada	GCP
18-OBE2109-003	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	Ukraine, USA	GCP
19-OBE2109-006	A double-blind, randomized, extension study to assess the long-term efficacy and safety of linzagolix in subjects with endometriosis associated pain	Ukraine, USA	GCP

2.3.2. Pharmacokinetics

18-OBE2109-003 (EDELWEISS 3)

Study Design

This was 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.

Study Population

The target population consisted of premenopausal women, aged 18 to 49 years (inclusive), with surgically and, if available, histologically confirmed pelvic endometriosis and with moderate to severe EAP. The subjects were enrolled in the United States (US) and Europe.

Approximately 150 subjects per group (i.e., 450 subjects in total) were planned to be randomized. 486 subjects were randomized; 2 subjects in the LGX 75 mg group discontinued prior to Day 1. The Pharmacokinetics (PK) Set (n=322) consisted of all subjects who received active study medication, had no major protocol deviations impacting PK evaluation and with available PK data.

Treatments

Linzagolix 2 dosage strengths (75 mg round tablet and 200 mg oblong tablet) or their corresponding placebos were supplied as film-coated tablets for oral administration. ABT or its corresponding placebo

was supplied as capsules for oral administration. Treatments were administered once daily for up to 6 months.

Objectives

The collection of pharmacokinetic (PK) and pharmacodynamic (PD) data of linzagolix for a separate modelling exercise was an exploratory objective in this study.

The overall study design and methodology of EDELWEISS 3 is acceptable for the exploratory PK objective described.

Sampling Timepoints

PK blood samples were to be collected from each subject for determining plasma levels of linzagolix and its metabolite KP017. On Day 1, blood samples for PK assessment were to be taken at least 1.5 h post-first dose. During the treatment period (on days of site visits at Months 1, 2, 3, 4 and 5) a PK sample was taken pre-dose.

Analysis of PK endpoint

Pharmacokinetic analyses were conducted using the PK Set.

For descriptive statistics of plasma concentrations mean (arithmetic and geometric), standard deviation (SD), median, 1st and 3rd quartiles, minimum, maximum, coefficient of variation (CV%) and number of observations were provided. Concentrations below the limit of quantification (LoQ) were assigned a value of zero. Missing values were not imputed, and if sufficient data were missing for a given subject, that subject may have been considered non-evaluable for PK analysis and would not be included in the PK Set. All plasma concentration data were displayed in listings.

The sparse PK sampling is acceptable for a modelling exercise, and the analysis of the PK endpoint is sufficient for this report. The MAH has indicated that the explorative analyses between plasma concentrations and intrinsic PK factors will be reported separately.

Pharmacokinetic results

Linzagolix

Post-dose samples were collected between 1.5 hours and 3.8 hours post IMP administration. Post-dose on Day 1, the geometric mean (CV%) LGX plasma levels were 7736.56 (56.93) ng/mL and 20898.40 (47.25) ng/mL in the LGX 75 mg and LGX 200 mg+ABT groups, respectively. During the treatment period, the pre-dose levels (geometric mean [CV%]) at the monthly visits were between 2980.76 (85.29) ng/mL and 3349.84 (82.78) ng/mL in the LGX 75 mg group. The pre-dose levels (geometric mean [CV%]) at the monthly visits were between 9030.41 (65.15) ng/mL and 10741.49 (71.22) ng/mL in the LGX 200 mg+ABT group (Table 3 below).

Table 3 PK plasma concentrations - PK analysis set

Parameters	LGX 75 mg (N=160)	LGX 200 mg + ABT (N=162)	Total (N=322)
LGX plasma level (ng/mL)			
Day 1 (Post-dose)			
n (missing)	148 (12)	150 (12)	298 (24)
Mean (SD)	8058.62 (4587.81)	22662.94 (10708.40)	15409.79 (11020.18)
Geometric Mean (CV%)	7736.56 (56.93)	20898.40 (47.25)	12903.99 (71.51)
Median	9170.00	25100.00	12200.00
Q1 ; Q3	4650.00; 11100.00	19000.00; 29800.00	7540.00; 25100.00
Min ; Max	0.0; 20800.0	0.0; 40500.0	0.0; 40500.0
Month 1 (Pre-dose)			
n (missing)	151 (9)	148 (14)	299 (23)
Mean (SD)	4109.97 (3402.30)	11873.42 (8157.45)	7952.74 (7332.73)
Geometric Mean (CV%)	3349.84 (82.78)	9297.32 (68.70)	5580.72 (92.20)
Median	3240.00	10040.00	5890.00
Q1 ; Q3	2070.00; 5040.00	6955.00; 16050.00	2720.00; 10600.00
Min ; Max	0.0; 18700.0	0.0; 42400.0	0.0; 42400.0
Month 2 (Pre-dose)			
n (missing)	142 (18)	156 (6)	298 (24)
Mean (SD)	3517.12 (2449.88)	10709.56 (6977.73)	7282.29 (6419.27)
Geometric Mean (CV%)	3168.81 (69.66)	9030.41 (65.15)	5502.10 (88.15)
Median	3125.00	9660.00	5385.00
Q1 ; Q3	1950.00; 4690.00	6155.00; 14250.00	2740.00; 10300.00
Min ; Max	0.0; 16300.0	0.0; 35200.0	0.0; 35200.0
Month 3 (Pre-dose)			
n (missing)	147 (13)	147 (15)	294 (28)
Mean (SD)	3628.93 (3094.97)	11211.14 (6909.18)	7420.03 (6556.03)
Geometric Mean (CV%)	2980.76 (85.29)	9597.19 (61.63)	5439.95 (88.36)
Median	3170.00	9600.00	5705.00
Q1 ; Q3	1790.00; 4880.00	6320.00; 14400.00	2920.00; 9860.00
Min ; Max	0.0; 23700.0	0.0; 31100.0	0.0; 31100.0
Month 4 (Pre-dose)			
n (missing)	139 (21)	141 (21)	280 (42)
Mean (SD)	3669.34 (3286.39)	12016.88 (8143.11)	7872.92 (7489.86)
Geometric Mean (CV%)	3321.64 (89.56)	10532.59 (67.76)	6033.72 (95.13)
Median	3110.00	9750.00	5390.00
Q1 ; Q3	1860.00; 4660.00	6770.00; 16100.00	2880.00; 10350.00
Min ; Max	0.0; 28400.0	0.0; 45400.0	0.0; 45400.0
Month 5 (Pre-dose)			
n (missing)	139 (21)	142 (20)	281 (41)
Mean (SD)	4131.14 (3673.71)	11782.68 (9221.25)	7997.75 (8009.88)
Geometric Mean (CV%)	3291.38 (88.93)	9270.53 (78.26)	5599.91 (100.15)
Median	3490.00	9655.00	5790.00
Q1 ; Q3	1800.00; 5590.00	6420.00; 15600.00	2990.00; 10300.00
Min ; Max	0.0; 26500.0	0.0; 55000.0	0.0; 55000.0
Month 6 (Pre-dose)			
n (missing)	122 (38)	128 (34)	250 (72)
Mean (SD)	4135.01 (3690.40)	12061.25 (8589.85)	8193.24 (7746.74)
Geometric Mean (CV%)	3327.29 (89.25)	10741.49 (71.22)	6083.57 (94.55)
Median	3280.00	10035.00	5955.00
Q1 ; Q3	1960.00; 5160.00	6885.00; 15050.00	2990.00; 10900.00
Min ; Max	0.0; 22600.0	0.0; 54100.0	0.0; 54100.0

LGX: LINZAGOLIX; ABT: Add-Back Therapy; CV: Coefficient of Variation.
Values below the limit of quantification (LOQ) are assigned as zero.
Geometric mean is defined as the nth root of the product of the n individual values. Values below the limit of quantification are excluded for the geometric mean.
At Day 1, PK assessments are included if sampling is done >=1.5 hours after the dose on the same day.
At other visits, PK assessments are included if done pre-dose or if no IMP is taken on the day of PK sampling, and if date is in the +/-10 days window of the theoretical visit and up to 2 days after last IMP intake for Month 6.
If the PK sampling time is missing, or the IMP intake on the same day is done and the IMP intake time is missing then assessments will not be included.
Samples analysed after the period of long term stability are excluded (Subjects 510009, Month 2; 511004, Month 6; 608001, Month 1).

KP017

Post-dose on Day 1, the geometric mean (CV%) KP017 plasma levels were 281.371 (71.729) ng/mL and 784.456 (63.907) ng/mL in the LGX 75 mg and LGX 200 mg+ABT groups, respectively. During the treatment period, the pre-dose levels (geometric mean [CV%]) at the monthly visits were between 163.879 (80.890) ng/mL and 192.381 (87.769) ng/mL in the LGX 75 mg group. The pre-dose levels (geometric mean [CV%]) at the monthly visits were between 371.685 (70.461) ng/mL and 438.518 (83.183) ng/mL in the LGX 200 mg+ABT group (Table 4 below).

Table 4 PK plasma concentrations - PK analysis set

Parameters	LGX 75 mg (N=160)	LGX 200 mg + ABT (N=162)	Total (N=322)
KP017 plasma level (ng/mL)			
Day 1 (Post-dose)			
n (missing)	148 (12)	150 (12)	298 (24)
Mean (SD)	319.311 (229.037)	985.596 (629.863)	654.689 (579.956)
Geometric Mean (CV%)	281.371 (71.729)	784.456 (63.907)	479.840 (88.585)
Median	329.000	989.000	488.000
Q1 ; Q3	99.050; 485.000	517.000; 1450.000	210.000; 994.000
Min ; Max	0.00; 880.00	0.00; 2410.00	0.00; 2410.00
Month 1 (Pre-dose)			
n (missing)	151 (9)	148 (14)	299 (23)
Mean (SD)	207.192 (152.324)	494.702 (377.500)	349.505 (320.482)
Geometric Mean (CV%)	185.468 (73.518)	423.190 (76.309)	279.740 (91.696)
Median	172.000	395.500	273.000
Q1 ; Q3	118.000; 264.000	288.500; 621.500	144.000; 442.000
Min ; Max	0.00; 722.00	0.00; 2030.00	0.00; 2030.00
Month 2 (Pre-dose)			
n (missing)	142 (18)	156 (6)	298 (24)
Mean (SD)	194.113 (133.723)	437.158 (308.026)	321.345 (269.797)
Geometric Mean (CV%)	175.792 (68.889)	371.685 (70.461)	260.812 (83.959)
Median	170.500	369.500	266.500
Q1 ; Q3	110.000; 261.000	263.500; 550.000	145.000; 404.000
Min ; Max	0.00; 708.00	0.00; 1570.00	0.00; 1570.00
Month 3 (Pre-dose)			
n (missing)	147 (13)	147 (15)	294 (28)
Mean (SD)	191.383 (154.810)	471.299 (327.117)	331.341 (291.406)
Geometric Mean (CV%)	163.879 (80.890)	412.064 (69.408)	262.930 (87.947)
Median	169.000	361.000	271.000
Q1 ; Q3	90.700; 262.000	276.000; 619.000	154.000; 422.000
Min ; Max	0.00; 1260.00	0.00; 1630.00	0.00; 1630.00
Month 4 (Pre-dose)			
n (missing)	139 (21)	141 (21)	280 (42)
Mean (SD)	200.368 (163.641)	496.489 (371.013)	349.486 (322.981)
Geometric Mean (CV%)	183.601 (81.670)	428.313 (74.727)	284.552 (92.416)
Median	170.000	386.000	264.000
Q1 ; Q3	106.000; 262.000	267.000; 598.000	152.000; 420.000
Min ; Max	0.00; 1300.00	0.00; 2160.00	0.00; 2160.00
Month 5 (Pre-dose)			
n (missing)	139 (21)	142 (20)	281 (41)
Mean (SD)	216.249 (189.799)	490.177 (387.369)	354.675 (334.875)
Geometric Mean (CV%)	183.622 (87.769)	406.466 (79.026)	276.101 (94.417)
Median	177.000	383.500	269.000
Q1 ; Q3	102.000; 278.000	258.000; 613.000	159.000; 434.000
Min ; Max	0.00; 1520.00	0.00; 2250.00	0.00; 2250.00
Month 6 (Pre-dose)			
n (missing)	122 (38)	128 (34)	250 (72)
Mean (SD)	224.421 (206.690)	508.802 (423.236)	370.024 (363.882)
Geometric Mean (CV%)	192.381 (92.099)	438.518 (83.183)	294.572 (98.340)
Median	181.500	422.000	275.000
Q1 ; Q3	112.000; 273.000	271.000; 574.500	151.000; 463.000
Min ; Max	0.00; 1560.00	0.00; 3190.00	0.00; 3190.00

LGX: LINZAGOLIX; ABT: Add-Back Therapy; CV: Coefficient of Variation.
Values below the limit of quantification (LOQ) are assigned as zero.
Geometric mean is defined as the nth root of the product of the n individual values. Values below the limit of quantification are excluded for the geometric mean.
At Day 1, PK assessments are included if sampling is done >=1.5 hours after the dose on the same day.
At other visits, PK assessments are included if done pre-dose or if no IMP is taken on the day of PK sampling, and if date is in the +/-10 days window of the theoretical visit and up to 2 days after last IMP intake for Month 6.
If the PK sampling time is missing, or the IMP intake on the same day is done and the IMP intake time is missing then assessments will not be included.
Samples analysed after the period of long term stability are excluded (Subjects 510009, Month 2; 511004, Month 6; 608001, Month 1).

19-OBE2109-006 (EDELWEISS 6)

Study Design

This was a prospective, randomized, double-blind study. Subjects who completed the 6-month treatment period in the 18-OBE2109-003 were invited to enter the present extension study. The Month

6 visit of the main study was a decision point for subjects to either end treatment and enter a post-treatment follow-up (part of the main study), or to opt for a 6-month treatment extension.

Study Population

All subjects who completed the full 6-month treatment period in the main study (EDELWEISS 3) and who met the inclusion criteria were offered entry to the current extension study.

The target population for EDELWEISS 3 consisted of premenopausal women, aged 18 to 49 years (inclusive), with surgically and, if available, histologically confirmed pelvic endometriosis and with moderate to severe EAP. The subjects were enrolled in the United States (US) and Europe.

Subjects who received placebo in the main study (EDELWEISS 3) were randomized to receive linzagolix 75 mg or linzagolix 200 mg + ABT.

Overall, 356 subjects entered the extension study and were treated. All treated subjects except for 2 were included in the extension PK set (n=354).

Treatments

Linzagolix (LGX) was supplied as film-coated tablets each containing 75 mg or 200 mg of active substance and administered orally once daily for 6 months. LGX 75 mg was administered in combination with ABT-matching placebo (one placebo capsule). LGX 200 mg was administered in combination with ABT.

Objectives

The collection of pharmacokinetic (PK) and pharmacodynamic (PD) data of linzagolix for a separate modelling exercise was an exploratory objective in this study.

The overall study design and methodology of EDELWEISS 6 is acceptable for the exploratory PK objective described.

Sampling Timepoints

PK blood samples were to be collected from each subject at each study visit during the treatment period for determining linzagolix and KP017 plasma levels. At the visits where IMP intake was at site, i.e. at Months 6, 7, 8, 9, 10 and 11 visits, PK sampling was to be performed before IMP intake.

The sparse PK sampling is acceptable for a modelling exercise, and the analysis of the PK endpoint is sufficient for this report.

Analysis of PK endpoint

Pharmacokinetic analyses were conducted using the Extension Pharmacokinetic Set.

For descriptive statistics of plasma concentrations mean (arithmetic and geometric), standard deviation (SD), median, 1st and 3rd quartiles, minimum, maximum, coefficient of variation (CV%) and number of observations were provided. Concentrations below the limit of quantification (LoQ) were assigned a value of zero. Missing values were not imputed, and if sufficient data were missing for a given subject, that subject may have been considered non-evaluable for PK analysis and would not be included in the PK Set. All plasma concentration data were displayed in listings.

Explorative analyses of correlations between plasma concentrations and intrinsic PK factors such as body weight/BMI, race, age could be performed, as appropriate, and will be reported separately.

Pharmacokinetic results

Linzagolix

Table 5 below details the plasma concentrations of linzagolix starting from Month 6, the final time-point in EDELWEISS 3, through to the end of EDELWEISS 6 at Month 12. During the 12-month treatment period, the pre-dose levels (geometric mean [CV%]) at the monthly visits ranged from 2526.64 (78.13) ng/mL and 3531.23 (75.62) ng/mL in the LGX 75 mg group. The pre-dose levels (geometric mean [CV%]) at the monthly visits were between 8492.43 (61.26) ng/mL and 10751.02 (67.85) ng/mL in the LGX 200 mg+ABT group.

Table 5 PK plasma concentrations – Extension Pharmacokinetic set

Parameters	Placebo / LGX 75 mg (N=57)	Placebo / LGX 200 mg + ABT (N=56)	LGX 75 mg (N=119)	LGX 200 mg + ABT (N=122)	Total (N=354)
Month 6 (Pre-dose)					
n (missing)			108 (11)	110 (12)	218 (136)
Mean (SD)			4305.47 (3757.41)	12604.18 (8552.20)	8492.89 (7809.93)
Geometric Mean (CV%)			3337.38 (87.27)	10751.02 (67.85)	6056.49 (91.96)
Median			3450.00	10450.00	6055.00
Q1 ; Q3			2055.00; 5195.00	7230.00; 15900.00	3210.00; 11100.00
Min ; Max			0.0; 22600.0	0.0; 54100.0	0.0; 54100.0
Month 7 (Pre-dose)					
n (missing)	49 (8)	46 (10)	114 (5)	114 (8)	323 (31)
Mean (SD)	4126.94 (2929.62)	10650.00 (5782.29)	3866.23 (2725.23)	11718.08 (7881.47)	7643.13 (6667.80)
Geometric Mean (CV%)	3182.66 (70.99)	9869.45 (54.29)	3037.30 (70.49)	9725.48 (67.26)	5494.81 (87.24)
Median	3840.00	10180.00	3385.00	10200.00	5980.00
Q1 ; Q3	1940.00; 5360.00	6350.00; 14400.00	2040.00; 4980.00	6650.00; 14500.00	3060.00; 10400.00
Min ; Max	0.0; 12700.0	0.0; 27100.0	0.0; 14300.0	0.0; 49800.0	0.0; 49800.0
Month 8 (Pre-dose)					
n (missing)	49 (8)	50 (6)	111 (8)	115 (7)	325 (29)
Mean (SD)	4292.20 (3015.57)	12413.80 (8707.93)	3773.13 (2672.09)	10469.86 (6413.31)	7550.33 (6548.27)
Geometric Mean (CV%)	3415.09 (70.26)	10395.90 (70.15)	3034.85 (70.82)	8492.43 (61.26)	5403.27 (86.73)
Median	3750.00	10200.00	3290.00	9240.00	5980.00
Q1 ; Q3	2200.00; 5710.00	6770.00; 15400.00	1930.00; 5090.00	6220.00; 13600.00	2980.00; 10100.00
Min ; Max	0.0; 13000.0	0.0; 36600.0	0.0; 11900.0	0.0; 32300.0	0.0; 36600.0
Month 9 (Pre-dose)					
n (missing)	48 (9)	50 (6)	104 (15)	113 (9)	315 (39)
Mean (SD)	4565.21 (3540.93)	11050.80 (8212.64)	3852.91 (2865.09)	11182.13 (6637.82)	7733.19 (6585.21)
Geometric Mean (CV%)	3985.27 (77.56)	9007.51 (74.32)	2893.42 (74.36)	9515.34 (59.36)	5633.28 (85.16)
Median	3335.00	8585.00	3250.00	9930.00	6090.00
Q1 ; Q3	2125.00; 6990.00	5970.00; 13700.00	1990.00; 5620.00	6640.00; 14600.00	2880.00; 10400.00
Min ; Max	0.0; 15200.0	0.0; 40200.0	0.0; 18700.0	0.0; 34400.0	0.0; 40200.0
Month 10 (Pre-dose)					
n (missing)	49 (8)	47 (9)	103 (16)	110 (12)	309 (45)
Mean (SD)	4237.12 (3359.58)	11069.57 (7980.98)	3536.52 (2762.93)	10511.36 (6730.02)	7276.38 (6473.73)
Geometric Mean (CV%)	3646.54 (79.29)	9283.96 (72.10)	2526.64 (78.13)	9652.53 (64.03)	5253.32 (88.97)
Median	3530.00	10600.00	3050.00	9655.00	5810.00
Q1 ; Q3	1890.00; 5960.00	5970.00; 15100.00	1710.00; 4840.00	6080.00; 12400.00	2640.00; 10600.00
Min ; Max	0.0; 13700.0	0.0; 45300.0	0.0; 15400.0	0.0; 47000.0	0.0; 47000.0
Month 11 (Pre-dose)					
n (missing)	48 (9)	46 (10)	94 (25)	103 (19)	291 (63)
Mean (SD)	5075.29 (6848.60)	10411.40 (7303.07)	4113.64 (3180.64)	10225.42 (6227.42)	7431.06 (6436.62)
Geometric Mean (CV%)	3668.35 (134.94)	7805.32 (70.14)	3501.31 (77.32)	9242.46 (60.90)	5668.60 (86.62)
Median	3435.00	9380.00	3420.00	9280.00	6120.00
Q1 ; Q3	1855.00; 6175.00	6140.00; 13300.00	2130.00; 5670.00	6250.00; 13700.00	2970.00; 9840.00
Min ; Max	0.0; 46700.0	0.0; 40800.0	0.0; 17900.0	0.0; 32200.0	0.0; 46700.0
Month 12 (Pre-dose)					
n (missing)	42 (15)	42 (14)	78 (41)	86 (36)	248 (106)
Mean (SD)	3362.14 (2378.89)	10677.05 (7360.09)	4440.22 (5586.87)	9959.65 (6096.41)	7227.88 (6485.99)
Geometric Mean (CV%)	3163.71 (70.76)	8673.49 (68.93)	2974.17 (125.82)	8871.43 (61.21)	5302.23 (89.74)
Median	2725.00	9705.00	3045.00	8635.00	5505.00
Q1 ; Q3	2140.00; 4710.00	6860.00; 13900.00	1840.00; 4750.00	5800.00; 13000.00	2535.00; 9955.00
Min ; Max	0.0; 11600.0	0.0; 38700.0	0.0; 32700.0	0.0; 32500.0	0.0; 38700.0

LGX: LINZAGOLIX; ABT: Add-Back Therapy; CV: Coefficient of Variation.
Values below the limit of quantification (LOQ) are assigned as zero.
Geometric mean is defined as the nth root of the product of the n individual values. Values below the limit of quantification are excluded for the geometric mean.
At Day 1, PK assessments are included if sampling is done >=1.5 hours after the dose on the same day.
At other visits, PK assessments are included if done pre-dose or if no IMP is taken on the day of PK sampling, and if date is in the +/-10 days window of the theoretical visit and up to 2 days after last IMP intake for Month 6 and Month 12.
If the PK sampling time is missing, or the IMP intake on the same day is done and the IMP intake time is missing then assessments will not be included.
Samples analysed after the period of long term stability are excluded.

KP017

Table 6 below details the plasma concentrations of KP017 starting from Month 6, the final time-point in EDELWEISS 3, through to the end of EDELWEISS 6 at Month 12. Post-dose on Day 1, the geometric mean (CV%) KP017 plasma levels were 294.776 (64.118) ng/mL and 850.404 (61.009) ng/mL in the LGX 75 mg and LGX 200 mg+ABT groups, respectively. During the 12-month treatment period, the pre-dose levels (geometric mean [CV%]) at the monthly visits were between 165.078 (65.394) ng/mL and 194.080 (90.661) ng/mL in the LGX 75 mg group. The pre-dose levels (geometric mean [CV%]) at the monthly visits were between 364.520 (71.095) ng/mL and 448.072 (72.956) ng/mL in the LGX 200 mg+ABT group.

Table 6 PK plasma concentrations – Extension Pharmacokinetic set

Parameters	Placebo / LGX 75 mg (N=57)	Placebo / LGX 200 mg + ABT (N=56)	LGX 75 mg (N=119)	LGX 200 mg + ABT (N=122)	Total (N=354)
KP017 plasma level (ng/mL)					
Month 6 (Pre-dose)					
n (missing)			108 (11)	110 (12)	218 (136)
Mean (SD)			234.881 (212.944)	528.494 (424.316)	383.034 (366.669)
Geometric Mean (CV%)			194.080 (90.661)	437.824 (80.288)	294.324 (95.727)
Median			183.500	422.000	278.000
Q1 ; Q3			116.000; 275.000	281.000; 602.000	169.000; 463.000
Min ; Max			0.00; 1560.00	0.00; 3190.00	0.00; 3190.00
Month 7 (Pre-dose)					
n (missing)	49 (8)	46 (10)	114 (5)	114 (8)	323 (31)
Mean (SD)	201.073 (159.659)	453.457 (228.090)	203.511 (134.780)	511.109 (437.945)	347.301 (326.245)
Geometric Mean (CV%)	170.509 (79.403)	431.999 (50.300)	172.070 (66.227)	407.047 (85.685)	267.638 (93.937)
Median	172.000	402.500	181.000	391.500	278.000
Q1 ; Q3	92.300; 258.000	308.000; 597.000	109.000; 278.000	282.000; 571.000	153.000; 431.000
Min ; Max	0.00; 711.00	0.00; 1150.00	0.00; 790.00	0.00; 2950.00	0.00; 2950.00
Month 8 (Pre-dose)					
n (missing)	49 (8)	50 (6)	111 (8)	115 (7)	325 (29)
Mean (SD)	203.137 (142.952)	513.340 (306.785)	197.644 (129.246)	450.770 (318.345)	336.608 (278.112)
Geometric Mean (CV%)	169.664 (70.372)	450.923 (59.762)	165.078 (65.394)	378.695 (70.623)	260.421 (82.622)
Median	150.000	469.500	178.000	362.000	273.000
Q1 ; Q3	94.500; 265.000	298.000; 692.000	92.900; 284.000	250.000; 553.000	150.000; 435.000
Min ; Max	0.00; 625.00	0.00; 1550.00	0.00; 604.00	0.00; 1680.00	0.00; 1680.00
Month 9 (Pre-dose)					
n (missing)	48 (9)	50 (6)	104 (15)	113 (9)	315 (39)
Mean (SD)	227.350 (166.052)	459.920 (328.252)	203.942 (142.972)	473.658 (312.598)	344.896 (281.544)
Geometric Mean (CV%)	202.896 (73.038)	390.944 (71.372)	183.949 (70.104)	399.574 (65.997)	281.238 (81.632)
Median	177.500	399.500	175.500	386.000	287.000
Q1 ; Q3	98.650; 325.000	246.000; 567.000	112.500; 293.500	273.000; 550.000	158.000; 435.000
Min ; Max	0.00; 640.00	0.00; 1630.00	0.00; 893.00	0.00; 1570.00	0.00; 1630.00
Month 10 (Pre-dose)					
n (missing)	49 (8)	47 (9)	103 (16)	110 (12)	309 (45)
Mean (SD)	222.986 (185.368)	463.772 (305.245)	189.206 (127.871)	444.984 (321.044)	327.379 (277.593)
Geometric Mean (CV%)	191.922 (83.130)	408.553 (65.818)	169.885 (67.583)	400.919 (72.147)	270.356 (84.793)
Median	158.000	486.000	164.000	359.500	270.000
Q1 ; Q3	103.000; 291.000	251.000; 571.000	113.000; 249.000	281.000; 511.000	143.000; 438.000
Min ; Max	0.00; 903.00	0.00; 1850.00	0.00; 599.00	0.00; 2320.00	0.00; 2320.00
Month 11 (Pre-dose)					
n (missing)	48 (9)	46 (10)	94 (25)	103 (19)	291 (63)
Mean (SD)	276.083 (411.897)	488.450 (365.666)	215.884 (145.299)	433.283 (299.552)	345.849 (314.320)
Geometric Mean (CV%)	197.243 (149.193)	421.900 (74.863)	192.114 (67.304)	383.691 (69.135)	279.579 (90.884)
Median	211.500	410.000	176.000	368.000	291.000
Q1 ; Q3	113.000; 319.500	277.000; 585.000	115.000; 302.000	248.000; 515.000	155.000; 428.000
Min ; Max	0.00; 2870.00	0.00; 1870.00	0.00; 732.00	0.00; 1780.00	0.00; 2870.00
Month 12 (Pre-dose)					
n (missing)	42 (15)	42 (14)	78 (41)	86 (36)	248 (106)
Mean (SD)	179.924 (131.724)	484.298 (351.664)	230.685 (264.198)	415.431 (295.352)	329.104 (297.859)
Geometric Mean (CV%)	168.846 (73.211)	404.082 (72.613)	175.552 (114.527)	364.520 (71.095)	260.677 (90.506)
Median	165.000	447.500	160.000	355.500	264.500
Q1 ; Q3	109.000; 224.000	276.000; 578.000	94.200; 299.000	248.000; 485.000	140.000; 417.000
Min ; Max	0.00; 695.00	0.00; 1950.00	0.00; 1620.00	0.00; 2100.00	0.00; 2100.00

LGX: LINZAGOLIX; ABT: Add-Back Therapy; CV: Coefficient of Variation.
Values below the limit of quantification (LOQ) are assigned as zero.
Geometric mean is defined as the nth root of the product of the n individual values. Values below the limit of quantification are excluded for the geometric mean.
At Day 1, PK assessments are included if sampling is done >=1.5 hours after the dose on the same day.
At other visits, PK assessments are included if done pre-dose or if no IMP is taken on the day of PK sampling, and if date is in the +/-10 days window of the theoretical visit and up to 2 days after last IMP intake for Month 6 and Month 12.
If the PK sampling time is missing, or the IMP intake on the same day is done and the IMP intake time is missing then assessments will not be included.
Samples analysed after the period of long term stability are excluded.

2.3.3. Discussion on clinical pharmacology

The overall study design and methodology for EDELWEISS 3 and EDELWEISS 6 are acceptable for the exploratory PK objectives described. The sparse PK sampling is acceptable for a modelling exercise, and the analysis of the PK endpoint is sufficient. The MAH has detailed that the planned additional exploratory analyses and modelling exercise were not performed as the data from the Edelweiss 3 and Edelweiss 6 studies were sufficiently robust to conclude on the safety and efficacy for this application, and as a result the additional analyses were unnecessary. This is overall acceptable.

For EDELWEISS 3, the geometric means for the PK plasma concentrations reported for linzagolix and KP017, for both the post-dose samples collected on Day 1 and the pre-dose samples (steady state trough concentrations) collected at the Months 1, 2, 3, 4, 5, and 6, are approximately dose proportional between the two groups. The geometric means for the pre-dose samples are similar at each time-point for both groups, although the CV% is high at each time-point.

For EDELWEISS 6, the geometric means for the PK plasma concentrations reported for linzagolix and KP017 are in line with what would be expected. In the linzagolix 75 mg and linzagolix 200 mg + ABT groups the steady state trough plasma concentrations remain consistent between the EDELWEISS 3 and EDELWEISS 6 up to Month 12. For the placebo/linzagolix 75 mg and placebo/linzagolix 200 mg + ABT, similar plasma concentrations are reached by the time of the sampling at Month 7 and are similar to the other groups up to Month 12.

The linzagolix and KP017 plasma concentration results for the linzagolix 200 mg + ABT group are consistent with the results from 16-OBE2109-008 (PRIMROSE 1) which investigated a similar linzagolix 200 mg + ABT group in premenopausal women with uterine fibroids. This suggests that the PK of linzagolix is similar between the uterine fibroids and endometriosis associated pain indications.

2.3.4. Conclusions on clinical pharmacology

The PK of linzagolix and its metabolite KP017 is similar between the currently approved uterine fibroids indication and the proposed endometriosis-associated pain indication.

2.4. Clinical efficacy

2.4.1. Dose response studies

Four Phase 2 studies (Study KLH1201, KLH1202, KLH1203, and KLH1204) were performed in Japanese patients with endometriosis-associated pain. These studies were previously submitted as part of the MAA in the indication of uterine fibroids and are summarized briefly here as they are discussed in the context of dose selection for the Phase 2b EDELWEISS 1 study.

All four studies included female patients aged ≥ 20 years, who had a diagnosis of endometriosis assessed by laparotomy/laparoscopy or documented by the presence of an ovarian chocolate cyst confirmed by diagnostic imaging, and had mild (moderate in KLH1202 and KLH1204) or worse pelvic pain during menstruation, slight (mild in KLH1202 and KLH1204) or worse pelvic pain during non-menstruation, and/or slight or worse Douglas pouch induration or limited uterine mobility based on the

objective findings. All treatment groups in the four studies were comparable for demographic characteristics. The primary efficacy variables in the three Phase 2a studies (Study KLH1201, KLH1202 and KLH1203) were the severity of pelvic pain measured with a 5-point verbal rating scale (VRS, 0-4), and the numeric rating scale (NRS, 0-10) of pelvic pain, assessed during menstruation and non-menstruation. The primary efficacy variable in the Phase 2b study (Study KLH1204) was the change in the average NRS (0- 10) score of pelvic pain at the end of 12 weeks.

Table 7 Response rates for pelvic pain, dysmenorrhoea, and non-menstrual pelvic pain in Study KLH1204

	Time point (wk)	Linzagolix				Placebo (N=86)	Leuprorelin (N=43)
		25 mg (N=77)	50 mg (N=85)	75 mg (N=74)	100 mg (N=84)		
Average pelvic pain (NRS), %	12	48.1	56.5	**67.6** *P=0.006**	**81.0** *P<0.001**	45.3	83.7
						—	—
	24	51.9	62.4	74.3	82.1	—	83.7
Dysmenorrhoea (NRS),%	12	**49.4** *P=0.006**	**65.9** *P<0.001**	**86.5** *P<0.001**	**86.9** *P<0.001**	27.9	100
						—	—
	24	54.5	64.7	81.1	86.9	—	97.7
NMPP (NRS), %	12	51.9	52.9	63.5	**72.6** *P=0.002**	50.0	74.4
						—	—
	24	57.1	65.9	68.9	77.4	—	76.7
Severity of pelvic pain (0-4 VRS), %	12	48.1	51.8	**66.2** *P=0.010*	**76.2** *P<0.001**	45.3	79.1
						—	—
	24	50.6	58.8	73.0	79.8	—	81.4

NMPP=non-menstrual pelvic pain
Analysis at both Week 12 and Week 24 is based on the FAS.
**Fisher exact test (vs. placebo) at the end of period 1 at Week 12. P-values are shown only for statistically significant results.*
The subjects with 30% or greater improvement of percent change from baseline are defined as responders.

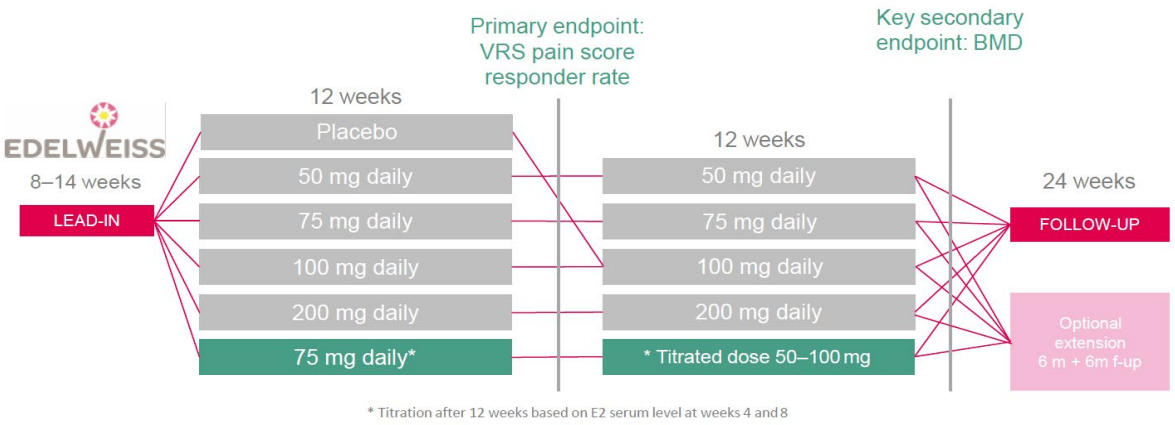
Responder rates achieved with leuprorelin were comparable to those observed with linzagolix 100 mg dose for pelvic pain (NRS), severity of pelvic pain (VRS), and NMPP (NRS) throughout the study period. Dose-dependent improvements were also noted in QoL measures such as all domains of the EHP-30 and PGIC. These improvements in pain and QoL scores were accompanied by a significant decrease in the use of analgesics at all linzagolix dose levels compared to placebo.

Phase 2b study 15-OBE2109-001 (EDELWEISS 1): dose-ranging clinical study of linzagolix in endometriosis patients

This was a randomized, double-blind, placebo-controlled, Phase 2b, dose-ranging study to assess the efficacy and safety of linzagolix in American and European subjects with endometriosis associated pain (15-OBE2109-001, EDELWEISS) who were treated for up to 52 weeks. In this trial, 328 women with moderate-to-severe EAP were recruited from 62 gynaecological clinics across the US and Europe and 327 were treated. Following a lead-in phase of two menstrual cycles to establish baseline pain level, patients were randomised to one of six treatment groups: placebo, fixed-dose groups of linzagolix 50, 75, 100 and 200 mg once daily, and a titrated-dose group of 75 mg once daily for up to 12 weeks, followed by 12 additional weeks of treatment at an up- or down-titrated dose.

Placebo was provided for 12 weeks after which all placebo subjects were crossed-over on to active treatment (100 mg daily). In the titrated-dose arm, all subjects started on 75 mg daily dose for 12 weeks after which the dose was titrated up or down to 100 or 50 mg, respectively, or remained at 75 mg for the following 12 weeks. Up- or down-titration depended on the mean of serum E2 assay results collected at Weeks 4 and 8. The study design is outlined in the figure below.

Figure 1 EDELWEISS 1 (15-OBE2109-001) study design



VRS – verbal rating scale

For the clinical study report for the EDELWEISS 1 study, and its addenda, were included in the previously submitted MAA in UF, demographics and baseline characteristics were comparable between groups with a mean baseline overall pain (VRS, 0-3) of 1.7, menstrual pain (VRS, 0-3) of 2.1, and non-menstrual pain (VRS, 0-3) of 1.6. Note that the 0-3 VRS scale was the same as the one used in Phase 3 studies.

Primary Endpoint Results:

The primary endpoint of the EDELWEISS 1 clinical trial was the percentage of subjects with a reduction of at least 30%, in combined menstrual and non-menstrual pelvic pain, recorded daily and assessed via electronic diary over the last 28 days of treatment prior to Week 12 on a verbal rating scale (VRS) of 0 (no pain) through 3 (severe pain). The primary endpoint was achieved for the three top doses (75 mg, 100 mg, and 200 mg). Subjects receiving a 75 mg dose had the highest responder rate of 61.5% compared to the placebo at 34.5% (Table 8).

Secondary Endpoint Results:

With respect to dysmenhorroea (DYS) (VRS) at Week 12, patients receiving a 200 mg dose reported the highest responder rate at 78.9%, compared to a placebo responder rate of 28.5%. Response to doses from 75 mg and above were highly statistically significant (Table 8). Responder rates for non-menstrual pelvic pain (NMPP) (VRS) at Week 12, were statistically significant for the 75 mg dose and the 100 mg dose and both doses showed comparable responder rates at 58.5% and 61.5%, respectively (Table 8).

Table 8 OPP, DYS and NMPP responder rates at Week 12 (EDELWEISS 1, FAS)

Dose (N=FAS)		Placebo (N=53)	50mg (N=49)	75mg (N=114)*	100mg (N=51)	200mg (N=56)
Overall Pelvic Pain[1]	Responder Rate	34.5%	49.4%	61.5%	56.4%	56.3%
	P-value	—	0.155	0.003	0.039	0.034
DYS[2]	Responder Rate	28.5%	43.3%	68.2%	68.6%	78.9%
	P-value	—	0.141	<0.001	<0.001	<0.001

NMPP[3]	Responder Rate	37.1%	46.2%	58.5%	61.5%	47.7%
	P-value	—	0.380	0.017	0.022	0.297

*The 75 mg group consists of the 75 mg fixed-dose group and 75 mg titrated dose group, as both received 75 mg up to Week 12. As of Week 12, subjects in the titrated group received 50, 75, or 100 mg depending on the subject's estradiol levels at Weeks 4 and 8.
FAS= Full Analysis Set. % responder rates are estimated proportions from the generalized linear model with repeated measures.
1 Primary endpoint: % of subjects with ≥ 30% reduction of mean Overall Pelvic Pain Score (0-3 VRS)
2 Key secondary endpoint: % of subjects with ≥ 30% reduction of mean DYS score (0-3 VRS)
3 Key secondary endpoint: % of subjects with ≥ 30% reduction of mean NMPP score (0-3 VRS)

In addition, the 75 mg, 100 mg and 200 mg doses of linzagolix significantly and consistently improved dyschezia and patient well-being as assessed by Endometriosis Health Profile-30 score (EHP- 30), Patient Global Impression of Change (PGIC) scale, Patient Global Impression of Severity (PGIS), the activity impairment score, and the modified Biberoglu & Behrman score. Dyspareunia was also improved for all doses and reached statistical significance at the 200 mg dose.

Median serum estradiol levels at Week 12 were 12 pg/ml for the 200 mg dose and 48 pg/ml for the 75mg dose, which indicates full suppression at the higher dose and partial suppression at the 75 mg dose.

Efficacy (Overall Pelvic Pain (OPP), DYS, NMPP) was maintained, or further improvements observed, at Week 24, compared to the positive Week 12 results (Table 9). Sustained efficacy was also observed with respect to additional endpoints such as daily activity, dyschezia and dyspareunia, as well as in the assessments of patient well-being, most notably the PGIC and EHP-30 questionnaire.

Table 9 OPP, DYS and NMPP responder rates at Week 12 and Week 24 (0-3 VRS) (EDELWEISS 1, FAS)

	Placebo /LGX 100 mg[a] (N=53)	LGX 50 mg (N=49)	LGX 75 mg (N=56)	LGX 75 mg TD[b] (N=58)	LGX 100 mg (N=51)	LGX 200 mg (N=56)
Week 12 (n)	48	45	53	54	45	51
Week 24 (n)	36	40	48	45	39	44
OPP Week 12	33.3%	51.1%	66.0%	57.4%	55.6%	54.9%
OPP Week 24	63.9%	52.5%	70.8%	66.7%	66.7%	77.3%
DYS Week 12	29.2%	44.4%	67.9%	68.5%	66.7%	78.4%
DYS Week 24	77.8%	47.5%	58.3%	71.1%	82.1%	84.1%
NMPP Week 12	35.4%	48.9%	66.0%	51.9%	60.0%	47.1%
NMPP Week 24	60.0%	50.0%	72.9%	64.4%	64.1%	72.7%

DYS = dysmenorrhoea; NMPP = non-menstrual pelvic pain; OPP = overall pelvic pain; TD = titrated dose
a: Placebo subjects were switched to 100 mg linzagolix treatment at week 12. Thus, the rates shown at Week 12 reflect the response while on placebo.
b: Subjects received 75mg linzagolix up to week 12 and thereafter their dose could be adjusted depending on their estradiol level at week 4 and 8.

Post-treatment follow-up after 24 weeks of treatment

After completing the 24-week treatment, subjects could either enter a 24-week post-treatment follow-up (PTFU) or, if willing, could enter an extension study to continue treatment with linzagolix up to Week 52. Of the 328 subjects randomized into the study, 253 (77.1%) completed the 24-week treatment period. Of these 253 subjects, 65 entered PTFU while most subjects (n=176) chose to continue linzagolix treatment in the extension study.

Efficacy endpoints were assessed at Week 36, i.e., 12 weeks after stopping treatment and half-way through the PTFU. Although the number of subjects in each treatment group in the PTFU was low (75 mg: n=8; 75 mg TD: n=16; 200 mg: n=12), the responder rates for OPP, DYS, and NMPP appeared to be maintained until Week 36 in the Follow-up FAS (EDELWEISS 1, CSR Addendum 1 [up to Week 48]).

Extension study

The extension study consisted of a further 28 weeks of treatment and a 24-week PTFU. As outlined above, 253 (77.1%) completed the 24-week treatment period and, of those, 176 subjects chose to participate in the treatment extension and received at least one dose of linzagolix during the extension phase of the study.

There were no statistical comparisons performed, however, the response rates observed were slightly numerically higher or similar to those reported at Week 12, where statistically significant improvements were noted in the mean OPP, DYS and NMPP scores in dose groups 75 mg and above compared to placebo.

In general, treatment effects apparent at Week 12 at all linzagolix doses were maintained or further improved at Week 24 – the decision point for entry into the optional treatment extension – and maintained until Week 52. The greatest improvements on all efficacy endpoints were reported at dose levels 75 mg and above. Among subjects who remained on treatment for 52 weeks, those treated with a 50 mg dose also showed improvement on several parameters, namely, in the scores for difficulty in performing daily activities, EHP-30, and PGIC, as well as reduction in the number of days with pelvic pain and severe-to-moderate pain, the use of analgesics, and dyschezia.

Subjects in the placebo/100 mg group received 40 weeks of linzagolix 100 mg dosing (between Week 12 and 52) and achieved high response rates at Week 52 in terms of OPP (72.7% and 81.8%), DYS (77.3% and 81.8%), and NMPP (63.6% and 81.8%), using VRS and NRS, respectively.

Subjects in the 50 mg, 75 mg FD and TD, 100 mg and 200/100 mg groups received up to 52 weeks of continuous dosing with linzagolix, therefore, the discussion of the long-term efficacy of linzagolix focuses on these groups. A summary of key findings is presented below:

- OPP responder rates — defined as the proportion of patients experiencing an OPP score reduction ≥30% from baseline using a verbal rating scale (0-3) — were 69.2% for the 75 mg FD once daily dose and 82.4% for the 200/100 mg once daily dose.
- DYS response rates — defined as the proportion of patients experiencing an DYS score reduction ≥30% from baseline using a verbal rating scale (0-3) — were improved between Week 24 and Week 52 at the 75 mg FD dose (55.6% to 69.2%, respectively, on VRS). At the 200/100 mg dose, improvements observed at Week 24 were maintained until Week 48 (90.0% to 85.0%, respectively, on VRS), but DYS response rate declined at Week 52 (64.7% on VRS).
- NMPP response rates — defined as the proportion of patients experiencing an NMPP score reduction ≥30% from baseline using a verbal rating scale (0-3) — were maintained between Week 24 and Week 52 in the 75 mg group (72.2% to 69.2%, respectively, on VRS) and improved in the 200/100 mg group (73.3% to 76.5%, respectively, on VRS).
- Mean dyspareunia scores were reduced between baseline and Week 52 at all linzagolix doses, with the greatest improvements at dose levels 75 mg and above; the mean change from baseline to Week 52 was -0.9, -0.7, and -0.9 for the 75 mg FD, 100 mg, and 200/100 mg groups using VRS, respectively.
- Mean dyschezia scores were reduced between baseline and Week 52 at all linzagolix doses, with the mean change from baseline to Week 52 ranging from -2.1 in the 75 mg group to - 2.9 in the 100 mg group using NRS.
- Menstruation was suppressed in a dose-dependent manner. At Week 24, the incidence of amenorrhea ranged between 16.7% at the 50 mg dose and 80.0% at the 200 mg dose. During treatment extension, incidence of amenorrhea was generally maintained in all linzagolix groups. At Week 52, the incidence of amenorrhea ranged from 16.7% at the 50 mg dose to 53.8% at the 100 mg dose.
- Subjects at all linzagolix doses reported improvements in the scores for difficulty in performing daily activities (0-10 NRS) between baseline and Week 52, ranging from -2.2 in the 50 mg group to -3.0 in the 100 mg group. Subjects at the 75 mg FD dose had an improved score by -2.4 by Week 52. Of note, subjects in the placebo/100 mg group reported an improvement of -3.4 after 40 weeks of linzagolix treatment.

Post-treatment follow-up after 52 weeks of treatment

Subjects who had opted to enrol into the 28-week treatment extension (up to Week 52, described above), upon completion, entered a 24-week post treatment follow-up (PTFU). The main conclusions are summarised below:

- 3 months after the end of treatment (Week 64), treatment effect was maintained for the OPP, NMPP, and dyschezia, but started to diminish for DYS and dyspareunia.

- Improvements relative to baseline were observed on all efficacy endpoints at the end of follow-up, including pain scores (OPP, NMPP, DYS), dyspareunia, dyschezia, quality of life measures, and severity of endometriosis symptoms.
- Treatment effect persisted for up to 3 months post-treatment enabling the patients to be potentially cycled on and off the drug, without a substantial loss of endometriosis symptom management, while allowing for BMD recovery

2.4.2. Main study

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: EDELWEISS 3 (18-OBE2109-003)

Methods

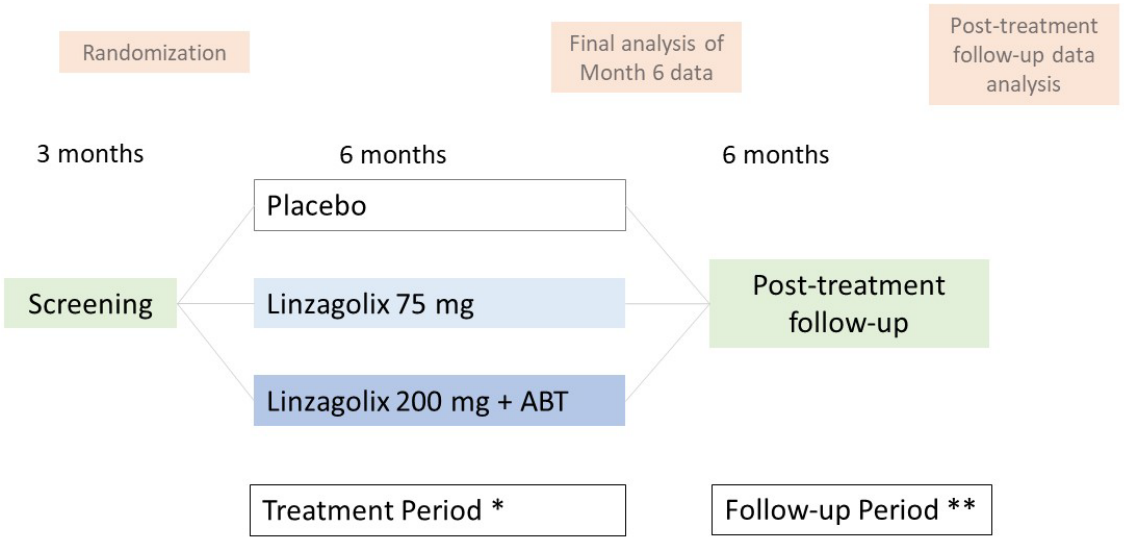
EDELWEISS 3 was a prospective, randomized, placebo-controlled, parallel-group, multicentre, double-blind, double-dummy study of linzagolix (LGX) administered once daily at a dose of 75 mg alone or at a dose of 200 mg in combination with add-back therapy (ABT) (E2 1 mg / NETA 0.5 mg) for up to 6 months for the management of moderate to severe EAP in women with surgically-confirmed endometriosis.

Eligibility, including baseline pain levels, was assessed over two menstrual cycles during a 3- month screening period. The inclusion and exclusion criteria are presented in detail below.

Subjects were randomised to one of three treatment groups in a 1:1:1 ratio for placebo, linzagolix 75 mg, and linzagolix 200 mg + ABT, with no stratification. Analgesic use during the treatment period was standardised per protocol. Permitted rescue analgesics included ibuprofen (200 mg) or a narcotic analgesic (5 mg hydrocodone + 300 mg acetaminophen); locally permitted equivalent narcotic analgesics were allowed.

At Month 6 of the treatment period, bone mineral density (BMD) change was assessed via dual energy X-ray absorptiometry (DXA) measurement. Eligible subjects who completed the 6-month treatment period could enter a separate extension study for 6 additional months of active treatment (no placebo control). In this extension study (EDELWEISS 6), subjects who previously received placebo were to be randomly switched to one of the two active treatments (75 mg alone or 200 mg + ABT). Subjects who received active treatment were to continue with the same treatment. Subjects who declined to participate in – or did not qualify for – the extension study and who had received at least 3 months of treatment were to enter a 6-month drug-free post-treatment follow-up (PTFU). Subjects who discontinued treatment prior to Month 3 of the treatment period were not to enter the follow-up period.

Figure 2 Study design EDELWEISS 3



* Subjects who discontinue treatment prior to Month 3 were not to enter the post-treatment Follow-up Period.
** At the end of the 6-month post-treatment Follow-up Period, subjects with a BMD decrease from baseline of >1.5% for lumbar spine and/or >2.5% for total hip were to have an additional DXA scan 6 months later.

Study participants

The subject population for the Phase 3 trial was chosen to reflect the majority of patients with endometriosis. The study population consisted of premenopausal women, aged 18 to 49 (inclusive), with surgically and, if available, histologically confirmed pelvic endometriosis and with moderate-to-severe EAP.

At the screening visit, moderate-to-severe EAP was defined as a score of at least 2 for DYS and at least 2 for NMPP for the previous month assessed using the modified Biberoglu & Behrman (mB&B) scale. The mB&B scale is a composite pelvic pain and physical sign score (0-15) of five domains (each domain rated from 0-3): dysmenorrhoea, deep dyspareunia, non-menstrual pelvic pain, pelvic tenderness, and induration, where the higher the score the more severe the pain and physical signs of endometriosis (Biberoglu 1981). In addition, for each of the two menstrual cycles during screening, the subject had to have a mean overall pelvic pain (OPP) of at least 4 (on the 0-10 numeric rating scale (NRS)) over the 5 days with the highest score for each cycle, at least 2 days with moderate or severe pain on the 0-3 verbal rating scale (VRS) for pelvic pain during uterine bleeding days and at least 2 days with moderate or severe pain on the 0-3 VRS for pelvic pain over the days without uterine bleeding.

Patients were excluded if they had an endometrial ablation resulting in amenorrhea, hysterectomy, bilateral oophorectomy, or any interventional surgery for endometriosis within 2 months prior to screening, or if the subject was scheduled for a surgical abdominal procedure during the course of the study. They were also excluded if they had a history of systemic glucocorticoid therapy for treatment of chronic diseases, or if they were at significant risk of osteoporosis or had history of osteoporosis or other metabolic bone disease.

Further exclusions included history of failed treatment of endometriosis with GnRH analogs, any contraindication to E2/NETA add-back therapy, or administration of the following therapies within specified periods prior to screening: GnRH antagonists (≤ 3 months), GnRH agonist injections/depots (≤ 3 and 6 months), oral contraceptives and other sex hormones (≤ 1 month), selective progesterone receptor modulators (SPRMs) or selective estrogen receptor modulators (SERMs) (≤3 months), acute system glucocorticoid treatments (≤ 1 month). The subjects were enrolled in Europe and the US.

Inclusion and exclusion criteria for the EDELWEISS 3 study

Inclusion criteria

1. The subject had to provide written informed consent prior to any study-related procedures.

2. The subject had to be female aged 18 years to 49 years, inclusive.

3. The subject had to have her most recent surgical and – if available – histological diagnosis of pelvic endometriosis (laparoscopy, laparotomy, vaginal fornix or other biopsy) up to 10 years before screening.

4. The subject had to agree to the washout intervals for prohibited therapies (if applicable).

5. The subject had to agree to switch from her usual analgesic rescue medication to only those permitted by the protocol during the Screening, Treatment and Follow-up Period.

6. The subject had moderate to severe EAP during the screening period defined as:

    a. At the screening visit, a score of at least 2 for DYS and at least 2 for NMPP for the previous month assessed with the modified Biberoglu & Behrman (mB&B) scale.

    b. Over two full menstrual cycles (i.e. from day 1 of the first menstruation going over two spontaneous menstrual cycles up to the day before the next menstruation i.e. the third menstruation) finishing just before the baseline visit:

        i. Mean overall pelvic pain (OPP) scores of at least 4 on the 0–10 NRS over the 5 days with the highest score for each cycle separately, i.e. required for both cycles;

        ii. At least two days with "moderate" or "severe" pain on the 0–3 VRS for pelvic pain over the days with uterine bleeding for each cycle separately, i.e. required for both cycles;

        iii. At least two days with "moderate" or "severe" pain on the 0–3 VRS for pelvic pain over the days without uterine bleeding for each cycle separately, i.e. required for both cycles.

7. The subject had to be compliant with eDiary completion i.e. has completed at least 75% of days during the screening period.

8. The subject had regular menstrual cycles and the total length of the two screening menstrual cycles should have been between 42 and 76 days inclusive.

9. The subject had a Body Mass Index (BMI) ≥18 kg/m2 at the screening visit.

10. If of childbearing potential, the subject agreed to use one of the following birth control methods during the Screening Period, the entire Treatment Period of the study and until 3 months after the end of treatment:

a. Sexual abstinence, if this is the subject's habitual practice and/or the subject is routinely abstinent from heterosexual intercourse.

b. Partner with a vasectomy with confirmed azoospermia.

c. Double non-hormonal barrier contraception such as condom or diaphragm each combined with

spermicide.

11. If of non-childbearing potential, the subject had to have had tubal ligation sterilization at least two months before the screening visit.

12. The subject ≥ 40 years of age at the screening visit had to have a normal mammogram within 1 year before randomization.

13. The subject had to be able to communicate well with the Investigator and research staff and to comply with the requirements of the study protocol.

Exclusion criteria

1. The subject was pregnant or breast-feeding or was planning a pregnancy within the duration of the Treatment Period of the study.

2. The subject was less than 6 months postpartum or 3 months post-abortion/miscarriage at the time of entry into the screening period.

3. The subject had a surgical history of:

a. Hysterectomy,

b. Bilateral oophorectomy,

c. Vagotomy, bowel resection or any surgical procedure (including gastric surgery) that might interfere with gastrointestinal motility, pH, or absorption,

d. Any major abdominal surgery (including laparotomy for endometriosis) within 6 months or any interventional surgery for endometriosis performed within a period of 2 months before screening, or the subject was scheduled for a surgical abdominal procedure during the course of the study.

4. The subject had a tubal sterilization which was performed with ESSURE™.

5. The subject had endometrial ablation resulting in amenorrhea.

6. The subject had at least one ovarian endometrioma with a diameter of 7 cm or greater.

7. The subject was likely to require treatment during the study OR received treatment within a specified period prior to screening with any of the medications listed below:

a. GnRH antagonists	3 months
b. GnRH agonist injections/3-month depot injections	3 months/6 months
c. Danazol	3 months
d. Oral contraceptives and other sex hormones	1 month
e. Depot contraceptives	10 months
f. Selective progesterone receptor modulators (SPRMs) and selective estrogen receptor modulators (SERMs) and aromatase inhibitors	3 months
g. Long-acting narcotics (i.e., requiring less than once daily dosing)	1 day
h. Systemic glucocorticoid treatments for acute diseases (not depot)	1 month
i. Medical (prescribed marijuana)	1 week
j. In situ copper intra-uterine device (IUD)	1 day
k. In situ IUD with progestogen	1 month

8. The subject was likely to use cannabinoids during the study washout, screening or treatment period.

9. The subject had required more than 2 weeks of continuous use of a narcotic analgesics for treatment of EAP within 6 months prior to Screening.

10. The subject received strong CYP3A4 inducers or inhibitors that (might potentially) interact with ABT within 1 month prior to randomization.

11. The subject had a contra-indication to ABT including:

a. Active deep vein thrombosis, pulmonary embolism, or history of these conditions,

b. Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction),

c. Known, suspected, or history of breast cancer,

d. Known or suspected estrogen-dependent neoplasia,

e. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden,

f. Migraine with aura,

g. History of porphyria,

h. Known hypersensitivity to the ingredients.

12. The subject had a history of or current systemic glucocorticoid therapy for the treatment of chronic diseases (e.g., Systemic Lupus Erythematosus (SLE), rheumatic arthritis). Inhaled glucocorticoids, e.g., for asthma, were not considered systemic glucocorticoids.

13. The subject did not respond to prior treatment with GnRH agonists or GnRH antagonists for endometriosis.

14. The subject had alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL) levels or gamma-glutamyl transpeptidase (GGT) level ≥ 2 times the upper limit of normal (ULN) and indicative of potential liver damage at Screening or Day 1 (subjects with abnormalities at Day 1 were to be withdrawn from the study on receipt of the results).

15. The subject had clinically significant abnormal electrocardiogram (ECG), or ECG with QTc using Fridericia's correction formula (QTcF) > 450 msec at Screening or Day 1 (prior to dosing).

16. The subject had a known positive human immunodeficiency virus (HIV) or viral Hepatitis serology.

17. The subject had abnormal uterine bleeding of undiagnosed cause.

18. The subject had clinically significant findings from a Papanikolaou (PAP) smear test performed within the past 12 months or at the screening visit which would require surgical intervention (e.g., Loop electrosurgical excision procedure (LEEP) or cervical conization).

19. The subject had chronic pelvic pain that, in the opinion of the Investigator, was not caused by endometriosis and required chronic analgesic or other chronic therapy which would have interfered with the assessment of EAP (e.g., interstitial cystitis, presumptive adenomyosis, fibroids, non-endometriosis related pelvic adhesive disease, post-tubal ligation, or irritable bowel syndrome).

20. The subject had any other clinically significant gynaecological condition identified during screening transvaginal ultrasound (TVUS) or endometrial biopsy which might have interfered with the study efficacy and safety objectives (e.g., endometritis, endometrial hyperplasia). However, uterine fibroids (as long as uterus size ≤ 12 weeks, i.e., equivalent gestational weeks) and adenomyosis were allowed

provided they did not interfere with the assessment of EAP (see previous criterion).

21. The subject had any known condition, including findings in the medical history or in the screening assessments, which in the opinion of the Investigator constituted a risk or a contraindication to the participation of the subject in the trial or that could have interfered with the trial objectives, conduct, or evaluation.

22. The subject had a history of, or known, osteoporosis, hyperparathyroidism or other metabolic bone disease:

a. Screening DXA results of the lumbar spine (L1–L4), femoral neck, or total hip bone mineral density (BMD) showed a z-score ≤ –1.5;

b. Any condition that would have interfered with obtaining adequate DXA measurements (e.g., weight [> 300 pounds or 136 kg], history of spinal surgery, spinal hardware, severe scoliosis);

c. Intercurrent bone disease;

d. History of hip fracture;

e. History of pathologic or compression fractures;

f. History of bilateral hip replacement.

23. The subject had a mental condition rendering her unable to understand the nature, scope and possible consequences of the study, or evidence of an uncooperative attitude.

24. The subject had a current problem with alcohol or drug abuse (including painkiller abuse).

25. The subject had been administered with any experimental drug in the 12 weeks before screening.

26. The subject had calcium level above the ULN range at screening, which was confirmed on repeat fasting testing at Screening.

27. The subject had a history of, or active malignancy (with or without systemic chemotherapy) (except treated basal carcinoma of the skin which was not an exclusion criterion).

28. The subject had a history of attempted suicide and/or a history of or known major psychiatric disorders that were not well controlled.

Table 10 Inclusion and exclusion criteria for the EDELWEISS 6 study

Inclusion criteria
1. The subject had to provide written informed consent specific to this study prior to starting the extension study treatment. 2. The subject must have completed the 6-month treatment in the main [EDELWEISS 3] study. 3. The subject was willing and able to continue to comply with the requirements of the study protocol for the duration of the extension study. 4. The subject agreed to continue to use only the analgesic rescue medication permitted by the protocol during the treatment and follow-up periods. 5. If of childbearing potential, the subject agreed to continue to use one of the following birth control methods during the entire treatment period of the study and until 3 months after the end of treatment: a. Sexual abstinence, if this was the subject's habitual practice and/or the subject was routinely abstinent from heterosexual intercourse. b. Partner with a vasectomy with confirmed azoospermia. c. Double non-hormonal barrier contraception such as condom or diaphragm each combined with spermicide.
Exclusion criteria
1. The subject was pregnant or was planning a pregnancy within the duration of the study (including the follow-up period). 2. The subject was likely to require treatment during the study with any of the medications listed below: a. GnRH antagonists b. GnRH agonist injections/3-month depot injections c. Danazol d. Oral contraceptives and other sex hormones e. Depot contraceptives f. SPRMs, SERMs and aromatase inhibitors g. Long-acting narcotics (i.e., requiring less than once daily dosing) h. Systemic glucocorticoid treatments for acute diseases (not depot) i. In situ copper intra-uterine device (IUD) j. In situ IUD with progestogen 3. The subject was likely to use cannabinoids during the study. 4. The subject had any other clinically significant gynecologic condition identified during the main study on TVUS, on endometrial biopsy or at the manual breast examination, which might interfere with the study efficacy and safety objectives. 5. The subject met any of the main [EDELWEISS 3] study discontinuation criteria including: a. Serum calcium level confirmed on a repeated test above 2.9 mmol/L. b. BMD decrease from baseline > 8% or a Z-score ≤ -2.5 at either femoral neck, hip or spine on the Month 6 DXA scan during the main study. c. QTcF > 500 ms or increase > 60 ms from the highest value prior to first dose during the main study. d. Any of the following elevation of hepatic enzymes: i. ALT or AST >8xULN ii. ALT or AST >5xULN for more than 2 weeks iii. ALT or AST >3xULN and (TBL >2xULN or INR* >1.5) iv. ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). 6. The subject had any condition that, in the opinion of the Investigator, constituted a risk or a contraindication to the participation of the subject in this extension study or that could interfere with the study objectives, conduct or assessments.

Treatments

EDELWEISS 3

Subjects were randomized to one of the three treatment groups in a 1:1:1 ratio with no stratification:

- LGX 75 mg: linzagolix 75 mg round tablet, linzagolix 200 mg matching placebo oblong tablet, and add-back matching placebo capsule;

- LGX 200 mg+ABT: linzagolix 200 mg oblong tablet, linzagolix 75 mg matching placebo round tablet, and add-back capsule; Placebo: linzagolix 75 mg matching placebo round tablet, linzagolix 200 mg matching placebo oblong tablet, and add-back matching placebo capsule.

For linzagolix, a treatment kit containing 1-month supply was dispensed on Day 1, Month 1, Month 2, Month 3, Month 4 and Month 5 visits, in a sealed child-proof labelled wallet card containing four blisters in total:

- Two blisters of 15 tablets each of 200 mg linzagolix or matching placebo,
- Two blisters of 15 tablets each of 75 mg linzagolix or matching placebo.

EDELWEISS 6 (extension of EDELWEISS 3)

Subjects who received placebo in the EDELWEISS 3 study were randomized in a 1:1 ratio to either linzagolix 75 mg alone (with ABT placebo) or linzagolix 200 mg with ABT, as per the main study randomization schedule.

Subjects who received active treatment continued with the same treatment (linzagolix 75 mg alone or linzagolix 200 mg with ABT).

In order to maintain the blind, the site was not required to perform any randomization activities. The kits were automatically allocated in the IWRS to the corresponding patients upon confirmation of their eligibility.

The Sponsor was unblinded to active treatment groups, following analysis of Month 6 visit data of the EDELWEISS 3 study, but was blinded to the treatment allocated to patients who previously received placebo. The randomization list was secured in a computer file with restricted access to only the designated personnel including those responsible for labelling and handling the study medication until the study database was locked and ready to be unblinded.

Objectives

The primary objective was to demonstrate the efficacy and safety of linzagolix administered orally once daily for up to 3 months at a dose of 75 mg alone or of 200 mg in combination with ABT (E2 1 mg / NETA 0.5 mg) versus placebo, while under randomized treatment, in the management of moderate to severe EAP in women with surgically confirmed endometriosis.

Outcomes/endpoints

Efficacy endpoints in the EDELWEISS 3 and EDELWEISS 6 studies

The two co-primary, composite, efficacy endpoints were clinically meaningful reduction from baseline to the last 28 days preceding the Month 3 visit (the 4-week period preceding Month 3 visit) or, for subjects who discontinued randomized treatment prior to the Month 3 visit, to the last 28 days of randomized treatment, along with a stable or decreased use of analgesics for EAP, in the mean daily assessment of 1) DYS and of 2) NMPP measured on a Verbal Rating Scale (VRS) using an electronic diary (eDiary).

Ranked secondary endpoints in the order to be tested were as follows:

1. Change from baseline to Month 6 in DYS (VRS).

2. Change from baseline to Month 6 in NMPP (VRS).

3. Change from baseline to Month 6 in dyschezia (NRS).

4. Change from baseline to Month 6 in overall pelvic pain (NRS).

5. Change from baseline to Month 6 in the interference of pain with the ability to perform daily activities, measured using the pain dimension of the Endometriosis Health Profile-30 (EHP-30).

6. Change from baseline to Month 6 in dyspareunia (VRS).

7. No analgesics use for EAP during the preceding 4-week period at Month 6.

8. No opiate use for EAP during the preceding 4-week period at Month 6.

Selected clinically important additional secondary efficacy endpoints included responder rates over time, pelvic pain scores over time, number of days with moderate-to-severe pain, dyschezia scores, dyspareunia scores, analgesic use, intention for surgery, and quality of life measures.

Sample size

The SAP states that the planned sample size for this study was 150 subjects per treatment group (450 subjects in total). An overall two-sided type I error of 0.05 was used. As there were two linzagolix versus placebo comparisons, Bonferroni corrected p-values were produced (raw p-values was multiplied by two prior to comparing to 0.05).

The planned sample size considers the hierarchical, fixed sequence testing of the ranked secondary endpoints as well as the co-primary endpoints. The assumptions used for the sample size calculations are based on analyses of clinically meaningful reduction in pain with a stable or decreased use of analgesics from the Phase 2b EDELWEISS study. Meaningful change thresholds of -1.0 in DYS and -0.7 in NMPP were derived using the phase 2b EDELWEISS study data. The proportion of participants in each EDELWEISS treatment group who achieved at least this degree of improvement with a stable or decreased use of analgesics for EAP were then calculated to obtain the response rates used as the basis for the EDELWEISS 3 sample size calculation. Calculations were performed using the software East6.5 software.

One hundred and fifty (150) subjects per treatment group was expected to provide a power greater than 95% to reject the null hypothesis for both co-primary endpoints for either treatment group, assuming for the DYS outcome:

- placebo response rate of 14.6%
- active treatment response rate of 48.6% (75 mg, EDELWEISS Phase II study results) or 64.7% (200 mg, EDELWEISS Phase II study result) for DYS

For the NMPP endpoint, a placebo response rate of 18.8%, an active treatment response rate of 42.1% (75 mg, EDELWEISS Phase II study result; the response rate (33.3%) for 200 mg in EDELWEISS was lower but was inconsistent with the other doses and other timepoints for the same dose and so was not used) for non-menstrual pelvic pain (NMPP).

In addition, 150 subjects per treatment group was expected to provide 85% power to reject the null hypotheses for all the ranked secondary endpoints based on the observed results from the placebo and 200 mg treatment group in the EDELWEISS study.

The values used for the sample size calculations assume that these responses rates are what would be seen on average when under treatment including taking into account any subjects who might withdraw from treatment early; therefore, the calculations were not further adjusted for dropouts.

Randomisation

Prior to the start of the EDELWEISS 3 study, a randomization list and two treatment kit lists (one for linzagolix/placebo, one for ABT/placebo) were generated by a designated statistician to be transmitted to the assigned clinical packaging organization for labelling and to a fully integrated interactive web response system (IWRS).

Blinded treatment kits were sent to the site and kept in controlled conditions. Once a patient was confirmed as eligible, the eligibility was entered into the IWRS system, which then allocated a treatment kit number with the randomised treatment at that site.

There were no randomisation stratification factors.

Blinding (masking)

Linzagolix and linzagolix-matching placebo treatments were packaged, labelled and administered in the same manner to protect the blinded nature of the trial. For ABT, the subject was given a sealed labelled carton box containing 14 labelled child-resistant blisters of seven capsules each of ABT or matching placebo at the Day 1 and Month 3 visits. This kit covered 98 days of treatment. ABT and ABT-matching placebo treatments were packaged, labelled and administered in the same manner to protect the blinded nature of the trial. Placebo treatments were identical in appearance to the active treatments. Treatment allocation was blinded to subjects, site staff, investigators, study management and the Sponsor.

The Sponsor and the study team were unblinded to active treatment groups after all subjects completed the initial 6-month treatment period and the database was locked. The investigators, site personnel, and subjects remained fully blinded to treatment allocation, individual progesterone (P4) and estradiol (E2) levels, serum levels of linzagolix, and eDiary (electronic diary) data (from Study Day 1) until the final database lock, which was performed after the last subject completed the post-extension-treatment follow-up period of the EDELWEISS 6 extension study.

Statistical methods

Estimand for the (Co)-primary Outcomes

The following components of the estimand strategy for the co-primary endpoints were stated:

- **Population:** Premenopausal women aged 18 to 49 years inclusive at Screening, with surgically and, if available, histologically confirmed pelvic endometriosis and with moderate to severe EAP.
- **Endpoint:** The 2 co-primary, composite efficacy endpoints are: clinically meaningful reduction from baseline to the last 28 days on randomized treatment, preceding the Month 3 visit or discontinuation, along with a stable or decreased use of analgesics for EAP, in the mean daily assessment of 1) DYS and of 2) NMPP measured on a VRS using an ediary.
- **Treatment:** linzagolix administered orally once daily for up to 3 months at a dose of 75 mg alone or of 200 mg in combination with ABT, versus placebo.
- **Population-level summary:** Odds ratio (OR) of proportions of responders of linzagolix versus placebo from a logistic regression model for each co-primary endpoint, with treatment group as the main effect (3 values) and including the baseline pain score as a covariate.

Intercurrent events (IC): Use of additional EAP analgesia is a non-response in the endpoint definition. Treatment discontinuations are assessed up to the time of discontinuation. Randomized treatment will be considered, regardless of lack of compliance to treatment or treatment assignment errors. The clinical question of interest is based on a **while-on-treatment strategy** for study treatment discontinuation and **composite strategy** for analgesics use. Lack of compliance to treatment and treatment assignment errors are handled using a **treatment policy strategy**.

In addition, a Full Analysis Set (FAS) was defined as: All randomized subjects who received at least one dose of double-blind study drug irrespective of the treatment received. This is the same as the Safety Set, but for the FAS, subjects will be analyzed according to randomized treatment.

Use of a composite strategy for analgesic use and treatment policy strategy for treatment assignment errors and lack of compliance to treatment are acceptable.

The applicant has presented a sensitivity analysis following a composite strategy in which study drug discontinuations were treated as non-responders and non-response imputation was applied to participants who withdraw from the study.

Statistical Methods for primary Outcome

The primary efficacy analysis was conducted using the FAS. The analysis of each co-primary endpoint was conducted using a logistic regression model, with treatment group as the main effect (three values) and including the baseline pain score as a covariate. Individual linzagolix versus placebo treatment group comparisons were made using the same logistic regression model. Estimated odds-ratios and 97.5% intervals of proportions of responders of linzagolix treatment groups versus placebo were presented, along with Bonferroni corrected p-values. Estimates of proportions of responders with 95% confidence intervals were also presented. In the statistical model baseline pain was included as a covariate for each outcome. A further analysis was planned using a per protocol (PP) set.

The pre-planned statistical analysis methods for the two co-primary endpoints were accepted by the CHMP.

Multiplicity

The applicant stated in the SAP that to maintain an overall type I error rate of 0.05, as there are two linzagolix versus placebo comparisons, Bonferroni corrected p-values were produced (raw p-values were to be multiplied by two prior to comparing to 0.05), along with corresponding 97.5% confidence intervals. This is taken to be equivalent to each hypothesis (75mg vs Placebo and 200mg vs Placebo) being tested at the two-sided 2.5% level.

For each linzagolix group that was statistically significantly more efficacious than placebo for the co-primary endpoints, a fixed-sequence testing strategy was to be used within the group to test the ranked secondary endpoints to maintain the family-wise type I error rate. That is, the comparison for each linzagolix group versus placebo for each ranked endpoint will only be declared statistically significant different if the raw p-value multiplied by two is less than or equal to 0.05 for that endpoint and for all preceding endpoints for that dose versus placebo.

Each linzagolix group needed to demonstrate a statistically significant difference for both co-primary endpoints for the group to be considered more efficacious than placebo, thus maintaining an overall type I error rate of 0.05. The approach to multiplicity of the two co-primary endpoints due to multiple treatment comparisons using a Bonferroni correction was acceptable.

Meaningful Clinical Threshold Analysis

Meaningful changes for the two primary endpoints (Change from Baseline in dysmenorrhea [DYS] and Change from Baseline in non-menstrual pelvic pain [NMPP] at Month 3) and for ranked secondary endpoints (Change from Baseline in DYS, NMPP, Overall Pelvic Pain [OPP], Endometriosis Health Profile 30 [EHP-30] Pain Impact domain, dyspareunia, and dyschezia at Month 6) were estimated.

The values of meaningful change (meaningful change thresholds, MCTs) were based on estimates both from blinded EDELWEISS 3 Month 3 and Month 6 data and from estimates for DYS and NMPP obtained previously from Phase 2b data.

The estimated MCTs were applied to the Phase 3 data in responder threshold analyses as described in the SAP.

The derivation of the MCTs for the co-primary endpoints was undertaken once all randomised patients had completed Month 3, using blinded data up to Month 3 on the Threshold Analysis Set and Threshold Analysis Set – Random Sample (TAS-R).

The derivation of the MCTs in Phase 3 for the ranked secondary endpoints was undertaken once all patients had completed Month 6, using blinded data up to Month 6 on the M6 Threshold Analysis Set.

The applicant has used a blinded data review BDR of a single pivotal study as a basis for defining the clinically meaningful effect for each co-primary endpoint. The essential purpose of the BDR is to evaluate assumptions around analyses/design. Since no assumptions were made with regards to the treatment effect, the approach was data driven to the extent that treatment induced effects could have become apparent when defining the relevant cut-off.

However, the applicant has provided detailed documentation of measures used to ensure blinding was not compromised by the conduct of analyses to estimate the meaningful change thresholds (MCTs) using the blinded interim EDELWEISS 3 data. This was acceptable to the CHMP.

Statistical Methods for Secondary and Other outcomes

A total of 8 ranked secondary outcomes were proposed along with a further 24 additional efficacy outcomes were proposed. Model based analyses were conducted and described in the SAP. In general, the statistical methods of analyses are acceptable. The multiplicity approach for the ranked secondary outcomes is based on a fixed sequence testing strategy within each co-primary outcome.

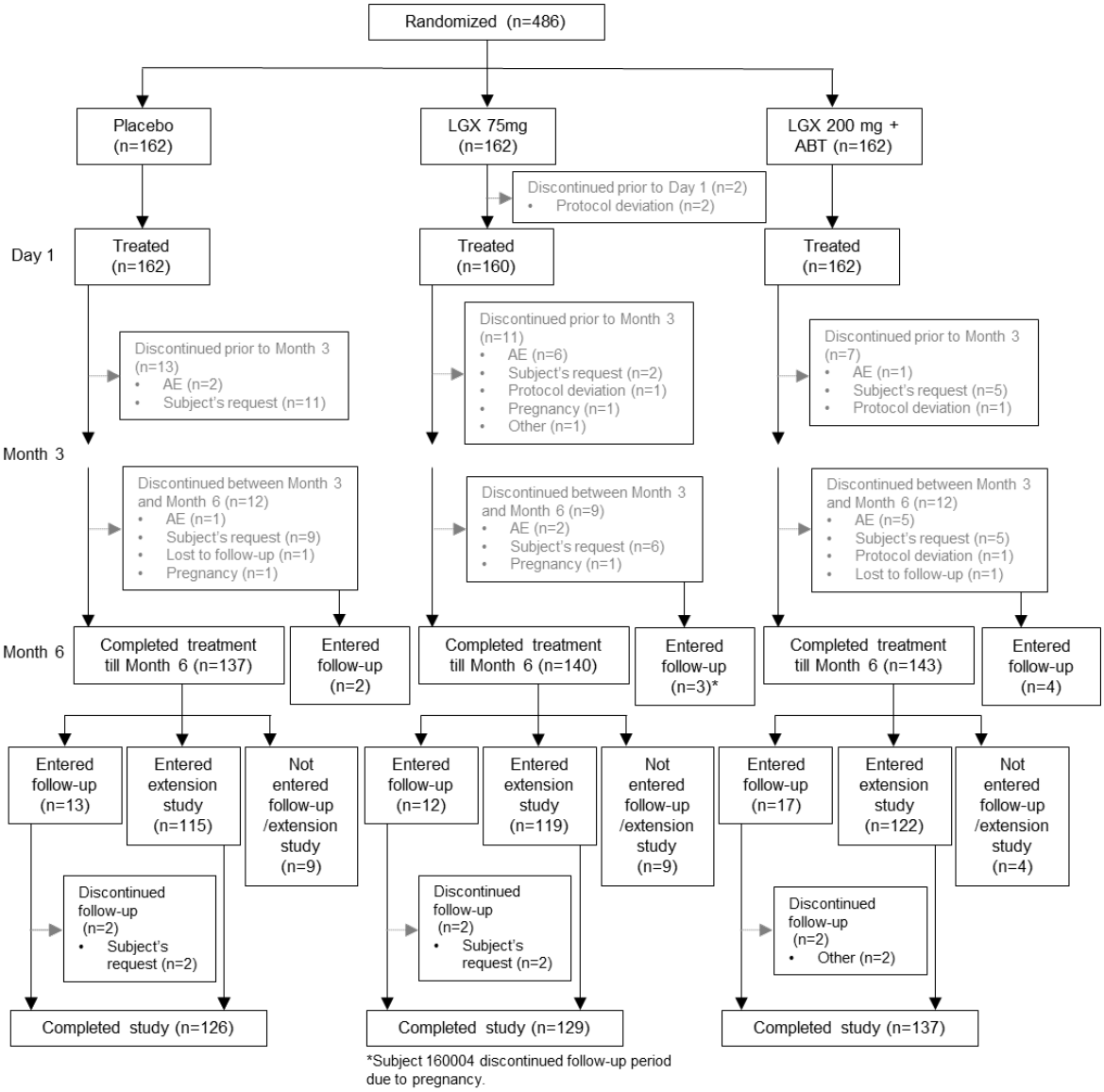
The pre-planned statistical analysis methods for the secondary endpoints were acceptable to the CHMP.

Estimand for Secondary Outcomes

No estimands for the secondary outcomes appear to have been defined. Analyses of ranked secondary and other secondary outcomes were based on the Full Analysis Set (FAS), which was accepted by the CHMP.

Results

Figure 3 Participant flow



LGX = linzagolix

Recruitment

- First patient enrolled (i.e., First subject screened): 13-Jun-2019
- First subject treated: 19-Sep-2019
- Last subject treated: 13-Oct-2021
- Last patient completed (i.e., Last subject last visit for 6month follow-up): 01-Apr-2022

The screen failure rate was lower than anticipated (actual rate of 43.1% vs expected rate of 60%). The predominant reason for screen failure (286/368; 77.7%) was entry criteria not being met, mainly inclusion criteria 6 (i.e. meeting the definition of moderate to severe EAP) and 7 (i.e. complying with eDiary completion).

Conduct of the study

Treated subjects

The rate of treatment completion was high: 86.8% (420 subjects) of the 484 treated subjects had completed the 6-month treatment period in the EDELWEISS 3 study. Treatment completion rates were comparable between the placebo (84.6%) and LGX groups (LGX 75 mg: 87.5%; LGX 200 mg+ABT: 88.3%).

Overall, 64 of the 484 subjects (13.2%) discontinued treatment during the 6-month Treatment Period. Discontinuation rates were similar during the first and second three-month intervals: 31/484 (6.4%) between Day 1 and Month 3, at which the coprimary efficacy endpoints were evaluated, compared to 33/484 (6.8%) between Month 3 and Month 6 visits. Of note, discontinuation rates were comparable if slightly lower in the LGX groups (75 mg: 12.5%; 200 mg+ABT: 11.7%) compared to placebo (15.4%) over the 6-month Treatment Period.

Subject's request was the most common reason for treatment discontinuation during the first 3-month interval (18/31; 58.1%) and the second 3-month interval (20/33; 60.6%). Subject's request was the reason for discontinuation more frequently given by subjects in the placebo group (6.8% in the first interval and 5.6% in the second interval) compared to LGX groups (≤3.1% in the first interval and ≤3.8% in the second interval).

Discontinuations due to adverse events were infrequent and reported in 17 subjects (17/64; 26.6%) over the 6-month Treatment Period, with equal frequency during the first and second 3-month interval (9 and 8 subjects, respectively). Overall, adverse events led to treatment discontinuation in 3 subjects in the placebo group, 8 subjects in the LGX 75 mg group (most [6/8] during the first 3-month interval), and 6 subjects in the LGX 200 mg+ABT group (most [5/6] during the second 3-month interval).

At the end of the 6-month treatment period, subjects could either enter an extension study (73.6%; n=356) or continue into drug-free follow-up period (10.5%; n=51), with the majority of subjects opting to continue treatment in the EDELWEISS 6 extension study.

Similar percentages of subjects in each group entered the follow-up period: 9.3% (15 subjects) in the placebo group, 9.4% (15 subjects) in the LGX 75 mg group, and 13.0% (21 subjects) in the LGX 200 mg+ABT group. Of the 51 subjects who entered the drug-free follow-up period, 7 (13.7%) discontinued the follow-up period, with similar discontinuation rates observed between the placebo (1.2%) and LGX groups (LGX 75 mg: 1.9%; LGX 200 mg+ABT: 1.2%).

Overall, 81.0% (n=392) of the randomised and treated subjects completed the EDELWEISS 3 study (i.e., after the 6-month treatment either entered the extension study or completed the follow-up period), with comparable completion rates between the placebo (77.8%) and LGX groups (LGX75 mg: 80.6%; LGX 200 mg+ABT: 84.6%).

Table 11 Exposure and treatment compliance up to Month 6 (EDELWEISS 3, FAS)

	Placebo (N=162)	LGX 75 mg (N=160)	LGX 200 mg + ABT (N=162)	Total (N=484)
Treatment duration[a] (weeks)				
n (missing)	162 (0)	160 (0)	162 (0)	484 (0)
Mean (SD)	22.22 (4.93)	22.18 (5.32)	22.72 (4.24)	22.37 (4.84)
Median	24.00	24.00	24.00	24.00
Q1; Q3	23.57; 24.14	23.57; 24.21	23.71; 24.14	23.57; 24.14
Min; Max	1.1; 25.9	0.1; 26.1	1.6; 27.9	0.1; 27.9
Grey blister (LGX 200 mg or matching placebo) compliance (%)				

	Placebo (N=162)	LGX 75 mg (N=160)	LGX 200 mg + ABT (N=162)	Total (N=484)
n (missing)	162 (0)	160 (0)	162 (0)	484 (0)
Mean (SD)	97.28 (7.02)	96.82 (9.19)	97.36 (7.34)	97.15 (7.89)
Median	100.00	100.00	100.00	100.00
Q1; Q3	98.18; 100.00	97.95; 100.00	98.20; 100.00	98.20; 100.00
Min; Max	40.5; 102.4	31.4; 103.7	38.0; 103.6	31.4; 103.7
Pink blister (LGX 75 mg or matching placebo) compliance (%)				
n (missing)	162 (0)	160 (0)	162 (0)	484 (0)
Mean (SD)	97.27 (7.03)	97.03 (9.13)	97.34 (7.40)	97.21 (7.88)
Median	100.00	100.00	100.00	100.00
Q1; Q3	98.18; 100.00	98.20; 100.00	98.20; 100.00	98.20; 100.00
Min; Max	40.5; 102.4	31.4; 109.9	38.0; 103.6	31.4; 109.9
ABT compliance (%)				
n (missing)	162 (0)	160 (0)	162 (0)	484 (0)
Mean (SD)	97.41 (7.38)	97.07 (9.26)	97.59 (7.36)	97.35 (8.03)
Median	100.00	100.00	100.00	100.00
Q1; Q3	98.20; 100.00	98.20; 100.00	98.20; 100.00	98.20; 100.00
Min; Max	40.5; 109.5	31.4; 110.5	38.0; 107.5	31.4; 110.5

ABT = add-back therapy; LGX = linzagolix; Q = quartile; SD = standard deviation
a: Duration of treatment (weeks) was defined as: [(date of last treatment administration) - (date of first administration as collected in eCRF) +1] / 7.

Note: If compliance for LGX/Placebo Grey blister (200 mg or matching placebo), LGX/Placebo Pink blister (75 mg or matching placebo) or Add-back therapy was missing from accountability data, then compliance was computed from daily diary data using the following definition: (number of days with pink tablet/grey tablet/Add-back capsule taken × 100) ÷ the number of days in the period (Month 6 visit date – 1 or last treatment administration date - Day 1) + 1.

Baseline data

Table 12 Baseline characteristics of the EDELWEISS 3 study population (FAS)

Characteristic mean (SD) unless specified	Placebo N=162	LGX 75 mg N=160	LGX 200 mg + ABT N=162	Total N=484
Demographics				
Age – years	34.9 (6.8)	35.1 (6.4)	34.6 (6.8)	34.9 (6.6)
Race, Black – n (%)	2 (1.2)	1 (0.6)	1 (0.6)	4 (0.8)
Race, White – n (%)	160 (98.8)	158 (98.8)	159 (98.1)	477 (98.6)
Weight – kg	65.81 (11.96)	67.73 (14.45)	65.75 (14.75)	66.42 (13.77)
BMI – kg/m^2	24.14 (4.44)	24.60 (5.23)	24.09 (5.17)	24.27 (4.95)
Menstrual cycles and pain assessment*				
Average number of days with uterine bleeding (days)	6.26 (2.34)	6.95 (2.58)	6.68 (2.14)	6.63 (2.37)
Overall Pelvic Pain (VRS)	1.90 (0.40)	1.87 (0.41)	1.92 (0.42)	1.90 (0.41)
DYS (VRS)	2.29 (0.43)	2.25 (0.40)	2.29 (0.43)	2.28 (0.42)
NMPP (VRS)	1.78 (0.44)	1.73 (0.46)	1.80 (0.46)	1.77 (0.45)
Analgesic use on bleeding days (pill count/day)	1.65 (1.45)	1.88 (1.69)	2.01 (1.95)	1.85 (1.71)
Analgesic use on non-bleeding days (pill count/day)	0.78 (0.98)	1.00 (1.23)	1.08 (1.26)	0.95 (1.17)
Endometriosis history and symptoms				

Characteristic mean (SD) unless specified	Placebo N=162	LGX 75 mg N=160	LGX 200 mg + ABT N=162	Total N=484
Time since first seeking medical diagnosis/treatment - years	4.94 (4.51)	5.15 (4.38)	5.50 (4.74)	5.20 (4.54)
Time since first surgical diagnosis - years	3.54 (3.40)	3.92 (3.71)	4.06 (3.77)	3.84 (3.63)
Dyspareunia** – n (%)	145 (89.5)	141 (88.1)	140 (86.4)	426 (88.0)
Dyschezia** – n (%)	88 (54.3)	83 (51.9)	76 (46.9)	247 (51.0)
Dysuria** – n (%)	45 (27.8)	37 (23.1)	44 (27.2)	126 (26.0)
Current adenomyosis – n (%)	46 (28.4)	46 (28.8)	53 (32.7)	145 (30.0)
Current rectovaginal endometriosis nodes – n (%)	27 (16.7)	28 (17.5)	33 (20.4)	88 (18.2)
Transvaginal ultrasound findings				
Endometrium thickness (mm)	7.97 (3.13)	8.06 (3.39)	8.40 (3.72)	8.14 (3.42)
Previous treatment for endometriosis				
Undergone pretreatment procedure for endometriosis, excluding diagnostic procedures – n (%)	129 (79.6)	130 (81.3)	127 (78.4)	386 (79.8)
Received pretreatment medication with progestin treatment, COC, or Levonorgestrel IUD – n (%)	70 (43.2)	55 (34.4)	75 (46.3)	200 (41.3)

ABT = add-back therapy; BMI = body mass index; COC = combined oral contraceptive; DYS = dysmenorrhoea; FAS = Full analysis set; IUD = intrauterine device; LGX = linzagolix; NMPP = non-menstrual pelvic pain; SD = standard deviation; VRS = verbal rating scale

*Based on the two selected screening menstrual cycles.

** Within 2 months of screening.

Subject characteristics for those entering the additional 6-month treatment period in the EDELWEISS 6 study

The demographic profile of subjects included in the EDELWEISS 6 study Treatment Extension Analysis Set (N=353) was nearly identical to that reported for the preceding EDELWEISS 3 study FAS (N=484). The mean (SD) age was 34.8 (6.7) years, with a median of 35.0 years. The women were mostly white (98.6%), and less than 1% were Black or African American. Only 2.3% of subjects identified as either hispanic or latino. The mean (SD) weight was 66.61 (13.87) kg and mean (SD) BMI was 24.25 (4.94) kg/m2.

Numbers analysed

Of the 854 subjects screened, 486 were randomised (460 subjects at sites in the EU; 26 at sites in the US). Between randomisation and Day 1 (i.e., first day of dosing), 2 subjects in the LGX 75 mg group discontinued due to protocol deviation. Thus, 484 randomised subjects were treated and comprised the Full Analysis Set (FAS) and Safety Analysis Set (SAF).

Table 12 Analysis set

	Placebo	LGX 75 mg	LGX 200 mg+ABT	Total
Randomized set	162 (100.0)	162 (100.0)	162 (100.0)	486 (100.0)
Full Analysis Set (FAS)	162 (100.0)	160 (98.8)	162 (100.0)	484 (99.6)
Per Protocol Set (PP)	133 (82.1)	134 (82.7)	139 (85.8)	406 (83.5)
Threshold Analysis Set	149 (92.0)	152 (93.8)	157 (96.9)	458 (94.2)
M6 Threshold Analysis Set	142 (87.7)	150 (92.6)	149 (92.0)	441 (90.7)
Safety Analysis Set (SAF)	162	160	162	484
Pharmacokinetic Set (PK)	0	160	162	322
Follow-up Set (FU)	15 (9.3)	15 (9.3)	21 (13.0)	51 (10.5)
Follow-up Safety Set (FU SAF)	15	15	21	51

ABT = add-back therapy; LGX = linzagolix

Outcomes and estimation

The two co-primary, composite, efficacy endpoints were clinically meaningful reductions from baseline to the last 28 days preceding the Month 3 visit (i.e., the 4-week period preceding Month 3 visit) or, for subjects who discontinued randomized treatment prior to the Month 3 visit, to the last 28 days of randomized treatment, along with a stable or decreased use of analgesics for EAP, in the mean daily assessment of 1) DYS and of 2) NMPP measured on a Verbal Rating Scale (VRS) using an electronic diary (eDiary).

Clinically meaningful reductions in DYS and NMPP were determined using the Meaningful Clinical Threshold (MCT) analysis performed on soft locked data at Month 3. This analysis was performed by an external group while the Sponsor remained blinded until database lock at Month 6. Anchor-based methods were used to estimate the MCT for each co-primary and ranked secondary endpoint. Both generic and specific anchors were used.

The anchor-based methods included estimation of mean within-group change, with 95% confidence intervals (CIs), and receiver operating characteristic (ROC) curves to identify best cut points (BCPs). The MCT determination also considered supportive information from cumulative distribution function (CDF) and probability distribution function (PDF) curves. Differences between the CDF curves at the 25th, 50th, and 75th percentiles were used to generate estimates of what constitutes a meaningful change. Lastly, shift tables were used, where appropriate, to examine the change in the endpoint by baseline and Month 3/6 anchor score.

Following the analyses to estimate the MCTs performed on soft locked data at Month 3, the criterion for defining a subject as a responder over the last 28 days of randomized treatment up to Month 3 was a reduction of 1.10 or greater from baseline pain for DYS; a reduction of 0.80 or greater from baseline pain for NMPP. These definitions of a clinically meaningful response were used for the primary efficacy analysis.

MCTs were estimated for additional supportive responder analyses on the ranked secondary endpoints based on the blinded data up to Month 6 using anchor-based methods. Following the MCT analysis, the recommendation for the final MCT estimates of the ranked secondary endpoints were as follows:

- Dysmenorrhea (VRS): -1.25
- Non-Menstrual Pelvic Pain (VRS): -0.85
- Dyschezia (Numeric Rating Scale - NRS): -1.5

- Overall pelvic pain (NRS): -2.7
- EHP-30 pain domain: -28
- Dyspareunia (VRS): -0.9

Subjects whose response could not be assessed for the co-primary efficacy endpoints, e.g. due to lack of on treatment pain data (i.e., subjects who received less than 28 days of treatment), were considered as non-responders.

The MCT estimates, based on soft-locked data at Month 3, were -1.10 for DYS (VRS) and -0.80 for NMPP (VRS). Thus, the criterion for defining a subject as a responder over the last 28 days of randomized treatment up to Month 3 was a reduction of 1.10 or greater from baseline pain for DYS; a reduction of 0.80 or greater from baseline pain for NMPP, and having a stable or decreased use of analgesics for EAP over this period.

Treatment with LGX 200 mg dose administered with ABT demonstrated statistically significant reductions in both co-primary endpoints of DYS and NMPP at 3 months with a stable or decreased use of analgesics for EAP. From the logistic regression analysis, the estimated percentage of responders:

- for DYS was 72.9% (95% CI: 65.3, 79.4) compared with 23.5% (95% CI: 17.5, 30.7) in the placebo group with an Odds Ratio (OR) vs placebo of 8.80 (97.5% CI: 4.86, 15.91) and a Bonferroni-corrected p-value of treatment effect <0.001.
- for NMPP was 47.3% (95% CI: 39.5, 55.3) compared with 30.9% (95% CI: 24.1, 38.6) in the placebo group with an OR vs placebo of 2.01 (97.5% CI: 1.18, 3.42) and a Bonferroni corrected p-value of treatment effect of 0.007.

Treatment with the 75 mg dose achieved statistically significant reduction in DYS but not in NMPP at 3 months. Therefore, in this application, the 75 mg linzagolix dose is not proposed for the treatment of endometriosis-associated pain.

Table 13 Reduction of DYS and NMPP (VRS) at Month 3 – responder analysis (EDELWEISS 3, FAS)

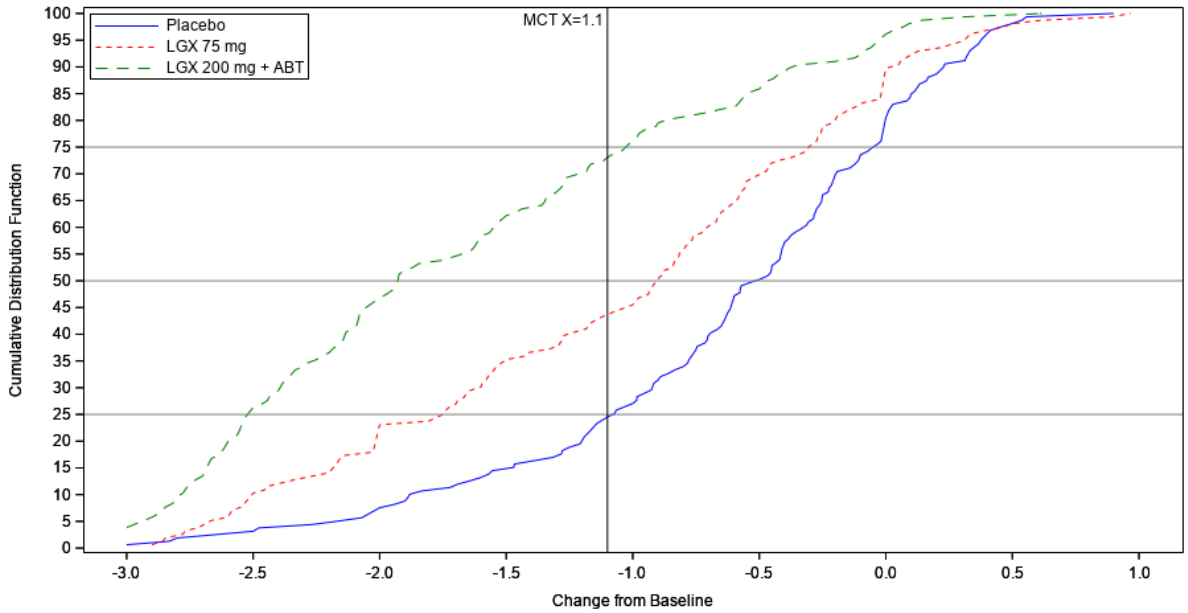
	Placebo (N=162)	LGX 75 mg (N=160)	LGX 200 mg + ABT (N=162)	Total (N=484)
Responders for DYS*				
n (missing)	159 (3)	156 (4)	156 (6)	471 (13)
Yes, n (%)	39 (24.5)	68 (43.6)	113 (72.4)	220 (46.7)
Logistic Regression – Responder analysis for DYS				
Odds Ratio vs Placebo [(1)]		2.56	8.80	
97.5% CI [(1)]		1.46; 4.49	4.86; 15.91	
p-value of treatment effect [(2)]		<0.001	<0.001	
Proportion of responders (95% CI) [(1)]	23.5 (17.5; 30.7)	44.0 (36.3; 52.0)	72.9 (65.3; 79.4)	
Responders for NMPP*				
n (missing)	159 (3)	156 (4)	156 (6)	471 (13)
Yes, n(%)	50 (31.4)	60 (38.5)	75 (48.1)	185 (39.3)
Logistic Regression – Responder analysis for NMPP				
Odds Ratio vs Placebo [(1)]		1.43	2.01	
97.5% CI [(1)]		0.83; 2.45	1.18; 3.42	
p-value of treatment effect [(2)]		0.279	0.007	

Proportion of responders (95% CI) [1]	30.9 (24.1; 38.6)	38.9 (31.5; 46.9)	47.3 (39.5; 55.3)	

ABT = add-back therapy; DYS = dysmenorrhoea; EAP = endometriosis-associated pain; LGX = linzagolix; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale
*Reduction of 1.1 (resp. 0.8) for DYS (resp. NMPP) in mean pelvic pain score within last 28 days prior to Month 3 or discontinuation, and stable or decreased use of analgesics for EAP within the same calendar days.
(1) Estimated with logistic regression model with Reduction of DYS or NMPP as response variable, treatment group as the main effect and including the baseline pain score as a covariate.
(2) Bonferroni corrected p-value.
Subjects with less than 43% of daily diary data completed were excluded.

The change from baseline for pelvic pain scores for DYS and NMPP for the last 28 days prior to Month 3 (or the last 28 days of treatment – or less – for subjects who discontinued) are illustrated as continuous variables by treatment group in the cumulative distribution functions (CDF) plots for DYS in Figure 4 and NMPP in Figure 5.

Figure 4 Cumulative distribution function – DYS (VRS) change at Month 3 (EDELWEISS 3, FAS)

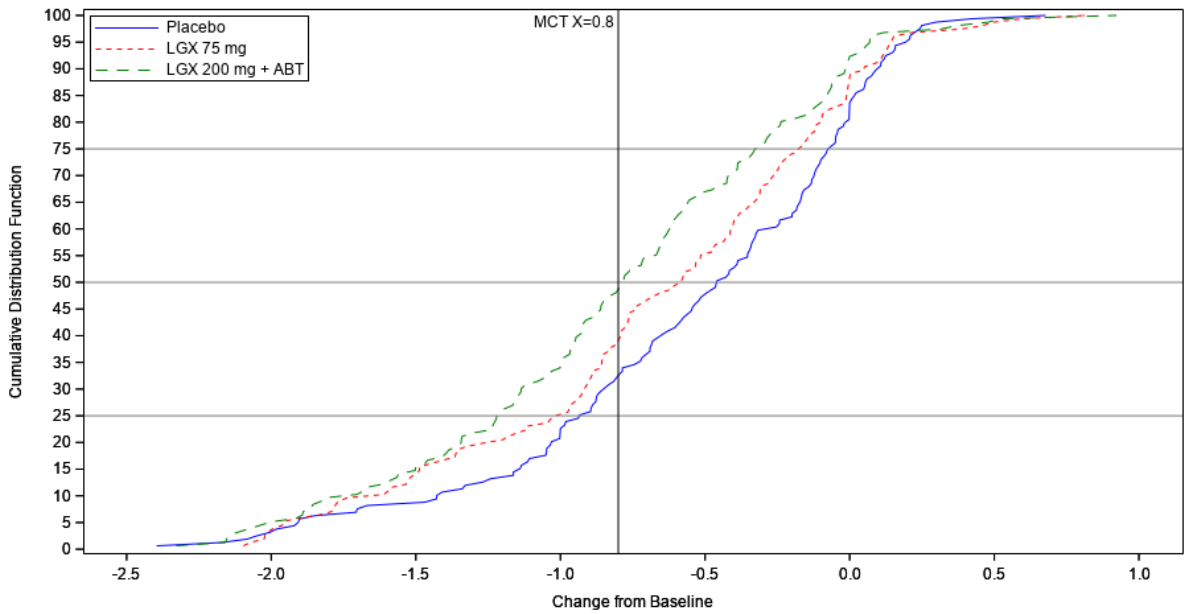


ABT = add-back therapy; DYS = dysmenorrhoea; FAS = Full analysis set; LGX = linzagolix; MCT = meaningful change threshold; VRS = verbal rating scale

Dysmenorrhoea (VRS) Change at Month 3 was derived as the average of the daily e-diary data scores over the last 28 days on treatment prior to Month 3 or discontinuation.

Subjects with less than 43% of daily diary data completed were excluded.

Figure 5 Cumulative distribution function – NMPP (VRS) change at Month 3 (EDELWEISS 3, FAS)



ABT = add-back therapy; FAS = Full analysis set; LGX = linzagolix; MCT = meaningful change threshold; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale

Non-Menstrual Pelvic Pain (VRS) Change at Month 3 was derived as the average of the daily e-diary data scores over the last 28 days on treatment prior to Month 3 or discontinuation.

Subjects with less than 43% of daily diary data completed were excluded.

Sensitivity analyses

Cochran-Mantel-Haenszel test (CMH)

The results of sensitivity analyses using CMH test confirmed the results of the primary analysis for the FAS. The estimated proportion of responders for DYS were 43.6% (95% CI: 35.7, 51.8) for the LGX75 mg group, 72.4% (95% CI: 64.7, 79.3) for the LGX 200 mg+ABT group, compared with 24.5% (95% CI: 18.1, 32.0) for placebo. Response rates for DYS were statistically significant in both LGX groups with CMH OR vs placebo of 2.38 (97.5% CI: 1.37, 4.12; p-value < 0.001) and 8.09(97.5% CI: 4.54, 14.39; p-value < 0.001) for the LGX 75 mg and LGX 200 mg+ABT groups, respectively. The risk (proportion) difference between each LGX group and placebo was 19.1 (97.5% CI: 7.3, 30.8) and 47.9 (97% CI: 36.8, 59.0) for the LGX 75 mg and LGX 200 mg+ABTgroups, respectively.

The estimated response rates for NMPP were 38.5% (95% CI: 30.8, 46.6) for the LGX 75 mg group, 48.1% (95% CI: 40.0, 56.2) for the LGX 200 mg+ABT group, compared with 31.4% (95%CI: 24.3, 39.3) for placebo. Response rates for NMPP were statistically significant only for the LGX 200 mg+ABT group with OR vs placebo of 2.02 (97.5% CI: 1.19, 3.41; p-value = 0.005), and not significant for the LGX 75 mg group with OR of 1.36 (97.5% CI: 0.80, 2.32). The risk(proportion) difference between each LGX group and placebo was 7.0 (97.5% CI: -5.0, 19.0) and 16.6 (97% CI: 4.4, 28.8) for the LGX 75 mg and LGX 200 mg+ABT groups, respectively.

Subjects who had completed at least 75% eDiary entries

The primary analysis was repeated using subjects with at least 75% (21 days of each 28-day period) of completed daily eDiaries for DYS, NMPP and analgesic use. The results of these analyses were consistent with the primary analysis that included subjects with at least 43% (12 days) of completed daily eDiaries.

Including analgesics for non-endometriosis associated pain

Sensitivity analyses which included in the definition of a responder any analgesic medication also taken for non-endometriosis associated pain (i.e., including those for EAP or not, as collected in eDiary and concomitant medications eCRF pages) yielded similar results to the primary analysis as shown for the FAS in the EDELWEISS 3 CSR.

Using the meaningful change thresholds derived in the EDELWEISS Phase 2b study

The results of the co-primary endpoints analysed using the meaningful change thresholds (MCTs) derived in the EDELWEISS Phase 2b study (i.e., -1.0 for DYS and -0.7 for NMPP) are shown in the table below. This sensitivity analysis confirmed that the LGX 200 mg+ ABT regimen resulted in meaningful reductions in dysmenorrhea (DYS) and non-menstrual pelvic pain (NMPP) at 3 months with a stable or decreased use of analgesics for endometriosis-associated pain (EAP). This analysis also confirmed that, although the linzagolix 75 mg dose resulted in meaningful reduction in DYS at 3 months, it did not reach statistical significance for reduction of NMPP.

Table 14 Reduction of dysmenorrhea and non-menstrual pelvic pain and stable or decreased use of analgesics for EAP on the last 28 days on treatment prior to Month 3 – Responder analysis from logistic regression using MCTs of -1.0 for DYS and -0.7 for NMPP (EDELWEISS 3 FAS)

	Placebo (N=162)	LGX 75 mg (N=160)	LGX 200 mg + ABT (N=162)	Total (N=484)
Responders for DYS*				
n (missing)	159 (3)	156 (4)	156 (6)	471 (13)
Yes	43 (27.0)	71 (45.5)	119 (76.3)	233 (49.5)
Logistic Regression – Responder analysis for DYS				
Odds Ratio vs Placebo [1]		2.40	9.30	
97.5% CI [1]		1.39; 4.15	5.13; 16.86	
p-value of treatment effect [2]		<0.001	<0.001	
Proportion of responders (95% CI) [1]	26.2 (19.9; 33.6)	46.0 (38.2; 53.9)	76.7 (69.4; 82.7)	
Responders for NMPP*				
n (missing)	159 (3)	156 (4)	156 (6)	471 (13)
Yes	57 (35.8)	71 (45.5)	84 (53.8)	212 (45.0)
Logistic Regression – Responder analysis for NMPP				
Odds Ratio vs Placebo [1]		1.55	2.08	
97.5% CI [1]		0.92; 2.61	1.23; 3.49	
p-value of treatment effect [2]		0.121	0.003	
Proportion of responders (95% CI) [1]	35.6 (28.5; 43.3)	46.1 (38.3; 54.0)	53.4 (45.5; 61.1)	

ABT = add-back therapy; DYS = dysmenorrhea; EAP = endometriosis-associated pain; LGX = linzagolix; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale

*Reduction of 1.0 (resp. 0.7) for DYS (resp. NMPP) in mean pelvic pain score within last 28 days prior to Month 3 or discontinuation, and stable or decreased use of analgesics for EAP within the same calendar days.

(1) Estimated with logistic regression model with Reduction of DYS or NMPP as response variable, treatment group as the main effect and including the baseline pain score as a covariate.

(2) Bonferroni corrected p-value.

Subjects with less than 43% of daily diary data completed were excluded.

Ancillary analyses

Supportive analyses

Discontinued subjects as non-responders

Results consistent with the primary analysis were obtained when subjects who discontinued treatment prior to Month 3 were considered as non-responders. These are composite endpoints that estimate the proportion of subjects with clinically meaningful reduction in pain, a stable or decreased use of rescue medication, and who complete 3 months of treatment. The primary analyses were performed using a composite strategy for discontinuation as opposed to a while-on treatment strategy used for the primary estimand.

From the logistic regression analysis, the estimated response rates for DYS were 42.0% (95% CI: 34.4, 50.1) for the LGX 75 mg group, 71.3% (95% CI: 63.6, 78.0) for the LGX 200 mg+ABT group, compared with 22.5% (95% CI: 16.6, 29.8) for placebo. Response rates for DYS were statistically significant in both LGX groups with OR vs placebo of 2.49 (97.5% CI: 1.41, 4.40; pvalue < 0.001) and 8.55 (97.5% CI: 4.72, 15.50; p-value < 0.001) for the LGX 75 mg and LGX 200 mg+ABT groups, respectively.

The estimated response rates for NMPP were 39.0% (95% CI: 31.5, 47.0) for the LGX 75 mg group, 46.9% (95% CI: 39.1, 54.9) for the LGX 200 mg+ABT group, compared with 29.6% (95% CI: 22.9, 37.2) for placebo. Response rates for NMPP were statistically significant only for the LGX 200 mg+ABT group with OR vs placebo of 2.11 (97.5% CI: 1.23, 3.59; p-value = 0.004), and not significant for the LGX 75 mg group with OR of 1.52 (97.5% CI: 0.88, 2.61).

Reference-based multiple imputation for discontinued subjects

In order to estimate the effect of treatment policy, a reference based multiple imputation approach was used for the co-primary endpoints for subjects who discontinued the study early, under the assumption that the efficacy of the linzagolix-treated subjects gradually transitions to that observed in the placebo subjects, i.e., using a treatment policy strategy for discontinuation as opposed to a while-on-treatment strategy used for the primary estimand.

DYS and NMPP mean scores changes, and ibuprofen and analgesic use (pill counts) were simultaneously imputed using multivariate imputation by a fully conditional specification method, with 20 burn-in iterations before each imputation. The predictive mean matching method for continuous variables was used where the imputed values were randomly taken from the 5 closest observed values whose predicted values were closest to the predicted value for the missing value from the simulated imputation model. The imputation model included baseline value as a covariate. Following imputation, the corresponding binary endpoints of response for DYS, NMPP including use of analgesics, were computed.

The results using reference-based multiple imputation for subjects who discontinued prior to Month 3 were consistent with those observed for the primary analysis (EDELWEISS 3 CSR, Table 14.2.2.34.1). From the logistic regression analysis, the estimated response rates for DYS were 44.2% (95% CI: 36.0, 52.4) for the LGX 75 mg group, 73.2% (95% CI: 66.0, 80.5) for the LGX 200 mg+ABT group, compared with 24.4% (95% CI: 17.5, 31.4) for placebo. Response rates for DYS were statistically significant in both LGX groups with OR vs placebo of 2.45 (97.5% CI: 1.38, 4.36; p-value < 0.001) and 8.47 (97.5% CI: 4.60, 15.60; p-value < 0.001) for the LGX 75 mg and LGX 200 mg+ABT groups, respectively. The estimated response rates for NMPP were 40.6% (95% CI: 32.5, 48.6) for the LGX 75 mg group, 48.5% (95% CI: 40.4, 56.6) for the LGX 200 mg+ABT group, compared with 32.1% (95% CI: 24.5, 39.7) for placebo. Response rates for NMPP were statistically significant only for the LGX 200 mg+ABT group with OR vs placebo of 1.99 (97.5% CI: 1.16, 3.44; p-value = 0.009) and not significant for the LGX 75 mg group with OR of 1.44 (97.5% CI: 0.83, 2.51).

Assessment of stable or decreased use of analgesics for EAP overall

An additional analysis of DYS and of NMPP was conducted where the assessment of stable or decreased use of analgesics for EAP was assessed over all days rather than separately for bleeding days and non-bleeding days. This same assessment was then incorporated into the DYS and NMPP endpoints. The same logistic regression analysis as for the primary analysis was performed. The results of this supplementary analysis were consistent with those observed for the primary analysis.

From the logistic regression analysis, the estimated response rates for DYS were 43.3% (95% CI: 35.6, 51.3) for the LGX 75 mg group, 70.9% (95% CI: 63.2, 77.6) for the LGX 200 mg+ABT group, compared with 22.3% (95% CI: 16.4, 29.4) for placebo. Response rates for DYS were statistically significant in both LGX groups with OR vs placebo of 2.67 (97.5% CI: 1.51, 4.71; p value < 0.001) and 8.53 (97.5% CI: 4.72, 15.41; p-value < 0.001) for the LGX 75 mg and LGX 200 mg+ABT groups, respectively. The estimated response rates for NMPP were 39.6% (95% CI: 32.1, 47.6) for the LGX 75

mg group, 47.9% (95% CI: 40.1, 55.9) for the LGX 200 mg+ABT group, compared with 30.2% (95% CI: 23.5, 37.9) for placebo. Response rates for NMPP were statistically significant only for the LGX 200 mg+ABT group with OR vs placebo of 2.13 (97.5% CI: 1.25, 3.63; p-value = 0.003), and not significant for the LGX 75 mg group with OR of 1.52 (97.5% CI: 0.88, 2.60).

Ranked secondary endpoints at Month 6

The LGX 200 mg+ABT group was shown to be statistically significantly more efficacious than placebo for the co-primary endpoints, thus a fixed-sequence testing strategy could continue to be used within the group to test the ranked secondary endpoints. The MCT estimates, based on Month 6 database lock (as described in the EDELWEISS 3 CSR, Section 9.7.6), used for the analyses of ranked secondary endpoints show statistically significant reductions (improvements) were observed in the following ranked secondary endpoints at 6 months in the LGX 200 mg+ABT group compared to placebo: DYS (VRS), NMPP (VRS), dyschezia (NRS), overall pelvic pain (NRS), and the ability to do daily activities measured using the pain dimension of EHP-30.

The corresponding proportions of responders were 77.2% (vs. 20.3% for placebo) for DYS, 56.3% (vs 38.0% for placebo) for NMPP, 51.9% (vs 43.7% for placebo) for dyschezia, 63.3% (vs 41.8% for placebo) for overall pelvic pain, and 62.6% (vs 34.8% for placebo) for EHP-30 pain dimension.

Treatment effect for dyspareunia was not statistically significant, with the corresponding proportion of responders of 52.9% (vs 46.2% for placebo).

Only 2.5% of subjects in the LGX 200 mg+ABT group did not use analgesics for EAP at baseline. The percentage of subjects not using analgesics for EAP rose to 45.3% at Month 6, with a statistically significant change from baseline (OR = 5.27; 97.5% CI: 2.83, 9.82; p<0.001).

Most subjects in the LGX 200 mg+ABT group did not use opiates for EAP at baseline (87.7%) and at Month 6 (93.7%).

Table 15 Summary of analyses of ranked secondary endpoints at Month 6 for the LGX 200 mg+ABT group (EDELWEISS 3, FAS)

Endpoints at Month 6	Month 6 MCT	Placebo (N=162)	LGX 200 mg + ABT (N=162)		
		LSM (95% CI)	LSM (95% CI)	Diff with PBO (97.5% CI)	p-val[1]
CfB in DYS (VRS)	-1.25	-0.66 (-0.79; -0.53)	-1.83 (-1.96; -1.70)	-1.17 (-1.38; -0.97)	<0.001
CfB in NMPP (VRS)	-0.85	-0.66 (-0.77; -0.56)	-0.92 (-1.03; -0.82)	-0.26 (-0.43; -0.09)	0.002
CfB in dyschezia (NRS)	-1.5	-1.41 (-1.71; -1.12)	-1.99 (-2.29; -1.70)	-0.58 (-1.05; -0.11)	0.012
CfB in OPP (NRS)	-2.7	-2.19 (-2.55; -1.84)	-3.39 (-3.74; -3.03)	-1.19 (-1.77; -0.62)	<0.001
CfB in EHP-30 pain dimension	-28	-19.47 (-22.66; -16.28)	-35.60 (-38.73; -32.48)	-16.13 (-21.24; -11.02)	<0.001
CfB in dyspareunia (VRS)	-0.9	-0.82 (-0.97; -0.66)	-1.01 (-1.18; -0.85)	-0.20 (-0.46; 0.07)	0.184
		% of responders (95% CI)	% of responders (95% CI)	OR[2] (97.5% CI)	p-val[1]
No analgesic use for EAP	n/a	13.2 (8.9; 19.2)	44.5 (36.3; 52.9)	5.27 (2.83; 9.82)	<0.001

Endpoints at Month 6	Month 6 MCT	Placebo (N=162)	LGX 200 mg + ABT (N=162)		
		LSM (95% CI)	LSM (95% CI)	Diff with PBO (97.5% CI)	p-val[(1)]
No opiate use for EAP	n/a	97.0 (92.5; 98.9)	97.0 (92.7; 98.8)	0.99 (0.22; 4.51)	1.000

CfB = change from baseline; DYS = dysmenorrhoea; MCT = meaningful threshold analysis (performed on Month 6 database lock); n/a = not applicable; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; OPP = overall pelvic pain; VRS = visual rating scale
endometriosis-associated pain; EHP-30 = Endometriosis Health Profile-30; LGX = linzagolix; LSM = least square mean; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; OPP = overall pelvic pain; OR = odds ratio; VRS = verbal rating scale
Scores were computed as mean of daily assessments on the last 28 days prior to Month 6 or discontinuation.
Analysis of covariance with change from Baseline as response variable, and baseline value, treatment as covariates.
EHP-30 Pain Score at Month 6 or discontinuation. EHP-30 Pain Score was computed as the sum of each pain question score/(number of items*4)*100 and ranges from 0 (best possible health status) to 100 (worst possible health status).
For dyspareunia, subjects not sexually active for other reasons than endometriosis have missing value.
Analgesic and opiate use for EAP as collected in eDiary and Concomitant Medication page on the last 28 days prior to Month 6 or discontinuation.
(1) Bonferroni corrected p-value. A fixed-sequence testing strategy was used to account for multiplicity. The LGX 200 mg+ABT group demonstrated statistically significant differences for both co-primary endpoints. The LGX 75 mg group was not found to be statistically significantly compared to placebo for the NMPP co-primary endpoint.
(2) Odds-ratios and 97.5% CI estimated with logistic regression model with no analgesic use/no opiate use in the last 28 days on treatment prior to Month 6 as response variable, treatment group as the main effect and including the baseline analgesic use/opiate use as a covariate.
Subjects with less than 43% of daily diary data completed were excluded.

Additional secondary efficacy endpoints at Month 6

A Bonferroni correction for p-values of comparison of treatment groups at each visit was used for the additional secondary endpoints. The analyses did not form part of the fixed-sequence strategy being used for the co-primary and ranked secondary endpoints and were not fully controlled for an overall type I error rate. However, to maintain consistency with the primary and secondary analyses, Bonferroni corrections were used because there were two linzagolix versus placebo comparisons for each endpoint / time point.

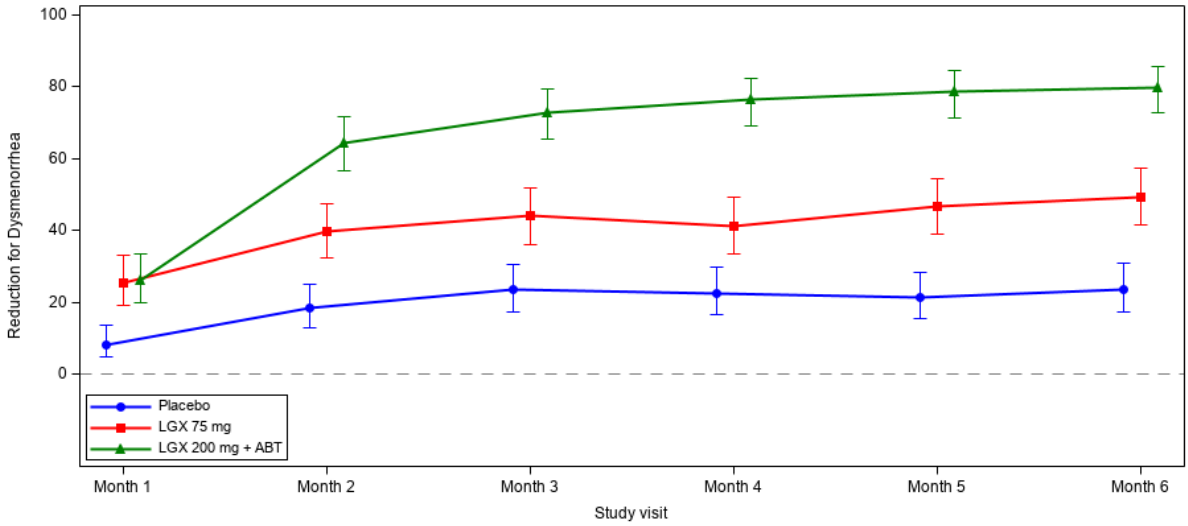
Given that the co-primary endpoint of NMPP reduction was not achieved with the administration of 75 mg of linzagolix alone, the supportive evidence of secondary efficacy endpoints at Month 6 outlined in this section is focused on the proposed dose regimen of linzagolix 200 mg coadministered with ABT.

The proportion of responders for DYS and NMPP based on daily eDiary data was reported at each visit (each 28-day period), as illustrated in Figure 2.7.3-9 and Figure 2.7.3-10, respectively. A responder for DYS was defined as having a change from baseline of at least -1.1, and responder for NMPP was defined as having a change from baseline of at least -0.8 (i.e., same definition as for the primary endpoint analysis).

DYS

The response to treatment was rapid. The proportion of subjects with a reduction in DYS (VRS) was higher in both LGX groups as early as Month 1 (Figure 6) compared to placebo. In the LGX 200 mg+ABT group, the proportion of responders rose sharply at Month 2 and continued to rise gradually until the end of treatment at Month 6.

Figure 6 Proportion of subjects with a reduction for DYS (VRS) (EDELWEISS 3, FAS)



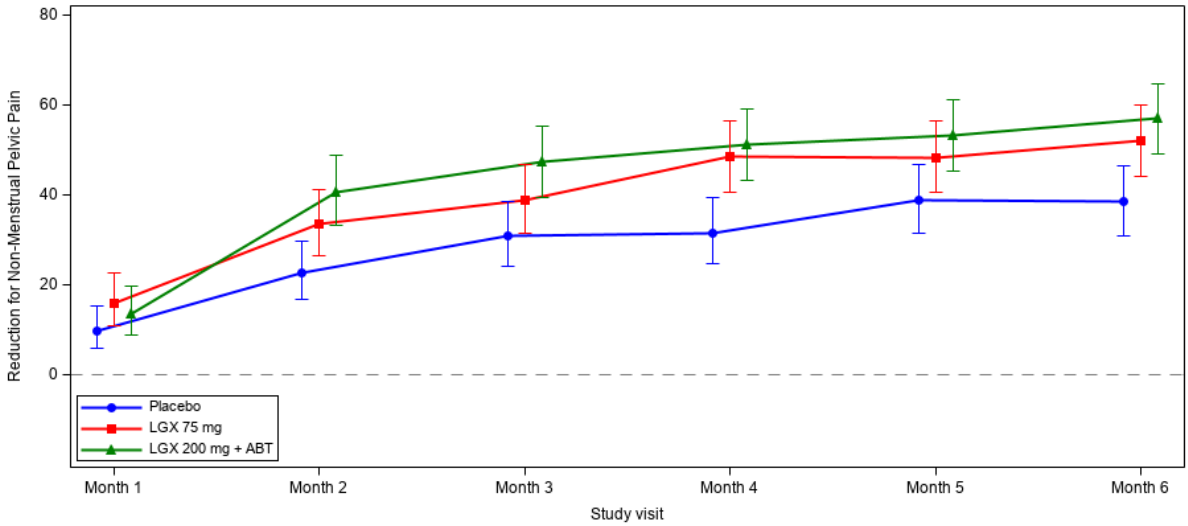
ABT = add-back therapy; DYS = dysmenorrhoea; EAP = endometriosis-associated pain; FAS = Full analysis set; LGX = linzagolix; VRS = verbal rating scale
Reduction of 1.1 for DYS (Month 3 MCT analysis) in mean pelvic pain score within last 28 days prior to each visit or discontinuation, and stable or decreased use of analgesics for EAP within the same calendar days.
Percentages and 95% CI of responders estimated with logistic regression model at each time point with reduction of DYS as response variable, treatment group as the main effect and including the baseline pain score as a covariate.
Subjects with less than 43% of daily diary data completed were excluded.

At Month 6, the proportion of DYS responders was 49.5% (95% CI: 41.6, 57.4) and 80.0% (95% CI: 73.0, 85.5) in the LGX 75 mg and LGX 200 mg+ABT group, respectively, compared to 23.5% (95% CI: 17.5, 30.8) in the placebo group. These results represented substantial DYS reduction in both LGX groups, with an odds ratio vs placebo of 3.18 (97.5% CI: 1.82, 5.56; p-value < 0.001) and 12.98 (97.5% CI: 7.00, 24.06; p-value < 0.001) in the LGX 75 mg and LGX 200 mg+ABT group, respectively.

NMPP

The proportion of subjects with a reduction in NMPP (VRS) was higher in both LGX groups at Month 2 (Figure 7) compared to placebo, with a consistently better response observed for the LGX 200 mg+ABT group, continuing to rise gradually until the end of treatment at Month 6.

Figure 7 Proportion of subjects with a reduction for NMPP (VRS) (EDELWEISS 3, FAS)



ABT = add-back therapy; EAP = endometriosis-associated pain; FAS = Full analysis set; LGX = linzagolix; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale
Reduction of 0.8 for NMPP (Month 3 MCT analysis) in mean pelvic pain score within last 28 days prior to the visit or discontinuation, and stable or decreased use of analgesics for EAP within the same calendar days.
Percentages and 95% CI of responders estimated with logistic regression model at each time point with reduction of NMPP as response variable, treatment group as the main effect and including the baseline pain score as a covariate.
Subjects with less than 43% of daily diary data completed were excluded.

At Month 6, the proportion of NMPP responders was 52.2% (95% CI: 44.1, 60.1) and 57.1% (95%CI: 49.0, 64.8) in the LGX 75 mg and LGX 200 mg+ABT group, respectively, compared to 38.5% (95% CI: 31.0, 46.4) in the placebo group. These results represented marked NMPP reduction in both LGX groups, with an odds ratio vs placebo of 1.75 (97.5% CI: 1.03, 2.96; p-value = 0.036) and 2.13 (97.5% CI: 1.26, 3.60; p-value = 0.003) in the LGX 75 mg and LGX 200 mg+ABT group, respectively.

Primary Efficacy Endpoints at Month 12 (EDELWEISS 6)

The co-primary endpoints at Month 12 were a clinically meaningful reduction in DYS and NMPP (analysed using both the Month 3 MCT and Month 6 MCT) with stable or decreased use of analgesics.

DYS

Month 3 MCT

At Month 12, the proportion of subjects with a reduction of 1.10 or greater in DYS (VRS) and stable or decreased use of analgesics was 55.9% in the LGX 75 mg group and 91.0% in the LGX200 mg+ABT group. The proportion of subjects with a reduction of 0.80 or greater in NMPP(VRS) was 59.5% in the LGX 75 mg group and 67.6% in the LGX 200 mg+ABT group.

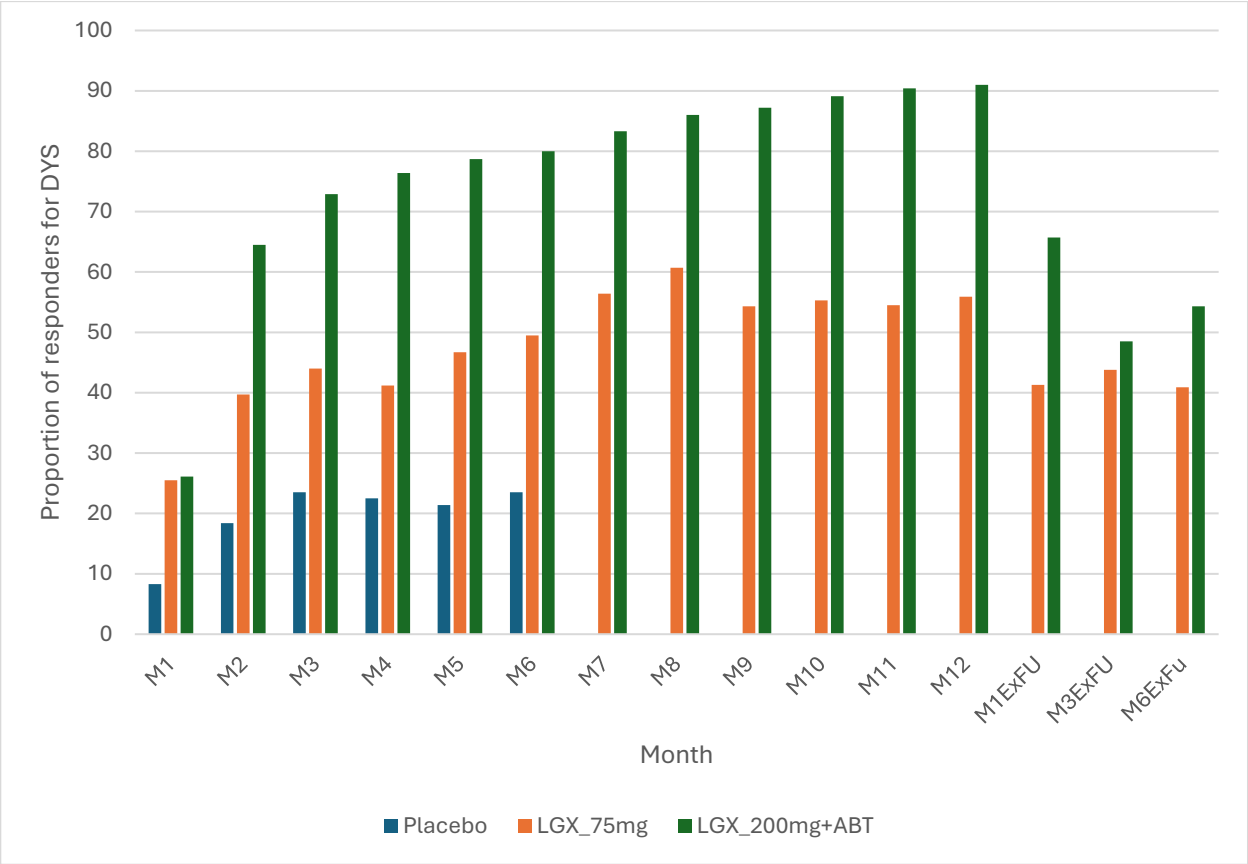
Month 6 MCT

At Month 12, the proportion of subjects with a reduction of 1.25 or greater in DYS (VRS) and stable or decreased use of analgesics was 50.5% in the LGX 75 mg group and 88.3% in the LGX 200 mg+ABT group. The proportion of subjects with a reduction of 0.85 or greater in NMPP (VRS) and stable or decreased use of analgesics was 55.9% in the LGX 75 mg group and 64.9% in the LGX 200 mg+ABT group. At Month 6, the proportion of DYS responders was 49.5% (95% CI: 41.6, 57.4) and 80.0% (95% CI: 73.0, 85.5) in the LGX 75 mg and LGX 200 mg+ABT group, respectively, compared to 23.5% (95% CI: 17.5, 30.8) in the placebo group in the FAS. These results represented substantial DYS reduction in both LGX groups, with an odds ratio vs placebo of 3.18 (97.5% CI: 1.82, 5.56; p

value< 0.001) and 12.98 (97.5% CI: 7.00, 24.06; p-value < 0.001) in the LGX 75 mg and LGX 200 mg+ABT group, respectively.

At the end of the 6-month drug-free follow-up period (Month 6 ExFU 6 months after drug cessation), subjects were still experiencing some lingering benefits of treatment compared to baseline, with the proportion of DYS responders with stable or decreased use of analgesics of 40.9% in the LGX 75 mg group and 54.3% in LGX 200 mg+ABT group (compared to 56.2% and 90.4% at Month 12, respectively) in the FuEAS.

Figure 8 Responder rates for DYS (VRS) using Month 3 MCT throughout treatment and follow-up (EDELWEISS 3, EDELWEISS 6)



ABT = Add-back therapy; DYS = dysmenorrhoea; ExFU = drug free follow-up after extension treatment; LGX = Linzagolix; M = month; MCT = meaningful change threshold; VRS = verbal rating scale

Subjects received treatment from Month 1 to Month 12. M1ExFU to M6ExFU denote drug-free follow-up.

Month 3 MCT for DYS was change from baseline of at least 1.1 (VRS)

NMPP

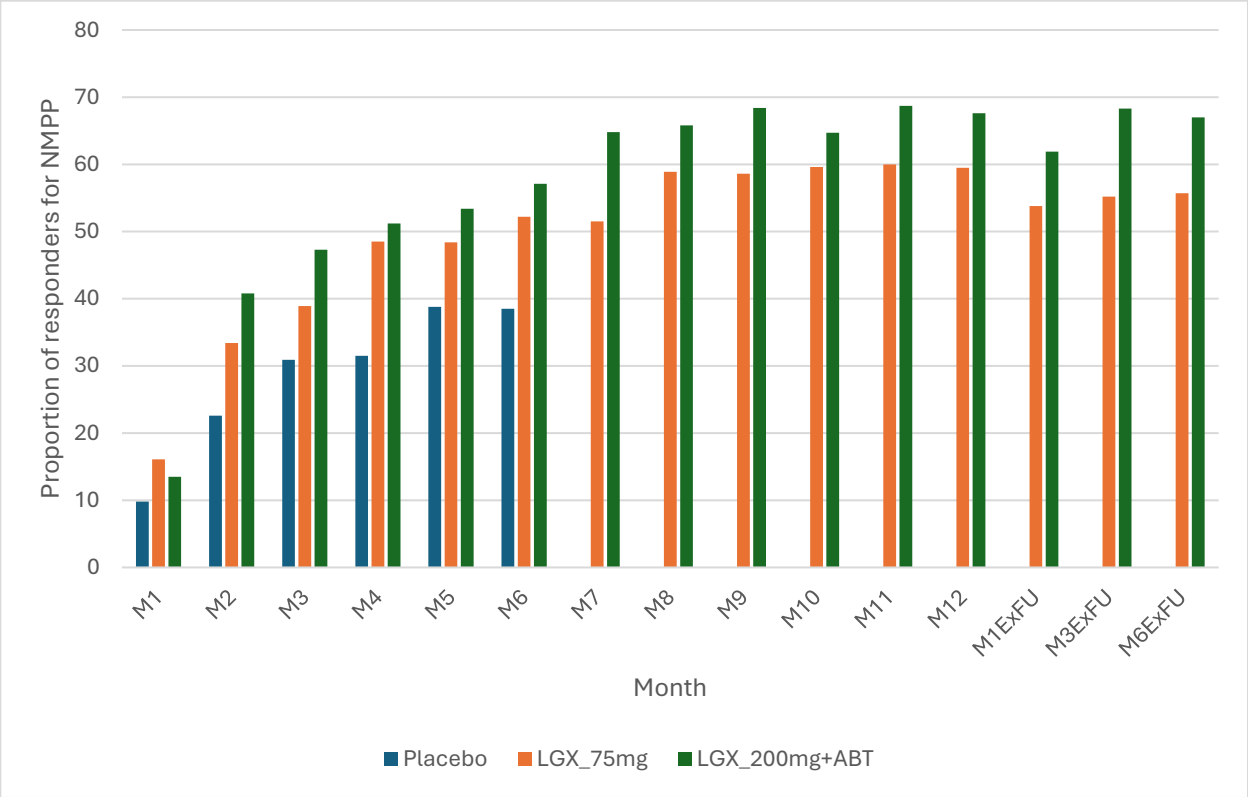
Substantial reductions in NMPP (VRS) scores were observed at Month 2 of treatment with 40.8% of responders in the LGX 200 mg+ABT group compared to 22.6% of responders in the placebo group (OR=2.36, 97.5% CI: 1.34, 4.16; p=0.001) in the FAS. The proportion of responders increased sharply at Month 2, then and continued to rise gradually until Month 6, stabilizing between Month 7 and the end of treatment at Month 12.

At Month 6, the proportion of NMPP responders was 52.2% (95% CI: 44.1, 60.1) and 57.1% (95% CI: 49.0, 64.8) in the LGX 75 mg and LGX 200 mg+ABT group, respectively, compared to 38.5% (95% CI: 31.0, 46.4) in the placebo group in the FAS. These results represented marked NMPP reduction in both LGX groups, with an odds ratio vs placebo of 1.75 (97.5% CI: 1.03, 2.96; p-value= 0.036) and 2.13 (97.5% CI: 1.26, 3.60; p-value = 0.003) in the LGX 75 mg and LGX 200 mg+ABT group, respectively.

At Month 12, the proportion of subjects with a reduction of 0.80 or greater in NMPP (VRS) was 59.5% in the LGX 75 mg group and 67.6% in the LGX 200 mg+ABT group in the TEAS.

At the end of the 6-month drug-free follow-up period (Month 6 ExFU), subjects were still experiencing some lingering benefits of treatment compared to baseline, with the proportion of NMPP responders was 55.7% in the LGX 75 mg group and 67.0% in the LGX 200 mg+ABT group (compared to 58.1% and 65.4% at Month 12, respectively) in the FuEAS.

Figure 9 Responder rates for NMPP (VRS) using Month 3 MCT throughout treatment and follow-up (EDELWEISS 3, EDELWEISS 6)



ABT = Add-back therapy; ExFU = drug free follow-up after extension treatment; LGX = Linzagolix; M = month; MCT = meaningful change threshold; NMPP = non-menstrual pelvic pain; VRS = verbal rating scale

Subjects received treatment from Month 1 to Month 12. M1ExFU to M6ExFU denote drug-free follow-up.

Month 3 MCT for NMPP was change from baseline of at least 0.8 (VRS)

Percentage of Responders Based on Month 6 MCT over Time

The percentage of responders over time for DYS, NMPP, dyschezia, OPP, EHP-30 pain domain, and dyspareunia evaluated based on Month 6 MCT are summarized in Table 16 using the FAS (Month 6), TEAS (Month 6 and Month 12), and FuEAS (Month 12 and Month 6 ExFU).

The response rates in the LGX 200 mg+ABT group were most robust for DYS (VRS), with 77.2% of responders at Month 6 and increasing up to 88.3% at Month 12, then declining by half 6 months after the cessation of treatment.

For EAP measures such as NMPP (VRS), OPP (NRS) and EHP-30 pain domain, responder rates were in the range of 56-63% at Month 6. Responder rates for NMPP rose from 56.3% at Month 6 to 64.9% at Month 12 and were maintained at Month 6 ExFU. OPP (NRS) responder rates rose to 78.4% at Month 12 and were maintained at Month 6 ExFU. When assessing pain using the EHP-30 pain domain questionnaire, the number of responders rose from 62.6% at Month 6 to 73.4% by Month 12, then declined to 62.5% by Month 6 ExFU.

Responder rates for other symptoms of endometriosis, such as dyschezia and dyspareunia, were more modest, at approximately 52-53% at Month 6, though rising to approximately 64% by Month 12. While response rates were maintained at Month 6 ExFU for dyschezia (62.8%), they fell to 54.4% for dyspareunia.

Table 16 Percentage of responders over time for DYS, NMPP, dyschezia, OPP, EHP-30 pain domain, and dyspareunia based on Month 6 MCT (EDELWEISS 3, EDELWEISS 6)

Study:	Month 6 MCT	EDELWEISS 3		EDELWEISS 6			
Analysis Set:		FAS		TEAS		FuEAS	
		Placebo	LGX 200 mg +ABT	LGX 200 mg+ABT			
		N=162	N=162	N=121		N=112	
Timepoint		Month 6	Month 6	Month 6	Month 12	Month 12	Month 6 ExFU
DYS (VRS)	-1.25	20.3	77.2	82.2	88.3	87.5	45.7
NMPP (VRS)	-0.85	38.0	56.3	60.2	64.9	62.5	64.9
Dyschezia (NRS)	-1.5	43.7	51.9	55.1	64.0	61.1	62.8
OPP (NRS)	-2.7	41.8	63.3	68.6	78.4	76.8	77.7
EHP-30 Pain domain*	-28	34.8	62.6	65.8	73.4	74.3	62.5
Dyspareunia (VRS)	-0.9	46.2	52.9	59.3	63.8	67.6	54.4

ABT = add-back therapy; DYS = dysmenorrhoea; EHP-30 = Endometriosis health profile-30; FAS = Full Analysis Set; FuEAS = Follow-up Extension Analysis Set; LGX = linzagolix; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; OPP = overall pelvic pain; TEAS = Treatment Extension Analysis Set; VRS = verbal rating scale
* Interference of pain with the ability to perform daily activities, measured using the pain dimension of EHP-30 Pain domain.

Mean change from baseline on other secondary efficacy outcomes

A summary of additional secondary efficacy endpoints of clinical interest is presented in Table 17. As the baseline values in the LGX 200 mg+ABT group for each measured outcome were similar between the FAS, TEAS, and FuEAS, only the baseline value for the FAS is shown. Mean change from baseline values are shown at Month 6 for the FAS and TEAS, to account for the fact that the population in the EDELWEISS 6 trial was self-selected and thus, predictably, it was expected that the subjects who derived most benefit from the treatment might voluntarily opt to continue treatment. As shown in Table 2.5-4, outcomes were marginally better for the TEAS compared to the FAS at Month 6. However, there was a clear trend on all of the efficacy endpoints of subjects deriving substantial treatment benefit at Month 6, which improved further by the end of treatment at Month 12. As could be expected, the effect of treatment diminished over the course of the 6-month drug-free post-treatment follow-up. It is noteworthy, however, that some benefit relative to baseline still persisted 6 months after the cessation of treatment with LGX 200 mg+ABT.

Additional Efficacy Endpoints over Time (EDELWEISS 3 and EDELWEISS 6)

Clinically Meaningful Reduction in DYS and NMPP over Time (Month 3 MCT)

Proportion of subjects with a reduction from baseline of at least 1.1 for DYS and at least 0.8 for NMPP (i.e., Month 3 MCT) is shown in Figure 2.5-3 and Figure 2.5-4, respectively. For illustration purposes, the largest available population was used for each period:

- Full Analysis Set (FAS, N=484, of those 162 subjects in the LGX 200 mg+ABT group) for the treatment period from Month 1 to Month 6 in the EDELWEISS 3 study,
- Treatment Extension Analysis Set (TEAS, N=353, of those 121 subjects in the LGX 200 mg+ABT group) from Month 7 to Month 12 in the EDELWEISS 6 study,
- Follow-up Extension Analysis Set (FuEAS, N=329, of those 112 subjects in the LGX 200 mg+ABT group) for the drug-free post-treatment follow-up Month 1 ExFU to Month 6 ExFU in the EDELWEISS 6 study.

Substantial reductions in DYS (VRS) scores were observed as early at Month 1 of treatment with 26.1% of responders in the LGX 200 mg+ABT group compared to 8.3% of responders in the placebo group (OR=3.90, 97.5% CI: 1.84, 8.27; p<0.001) in the FAS. The proportion of responders increased sharply at Month 2, then more gradually until the end of treatment at Month 12.

Table 17 Mean change from baseline for efficacy variables throughout treatment and follow-up for the LGX 200 mg+ABT group (EDELWEISS 3, EDELWEISS 6)

Study:	EDELWEISS 3		EDELWEISS 6			
Analysis Set:	FAS (N=162)		TEAS (N=121)		FuEAS (N=112)	
Bsl and Mean change from Bsl in:	Bsl	Month 6	Month 6	Month 12	Month 12	Month 6 ExFU
DYS (VRS)	2.29	-1.84	-1.98	-2.02	-2.00	-1.25
DYS (NRS)	7.08	-5.76	-6.27	-6.43	-6.31	-4.28
NMPP (VRS)	1.80	-0.94	-1.00	-1.16	-1.14	-1.08
NMPP (NRS)	5.81	-3.22	-3.49	-4.07	-3.95	-3.80
OPP (VRS)	1.92	-1.02	-1.10	-1.27	-1.25	-1.12
OPP (NRS)	6.12	-3.43	-3.76	-4.35	-4.23	-3.90
Worst pelvic pain (NRS)	8.28	-4.54	-4.99	-5.71	-5.63	-4.64
Number of days with moderate-to-severe pain (VRS)	19.0	-13.28	-14.75	-16.13	-15.86	-15.29
Number of pelvic pain-free days (VRS)	1.16	+7.99	+8.38	+11.84	+11.94	+9.06
Dyschezia (NRS)	4.07	-2.00	-2.20	-2.72	-2.60	-2.16
Dyspareunia (VRS)	2.09	-1.05	-1.16	-1.33	-1.41	-1.11
Number of days with uterine bleeding	6.68	-4.22	-5.03	-5.26	-5.13	-1.37
Ibuprofen use (mean daily pill count)	1.27	-0.98	-1.04	-1.09	-1.06	-0.97
Number of days with analgesic use	13.12	-9.53	-10.28	-10.23	-10.18	-9.78
Difficulty to perform daily activities (NRS)	5.65	-3.12	-3.46	-4.00	-3.89	-3.54
EHP-30						
Pain	52.37	-35.98	-37.70	-41.89	-41.83	-34.38
Control and powerlessness	60.65	-38.63	-41.56	-48.28	-47.69	-39.93
Emotional well-being	47.27	-22.26	-24.50	-27.74	-28.25	-24.61
Social support	47.05	-26.37	-26.83	-30.90	-31.25	-26.97
Self-image	43.97	-20.95	-22.34	-25.15	-25.58	-21.84
Modular sexual relationship	59.96	-27.93	-28.49	-36.90	-37.61	-27.92
EQ-5D-5L Index value	0.74	+0.12	+0.14	+0.17	+0.17	+0.16
EQ-5D-5L VAS score	62.0	+15.0	+17.5	+18.0	+19.5	+20.3
PSIQ	4.4	-1.7	-2.0	-2.7	n/a	n/a
SSIQ	5.5	-1.7	-1.9	-1.9	n/a	n/a
PROMIS Fatigue total score	19.9	-6.6	-7.5	-8.4	-8.6	-8.2

ABT = add-back therapy; Bsl = baseline; cfb = change from baseline; DYS = dysmenorrhoea; EHP-30 = Endometriosis health profile-30; FAS = Full Analysis Set; FuEAS = Follow-up Extension Analysis Set; LGX = linzagolix; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; OPP = overall pelvic pain; PSIQ = Physician Surgery Intention Questionnaire; SSIQ = Subject Surgery Intention Questionnaire; TEAS = Treatment Extension Analysis Set; VRS = verbal rating scale

Efficacy in Subgroups

Subgroup analyses were performed for co-primary endpoints of reduced DYS and NMPP without increase in analgesic use for EAP on the EDELWEISS 3 FAS population, as prespecified in the Statistical Analysis Plan (SAP) (version 5.0, issued on 13 June 2022), including the following:

- By age: for subjects with <median age of 35 and ≥median age of 35 years (Age Group 1), and more granular age group categories (Age Group 2: <25, ≥25 to <35, ≥35 to <45, ≥45 years),
- By weight: for subjects with <median weight of 63 kg and ≥median weight of 63 kg,
- By BMI: for subjects with <median of 23 and ≥median 23 kg/m2 (BMI Group 1), and for more granular categories (BMI Group 2: <20, ≥20 to <25, ≥25 to <30, and ≥30 kg/m2),
- By baseline VRS scores for DYS: for subjects with <median baseline DYS (VRS) score of 2.29 and ≥median baseline DYS (VRS) score of 2.29,
- By baseline pain VRS scores for NMPP: for subjects with <median baseline NMPP (VRS) score of 1.83 and ≥median baseline NMPP (VRS) score of 1.83,
- By time since diagnosis of endometriosis: for subjects diagnosed <2 years, ≥2 and <5 years, and ≥5 years prior to the study.

At the pre-submission meeting held between HPRA and Theramex in June 2023, additional subgroup analyses were requested to determine the patient population which could benefit the most from this new treatment option based on the patient's previous treatment [HPRA meeting minutes].

Several subgroups were identified, as outlined in the Addendum to the SAP issued on 24 October 2023. The co-primary endpoints were analysed, as described above using the Month 3 MCT, for the following two subgroups:

- Any documented pretreatment procedure for endometriosis, excluding diagnostic procedures: Yes/ No
- Any pretreatment medication with progestin treatment, Combined Oral Contraceptive (COC), or Levonorgestrel intra-uterine device (IUD): Yes/ No

Table 18 Reduction of Dysmenorrhea at month 3 by pre-treatment procedure and medication groups

Subgroup/ Sensitivity analysis	Placebo events n/N (%)	Treatment events n/N (%)	Treatment	Odds ratio [95%CI]
Pretreatment (Procedure)				
Yes	33/127 (26.0)	54/127 (42.5)	LGX 75 mg	2.35 [1.26;4.37]
		92/124 (74.2)	LGX 200 mg + ABT	8.95 [4.61;17.37]
No	6/32 (18.8)	14/29 (48.3)	LGX 75 mg	3.44 [0.89;13.26]
		21/32 (65.6)	LGX 200 mg + ABT	8.39 [2.16;32.54]
Pretreatment (Medication)				
Yes	15/70 (21.4)	20/54 (37.0)	LGX 75 mg	2.86 [1.10;7.46]
		57/72 (79.2)	LGX 200 mg + ABT	17.46 [6.49;46.93]
No	24/89 (27.0)	48/102 (47.1)	LGX 75 mg	2.38 [1.18;4.81]
		56/84 (66.7)	LGX 200 mg + ABT	5.57 [2.62;11.85]

Table 19 Reduction of Non-menstrual Pelvic pain at month 3 by pre-treatment procedure and medication groups

Subgroup/ Sensitivity analysis	Placebo events n/N (%)	Treatment events n/N (%)	Treatment	Odds ratio [95%CI]
Pretreatment (Procedure)				
Yes	41/127 (32.3)	47/127 (37.0)	LGX 75 mg	1.32 [0.72;2.40]
		55/124 (44.4)	LGX 200 mg + ABT	1.69 [0.94;3.06]
No	9/32 (28.1)	13/29 (44.8)	LGX 75 mg	1.42 [0.39;5.24]
		20/32 (62.5)	LGX 200 mg + ABT	3.61 [0.99;13.19]
Pretreatment (Medication)				
Yes	21/70 (30.0)	24/54 (44.4)	LGX 75 mg	2.29 [0.95;5.53]
		40/72 (55.6)	LGX 200 mg + ABT	3.22 [1.43;7.25]
No	29/89 (32.6)	36/102 (35.3)	LGX 75 mg	1.10 [0.55;2.20]
		35/84 (41.7)	LGX 200 mg + ABT	1.38 [0.67;2.83]

Dysmenorrhea

In the LGX 75 mg group, the reductions in DYS at Month 3 by at least 1.1 (VRS) (as defined by MCT analysis) were similar in all the subgroups studied. In the LGX 200 mg+ABT group, there was a slight trend towards higher ORs for reduction of DYS at Month 3 in the following subgroups:

(1) ≥ median age of 35 (OR = 14.81; 95% CI: 6.09, 36.02; p-value < 0.001) compared to those <35 years of age (OR = 5.41; 95% CI: 2.41, 12.14; p-value of treatment effect <0.001);

(2) < median weight of 63 kg (OR =13.74; 97.5% CI: 5.69, 33.17; p-value < 0.001) compared to those weighing ≥63 kg (OR = 5.29; 97.5% CI: 2.33, 11.99; p-value < 0.001);

(3) < median BMI of 23 kg/m2 (OR = 15.54; 97.5% CI: 6.12, 39.48; p-value <0.001), compared to those with BMI ≥23 kg/m2; (OR = 5.49; 97.5% CI: 2.48, 12.14; p-value <0.001);

(4) longer time (≥5 years) since the diagnosis of endometriosis (OR = 12.69; 97.5% CI: 3.60, 44.75; p-value <0.001) compared to those more recently diagnosed (OR ≤ 7.86).

(5) pretreatment medication (OR = 17.46; 97.5% CI: 6.49, 46.93; p-value <0.001), compared to no pretreatment medication; (OR = 5.57; 97.5% CI: 2.62, 11.85; p-value <0.001).

Non-Menstrual Pelvic Pain

There was no strong evidence to suggest different response in any of the subgroups in terms of reductions in NMPP at Month 3 by at least 0.8 (VRS) (as defined by MCT analysis).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20 Summary of efficacy for trial 18-OBE2109-003

Title: 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			
Study identifier	Protocol identification number: 18-OBE2109-003 EudraCT number: 2019-000283-26 ClinicalTrials.gov identifier: NCT03992846 Study name: EDELWEISS 3		
Design	Prospective, randomized, placebo-controlled, parallel-group, multicenter, double-blind, double-dummy study in women with surgically confirmed endometriosis moderate to severe endometriosis associated pain.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Up to 6 months Up to 3 months Optional 6 months treatment extension in EDELWEISS 6 study or – if no extension – followed by 6 months of treatment free Follow-Up
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo linzagolix 75 mg + placebo linzagolix 200mg + placebo ABT 6 months, 162 subjects
	Linzagolix (LGX) 75 mg		Linzagolix 75 mg + Placebo linzagolix 200mg + Placebo ABT 6 months, 160 subjects
	Linzagolix (LGX) 200 mg + ABT		Linzagolix 200 mg + ABT (E2 1 mg/NETA 0.5 mg) + Placebo linzagolix 75 mg + 6 months, 162 subjects
Endpoints and definitions Database lock	Co-Primary endpoint	Dysmenorrhea (DYS) responder rate	Percentage of subjects who met a clinically meaningful reduction from baseline to Month 3 visit (last 28 days prior to Month 3 visit) in the mean daily assessment of DYS without increased use of analgesics. The meaningful reduction at Month 3 was established as a reduction in dysmenorrhea scores of 1.1 measured on a 4-point verbal rating scale (VRS).
	Co-Primary endpoint	Non-menstrual pelvic pain (NMPP) responder rate	Percentage of subjects who met a clinically meaningful reduction from baseline to Month 3 visit (last 28 days prior to Month 3 visit) in the mean daily assessment of NMPP without increased use of analgesics. The meaningful reduction at Month 3 was established as a reduction in non-menstrual pelvic pain scores of -0.8 measured on a 4-point verbal rating scale
	Ranked secondary endpoint	Change in DYS (VRS)	Change from baseline to Month 6 in DYS (measured on a VRS)

	Ranked secondary endpoint	Change in NMPP (VRS)	Change from baseline to Month 6 in NMPP (measured on a VRS)
	Ranked secondary endpoint	Change in dyschezia (NRS)	Change from baseline to Month 6 in dyschezia (measured on an 11-point numerical rating scale (NRS))
	Ranked secondary endpoint	Change in OPP (NRS)	Change from baseline to Month 6 in the mean overall pelvic pain (OPP) NRS
	Ranked secondary endpoint	Change in EHP-30 pain dimension	Change from baseline to Month 6 in the interference of pain with the ability to perform daily activities assessing the pain dimension of the Endometriosis Health Profile-30 (EHP-30)
	Ranked secondary endpoint	Change in dyspareunia (VRS)	Change from baseline to Month 6 in mean dyspareunia VRS score
	Ranked secondary endpoint	No analgesics use	Proportion of patients who are not using protocol-specified analgesics for EAP during the preceding 4-week period at Month 6
	Ranked secondary endpoint	No opiate use	Proportion of patients who are not using protocol-specified opiates for EAP during the preceding 4-week period at Month 6.
	Additional secondary endpoints	Dysmenorrhea (DYS) responder rates	Percentage of subjects who met a clinically meaningful reduction from baseline to Month 6 in DYS based on Month 3 meaningful change thresholds (MCT)
	Additional secondary endpoints	Non-menstrual pelvic pain (NMPP) responder rates	Percentage of subjects who met a clinically meaningful reduction from baseline to Month 6 in NMPP based on Month 3 MCTs
	Additional secondary endpoints	Mean pelvic pain scores for worst pelvic pain	Change from baseline to Month 6 in the mean worst pelvic pain scores (defined as the mean of the 5 highest daily pain scores reported during the previous 4-week period assessed on the NRS)
	Additional secondary endpoints	Number of pelvic pain-free days	Change from baseline to Month 6 in the number of pelvic pain-free days (assessed on the VRS)
	Additional secondary endpoints	Number of days with moderate-to severe pelvic pain	Change from baseline to Month 6 in the number of days with moderate-to-severe pain (assessed on the VRS)
	unblinding: 26.11.2021 (partial database lock) Final database lock: 22.12.2022		

<table>
<tr><td colspan="5"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description</td><td colspan="4">Co-Primary Analysis – pre-specified</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="4">Full Analysis Set
(defined as all randomized subjects who received at least one dose of double-blind study drug irrespective of the treatment received)
Month 3</td></tr>
<tr><td rowspan="6">Descriptive statistics and estimate variability</td><td colspan="2">Treatment group</td><td>Placebo</td><td>LGX 200 mg + ABT</td></tr>
<tr><td colspan="2">Number of subject</td><td>162</td><td>162</td></tr>
<tr><td colspan="2">Dysmenorrhea (DYS) responder rate
(logistic regression)</td><td>23.5%</td><td>72.9%</td></tr>
<tr><td colspan="2">95% confidence interval</td><td>17.5%; 30.7%</td><td>65.3%; 79.4%</td></tr>
<tr><td colspan="2">Non-menstrual pelvic pain (NMPP) responder rate
(logistic regression)</td><td>30.9%</td><td>47.3%</td></tr>
<tr><td colspan="2">95% confidence interval</td><td>24.1%; 38.6%</td><td>39.5%; 55.3%</td></tr>
<tr><td rowspan="8">Effect estimate per comparison</td><td rowspan="4">Co-Primary endpoint DYS responder rate</td><td>Comparison groups</td><td colspan="2">LGX 200 mg + ABT vs. Placebo</td></tr>
<tr><td>Odds Ratio for DYS</td><td colspan="2">8.80</td></tr>
<tr><td>97.5% CI</td><td colspan="2">4.86; 15.91</td></tr>
<tr><td>P-value</td><td colspan="2"><0.001</td></tr>
<tr><td rowspan="4">Co-Primary endpoint NMPP responder rate</td><td>Comparison groups</td><td colspan="2">LGX 200 mg + ABT vs. Placebo</td></tr>
<tr><td>Odds Ratio for DYS</td><td colspan="2">2.01</td></tr>
<tr><td>97.5% CI</td><td colspan="2">1.18; 3.42</td></tr>
<tr><td>P-value</td><td colspan="2">0.007</td></tr>
<tr><td>Notes</td><td colspan="4">A responder for each of the co-primary endpoints needed to demonstrate both a reduction in pain (DYS or NMPP, depending on the endpoint) and a stable or decreased use of analgesics for EAP (assessed separately for DYS and NMPP). Any subject who did not meet both of these criteria was defined as a non-responder, including subjects whose response could not be assessed due to lack of on-treatment pain data.

As there were 2 linzagolix versus placebo comparisons, Bonferroni-corrected p-values were produced (raw p-values were multiplied by 2 prior to comparing to 0.05).

Responder threshold analysis was performed for the co-primary endpoints using the MCTs estimated based on the blinded, soft-locked data at Month 3. The threshold for response in the responder analysis was chosen to represent a clinically meaningful reduction in pain and was foreseen to be different for each endpoint (DYS and NMPP). Following the analyses to estimate the MCTs, the criterion for defining a subject as a responder was a reduction of 1.10 or greater from baseline pain for DYS; a reduction of 0.80 or greater from baseline pain for NMPP.

The primary efficacy analysis was conducted using the FAS and repeated using the Per Protocol Set. Several sensitivity analyses were conducted assessing the impact of missing eDiary entries and different methods of handling missing data, assessing the influence of different subgroups (race, age, BMI etc.) and using a different statistical approach (Cochran-Maental-Haenszel test).

Study completion rate and reasons for patient drop-outs were balanced across the three treatment arms.</td></tr>
<tr><td>Analysis description</td><td colspan="4">Secondary analysis – ranked secondary endpoints – pre-specified:</td></tr>
</table>

Analysis population and description	Full Analysis Set (defined as all randomized subjects who received at least one dose of double-blind study drug irrespective of the treatment received). Month 6		
Descriptive statistics and estimate variability	Treatment group	Placebo	LGX 200 mg + ABT
	Number of subject	162	162
	Change from baseline in DYS (VRS) LS Mean (95% CI)	-0.66 (-0.79; -0.53)	-1.83 (-1.96; -1.70)
	Change from baseline in NMPP (VRS) LS Mean (95% CI)	-0.66 (-0.77; -0.56)	-0.92 (-1.03; -0.82)
	Change in dyschezia (NRS) LS Mean (95% CI)	-1.41 (-1.71; -1.12)	-1.99 (-2.29; -1.70)
	Change in OPP (NRS) LS Mean (95% CI)	-2.19 (-2.55; -1.84)	-3.39 (-3.74; -3.03)
	Change in EHP-30 pain dimension LS Mean (95% CI)	-19.47 (-22.66; -16.28)	-35.60 (-38.73; -32.48)
	Change in dyspareunia (VRS) LS Mean (95% CI)	-0.82 (-0.97; -0.66)	-1.01 (-1.18; -0.85)
	No analgesic use for EAP % of responders (95% CI)	13.2 (8.9; 19.2)	44.5 (36.3; 52.9)
	No opiate use for EAP % of responders (95% CI)	97.0 (92.5; 98.9)	97.0 (92.7; 98.8)

Effect estimate per comparison	Change from baseline to Month 6 in DYS (VRS)	Comparison groups	LGX 200 mg + ABT vs. Placebo
		Diff in LSM with PBO	-1.17
		97.5% Confidence Intervals	-1.38; -0.97
		p-value	<0.001
	Change from baseline to Month 6 in NMPP (VRS)	Comparison groups	LGX 200 mg + ABT vs. Placebo
		Diff in LSM with PBO	-0.26
		97.5% Confidence Intervals	-0.43; -0.09
		p-value	0.002
	Change in dyschezia (NRS)	Comparison groups	LGX 200 mg + ABT vs. Placebo
		Diff in LSM with PBO	-0.58
		97.5% Confidence Intervals	-1.05; -0.11
		p-value	0.012
	Change in OPP (NRS)	Comparison groups	LGX 200 mg + ABT vs. Placebo
		Diff in LSM with PBO	-1.19
		97.5% Confidence Intervals	-1.77; -0.62
		p-value	<0.001
	Change in EHP-30 pain dimension	Comparison groups	LGX 200 mg + ABT vs. Placebo
		Diff in LSM with PBO	-16.13
		97.5% Confidence Intervals	-21.24; -11.02
		p-value	<0.001
	Change in dyspareunia (VRS)	Comparison groups	LGX 200 mg + ABT vs. Placebo
		Diff in LSM with PBO	-0.20
		97.5% Confidence Intervals	-0.46; 0.07
		p-value	0.184
	No analgesic use for EAP	Comparison groups	LGX 200 mg + ABT vs. Placebo
		OR	5.27
		97.5% Confidence Intervals	2.83; 9.82
		p-value	<0.001
	No opiate use for EAP	Comparison groups	LGX 200 mg + ABT vs. Placebo
		OR	0.99
		97.5% Confidence Intervals	0.22; 4.51
		p-value	1.000

Analysis description	Additional secondary endpoints – pre-specified		
Analysis population and description	Full Analysis Set (defined as all randomized subjects who received at least one dose of double-blind study drug irrespective of the treatment received) Month 6		
Descriptive statistics and estimate variability	Treatment group	Placebo	LGX 200 mg + ABT
	Number of subject	162	162
	Dysmenorrhea (DYS) responder rates % of responders (95% CI)	23.5% (17.5%; 30.8%)	80.0% (73.0%; 85.5%)
	Non-menstrual pelvic pain (NMPP) responder rates % of responders (95% CI)	38.5% (31.0%; 46.4%)	57.1% (49.0%; 64.8%)
	Change from baseline in mean pelvic pain scores for worst pelvic pain LS Mean (95% CI)	-2.40 (-2.81; -1.99)	-4.49 (-4.90; -4.08)
	Change from baseline in number of pelvic pain-free days (VRS) LS Mean (95% CI)	5.48 (4.09; 7.33)	8.81 (6.60; 11.75)
	Change from baseline in number of days with moderate-to severe pelvic pain LS Mean (95% CI)	9.15 (7.39; 11.32)	4.75 (3.81; 5.92)

Effect estimate per comparison	Dysmenorrhea (DYS) responder rates	Comparison groups	LGX 200 mg + ABT vs. Placebo
		OR vs placebo	12.98
		97.5% Confidence Intervals	7.00; 24.06
		p-value	<0.001
	Non-menstrual pelvic pain (NMPP) responder rates	Comparison groups	LGX 200 mg + ABT vs. Placebo
		OR vs placebo	2.13
		97.5% Confidence Intervals	1.26; 3.60
		p-value	0.003
	Change from baseline in mean pelvic pain scores for worst pelvic pain (NRS)	Comparison groups	LGX 200 mg + ABT vs. Placebo
		Diff in LSM with PBO	-2.09
		97.5% Confidence Intervals	-2.76; -1.43
		p-value	<0.001
	Change from baseline in number of pelvic pain-free days (VRS)	Comparison groups	LGX 200 mg + ABT vs. Placebo
		Ratio of number of days vs placebo	1.61
		97.5% Confidence Intervals	1.01; 2.57
		p-value	0.047
	Change from baseline in number of days with moderate-to severe pelvic pain (VRS)	Comparison groups	LGX 200 mg + ABT vs. Placebo
		Ratio of number of days vs PBO	0.52
		97.5% Confidence Intervals	0.36; 0.74
		p-value	<0.001

Notes	A number of analyses were conducted at additional timepoints and with different rating scales (NRS instead of VRS) as well as responder analyses for DYS, NMPP, dyschezia, OPP and dyspareunia at Month 6 meaningful change thresholds (MCT). Quality of Life was assessed for additional EHP-30 dimensions (control and powerless, emotional wellbeing, social support and self-image).

Supportive study

The open label extension study EDELWEISS 6 is supportive, and the study and results are presented with the results of the pivotal trial above.

2.4.3. Discussion on clinical efficacy

Yselty is indicated in adult women of reproductive age for the treatment of moderate to severe symptoms of uterine fibroids. The initial extension of indication sought was for the treatment of endometriosis-associated pain and recommended a dose of 200mg once daily with concomitant hormonal add-back therapy.

Clinical guidelines do not recommend starting treatment for endometriosis associated pain with a GnRH agonist or antagonist due to the possible adverse effects on bone mineral density. Instead, prescription as second line (for example if hormonal contraceptives or progestogens have been ineffective) is indicated.

Hence, and consistent with the population enrolled to the EDELWEISS 3 study, the proposed indication was revised during the assessment, to second line treatment of symptoms of endometriosis in women who have had prior surgical or medical treatment.

Design and conduct of clinical studies

There was one pivotal trial, EDELWEISS 3, submitted to support the indication with an open labelled extension for a further 6 months.

The doses chosen for the pivotal trial were supported by dose finding studies in women with endometriosis. EDELWEISS 1 trial compared improvement in dysmenorrhoea and non-menstrual pelvic pain in women treated with Linzagolix at doses from 25 mg to 200mg. Four Phase 2 studies (KLH1201, KLH1202, KLH1203 and KLH1204) conducted in Japan and a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study conducted in EU/US in adult women with endometriosis-associated pain who were treated for up to 52 weeks (Study 15-OBE2109-001, EDELWEISS 1) showed that daily doses of 75 mg (minimally effective dose), 100 mg and 200 mg (maximally effective dose tested) could provide clinically meaningful reductions in pelvic pain. The 200 mg dose demonstrated efficacy vs placebo in reducing DYS, NMPP and other symptoms of endometriosis. As the 200 mg dose suppresses serum E2 to postmenopausal levels (<20 pg/mL), the expected hypoestrogenic effects including levels of BMD decrease that necessitates concomitant hormonal ABT for long term use were demonstrated. For the Phase 3 study, the 200 mg of LGX dose was chosen with concomitant hormonal ABT - oral estradiol (E2) 1 mg + norethisterone acetate (NETA) 0.5 mg once daily. LGX 75 mg dose was also investigated in the Phase 3 study.

The pivotal clinical trial, i.e. EDELWEISS 3, was a randomised double-blind controlled trial in women of reproductive age with a surgical and if available histological diagnosis of endometriosis.

Participants were adult women with surgically confirmed endometriosis, with moderate to severe EAP over two full menstrual cycles before the baseline visit. Study was conducted in the US and Europe. There were three treatment groups: LGX 75 mg, LGX 200 mg + ABT (E2 1 mg/NETA 0.5 mg), placebo. Permitted analgesic rescue treatments were defined and included narcotic analgesics.

Women with moderate to severe endometriosis associated pain were included in the trial, i.e. at the screening visit, moderate-to-severe EAP was defined as a score of at least 2 for DYS and at least 2 for NMPP for the previous month assessed using the modified Biberoglu & Behrman (mB&B) scale. The mB&B scale is a composite pelvic pain and physical sign score (0-15) of five domains (each domain rated from 0-3): dysmenorrhoea, deep dyspareunia, non-menstrual pelvic pain, pelvic tenderness, and induration, where the higher the score the more severe the pain and physical signs of endometriosis (Biberoglu 1981). In addition, for each of the two menstrual cycles during screening, the subject had to have a mean overall pelvic pain (OPP) of at least 4 (on the 0-10 numeric rating scale (NRS)) over the 5 days with the highest score for each cycle, at least 2 days with moderate or severe pain on the 0-3 verbal rating scale (VRS) for pelvic pain during uterine bleeding days and at least 2 days with moderate or severe pain on the 0-3 VRS for pelvic pain over the days without uterine bleeding.

All women in the clinical trial had dysmenorrhea but due to the length of time since diagnostic laparoscopy or surgery, it was not possible to determine whether all women had endometriosis outside of the pelvis. However, women with NMPP responded better to the higher dose of Linzagolix, i.e. 200mg plus ABT.

The population treated in the clinical trial included women who had had their endometriosis treated prior to taking part in the trial and those who had not. Most subjects had their endometriosis treated previously with medication or a surgical procedure. At least 80% of subjects included in the Full Analysis Set had confirmed prior interventional surgeries or procedures for endometriosis or endometriosis symptoms and this percentage was consistent across all treatment groups.

Overall, about 64% of women in the clinical trial had their endometriosis treated with medication prior to treatment in the trial and this percentage was consistent across treatment groups. Of those, 42% received prior hormonal treatments (ATC1 class: genito-urinary system and sex hormones) and 8% received prior treatment with GnRH-agonists, aromatase inhibitors (ATC1 class: antineoplastic and immunomodulating agents). Overall, 36% received prior anti-inflammatory medications and 7% received centrally acting analgesics. Since he population in the clinical trial were treated in the second line, this was reflected in the indication accordingly.

Two dosing regimens were investigated in the trial: LGX 75 mg alone and LGX 200 mg co-administered with ABT.

After completion of the pivotal study, participants could continue treatment in the OLE study (19-OBE2109-306, EDELWEISS 6) for additional 6 months or enter a post-treatment follow-up period.

The comparator used in the pivotal trial was placebo. The rationale for using placebo as comparator was not provided nor was it clear whether subjects in the pivotal clinical trial had responded to previous treatment. Since the clinical guidelines do not recommend treating women with this diagnosis in the first line with a GNRH antagonist, the Applicant has updated the indication in line with the majority of the population treated in the pivotal clinical trial, i.e. second line therapy, as well as with that of the recently authorised GnRH antagonist Ryeqo.. As linzagolix is not analgesic per se, but rather affects the hormonal state of the subject which is subsequently expected to result in a reduction of symptoms of disease, most importantly pain, an indication for symptomatic treatment is considered appropriate.

Efficacy data and additional analyses

Out of 854 screened, a total of 486 participants were randomised. The rate of screen failures (43%) is expected in the concerned clinical setting, and happened mostly because eligibility criteria were not met. A total of 484 participants were randomised and treated as two participants were discontinued from the study due to protocol deviations. Discontinuation rates were similar at Month 3 and Month 6 (6.4% and 6.8%) and were slightly lower in LGX groups compared to placebo group. Most common reason for discontinuation was subject's request. A total of 392 participants (81%) completed the Month 6 treatment period, with no difference between groups. At the end of treatment period, 356 participants entered the OLE study, and 51 participants continued into FU period without active treatment. Numbers of participants with at least one major protocol deviation leading to exclusion from PP set were low among study arms (overall N=17, 3.5%), and it is not expected to influence the interpretation of the results. Treatment compliance was high in all study arms.

With regards to the **primary endpoint:**

The two co-primary efficacy endpoints were clinically meaningful reductions from baseline to the last 28 days preceding the Month 3 visit (i.e., the 4-week period preceding Month 3 visit) or study drug discontinuation in the mean daily assessment of 1) DYS and of 2) NMPP measured on a Verbal Rating Scale (VRS) using an electronic diary (eDiary) along with a stable or decreased use of analgesics for EAP.

The MCT estimates, based on soft-locked data at Month 3, were -1.10 for DYS (VRS) and -0.80 for NMPP (VRS). Thus, the criterion for defining a subject as a responder over the last 28 days of randomized treatment up to Month 3 was a reduction of 1.10 or greater from baseline pain for DYS; a reduction of 0.80 or greater from baseline pain for NMPP, and having a stable or decreased use of analgesics for EAP over this period.

Treatment with LGX 200 mg dose administered with ABT demonstrated statistically significant reductions in both co-primary endpoints of DYS and NMPP at 3 months with a stable or decreased use of analgesics for EAP. From the logistic regression analysis, the estimated percentage of responders:

- for DYS was 72.9% (95% CI: 65.3, 79.4) compared with 23.5% (95% CI: 17.5, 30.7) in the placebo group with an Odds Ratio (OR) vs placebo of 8.80 (97.5% CI: 4.86, 15.91) and a Bonferroni-corrected p-value of treatment effect <0.001.
- for NMPP was 47.3% (95% CI: 39.5, 55.3) compared with 30.9% (95% CI: 24.1, 38.6) in the placebo group with an OR vs placebo of 2.01 (97.5% CI: 1.18, 3.42) and a Bonferroni corrected p-value of treatment effect of 0.007.

Treatment with the 75 mg dose achieved statistically significant reduction in DYS but not in NMPP at 3 months. Therefore, in this application, the 75 mg linzagolix dose is not proposed for the treatment of endometriosis-associated pain.

The dose of 200mg plus add back therapy was chosen as it was shown that it was more effective in treating both dysmenorrhoea and non-menstrual pelvic pain.

Results for the co-primary endpoints were driven by the DYS and NMPP components: independent from a decrease in endometriosis associated pain, most subjects showed stable or decreased use of analgesics, particularly during bleed days.

Subgroup analyses are generally consistent with the primary analysis with point estimates for OR in favour of LGX treatment compared to placebo. During pre-submission interactions, it was suggested that the MAH should explore which EAP subpopulation might benefit the most (HPRA, 2023). It is not possible to indicate the EAP subpopulation that would benefit the most from LGX treatment based on

the presented subgroup (post hoc) analysis. There are some trends for reduced effects in LGX 200 mg+ABT group in patients aged <25 years for the effect on DYS and <35 years for the effect on NMPP, those with BMI between 25 and 30 m^2/kg for the effect on DYS and NMPP, those with higher NMPP scores at baseline for the effect on DYS and NMPP, those with higher DYS scores at baseline for the effect on NMPP, and those with medication pre-treatment for the effect on NMPP. However, no conclusion on the possibly different effects in some subgroups can be made as subgroup analysis caveats preclude such.

Ranked secondary endpoints at month 6

Statistically significant reductions (improvements) were observed in the following ranked secondary endpoints at 6 months in the LGX 200 mg+ABT group compared to placebo: DYS (VRS), NMPP (VRS), dyschezia (NRS), overall pelvic pain (NRS), and the ability to do daily activities measured using the pain dimension of EHP-30.

Several concerns were raised related to the methodology used to calculate the MCT which were adequately addressed by the MAH.

The corresponding proportions of responders were 77.2% (vs. 20.3% for placebo) for DYS, 56.3% (vs 38.0% for placebo) for NMPP, 51.9% (vs 43.7% for placebo) for dyschezia, 63.3% (vs 41.8% for placebo) for overall pelvic pain, and 62.6% (vs 34.8% for placebo) for EHP-30 pain dimension.

The treatment effect for dyspareunia was not statistically significant, with the corresponding proportion of responders of 52.9% (vs 46.2% for placebo).

Only 2.5% of subjects in the LGX 200 mg+ABT group did not use analgesics for EAP at baseline. The percentage of subjects not using analgesics for EAP rose to 45.3% at Month 6, with a statistically significant change from baseline (OR = 5.27; 97.5% CI: 2.83, 9.82; p<0.001).

Most subjects in the LGX 200 mg+ABT group did not use opiates for EAP at baseline (87.7%) and at Month 6 (93.7%).

Primary Efficacy Endpoint at Month 12 (EDELWEISS 6)

The co-primary endpoints at Month 12 were a clinically meaningful reduction in DYS and NMPP (analysed using both the Month 3 MCT and Month 6 MCT) with stable or decreased use of analgesics.

Month 3 MCT

At Month 12, the proportion of subjects with a reduction of 1.10 or greater in DYS (VRS) and stable or decreased use of analgesics was 55.9% in the LGX 75 mg group and 91.0% in the LGX 200 mg+ABT group. The proportion of subjects with a reduction of 0.80 or greater in NMPP (VRS) was 59.5% in the LGX 75 mg group and 67.6% in the LGX 200 mg+ABT group.

Month 6 MCT

At Month 12, the proportion of subjects with a reduction of 1.25 or greater in DYS (VRS) and stable or decreased use of analgesics was 50.5% in the LGX 75 mg group and 88.3% in the LGX 200 mg+ABT group. The proportion of subjects with a reduction of 0.85 or greater in NMPP (VRS) and stable or decreased use of analgesics was 55.9% in the LGX 75 mg group and 64.9% in the LGX 200 mg+ABT group.

Additional Efficacy Endpoints over Time (EDELWEISS 3 and EDELWEISS 6)

Clinically Meaningful Reduction in DYS and NMPP over Time (Month 3 MCT)

Full Analysis Set (FAS, N=484, of those 162 subjects in the LGX 200 mg+ABT group) for the treatment period from Month 1 to Month 6 in the EDELWEISS 3 study,

- Treatment Extension Analysis Set (TEAS, N=353, of those 121 subjects in the LGX 200 mg+ABT group) from Month 7 to Month 12 in the EDELWEISS 6 study,
- Follow-up Extension Analysis Set (FuEAS, N=329, of those 112 subjects in the LGX 200 mg+ABT group) for the drug-free post-treatment follow-up Month 1 ExFU to Month 6 ExFU in the EDELWEISS 6 study.

Substantial reductions in DYS (VRS) scores were observed as early at Month 1 of treatment with 26.1% of responders in the LGX 200 mg+ABT group compared to 8.3% of responders in the placebo group (OR=3.90, 97.5% CI: 1.84, 8.27; p<0.001) in the FAS. The proportion of responders increased sharply at Month 2, then more gradually until the end of treatment at Month 12.

At Month 6, the proportion of DYS responders was 49.5% (95% CI: 41.6, 57.4) and 80.0% (95% CI: 73.0, 85.5) in the LGX 75 mg and LGX 200 mg+ABT group, respectively, compared to 23.5% (95% CI: 17.5, 30.8) in the placebo group in the FAS. These results represented substantial DYS reduction in both LGX groups, with an odds ratio vs placebo of 3.18 (97.5% CI: 1.82, 5.56; p-value < 0.001) and 12.98 (97.5% CI: 7.00, 24.06; p-value < 0.001) in the LGX 75 mg and LGX 200 mg+ABT group, respectively.

At Month 12, the proportion of subjects with a reduction of 1.10 or greater in DYS (VRS) and stable or decreased use of analgesics was 55.9% in the LGX 75 mg group and 91.0% in the LGX 200 mg+ABT group in the TEAS.

At the end of the 6-month drug-free follow-up period (Month 6 ExFU), subjects were still experiencing some lingering benefits of treatment compared to baseline, with the proportion of DYS responders with stable or decreased use of analgesics of 40.9% in the LGX 75 mg group and 54.3% in LGX 200 mg+ABT group (compared to 56.2% and 90.4% at Month 12, respectively) in the FuEAS.

2.4.4. Conclusions on the clinical efficacy

The data presented form the pivotal trial support the efficacy of Linzagolix for the treatment of endometriosis associated pain. For non-menstrual pelvic pain, the higher dose of 200mg plus add back therapy was more effective. There were higher proportion of patients who met the responder criteria for reduction in dysmenorrhea and non-menstrual pelvic pain with stable or decreased use of analgesics over 6 months of treatment. Those co-primary endpoints are supported by results of five of eight hierarchically tested key secondary endpoints: DYS (VRS), NMPP (VRS), dyschezia (NRS), OPP (NRS) and EHP-30 Pain Dimension. The effect of linzagolix 200 mg+ABT was maintained over additional 6 months (treatment duration of 12 months in total) for the co-primary and the key secondary endpoints, studied in the controlled, double-blinded extension study.

2.5. Clinical safety

Introduction

The most common side effects are hot flushes (which may affect more than 1 in 10 people) and headache (which may affect up to 1 in 10 people), but Yselty may also impact bone mineral density (BMD). Based on data from two clinical trials (PRIMROSE 1 and 2), there appears to be some slowing of the rate of bone loss in the 24–52-week period. However, the rate of continued BMD loss with treatment for > 52 weeks is not known. Therefore, the product information includes recommendations on how to monitor patients for bone loss. In patients with risk factors for osteoporosis or bone loss, a dual X-ray absorptiometry (DXA) scan is recommended prior to starting Yselty treatment, whereas a DXA scan is recommended after 1 year of treatment for all women.

Patient exposure

To date, 2882 subjects have been exposed to different daily doses of linzagolix in completed clinical trials (12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, 400 mg and 700 mg). Of these, 744 patients have been treated with the dose proposed for the EAP indication: linzagolix 200 mg + ABT, either as an initial dosing regimen or upon switching after 6 months from either the placebo group or the 200 mg alone group. Although linzagolix has been authorized throughout the EU (European Union) and United Kingdom (UK) for the treatment of uterine fibroids (UF), it has not yet been launched in any countries at the time of this extension of indication application.

The safety of linzagolix in patients with endometriosis associated pain has been evaluated in 2 pivotal phase 3 studies.

Study 18-OBE2109-003 (EDELWEISS 3) – (Endometriosis study in Europe and US), was a prospective, randomized, placebo-controlled, parallel-group, multicentre, double-blind, double-dummy study of linzagolix (LGX) administered once daily at a dose of 75 mg alone or at a dose of 200 mg in combination with add-back therapy (ABT) (E2 1 mg / NETA 0.5 mg) for up to 6 months for the management of moderate to severe EAP in women with surgically-confirmed endometriosis. The Safety Analysis Set (SAF) consisted of 484 subjects (placebo: 162; LGX 75 mg: 160; LGX 200 mg+ABT: 162).

Study 19-OBE2109-006 (EDELWEISS 6) was a prospective, randomised, double-blind, optional treatment extension study in women with moderate-to-severe endometriosis.

There are also two prematurely terminated trials which contribute data to the safety, but not efficacy, analysis: 18-OBE2109-002 (EDELWEISS 2) Phase 3, double-blind, randomised, placebo controlled, prospective, multicentre, in women with surgically confirmed endometriosis and 19-OBE2109-005 (EDELWEISS 5) a treatment extension of EDELWEISS 2 was opened in the USA and Canada but prematurely terminated due to poor recruitment.

The pooled analysis of all the Phase 3 linzagolix trials (EDELWEISS 3/2/6/5, and PRIMROSE 1/2) was performed for the groups exposed to 200 mg+ABT or placebo for treatment exposure, demographic characteristics, and adverse events for the following two periods:

- Period 1 (from Day 1 of treatment to Month 6): pooled analysis of data from EDELWEISS 3 (Day 1 to Month 6), EDELWEISS 2 (Day 1 to Month 6), PRIMROSE 1 (Day 1 to Week 24), and PRIMROSE 2 (Day 1 to Week 24);

- Period 2 (from Month 6 to Month 12): pooled analysis of data from EDELWEISS 6 (Month 6 to Month 12), EDELWEISS 5 (Month 6 to Month 12), PRIMROSE 1 (Week 24 to Week 52), and PRIMROSE 2 (Week 24 to Week 52).

Subject disposition

In total 568 patients with endometriosis are included in the safety analysis set (SAF) for Period 1 (from Day 1 to Month 6). Of those, 386 patients with endometriosis are included in the extension safety analysis set (ESAF) for Period 2 (from Month 6 to Month 12). The total exposure to linzagolix 200mg+ABT in patients with endometriosis in all 4 EDELWEISS studies is 252 participants. The median treatment duration in EDELWEISS 3 and EDELWEISS 6 studies was 24 weeks for each treatment group.

The pooled safety sets concentrate on patients with endometriosis and uterine fibroids who were treated with linzagolix 200mg+ABT or placebo in either Period 1 (SAFP1) or Period 2 (SAFP2). SAFP1 contains 797 patients with a median treatment duration of 24 weeks while SAFP2 contains 662 patients with the median treatment duration of 26 weeks.

The differences in baseline characteristics between women enrolled in the Phase 3 endometriosis trials compared to those enrolled in previously submitted Phase 3 trials in women with uterine fibroids (UF) were that endometriosis patients tended to be younger (age range of 18 to 49 years; treatment group medians between 31.0 and 35.5 years) than women with UF (age range 20 to 58 years; median 43 years) enrolled in PRIMROSE 1/2 trials. Endometriosis patients enrolled in the EDELWEISS 3 trial, who account for most of the endometriosis safety population, tended to have lower mean body weight than women with UF: mean (± SD) weight of 66.42 (13.77) kg in the EDELWEISS 3 study vs 81.29 (19.13) kg in the PRIMROSE 1/2 trials.

EDELWEISS 2 and 3:

In both trials, subjects were predominantly white (98.6% vs 82.1%, respectively). Endometriosis is more common in white women so this fits with the disease phenotype.

There was a similar mean (SD) age, 34.9 (6.6) vs. 32.7 (6.8) years, respectively.

Weight and body mass index (BMI) were slightly lower in the predominantly European population in EDELWEISS 3 compared to the North American population in EDELWEISS 2: mean (SD) weight of 66.42 (13.77) kg vs 75.4 (17.9) kg, respectively, and mean (SD) BMI of 24.27 (4.95) kg/m2 vs 28.10 (6.79) kg/m2, respectively. This is in line with the expected population demographics in these regions.

EDELWEISS 6 and EDELWEISS 5 were extension studies of EDELWEISS 3 and EDELWEISS 2, respectively, the demographic and other baseline characteristics were similar between the Safety Analysis Sets in the parent study. Most of the eligible subjects in the EDELWEISS 3 parent study opted to continue treatment in the extension study (356/484). Eligibility criteria for entry into extension studies excluded subjects with BMD decrease from baseline >8% or a Z-score ≤ -2.5 at either femoral neck, hip or spine on the Month 6 DXA scan during the parent study.

Endometriosis history

Endometriosis history was comparable between the treatment groups in both the EDELWEISS 3 and EDELWEISS 2 trials. The median time since first seeking medical diagnosis/ treatment was 3.88 vs 4.80 years, respectively. The median time since first surgical diagnosis was 2.65 vs 3.52 years, respectively.

Within 2 months prior to screening, most subjects in the EDELWEISS 3 and EDELWEISS 2, respectively, reported dyspareunia (88.0% vs 84.5%), approximately half (51.0% vs 44.0%) reported dyschezia, and approximately a quarter (26.0% vs 28.6%) reported dysuria, with comparable frequencies across the treatment groups. Most subjects had no adenomyosis (70.0% vs 92.9%) or rectovaginal endometriosis nodes (81.8% vs 97.6%).

Endometriosis Associated Pain and menstrual cycle

In the EDELWEISS 3 and EDELWEISS 2 trials, the study population is representative of women with established disease and suffering with moderate-to-severe endometriosis-associated pain (EAP).

The average duration of menstrual cycles and the average number of days with uterine bleeding were similar across treatment groups in both studies, with an overall mean (SD) of 27.87 (3.13) days vs 28.18 (3.15) days average length of a menstrual cycle in EDELWEISS 3 and EDELWEISS 2, respectively, and overall mean (SD) of 6.63 (2.37) days vs 6.99 (1.94) uterine bleeding days, respectively.

Baseline pain evaluation was similar between the treatment groups, with median OPP rated 1.95 vs 1.79 in EDELWEISS 3 vs EDELWEISS 2, respectively, median DYS 2.29 vs 2.18, and median NMPP 1.83 vs 1.65, based on the e-diary daily answers of Endometriosis Related Pelvic Pain (PP VRS Questionnaire), in which responses of "None," "Mild," "Moderate," and "Severe" were assigned a score of 0, 1, 2, and 3, respectively.

In both the EDELWEISS 3 and EDELWEISS 2 trials, respectively, baseline use of analgesics was comparable between the treatment groups during both the bleeding days (median 1.33 vs 1.93 pills/day) and the non-bleeding days (0.53 vs 0.90 pills/day).

In the EDELWEISS 3 study, the predominant analgesic used at baseline was ibuprofen, accounting for most of analgesic use during both the bleeding days (median 1.31 pills/day) and the nonbleeding days (0.50 pills/day). The use of narcotic analgesic at baseline was negligible on both the bleeding days (median 0 pills/day, mean (SD) of 0.05 (0.26) pills per day) and the non-bleeding days (median 0 pills/day, mean (SD) of 0.02 (0.12) pills/day).

In the EDELWEISS 2 study, the predominant analgesic used at baseline was ibuprofen during both the bleeding days (median 1.79 pills/day) and the non-bleeding days (0.84 pills/day), while the use of narcotic analgesics was negligible (median 0 pills/day).

In can be concluded that women in the study had moderate to severe endometriosis with prolonged cycle lengths, with an increased requirement for analgesia on uterine bleeding days, which is expected.

Baseline BMD

The BMD at baseline was comparable across all treatment groups in both the EDELWEISS 3 and EDELWEISS 2 studies. Median DXA readings ranged from 1.110 to 1.206 g/cm2 for the lumbar spine, from 0.867 to 0.994 g/cm2 for the femoral neck, and from 0.966 to 1.030 g/cm2 for the total hip. Median Z-scores ranged from 0.07 to 0.82 for the lumbar spine, from -0.09 to 0.46 for the femoral neck, and from 0.12 to 0.81 for the total hip. There were no subjects with minimum Z-scores lower than -2.0.

The BMD (median ≥ 0.867 g/cm2) and Z-score (≥ -0.09) at baseline suggest that the EDELWEISS 3 and EDELWEISS 2 study populations were generally in good bone health as would be expected for the general population of the same age, race, and BMI. BMD at baseline was comparable across all

treatment groups in both the EDELWEISS 6 and EDELWEISS 5 Extension Safety Analysis Sets, and similar to those observed for the Safety Analysis Sets in the respective parent studies. Eligibility criteria for entry into extension studies excluded subjects with BMD decrease from baseline >8% or a Z-score ≤ -2.5 at either femoral neck, hip or spine on the Month 6 DXA scan during the parent study. Three subjects were discontinued from the EDELWEISS 6 study once their DXA results confirmed that they met these exclusion criteria for entry into the extension study. None were discontinued from EDELWEISS 5 based on this criterion.

Adverse events

Treatment emergent adverse events

EDELWEISS 3 and EDELWEISS 2

Table 21 Summary of TEAEs reported between Day 1 and Month 6 (EDELWEISS 3, EDELWEISS 2, SAFs; Pooled SAF for Period 1)

Subjects with:	N (%) of subjects							
	EDELWEISS 3			EDELWEISS 2			E3/E2/P1/P2	
	Placebo (N=162)	LGX 75 mg (N=160)	LGX 200 mg +ABT (N=162)	Placebo (N=27)	LGX 75 mg (N=28)	LGX 200 mg +ABT (N=29)	Placebo (N=398)	LGX 200 mg +ABT (N=399)
Any TEAE	76 (46.9)	75 (46.9)	92 (56.8)	14 (51.9)	14 (50.0)	15 (51.7)	194 (48.7)	223 (55.9)
Severe TEAE	2 (1.2)	5 (3.1)	3 (1.9)	2 (7.4)	0	0	15 (3.8)	9 (2.3)
TEAE related to LGX	40 (24.7)	45 (28.1)	56 (34.6)	4 (14.8)	4 (14.3)	7 (24.1)	74 (18.6)	121 (30.3)
TEAE related to ABT	33 (20.4)	33 (20.6)	45 (27.8)	4 (14.8)	4 (14.3)	5 (17.2)	60 (15.1)	90 (22.6)
Serious TEAE	0	1 (0.6)	2 (1.2)	0	0	0	5 (1.3)	6 (1.5)
Serious TEAE related to LGX	0	0	0	0	0	0	n/a	n/a
Serious TEAE related to ABT	0	0	0	0	0	0	n/a	n/a
TEAE leading to permanent discontinuation of IMP	4 (2.5)	9 (5.6)	5 (3.1)	2 (7.4)	1 (3.6)	2 (6.9)	23 (5.8)	23 (5.8)
Fatal TEAE	0	0	0	0	0	0	0	0
ABT = add-back therapy (E2 1 mg/ NETA 0.5 mg); E = EDELWEISS study in endometriosis; LGX = linzagolix; P = PRIMROSE study in uterine fibroids; SAE = serious adverse event; TEAE = treatment-emergent adverse event								

Approximately half of the study population reported TEAEs. The percentage of subjects reporting one or more TEAEs was similar between the placebo (46.9% to 51.9%) and LGX 75 mg groups (46.9% to 50.0%) across E3/E2 studies and slightly higher in the LGX 200 mg+ABT group (E3: 56.8%) during the 6-month treatment period. Notably, the TEAE rate in the LGX 200 mg+ABT group in the endometriosis patients was similar to that previously reported in patients with uterine fibroids (pooled P1/P2: 55.3%).

Severe TEAEs were infrequent and reported with similar frequency in the placebo (1.2% to 7.4%) and linzagolix (0 to 3.1%) arms. The incidence of TEAEs considered by the Investigators to be related to linzagolix or ABT was comparable between placebo and LGX 75 mg groups, and slightly higher in the LGX 200 mg+ABT group. This is consistent with a previous finding in uterine fibroids, where the incidence of treatment-related TEAEs was found to be dose-dependent.

Overall, 3 subjects in the endometriosis trials (E3/E2) reported treatment-emergent SAEs: 1 (0.6%) in the LGX 75 mg group and 2 (1.2%) in the LGX 200 mg+ABT group. This is consistent with the rate of

treatment-emergent SAEs reported in patients with uterine fibroids treated with linzagolix 200 mg+ABT (P1/P2: 4 subjects, 1.9%).

Treatment discontinuations due to TEAEs were infrequent and similar between the placebo (2.5% to 7.4%) and linzagolix groups (3.1% to 6.9%). Notably, the rates of discontinuations due to TEAEs in the LGX 200 mg+ABT group were higher in the pooled P1/P2 studies in uterine fibroids (8.2%) compared to that observed in the pivotal EDELWEISS 3 study (3.1%).

No fatal TEAEs were reported in the Phase 3 linzagolix trials.

EDELWEISS 6 and EDELWEISS 5

Table 22 Summary of TEAEs reported between Month 6 and Month 12 in the extension studies (EDELWEISS 6 and EDELWEISS 5 ESAFs)

Subjects with:	Number (%) of subjects							
	EDELWEISS 6				EDELWEISS 5			
	Placebo/ LGX 75 mg (N=58)	Placebo/ LGX 200 mg+ABT (N=57)	LGX 75 mg (N=119)	LGX 200 mg +ABT (N=122)	Placebo/ LGX 75 mg (N=3)	Placebo/LGX 200 mg +ABT (N=4)	LGX 75 mg (N=13)	LGX 200 mg +ABT (N=10)
Any TEAE	27 (46.6)	27 (47.4)	53 (44.5)	49 (40.2)	0	0	3 (23.1)	4 (40.0)
Severe TEAE	1 (1.7)	2 (3.5)	1 (0.8)	1 (0.8)	0	0	1 (7.7)	0
TEAE related to LGX	13 (22.4)	14 (24.6)	19 (16.0)	23 (18.9)	0	0	0	1 (10.0)
TEAE related to ABT	10 (17.2)	8 (14.0)	14 (11.8)	13 (10.7)	0	0	0	1 (10.0)
Serious TEAE	0	1 (1.8)	3 (2.5)	0	0	0	0	0
Serious TEAE related to LGX	0	0	0	0	0	0	0	0
Serious TEAE related to ABT	0	0	1 (0.8)	0	0	0	0	0
TEAE leading to permanent discontinuation of IMP	2 (3.4)	2 (3.5)	3 (2.5)	2 (1.6)	0	0	0	0
Fatal TEAE	0	0	0	0	0		0	0

ABT = add-back therapy; ESAF = Extension Safety Analysis Set; LGX = linzagolix; TEAE = treatment-emergent adverse event

In the EDELWEISS 6 trial, 43.8% of subjects reported TEAEs between Month 6 and the end of treatment period at Month 12. The percentage of subjects reporting one or more TEAEs was slightly higher among subjects who initiated linzagolix treatment at Month 6 (placebo/LGX 75 mg: 46.6%; placebo/LGX 200 mg+ABT: 47.4%) compared to those continuing their linzagolix regimen (LGX 75 mg: 44.5%; LGX 200 mg+ABT: 40.2%)

Most TEAEs (98.6% overall) were mild or moderate in intensity. The incidence of severe TEAEs was low (≤3.5%) across the treatment groups and lowest (0.8%) among subjects treated with linzagolix from Day 1 of the parent EDELWEISS 3 trial, at both dosing regimens.

SAEs were reported in 1 subject in the placebo/LGX 200 mg+ABT group and 3 subjects in the LGX 75 mg group.

None of the SAEs were considered by the Investigators as being related to LGX. One serious TEAE reported in the LGX 75 mg group was considered as being related to ABT treatment.

Between Month 6 and Month 12, the discontinuation rate due to AEs was 2.5% overall, with ≤3.5% in the placebo/LGX groups and lower (≤2.5%) among subjects continuing LGX from Day 1, while the

lowest (1.6%) in the LGX 200 mg+ABT group, suggesting long-term tolerability of linzagolix Treatment.

The percentage of subjects reporting one or more TEAEs related to either LGX (total 19.4%) or ABT (total 12.6%) treatment was comparable across the treatment group.

No TEAEs leading to death were reported.

Pooled dataset (EDELWEISS 6, EDELWEISS 5, PRIMROSE 1, PRIMROSE 2)

Table 23 Summary of TEAEs reported between Month 6 and Month 12 (E6, E5, P1, P2; Pooled SAFs for Period 2)

Subjects with:	Number (%) of subjects					
	EDELWEISS 6/EDELWEISS 5/PRIMROSE 1/PRIMROSE 2					
	Placebo - Placebo (N=31)	Placebo - LGX 200mg + ABT (N=184)	LGX 200mg - LGX 200mg + ABT (N=161)	LGX 200mg + ABT - LGX 200mg + ABT (N=286)	Total LGX 200mg + ABT (N=631)	Total (N=662)
Any TEAE	12 (38.7)	79 (42.9)	77 (47.8)	108 (37.8)	264 (41.8)	276 (41.7)
Severe TEAE	0	6 (3.3)	5 (3.1)	6 (2.1)	17 (2.7)	17 (2.6)
TEAE related to LGX	1 (3.2)	28 (15.2)	25 (15.5)	44 (15.4)	97 (15.4)	98 (14.8)
TEAE related to ABT	2 (6.5)	20 (10.9)	17 (10.6)	27 (9.4)	64 (10.1)	66 (10.0)
Serious TEAE	0	5 (2.7)	6 (3.7)	3 (1.0)	14 (2.2)	14 (2.1)
TEAE leading to permanent discontinuation of IMP	1 (3.2)	10 (5.4)	14 (8.7)	4 (1.4)	28 (4.4)	29 (4.4)
Fatal TEAE	0	0	0	0	0	0

ABT = add-back therapy; LGX = linzagolix; TEAE = treatment-emergent adverse event

In the Pooled SAF for Period 2 (N=662), the proportion of subjects reporting adverse events appeared similar between subjects treated with Total LGX 200 mg+ABT (41.8%) and placebo (38.7%).

In the Total LGX 200 mg+ABT group, the frequency of severe TEAEs, serious TEAEs, and TEAEs leading to the permanent discontinuation of study drugs was low at 2.7%, 2.2%, and 4.4%, respectively, between Month 6 and Month 12 of treatment. In this pooled group, the rates of TEAEs related to linzagolix (15.4%) or ABT (10.1%) were similar as those observed in the LGX 200 mg+ABT group in the EDELWEISS 6 study (18.9% and 10.7%, respectively).

Post treatment follow up (PTFU)

For EDELWEISS 2 PTFU, of the 3 subjects in the FU SAF, 1 subject in the LGX 200 mg+ABT group reported TEAEs of nausea and vomiting, both considered mild in intensity and related to linzagolix within 30 days of EOT. No other AEs were reported during the follow-up period.

For EDELWEISS 3 and EDELWEISS 6 ExFU, the data is mentioned in the following table:

Table 24 Summary of TEAEs and post-treatment AEs during the PTFU in EDELWEISS 3 and ExFU in EDELWEISS 6 (EDELWEISS 3 FU SAF; EDELWEISS 6 ExFU SAF)

Subjects with:	Number (%) of subjects						
	EDELWEISS 3 PTFU			EDELWEISS 6 ExFU			
	Placebo (N=15)	LGX 75 mg (N=15)	LGX 200 mg +ABT (N=21)	Placebo / LGX 75 mg (N=54)	Placebo/ LGX 200 mg +ABT (N=50)	LGX 75 mg (N=112)	LGX 200 mg +ABT (N=113)
Any AE	5 (33.3)	7 (46.7)	8 (38.1)	17 (31.5)	9 (18.0)	31 (27.7)	41 (36.3)
Any TEAE	1 (6.7)	4 (26.7)	5 (23.8)	7 (13.0)	3 (6.0)	11 (9.8)	11 (9.7)
Any post-treatment AE	5 (33.3)	4 (26.7)	5 (23.8)	11 (20.4)	6 (12.0)	22 (19.6)	35 (31.0)
Severe TEAE	0	0	0	0	0	0	0
TEAE related to LGX	0	0	1 (4.8)	1 (1.9)	0	2 (1.8)	4 (3.5)
TEAE related to ABT	0	0	0	0	0	0	1 (0.9)
Serious TEAE	0	0	0	0	0	0	0
Fatal TEAE	0	0	0	0	0	0	0

ABT = add-back therapy; AE = adverse event; ExFU = post-extension-treatment follow-up; LGX = linzagolix; PTFU = post-treatment follow-up; TEAE = treatment-emergent adverse event
Adverse events that occur within 30 days after the end of treatment are considered as treatment emergent adverse events
Adverse events starting more than 30 days after the end of treatment are considered as post-treatment adverse events.

For EDELWEISS 6 ExFU specifically, a total of 7 subjects had a TEAE related to LGX:

- 5 subjects reported bone density decreased: 1 (1.9%) in the placebo/LGX 75 mg group, 2 (1.8%) in the LGX 75 mg group, and 2 (1.8%) in the LGX 200 mg+ABT group
- 1 subject (0.9%) in the LGX 200 mg+ABT group reported hot flush
- 1 subject (0.9%) in the LGX 200 mg+ABT group reported adnexa uteri pain. This TEAE was considered related to ABT.

It is noted that the incidence of TEAEs was lower in EDELWEISS 6 compared to EDELWEISS 3. This finding is in accordance to previously reported data, in which the rates of TEAEs, particularly those related to the known hypoestrogenic effects of GnRH antagonists, was highest during the first 12 weeks of treatment and attenuated over time.

In EDELWEISS 3 and 2, overall TEAEs are consistent with previous findings in uterine fibroids, where the incidence of treatment-related TEAEs appears to be dose-dependent. The percentage of participants reporting at least one TEAE in EDELWEISS 3 study (E3) was higher in those receiving linzagolix 200mg+ABT compared to placebo but comparable to the pooled Phase 3 (E3/E2/P1/P2) set (56.8% vs 46.9% vs 55.9%, respectively). A comparable rate of TEAE in LGX 200mg+ABT was previously reported in patients with uterine fibroids (55.3%).

For EDELWEISS 5 ExFU, of the 12 subjects in the ExFU SAF, 1 subject in the placebo/LGX 200 mg+ABT group reported 1 TEAE (COVID-19) within 30 days of the EOT, which was not considered serious, severe in intensity, or related to treatment. There were no other AEs reported during the follow-up.

Common TEAEs

EDELWEISS 2 and EDELWEISS 3

In the EDELWEISS 3 trial, up to Month 6, the most commonly (≥5% in any arm) reported TEAEs were headache, hot flush, fatigue, anaemia, mood swings and arthralgia. An anticipated hypoestrogenic

effect of GnRH antagonists, such as hot flush, was reported more frequently in the LGX groups (75 mg: 7.5%; 200 mg+ABT: 6.8%) compared to the placebo group (2.5%).

Both mood swings and arthralgia were more common in the LGX 75 mg group (5.0% for both TEAEs), compared to the placebo (1.9%, 1.2%, respectively) and LGX 200 mg+ABT (3.1%, 1.9%, respectively) groups.

TEAEs reported with a similar frequency in the placebo and LGX mg groups were headache (≤10.5%) and fatigue (≤6.8%).

Anaemia was more frequently reported in the placebo group (6.2%) compared to the LGX groups (75 mg: 3.1%; 200 mg+ABT: 2.5%), which is supports the finding that both LGX regimens reduced the number of bleeding days.

Nausea was another common TEAE, reported with ≤4.3% incidence in all treatment groups, including placebo.

In terms of System Organ Classes (SOCs), TEAEs were most often reported in the following SOCs:

- Gastrointestinal disorders (14.0%): overall 68 subjects reported TEAEs in this SOC with a higher incidence observed in the LGX groups (75 mg: 14.4%; 200 mg+ABT: 17.3%) compared to placebo (10.5%). Most common TEAE in this SOC was nausea, which was reported with a similar incidence in the placebo (4.3%), and LGX groups (3.7-3.8%). In general, the TEAEs in this SOC were reported with a similar frequency between the placebo and LGX groups, with the exception of abdominal distension and constipation which occurred slightly more frequently in the LGX 200 mg+ABT group.
- Infections and infestations (12.8%): overall 62 subjects reported TEAEs in this SOC, with the same incidence observed between the placebo and LGX 75 mg groups (10.5-10.6%) and slightly higher rate observed in the LGX 200 mg+ABT group (17.3%). Most common infections aside from COVID-19 (which was reported with a similar frequency in all groups) were urinary tract infection and vaginal infection, both reported predominantly in the LGX groups.
- Nervous system disorders (11.6%): overall 56 subjects reported TEAEs in this SOC, with a similar incidence observed in placebo (10.5%) and LGX 75 mg (8.8%) groups and slightly higher in the LGX 200 mg+ABT group (15.4%). The most common TEAE was headache, which was reported with the same incidence in the placebo and LGX 75 mg groups (8.0-8.1%) and only slightly more frequently in the LGX 200 mg+ABT group (10.5%). The only other TEAEs in this SOC reported by more than 1 subject overall were disturbance in attention and dizziness, both occurring with a similar incidence between the placebo and LGX groups (all <2%).
- Reproductive system and breast disorders (9.5%): overall 46 subjects reported TEAEs in this SOC, with a similar incidence between placebo (9.9%) and LGX groups (75 mg: 6.9%; 200 mg+ABT: 11.7%). The most common TEAEs in this SOC were vaginal haemorrhage (reported predominantly in the LGX groups) and breast pain (reported more frequently in the placebo group).
- Psychiatric disorders (8.3%): overall 40 subjects reported TEAEs in this SOC with a higher incidence observed in the LGX groups (75 mg: 10.6%; 200 mg+ABT: 8.6%) compared to placebo (5.6%). The most common TEAE in this SOC was mood swings, which was reported slightly more frequently in the LGX 75 mg group (5.0%) compared to the placebo (1.9%) and LGX 200 mg+ABT (3.1%) groups. All other TEAEs in this SOC were reported with comparable frequencies across all groups.

Up to the study termination of EDELWEISS 2, TEAEs most often reported were nausea, headache, and fatigue, all with similar incidence across all treatment groups, including placebo.

Pooled dataset (EDELWEISS 3, EDELWEISS 2, PRIMROSE 1, PRIMROSE 2)

In the Pooled SAF for Period 1 (N=797), the most commonly (≥5% in any arm) reported TEAEs were headache (7.8%), hot flush (6.0%) and anaemia (5.3%). nausea (3.3%), fatigue (2.9%), vaginal haemorrhage (2.1%) nasopharyngitis (2.1%), COVID-19 (2.0%), pelvic pain (1.9%), arthralgia (1.9%), hypertension (1.8%), urinary tract infection (1.5%), and blood creatine phosphokinase increased (1.5%).

Of these, the TEAEs reported more frequently (with a difference of at least 1.5%) in the LGX 200mg+ABT group compared to placebo group were: hot flush (8.0% vs 4.0%, respectively), headache (8.8% vs 6.8%), vaginal haemorrhage (3.3% vs 1.0%), and urinary tract infection (2.3% vs 0.8%). Conversely, anaemia was reported more frequently in the placebo group (6.3%) compared to the LGX 200 mg+ABT group (4.3%). All other TEAEs that were considered as common, occurred with a similar frequency between the placebo and LGX 200 mg+ABT groups.

EDELWEISS 6

In the EDELWEISS 6 extension trial, between Month 6 to Month 12, the most commonly (≥5% in any treatment arm) reported TEAEs were COVID-19, headache, hot flush, anaemia, vaginal haemorrhage, and vulvovaginal mycotic infection. All of these TEAEs were reported in fewer than 7% of subjects in any treatment group.

Headache, vaginal haemorrhage, and vulvovaginal mycotic infection were each reported in ≤5.3% in any treatment group.

Hot flushes were most frequent in subjects who started LGX 75 mg at Month 6 (i.e., placebo/LGX 75 mg group) at 6.9%, while the incidence of hot flushes was lower among subjects on LGX regimens from Day 1 in the EDELWEISS 3 trial (≤4.1%).

Anaemia was reported in the LGX 75 mg group (5.9%), placebo/LGX 75 mg group (5.2%) and placebo/LGX 200 mg+ABT group (3.5%).

Between Month 6 and Month 12, TEAEs were reported most frequently in the following SOCs:

- Infections and infestations (16.3%): A total of 58 subjects reported TEAEs in this SOC overall; incidence was similar across treatment groups (between 15.1% and 17.2%). Most common TEAE in this SOC was COVID-19 (4.2%).
- Investigations (8.1%): A total of 29 subjects reported TEAEs in this SOC overall; the incidence was 13.8% in the placebo/LGX 75 mg group, while lower in all other treatment arms (5.7% to 8.8%). Most common TEAE in this SOC was bone density decreased (3.1%), which was reported less frequently in the LGX 200 mg+ABT group (1.6%) compared to the other treatment groups (placebo/LGX 75 mg: 3.4%; Placebo/ LGX 200 mg+ABT: 3.5%; LGX 75 mg: 4.2%).
- Gastrointestinal disorders (7.0%): A total of 25 subjects reported TEAEs in this SOC overall; a lower incidence was observed in the placebo/LGX 75 mg and LGX 75 mg groups (5.2% and 4.1%, respectively) compared to the placebo/LGX 200 mg+ABT and LGX 200 mg+ABT groups (10.5% and 9.2%, respectively). Most common TEAE in this SOC was nausea (2.2%), reported by 1 to 3 subjects in any treatment group.

EDELWEISS 5

In the terminated EDELWEISS 5 extension trial, 7 of the 30 subjects (23.3%) reported TEAEs. In the LGX 200 mg+ABT group, 4/10 subjects reported TEAEs: 2 subjects had COVID-19, and 1 subject each reported menstruation irregular and vaginal discharge. In the LGX 75 mg group, 3/13 subjects reported TEAEs: 1 subject each reported a urinary tract infection, pelvic pain, and tendon injury. No TEAEs were reported by the 3 subjects in the placebo/LGX 75 mg group and by the 4 subjects in the placebo/LGX 200 mg+ABT group.

Pooled dataset (EDELWEISS 6, EDELWEISS 5, PRIMROSE 1, PRIMROSE 2)

In the Pooled SAF for Period 2 (N=662), the only TEAEs reported with ≥5% frequency in any active arm was bone density decreased and anaemia. Decrease in bone density was reported in 2.9% of the Total LGX 200 mg+ABT arm (N=631) though with a lower frequency (1.7%) in the LGX 200 mg+ABT/LGX200 mg+ABT group (N=286) which consisted of subjects exposed to the 200 mg+ABT regimen for up to 12 months. Anaemia was reported in 2.7% of subjects in the Total LGX 200 mg+ABT group.

Severe TEAEs

EDELWEISS 2 and EDELWEISS 3

In the EDELWEISS 2 study, none of the subjects in the linzagolix groups reported severe TEAEs. Two subjects in the placebo group reported TEAEs rated as severe in intensity: 1 subject reported abscess limb and 1 subject reported menorrhagia and dysmenorrhea.

In EDELWEISS 3, the majority of TEAEs were mild or moderate in intensity. Of the 243 subjects who reported TEAEs, 184 (38.0% of SAF) subjects reported mild TEAEs, 125 (25.8% of SAF) reported moderate TEAEs, while 10 subjects (i.e., 2.1% of SAF) reported severe TEAEs.

The incidence of severe TEAEs was comparable across study groups: 1.2% (2 subjects) in the placebo group reported severe TEAEs, 3.1% (5 subjects) in the LGX 75 mg group, and 1.9% (3 subjects) in the LGX 200 mg+ABT group.

- The severe TEAEs reported in the placebo group included nausea and ligament rupture (each reported by 1 subject).
- The severe TEAEs reported in the LGX 75 mg group included dysmenorrhea, COVID-19, vaginal infection, blood pressure increased, hot flush (all reported by 1 subject each), and headache (reported by 2 subjects).
- The severe TEAEs reported in the LGX 200 mg+ABT group included menstruation irregular, vulvovaginal dryness, and abdominal pain (each reported by 1 subject).

Pooled dataset (EDELWEISS 3, EDELWEISS 2, PRIMROSE 1, PRIMROSE 2)

In the pooled dataset of 797 subjects, 3.0% of subjects reported severe TEAEs while the majority of subjects reporting TEAEs rated them either as moderate (22.6% of subjects) or mild (26.7%). A higher proportion of severe TEAEs was reported in the placebo group (3.8%) compared to the LGX 200 mg+ABT group (2.3%). Aside from anaemia, reported by 1 subject each in the placebo and LGX 200 mg+ABT group, all other TEAEs were reported by no more than 1 subject.

Overall, pooling did not reveal any differences with regard to the safety profile for the linzagolix 200 mg+ABT regimen.

Table 25 Severe TEAEs reported in Phase 3 linzagolix trials up to Month 6 (E3/E2/P1/P2 Pooled SAF for Period 1)

Maximum Severity Preferred Term	Number (%) of subjects		
	Placebo (N=398)	LGX 200mg + ABT (N=399)	Total (N=797)
Subjects with at least one TEAE	**194 (48.7)**	**223 (55.9)**	**417 (52.3)**
Severe	15 (3.8)	9 (2.3)	24 (3.0)
Moderate	83 (20.9)	97 (24.3)	180 (22.6)
Mild	96 (24.1)	117 (29.3)	213 (26.7)
Maximum Severity: Severe	**15 (3.8)**	**9 (2.3)**	**24 (3.0)**
Anaemia	1 (0.3)	1 (0.3)	2 (0.3)
Dysmenorrhoea	1 (0.3)	0	1 (0.1)
Menorrhagia	1 (0.3)	0	1 (0.1)
Menstruation irregular	0	1 (0.3)	1 (0.1)
Uterine haemorrhage	0	1 (0.3)	1 (0.1)
Vaginal haemorrhage	1 (0.3)	0	1 (0.1)
Vulvovaginal dryness	0	1 (0.3)	1 (0.1)
Abdominal pain	0	1 (0.3)	1 (0.1)
Abdominal pain upper	1 (0.3)	0	1 (0.1)
Nausea	1 (0.3)	0	1 (0.1)
Abscess limb	1 (0.3)	0	1 (0.1)
Influenza	1 (0.3)	0	1 (0.1)
Pharyngitis	0	1 (0.3)	1 (0.1)
Ankle fracture	1 (0.3)	0	1 (0.1)
Ligament rupture	1 (0.3)	0	1 (0.1)
Traumatic fracture	0	1 (0.3)	1 (0.1)
Blood creatine phosphokinase increased	1 (0.3)	0	1 (0.1)
Bone density decreased	1 (0.3)	0	1 (0.1)
Hepatic enzyme increased	1 (0.3)	0	1 (0.1)
Acute myocardial infarction	1 (0.3)	0	1 (0.1)
Migraine	1 (0.3)	0	1 (0.1)
Libido decreased	0	1 (0.3)	1 (0.1)
Hyperhidrosis	1 (0.3)	0	1 (0.1)
Hot flush	0	1 (0.3)	1 (0.1)

ABT = add-back therapy; LGX = linzagolix.
TEAEs in Period 1 are AEs with a start date on or after the first dose of study drug in Period 1 through switch to Period 2 or 30 days after discontinuation of study drug or the end date of study drug whatever comes first, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the investigator in Period 1 through switch to Period 2 or 30 days after discontinuation of study drug or the end date of study drug whatever comes first.
Subjects with one or more AEs within a level of MedDRA are counted only once in that level taking the most severe incident.
System Organ Class and Preferred Terms are sorted in decreasing frequency. MedDRA Dictionary (Version 23.0).

EDELWEISS 5 and EDELWEISS 6

In the EDELWEISS 5 trial, 1 subject (7.7%) in the LGX 75 mg group reported severe pelvic pain. All other TEAEs were mild or moderate in intensity.

Pooled dataset (EDELWEISS 6, EDELWEISS 5, PRIMROSE 1, PRIMROSE 2)

In the pooled dataset of 662 subjects, 2.6% of subjects reported severe TEAEs while the majority of subjects reporting TEAEs rated them either as moderate (17.2% of subjects) or mild (21.9%). Aside from menorrhagia (3 subjects), anaemia (2 subjects), and abdominal pain (2 subjects), all other TEAEs were reported by no more than 1 subject.

Table 26 Severe TEAEs reported in Phase 3 linzagolix trials between Month 6 and Month 12 (E6/E5/P1/P2 Pooled SAF for Period 2)

Maximum Severity Preferred Term	Number (%) of subjects					
	Placebo - Placebo (N=31)	Placebo - LGX 200mg + ABT (N=184)	LGX 200mg - LGX 200mg + ABT (N=161)	LGX 200mg + ABT - LGX 200mg + ABT (N=286)	Total LGX 200mg + ABT (N=631)	Total (N=662)
Subjects with at least one TEAE	**12 (38.7)**	**79 (42.9)**	**77 (47.8)**	**108 (37.8)**	**264 (41.8)**	**276 (41.7)**
Severe	0	6 (3.3)	5 (3.1)	6 (2.1)	17 (2.7)	17 (2.6)
Moderate	7 (22.6)	37 (20.1)	31 (19.3)	39 (13.6)	107 (17.0)	114 (17.2)
Mild	5 (16.1)	36 (19.6)	41 (25.5)	63 (22.0)	140 (22.2)	145 (21.9)
Maximum Severity: Severe	**0**	**6 (3.3)**	**5 (3.1)**	**6 (2.1)**	**17 (2.7)**	**17 (2.6)**
Menorrhagia	0	2 (1.1)	1 (0.6)	0	3 (0.5)	3 (0.5)
Anaemia	0	1 (0.5)	0	1 (0.3)	2 (0.3)	2 (0.3)
Abdominal pain	0	1 (0.5)	0	1 (0.3)	2 (0.3)	2 (0.3)
Dysmenorrhoea	0	1 (0.5)	0	0	1 (0.2)	1 (0.2)
Genital haemorrhage	0	1 (0.5)	0	0	1 (0.2)	1 (0.2)
Vaginal haemorrhage	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Femur fracture	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Meniscus injury	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Road traffic accident	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Hot flush	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Hypertensive crisis	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
ALT increased	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
AST increased	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Blood lactate dehydrogenase increased	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Gamma-glutamyltransferase increased	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Osteoporosis	0	1 (0.5)	0	0	1 (0.2)	1 (0.2)
Breast cancer	0	1 (0.5)	0	0	1 (0.2)	1 (0.2)
Headache	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)

ABT = add-back therapy; LGX = linzagolix
TEAEs in Period 2 are AEs with a start date on or after the first dose of study drug in Period 2 through 30 days after discontinuation of study drug or the end date of study drug, or any event that was present at the first visit in Period 2 worsened in intensity or was subsequently considered drug-related by the investigator in Period 2 through 30 days after discontinuation of study drug or the end date of study drug.
Subjects with one or more AEs within a level of MedDRA are counted only once in that level taking the most severe incident.
MedDRA Dictionary (Version 23.0).

Drug related TEAEs

Linzagolix-related TEAEs- EDELWEISS 2 and EDELWEISS 3

In the EDELWEISS 2 trial, the percentage of subjects reporting TEAEs considered related to linzagolix was similar between placebo (4 subjects) and LGX 75 mg (4 subjects) groups, while slightly higher in the LGX 200 mg+ABT group (24.1%).

Most TEAEs considered related to linzagolix were reported by 1 subject in any treatment group. Only dizziness and vaginal haemorrhage were reported by 2 subjects each, both in the LGX 200 mg+ABT group.

In the EDELWEISS 3 study, 29.1% of the subjects in the SAF reported TEAEs considered related to linzagolix. The percentage of subjects reporting TEAEs considered related to linzagolix was comparable between placebo (24.7%) and LGX 75 mg (28.1%) groups, while slightly higher in the LGX 200 mg+ABT group (34.6%). The common (i.e., in at least 2% of the SAF) linzagolix-related TEAEs included headache (5.8%), hot flush (5.6%), fatigue (3.3%), nausea (3.1%), mood swings (2.9%),

and abdominal distension (2.5%). Headache, hot flush, fatigue, and mood swings were reported more frequently in the LGX groups compared with placebo.

In the E3/E2/P1/P2 Pooled SAF for Period 1 (N=797), 24.5% reported TEAEs related to linzagolix: 30.3% in the LGX 200 mg+ABT group compared to 18.6% in the placebo group. The commonly (≥2% in any active arm) reported linzagolix-related TEAEs were hot flush (8.0% in the LGX 200 mg+ABT group vs 3.3% in the placebo group), headache (4.0% vs 2.8%, respectively), vaginal haemorrhage (2.8% vs 0.5%), nausea (2.5% vs 1.5%), and fatigue (2.3% vs 1.5%).

Table 27 TEAEs suspected to be linzagolix-related reported up to Month 6 by ≥1% in any arm in EDELWEISS 3 and/or Pooled SAF1 (E3 and E2 SAF; E3/E2/P1/P2 Pooled SAF for Period 1)

	Number (%) of subjects							
	EDELWEISS 3			EDELWEISS 2			E3/E2/P1/P2	
	Placebo (N=162)	LGX 75 mg (N=160)	LGX 200 mg + ABT (N=162)	Placebo (N=27)	LGX 75 mg (N=28)	LGX 200 mg +ABT (N=29)	Placebo (N=398)	LGX 200 mg +ABT (N=399)
Subjects with at least 1 linzagolix-related TEAE	40 (24.7)	45 (28.1)	56 (34.6)	4 (14.8)	4 (14.3)	7 (24.1)	74 (18.6)	121 (30.3)
Gastrointestinal disorders	**12 (7.4)**	**13 (8.1)**	**16 (9.9)**	**1 (3.7)**	**0**	**2 (6.9)**	**17 (4.3)**	**27 (6.8)**
Nausea	5 (3.1)	5 (3.1)	5 (3.1)	1 (3.7)	0	1 (3.4)	6 (1.5)	10 (2.5)
Abdominal distension	3 (1.9)	4 (2.5)	5 (3.1)	0	0	0	6 (1.5)	5 (1.3)
Diarrhoea	2 (1.2)	2 (1.3)	2 (1.2)	0	0	1 (3.4)	3 (0.8)	4 (1.0)
Constipation	1 (0.6)	2 (1.3)	1 (0.6)	0	0	0	1 (0.3)	2 (0.5)
Vomiting	2 (1.2)	0	1 (0.6)	0	0	0	2 (0.5)	2 (0.5)
Abdominal pain upper	0	0	2 (1.2)	0	0	1 (3.4)	0	3 (0.8)
Nervous system disorders	**9 (5.6)**	**12 (7.5)**	**16 (9.9)**	**1 (3.7)**	**2 (7.1)**	**2 (6.9)**	**18 (4.5)**	**24 (6.0)**
Headache	6 (3.7)	12 (7.5)	10 (6.2)	0	1 (3.6)	1 (3.4)	11 (2.8)	16 (4.0)
Dizziness	2 (1.2)	1 (0.6)	3 (1.9)	0	1 (3.6)	2 (6.9)	2 (0.5)	5 (1.3)
Disturbance in attention	2 (1.2)	1 (0.6)	1 (0.6)	0	0	0	2 (0.5)	1 (0.3)
Psychiatric disorders	**8 (4.9)**	**15 (9.4)**	**13 (8.0)**	**2 (7.4)**	**0**	**2 (6.9)**	**12 (3.0)**	**20 (5.0)**
Mood swings	2 (1.2)	8 (5.0)	4 (2.5)	1 (3.7)	0	0	4 (1.0)	5 (1.3)
Depressed mood	2 (1.2)	2 (1.3)	2 (1.2)	0	0	0	2 (0.5)	2 (0.5)
Sleep disorder	1 (0.6)	2 (1.3)	3 (1.9)	0	0	0	1 (0.3)	3 (0.8)
Insomnia	1 (0.6)	2 (1.3)	1 (0.6)	0	0	1 (3.4)	2 (0.5)	2 (0.5)
Libido decreased	0	2 (1.3)	1 (0.6)	0	0	0	0	3 (0.8)
Reproductive system and breast disorders	**9 (5.6)**	**9 (5.6)**	**14 (8.6)**	**0**	**2 (7.1)**	**3 (10.3)**	**13 (3.3)**	**35 (8.8)**
Vaginal haemorrhage	1 (0.6)	3 (1.9)	5 (3.1)	0	0	2 (6.9)	2 (0.5)	11 (2.8)
Breast pain	5 (3.1)	1 (0.6)	1 (0.6)	0	0	0	5 (1.3)	1 (0.3)
Vulvovaginal dryness	0	2 (1.3)	3 (1.9)	0	0	0	0	3 (0.8)
Metrorrhagia	1 (0.6)	2 (1.3)	1 (0.6)	0	0	0	1 (0.3)	5 (1.3)
Amenorrhoea	0	1 (0.6)	1 (0.6)	0	1 (3.6)	0	0	3 (0.8)
Pelvic pain	0	0	2 (1.2)	0	1 (3.6)	0	1 (0.3)	4 (1.0)
Uterine haemorrhage	0	0	2 (1.2)	0	0	0	0	3 (0.8)
Vascular disorders	**4 (2.5)**	**12 (7.5)**	**11 (6.8)**	**1 (3.7)**	**1 (3.6)**	**1 (3.4)**	**13 (3.3)**	**34 (8.5)**
Hot flush	4 (2.5)	12 (7.5)	11 (6.8)	1 (3.7)	1 (3.6)	1 (3.4)	13 (3.3)	32 (8.0)
General disorders and administration site conditions	**7 (4.3)**	**6 (3.8)**	**9 (5.6)**	**1 (3.7)**	**0**	**0**	**13 (3.3)**	**12 (3.0)**
Fatigue	3 (1.9)	5 (3.1)	8 (4.9)	1 (3.7)	0	0	6 (1.5)	9 (2.3)
Asthenia	1 (0.6)	1 (0.6)	2 (1.2)	0	0	0	1 (0.3)	3 (0.8)
Skin and subcutaneous tissue disorders	**7 (4.3)**	**2 (1.3)**	**7 (4.3)**	**0**	**0**	**0**	**10 (2.5)**	**9 (2.3)**
Acne	4 (2.5)	1 (0.6)	2 (1.2)	0	0	0	5 (1.3)	2 (0.5)
Alopecia	2 (1.2)	1 (0.6)	3 (1.9)	0	0	0	3 (0.8)	4 (1.0)
Investigations	**6 (3.7)**	**2 (1.3)**	**4 (2.5)**	**0**	**0**	**0**	**12 (3.0)**	**11 (2.8)**
Bone density decreased	2 (1.2)	1 (0.6)	3 (1.9)	0	0	0	3 (0.8)	3 (0.8)

	Number (%) of subjects							
	EDELWEISS 3			EDELWEISS 2			E3/E2/P1/P2	
	Placebo (N=162)	LGX 75 mg (N=160)	LGX 200 mg + ABT (N=162)	Placebo (N=27)	LGX 75 mg (N=28)	LGX 200 mg +ABT (N=29)	Placebo (N=398)	LGX 200 mg +ABT (N=399)
Blood triglycerides increased	2 (1.2)	0	0	0	0	0	2 (0.5)	0
Musculoskeletal and connective tissue disorders	**2 (1.2)**	**6 (3.8)**	**3 (1.9)**	**1 (3.7)**	**0**	**0**	**6 (1.5)**	**6 (1.5)**
Arthralgia	2 (1.2)	6 (3.8)	1 (0.6)	0	0	0	2 (0.5)	3 (0.8)

ABT = add-back therapy; E = EDELWEISS (3 or 2) trial in endometriosis; LGX = linzagolix; P = PRIMROSE (1 or 2) trial in uterine fibroids
Due to the low number of subjects per group in the prematurely terminated Edelweiss 2 study, the cut-off was not applied to the Edelweiss 2 SAF as 1 subject per group represents over 3%.
If a subject had multiple events within a system organ class or preferred term, the subject was counted once.
Events were sorted in decreasing order of frequency in the total column, by SOC and within a SOC by PT. In case of equal frequency, alphabetic order was used. The causality assessment of an AE to linzagolix was performed by the investigator.
Dictionary Coding: MedDRA Version 23.0.

EDELWEISS 5 and EDELWEISS 6

In the EDELWEISS 5 study, 1 subject (10%) in the LGX 200 mg+ABT reported irregular menstruation which was considered by the Investigator to be related to both linzagolix and ABT.

In the EDELWEISS 6 study, 19.4% of the subjects in the ESAF reported TEAEs considered related to linzagolix from Month 6 to Month 12. The percentage of subjects reporting TEAEs related to linzagolix was slightly higher in the Placebo/LGX groups (Placebo/LGX 75 mg: 22.4%; Placebo/ LGX 200 mg+ABT: 24.6%; LGX 75 mg: 16.0%; LGX 200 mg+ABT: 18.9%).

Most TEAEs related to linzagolix were reported by 1-2 subjects in any treatment group with no discernible pattern. The common (i.e., in at least 2% of the ESAF) linzagolix-related TEAEs included bone density decreased (3.1%), hot flush (3.1%), and mood swings (2.0%).

In the E6/E5/P1/P2 Pooled SAF for Period 2 (N=662), TEAEs suspected to be related to linzagolix were reported in 15.4% of subjects in the Total LGX 200 mg+ABT group. The commonly (≥2% in any active arm) reported linzagolix-related TEAEs in the Total LGX 200 mg+ABT group were bone density decreased (2.5%), hot flush (1.7%), vaginal haemorrhage (1.6%), vulvovaginal dryness (1.0%), and uterine haemorrhage (0.8%).

Table 28 TEAEs suspected to be linzagolix-related reported between Month 6 and Month 12 by ≥1% in any active treatment arm (EDELWEISS 6 ESAF; E6/E5/P1/P2 Pooled SAF for Period 2)

System Organ Class Preferred Term	Number (%) of subjects								
	EDELWEISS 6				E6/E5/P1/P2				
	Placebo / LGX 75 mg (N=58)	Placebo / LGX 200 mg +ABT (N=57)	LGX 75 mg (N=119)	LGX 200 mg+ ABT (N=122)	Placebo / Placebo (N=31)	Placebo / LGX 200 mg + ABT (N=184)	LGX 200 mg/ LGX 200 mg + ABT (N=161)	LGX 200 mg + ABT / LGX 200 mg + ABT (N=286)	Total LGX 200 mg + ABT (N=631)
Subjects with at least 1 LGX-related TEAE	13 (22.4)	14 (24.6)	19 (16.0)	23 (18.9)	1 (3.2)	28 (15.2)	25 (15.5)	44 (15.4)	97 (15.4)
Investigations	**5 (8.6)**	**4 (7.0)**	**5 (4.2)**	**4 (3.3)**	**1 (3.2)**	**8 (4.3)**	**7 (4.3)**	**13 (4.5)**	**28 (4.4)**
Bone density decreased	2 (3.4)	2 (3.5)	5 (4.2)	2 (1.6)	1 (3.2)	4 (2.2)	7 (4.3)	5 (1.7)	16 (2.5)
ALT increased	1 (1.7)	1 (1.8)	0	1 (0.8)	0	1 (0.5)	0	5 (1.7)	6 (1.0)
aPTT prolonged	1 (1.7)	0	0	1 (0.8)	0	0	0	1 (0.3)	1 (0.2)
AST increased	0	1 (1.8)	0	1 (0.8)	0	1 (0.5)	0	4 (1.4)	5 (0.8)

System Organ Class Preferred Term	Number (%) of subjects								
	EDELWEISS 6				E6/E5/P1/P2				
	Placebo / LGX 75 mg (N=58)	Placebo / LGX 200 mg +ABT (N=57)	LGX 75 mg (N=119)	LGX 200 mg+ ABT (N=122)	Placebo / Placebo (N=31)	Placebo / LGX 200 mg + ABT (N=184)	LGX 200 mg/ LGX 200 mg + ABT (N=161)	LGX 200 mg + ABT / LGX 200 mg + ABT (N=286)	Total LGX 200 mg + ABT (N=631)
Blood CPK increased	0	1 (1.8)	0	0	0	1 (0.5)	0	2 (0.7)	3 (0.5)
Blood pressure increased	0	1 (1.8)	0	0	0	1 (0.5)	0	0	1 (0.2)
Hepatic enzyme increased	1 (1.7)	0	0	0	0	0	0	0	0
Psychiatric disorders	**3 (5.2)**	**2 (3.5)**	**3 (2.5)**	**7 (5.7)**	**0**	**3 (1.6)**	**0**	**8 (2.8)**	**11 (1.7)**
Mood swings	2 (3.4)	1 (1.8)	1 (0.8)	3 (2.5)	0	2 (1.1)	0	3 (1.0)	5 (0.8)
Depressed mood	0	1 (1.8)	0	1 (0.8)	0	1 (0.5)	0	1 (0.3)	2 (0.3)
Nervousness	1 (1.7)	1 (1.8)	0	0	0	1 (0.5)	0	0	1 (0.2)
Reproductive system and breast disorders	**0**	**5 (8.8)**	**5 (4.2)**	**2 (1.6)**	**0**	**12 (6.5)**	**11 (6.8)**	**8 (2.8)**	**31 (4.9)**
Vaginal haemorrhage	0	2 (3.5)	1 (0.8)	1 (0.8)	0	3 (1.6)	6 (3.7)	1 (0.3)	10 (1.6)
Vulvovaginal dryness	0	2 (3.5)	0	1 (0.8)	0	4 (2.2)	0	2 (0.7)	6 (1.0)
Ovarian cyst	0	0	2 (1.7)	0	0	0	0	0	0
Genital haemorrhage	0	1 (1.8)	0	0	0	1 (0.5)	0	0	1 (0.2)
Uterine haemorrhage	0	0	0	0	0	4 (2.2)	1 (0.6)	0	5 (0.8)
Menorrhagia	0	0	1 (0.8)	0	0	2 (1.1)	1 (0.6)	1 (0.3)	4 (0.6)
Metrorrhagia	0	0	0	0	0	0	2 (1.2)	0	2 (0.3)
Vascular disorders	**3 (5.2)**	**0**	**4 (3.4)**	**5 (4.1)**	**0**	**3 (1.6)**	**0**	**9 (3.1)**	**12 (1.9)**
Hot flush	3 (5.2)	0	4 (3.4)	4 (3.3)	0	3 (1.6)	0	8 (2.8)	11 (1.7)
Gastrointestinal disorders	**3 (5.2)**	**4 (7.0)**	**2 (1.7)**	**2 (1.6)**	**0**	**5 (2.7)**	**1 (0.6)**	**2 (0.7)**	**8 (1.3)**
Nausea	2 (3.4)	2 (3.5)	1 (0.8)	1 (0.8)	0	3 (1.6)	1 (0.6)	1 (0.3)	5 (0.8)
Abdominal distension	1 (1.7)	1 (1.8)	0	0	0	1 (0.5)	0	0	1 (0.2)
Abdominal pain	0	1 (1.8)	0	1 (0.8)	0	1 (0.5)	0	1 (0.3)	2 (0.3)
Constipation	1 (1.7)	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	**3 (5.2)**	**1 (1.8)**	**0**	**3 (2.5)**	**0**	**3 (1.6)**	**1 (0.6)**	**4 (1.4)**	**8 (1.3)**
Acne	0	1 (1.8)	0	2 (1.6)	0	1 (0.5)	0	2 (0.7)	3 (0.5)
Alopecia	2 (3.4)	0	0	0	0	0	0	1 (0.3)	1 (0.2)
Hyperhidrosis	1 (1.7)	0	0	1 (0.8)	0	2 (1.1)	0	1 (0.3)	3 (0.5)
General disorders and administration site conditions	**1 (1.7)**	**2 (3.5)**	**3 (2.5)**	**0**	**0**	**2 (1.1)**	**0**	**0**	**2 (0.3)**
Fatigue	0	1 (1.8)	1 (0.8)	0	0	1 (0.5)	0	0	1 (0.2)
Peripheral swelling	0	1 (1.8)	1 (0.8)	0	0	1 (0.5)	0	0	1 (0.2)
Oedema	1 (1.7)	0	0	0	0	0	0	0	0
Nervous system disorders	**1 (1.7)**	**2 (3.5)**	**1 (0.8)**	**1 (0.8)**	**0**	**3 (1.6)**	**3 (1.9)**	**1 (0.3)**	**7 (1.1)**
Headache	1 (1.7)	2 (3.5)	1 (0.8)	1 (0.8)	0	2 (1.1)	2 (1.2)	1 (0.3)	5 (0.8)
Metabolism and nutrition disorders	**0**	**2 (3.5)**	**0**	**2 (1.6)**	**0**	**2 (1.1)**	**1 (0.6)**	**2 (0.7)**	**5 (0.8)**
Increased appetite	0	2 (3.5)	0	1 (0.8)	0	2 (1.1)	1 (0.6)	1 (0.3)	4 (0.6)
Musculoskeletal and connective tissue disorders	**2 (3.4)**	**0**	**0**	**2 (1.6)**	**0**	**2 (1.1)**	**4 (2.5)**	**4 (1.4)**	**10 (1.6)**
Arthralgia	1 (1.7)	0	0	1 (0.8)	0	0	2 (1.2)	2 (0.7)	4 (0.6)
Spinal pain	1 (1.7)	0	0	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.7)	0	0	0	**0**	**0**	**0**	**0**	**0**
Uterine leiomyoma	1 (1.7)	0	0	0	0	0	0	0	0

ABT = add-back therapy; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CPK = creatine phosphokinase; ESAF = Extension Safety Analysis Set; LGX = linzagolix
TEAE = treatment-emergent adverse event
If a subject had multiple events within an SOC or PT, the subject was counted once.

System Organ Class Preferred Term	Number (%) of subjects								
	EDELWEISS 6				E6/E5/P1/P2				
	Placebo / LGX 75 mg (N=58)	Placebo / LGX 200 mg +ABT (N=57)	LGX 75 mg (N=119)	LGX 200 mg+ ABT (N=122)	Placebo / Placebo (N=31)	Placebo / LGX 200 mg + ABT (N=184)	LGX 200 mg/ LGX 200 mg + ABT (N=161)	LGX 200 mg + ABT / LGX 200 mg + ABT (N=286)	Total LGX 200 mg + ABT (N=631)
Events were sorted in decreasing order of frequency in the total column, by SOC and within a SOC by PT. In case of equal frequency, alphabetic order was used. The causality assessment of an AE to linzagolix was performed by the investigator. For subjects not entering the Extension Follow-up, AE were included in this summary up to 30 days after end of extension treatment. Dictionary Coding: MedDRA Version 23.0.									

ABT-related TEAEs

EDELWEISS 2 and EDELWEISS 3

In the EDELWEISS 2 trial, the number of subjects reporting TEAEs considered related to ABT was similar between the placebo (4 subjects), LGX 75 mg (4 subjects), and LGX 200 mg+ABT (5 subjects) groups.

- In the placebo group, the following TEAEs were reported by 1 subject each: nausea, headache, chest discomfort, anxiety, and pain in extremity.
- In the LGX 75 mg group, the following TEAEs were reported by 1 subject each: nausea, abdominal distension, vomiting, headache, breast tenderness, and non-cardiac chest pain.
- In the LGX 200 mg+ABT group, 2 subjects reported dizziness. The following TEAEs were reported by 1 subject each: nausea, upper abdominal pain, diarrhoea, headache, menstrual disorder, vaginal haemorrhage, nervousness, and dyspnoea.

In the EDELWEISS 3 trial, 22.9% of the subjects in the SAF reported TEAEs considered related to ABT. The percentage of subjects reporting TEAEs considered related to ABT was nearly identical in the placebo (20.4%) and LGX 75 mg (20.6%) groups, while slightly higher in the LGX 200 mg+ABT group (27.8%).

Most TEAEs considered related to ABT were reported by 1-2 subjects in any treatment group with no discernible pattern. The common (i.e., in at least 2% of the SAF) ABT-related TEAEs included headache (5.8%), fatigue (2.9%), nausea (2.9%), and hot flush (2.7%). Nausea was observed with similar frequency in the placebo and LGX groups. Headache, fatigue and hot flush were reported more frequently in the LGX groups compared with placebo.

In the E3/E2/P1/P2 Pooled SAF for Period 1, TEAEs suspected to be related to ABT were reported in 22.6% of subjects in the LGX 200 mg+ABT group and 15.1% of subjects in the placebo group. The commonly (≥2% in any active arm) reported ABT-related TEAEs were headache (4.3% in the LGX 200 mg+ABT group vs 2.5% in the placebo group), hot flush (2.8% vs 1.8%, respectively), nausea (2.3% vs 1.3%), and vaginal haemorrhage (2.5% vs 0.8%).

Table 29 TEAEs suspected to be ABT-related up to Month 6 by ≥1% in any arm (E3/E2/P1/P2 Pooled SAF for Period 1)

Preferred Term	Number (%) of subjects		
	Placebo (N=398)	LGX 200mg + ABT (N=399)	Total (N=797)
Subjects with at least one TEAE related to ABT	60 (15.1)	90 (22.6)	150 (18.8)
Headache	10 (2.5)	17 (4.3)	27 (3.4)
Hot flush	7 (1.8)	11 (2.8)	18 (2.3)

Preferred Term	Number (%) of subjects		
	Placebo (N=398)	LGX 200mg + ABT (N=399)	Total (N=797)
Nausea	5 (1.3)	9 (2.3)	14 (1.8)
Vaginal haemorrhage	3 (0.8)	10 (2.5)	13 (1.6)
Fatigue	3 (0.8)	7 (1.8)	10 (1.3)
Abdominal distension	5 (1.3)	4 (1.0)	9 (1.1)
Breast pain	6 (1.5)	1 (0.3)	7 (0.9)
Dizziness	2 (0.5)	4 (1.0)	6 (0.8)
Acne	5 (1.3)	2 (0.5)	7 (0.9)
Metrorrhagia	1 (0.3)	4 (1.0)	5 (0.6)

ABT = add-back therapy; LGX = linzagolix.
TEAEs in Period 1 are AEs with a start date on or after the first dose of study drug in Period 1 through switch to Period 2 or 30 days after discontinuation of study drug or the end date of study drug whatever comes first, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the investigator in Period 1 through switch to Period 2 or 30 days after discontinuation of study drug or the end date of study drug whatever comes first.
For the Subjects columns, if a subject experienced more than one event in a given category, that subject is counted only once in that category.
MedDRA Dictionary (Version 23.0).

EDELWEISS 5 and EDELWEISS 6

In the EDELWEISS 5 study, 1 subject (10%) in the LGX 200 mg+ABT reported irregular menstruation which was considered by the Investigator to be related to both linzagolix and ABT.

In the EDELWEISS 6 study, 12.6% of the subjects in the ESAF reported TEAEs considered related to ABT from Month 6 to Month 12. The percentage of subjects reporting TEAEs related to ABT was slightly higher in the Placebo/LGX 75 mg group (17.2%, compared to Placebo/LGX 200mg+ABT: 14.0%; LGX 75 mg: 11.8%; LGX 200 mg+ABT: 10.7%).

Most TEAEs related to ABT were reported by 1-2 subjects in any treatment group with no clustering in any particular System Organ Class (SOC). The most common (i.e., in at least 1% of the ESAF) ABT-related TEAEs included vaginal haemorrhage (1.7%), hot flush (1.4%), and nausea (1.4%).

In the E6/E5/P1/P2 Pooled SAF for Period 2, TEAEs suspected to be related to ABT were reported in 10.1% of subjects in the Total LGX 200 mg+ABT group. The most commonly (≥2% in any active arm) reported ABT-related TEAEs were vaginal haemorrhage (1.7% in the Total LGX 200 mg+ABT group) and uterine haemorrhage (0.8%).

Table 30 TEAEs suspected to be ABT-related between Month 6 and Month 12 by ≥1% in any active arm (E6/E5/P1/P2 Pooled SAF for Period 2)

Preferred Term	Number (%) of subjects					
	Placebo / Placebo (N=31)	Placebo / LGX 200 mg + ABT (N=184)	LGX 200 mg / LGX 200 mg + ABT (N=161)	LGX 200 mg + ABT / LGX 200 mg + ABT (N=286)	Total LGX 200 mg + ABT (N=631)	Total (N=662)
Subjects with at least one TEAE Related to ABT	2 (6.5)	20 (10.9)	17 (10.6)	27 (9.4)	64 (10.1)	66 (10.0)
Vaginal haemorrhage	0	3 (1.6)	7 (4.3)	1 (0.3)	11 (1.7)	11 (1.7)
Uterine haemorrhage	0	4 (2.2)	1 (0.6)	0	5 (0.8)	5 (0.8)
Bone density decreased	0	1 (0.5)	3 (1.9)	1 (0.3)	5 (0.8)	5 (0.8)
Nausea	0	3 (1.6)	1 (0.6)	1 (0.3)	5 (0.8)	5 (0.8)
Blood CPK increased	0	1 (0.5)	0	3 (1.0)	4 (0.6)	4 (0.6)
ALT increased	0	1 (0.5)	0	3 (1.0)	4 (0.6)	4 (0.6)
Menorrhagia	0	2 (1.1)	1 (0.6)	1 (0.3)	4 (0.6)	4 (0.6)
Vulvovaginal dryness	0	2 (1.1)	0	2 (0.7)	4 (0.6)	4 (0.6)
Headache	0	2 (1.1)	2 (1.2)	0	4 (0.6)	4 (0.6)

Preferred Term	Number (%) of subjects					
	Placebo / Placebo (N=31)	Placebo / LGX 200 mg + ABT (N=184)	LGX 200 mg / LGX 200 mg + ABT (N=161)	LGX 200 mg + ABT / LGX 200 mg + ABT (N=286)	Total LGX 200 mg + ABT (N=631)	Total (N=662)
Anaemia	0	2 (1.1)	0	0	2 (0.3)	2 (0.3)

ABT = add-back therapy; ALT = alanine aminotransferase; CPK = creatine phosphokinase; LGX = linzagolix; TEAE = treatment-emergent adverse event
TEAEs in Period 2 are AEs with a start date on or after the first dose of study drug in Period 2 through 30 days after discontinuation of study drug or the end date of study drug, or any event that was present at the first visit in Period 2 worsened in intensity or was subsequently considered drug-related by the investigator in Period 2 through 30 days after discontinuation of study drug or the end date of study drug.
For the Subjects columns, if a subject experienced more than one event in a given category, that subject is counted only once in that category.
MedDRA Dictionary (Version 23.0).

Serious adverse event/deaths/other significant events

Overall, the incidence of SAEs was low (approximately 2%) in Phase 3 and Phase 2 studies.

During the first 6 months of treatment, the incidence of SAEs was similar between the LGX 75 mg (0.6%) and LGX 200 mg+ABT group (1.2%) in the Phase 3 EDELWEISS 3 trial. No serious TEAEs were reported in the EDELWEISS 2 trial.

EDELWEISS 2 and EDELWEISS 3

No serious TEAEs were reported in the EDELWEISS 2 study.

In the EDELWEISS 3 trial, 3 subjects (0.6%) reported serious TEAEs, all in the LGX groups.

Serious TEAEs were reported with a comparable incidence between the LGX 75 mg group (0.6%) and the LGX 200 mg+ABT group (1.2%). One subject in the LGX 75 mg group reported serious TEAEs of peritonitis and endometriosis. Pneumonia and abdominal pain were reported as serious TEAEs, by one subject each, in the LGX 200 mg+ABT group. None of the serious TEAEs were considered related to either LGX or AB.

Pooled dataset (EDELWEISS 3, EDELWEISS 2, PRIMROSE 1, PRIMROSE 2)

In the Pooled SAF for Period 1, the rate of serious TEAEs was similar between the LGX 200 mg+ABT group (1.5%) and placebo (1.3%) among subjects treated for up to 6 months.

Each serious TEAE was reported by 1 subject.

Table 31 Serious TEAEs reported up to Month 6 in the Phase 3 linzagolix trials (E3/E2/P1/P2 Pooled SAF for Period 1)

Preferred Term	Number (%) of subjects		
	Placebo (N=398)	LGX 200mg + ABT (N=399)	Total (N=797)
Subjects with at least one Serious TEAE	5 (1.3)	6 (1.5)	11 (1.4)
Intervertebral disc injury	1 (0.3)	0	1 (0.1)
Traumatic fracture	0	1 (0.3)	1 (0.1)
Anaemia	0	1 (0.3)	1 (0.1)
Acute myocardial infarction	1 (0.3)	0	1 (0.1)
Vertigo	1 (0.3)	0	1 (0.1)
Abdominal pain	0	1 (0.3)	1 (0.1)

Preferred Term	Number (%) of subjects		
	Placebo (N=398)	LGX 200mg + ABT (N=399)	Total (N=797)
Chest pain	0	1 (0.3)	1 (0.1)
Pneumonia	0	1 (0.3)	1 (0.1)
Intervertebral disc disorder	1 (0.3)	0	1 (0.1)
Nystagmus	1 (0.3)	0	1 (0.1)
Urinary incontinence	0	1 (0.3)	1 (0.1)
Ovarian vein thrombosis	1 (0.3)	0	1 (0.1)

ABT = add-back therapy; LGX = linzagolix; TEAE = treatment-emergent adverse event
TEAEs in Period 1 are AEs with a start date on or after the first dose of study drug in Period 1 through switch to Period 2 or 30 days after discontinuation of study drug or the end date of study drug whatever comes first, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the investigator in Period 1 through switch to Period 2 or 30 days after discontinuation of study drug or the end date of study drug whatever comes first.
For the Subjects columns, if a subject experienced more than one event in a given category, that subject is counted only once in that category.
MedDRA Dictionary (Version 23.0).

EDELWEISS 5 and EDELWEISS 6

In the EDELWEISS 5 study, there were no treatment-emergent SAEs during the study extension. One subject (703001) in the LGX 75 mg group reported an SAE of gallbladder polyp, which required hospitalization and occurred more than 30 days post-treatment.

In the EDELWEISS 6 trial, 4 subjects (1.1% of ESAF) reported serious TEAEs between Month 6 and Month 12 of the treatment period: 1.8% (1 subject) of the placebo/LGX 200 mg+ABT group and 2.5% (3 subjects) of the LGX 75 mg group.

- In the Placebo/LGX 200 mg+ABT group, 1 subject reported a serious TEAE of genital haemorrhage.
- In the LGX 75 mg group, serious TEAEs of vaginal haemorrhage, cholelithiasis, and anxiety were reported by 1 subject each.

Pooled dataset (EDELWEISS 6, EDELWEISS 5, PRIMROSE 1, PRIMROSE 2)

In the Pooled SAF for Period 2, 2.2% of subjects treated with LGX 200 mg+ABT reported serious TEAEs between Month 6 and Month 12 of the treatment period (Table 2.7.4-25). Aside for menorrhagia, reported in 3 subjects, all other serious TEAEs were reported by 1 subject each.

Table 32 Serious TEAEs reported between Month 6 and Month 12 in the Phase 3 linzagolix trials (E6/E5/P1/P2 Pooled SAF for Period 2)

Preferred Term	Number (%) of subjects					
	Placebo - Placebo (N=31)	Placebo / LGX 200mg + ABT (N=184)	LGX 200mg / LGX 200mg + ABT (N=161)	LGX 200mg + ABT / LGX 200mg + ABT (N=286)	Total LGX 200mg + ABT (N=631)	Total (N=662)
Subjects with at least one Serious TEAE	0	5 (2.7)	6 (3.7)	3 (1.0)	14 (2.2)	14 (2.1)
Menorrhagia	0	2 (1.1)	1 (0.6)	0	3 (0.5)	3 (0.5)
Genital haemorrhage	0	1 (0.5)	0	0	1 (0.2)	1 (0.2)

Preferred Term	Number (%) of subjects					
	Placebo - Placebo (N=31)	Placebo / LGX 200mg + ABT (N=184)	LGX 200mg / LGX 200mg + ABT (N=161)	LGX 200mg + ABT / LGX 200mg + ABT (N=286)	Total LGX 200mg + ABT (N=631)	Total (N=662)
Vaginal haemorrhage	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Femur fracture	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Joint dislocation	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Road traffic accident	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Deep vein thrombosis	0	1 (0.5)	0	0	1 (0.2)	1 (0.2)
Hypertensive crisis	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Anaemia	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Cholelithiasis	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Pneumonia viral	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Breast cancer	0	1 (0.5)	0	0	1 (0.2)	1 (0.2)
Emphysema	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)

ABT = add-back therapy; LGX = linzagolix; TEAE = treatment-emergent adverse event
TEAEs in Period 2 are AEs with a start date on or after the first dose of study drug in Period 2 through 30 days after discontinuation of study drug or the end date of study drug, or any event that was present at the first visit in Period 2 worsened in intensity or was subsequently considered drug-related by the investigator in Period 2 through 30 days after discontinuation of study drug or the end date of study drug.
For the Subjects columns, if a subject experienced more than one event in a given category, that subject is counted only once in that category.
MedDRA Dictionary (Version 23.0).

When investigating the causality in cases of vaginal and genital haemorrhage, those SAE were correlated to the add back therapy.

AESI

No AESIs were identified prior to commencement of the study.

Adverse events related to GnRH antagonists

Hypertension

The clinical database was searched for the PTs hypertension and blood pressure increased. During Period 1, PTs of hypertension or blood pressure increased were reported by 10 subjects (2.5%) treated with LGX 200 mg+ABT compared to 6 subjects (1.5%) who received placebo.

During Period 2, PTs of hypertension or blood pressure increased were reported by 15 subjects (2.4%) treated with LGX 200 mg+ABT and none in the placebo/placebo group. Of the 15 subjects, 5 subjects (1.7%) were in the LGX 200 mg+ABT/LGX 200 mg+ABT group and thus received the recommended regimen for up to 12 months.

Decreased libido

During Period 1, decreased libido was reported by 3 subjects (0.8%) treated with LGX 200 mg+ABT and by none of the subjects who received placebo.

During Period 2, decreased libido was reported by 2 subjects (0.3%) treated with LGX 200 mg+ABT and by none of the subjects who received placebo. Both subjects were in the LGX 200 mg+ABT/LGX 200 mg+ABT group (0.7%) and thus received the recommended regimen for up to 12 months.

Mood disorders

An increase in mood related disorders is consistent with the mechanism of action and warnings in GnRH agonists and antagonists, and mood disorders – as an umbrella term – were listed in Section 4.8 in the SmPC.

Overall, there were low incidences of mood disorder related PTs reported through the programme as a whole, and all cases were not severe, with no deaths/suicides. In order to enhance the understanding of the incidence of mood related disorders, the clinical database was searched for the following PTs: mood swings, anxiety, depressed mood, affect lability, depression, emotional disorder, irritability, nervousness, mood altered, and flat affect.

During Period 1, the PTs suggestive of mood disorders were reported with a similar frequency between the LGX 200 mg+ABT group and the placebo group: 18 subjects (4.5%) treated with LGX 200 mg+ABT compared to 12 subjects (3.0%) who received placebo.

During Period 2, the PTs suggestive of mood disorders were reported by 12 subjects (1.9%) treated with LGX 200 mg+ABT and by none of the subjects in the placebo/placebo group. Of the 12 subjects, 7 subjects (2.4%) were in the LGX 200 mg+ABT/LGX 200 mg+ABT group and thus received the recommended regimen for up to 12 months. Of note, PT of mood swings was the most frequently reported among the PTs included in the search (4/7 subjects in the LGX 200 mg+ABT/LGX 200 mg+ABT group reported mood swings).

Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire

In the EDELWEISS Phase 3 trials, treatment-emergent suicidal ideation and behaviour was prospectively assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire, which was administered at Screening, Day 1, and monthly during the treatment and follow-up periods.

Fewer subjects reported any suicidal ideation or behaviour post-baseline than at baseline.

Vaginal haemorrhage

During Period 1, the PTs listed above were reported more frequently in the LGX 200 mg+ABT group (23 subjects; 5.8%) compared to the placebo group (11 subjects; 2.8%). In the LGX 200 mg+ABT group, the most commonly reported PTs were vaginal haemorrhage (13 subjects; 3.3%) and metrorrhagia (6 subjects; 1.5%).

During Period 2, the PTs listed above were reported by 35 subjects (5.5%) treated with LGX 200 mg+ABT and by none of the subjects in the placebo/placebo group. Of the 35 subjects, 6 subjects (2.1%) were in the LGX 200 mg+ABT/LGX 200 mg+ABT group and thus received the recommended regimen for up to 12 months. The most commonly reported PT was vaginal haemorrhage (5/6 subjects in the LGX 200 mg+ABT group).

Change in menstrual bleeding pattern

The clinical database was searched for the following PTs: amenorrhoea, oligomenorrhoea, irregular menstruation, menstruation delayed, menstruation irregular, and menstrual disorder.

During Period 1, the PTs listed above were reported by 7 subjects (1.8%) treated with LGX 200 mg+ABT compared to 1 subject (0.3%) who received placebo. The most commonly reported PT in the LGX 200 mg+ABT group was menstruation irregular (5/7 subjects).

During Period 2, the only reported PT of those listed above was menstruation irregular. This PT was reported by 1 subject (0.2%) treated with LGX 200 mg+ABT and 1 subject (3.2%) in the placebo/placebo group. Of note, the 1 subject (0.3%) was in the LGX 200 mg+ABT/LGX 200 mg+ABT group and thus received the recommended regimen for up to 12 months.

Elevated liver enzymes

Overall multiple dose studies, in some subjects, an increase in transaminase values was observed under treatment, however this increase was generally reversible under treatment and was never

associated with any increase in bilirubin. No subjects met the criteria for Hy's law (i.e., no subject had ALT or AST ≥3×ULN [upper limit of normal] with concomitant total bilirubin ≥2×ULN or international normalized ratio [INR]>1.5) at any time point during linzagolix treatment.

During Period 1, the PTs listed above were reported with a similar frequency between the LGX 200 mg+ABT group and the placebo group: 14 subjects (3.5%) treated with LGX 200 mg+ABT compared to 11 subjects (2.8%) who received placebo. The most commonly reported PTs in the LGX 200 mg+ABT group was ALT increased (7/14 subjects) and AST increased (6/14 subjects).

During Period 2, elevated liver enzymes were reported by 14 subjects (2.2%) treated with LGX 200 mg+ABT and by none of the subjects in the placebo/placebo group. Of the 14 subjects, 8 subjects (2.8%) were in the LGX 200 mg+ABT/LGX 200 mg+ABT group and thus received the recommended regimen for up to 12 months. The most commonly reported PTs in the LGX 200 mg+ABT/LGX 200 mg+ABT group was ALT increased (7/8 subjects) and AST increased (6/8 subjects).

BMD decrease

Reduction in BMD is an observed side effect of all GnRH agonists and antagonists due to its mechanism of action. The clinical database was searched for the following PTs: bone density decreased, bone loss, osteopenia, osteoporosis, and BMD decrease.

During Period 1, the PTs listed above signalling BMD decrease were reported with a similar frequency between the LGX 200 mg+ABT group and the placebo group: 5 subjects (1.3%) treated with LGX 200 mg+ABT compared to 4 subjects (1.0%) who received placebo.

During Period 2, the PTs signalling BMD decrease were reported by 24 subjects (3.8%) treated with LGX 200 mg+ABT and 1 subject (3.2%) in the placebo/placebo group. Of the 24 subjects, 7 subjects (2.4%) were in the LGX 200 mg+ABT/LGX 200 mg+ABT group and thus received the recommended regimen for up to 12 months.

For most AEs related to GnRH antagonists, rates are higher in the treated population compared to placebo, as expected. The AEs were captured in section 4.8 of the SmPC.

The applicant provided justification for not including some TEAEs as ADRs.

TEAEs leading to discontinuation

EDELWEISS 2 and EDELWEISS 3

In the EDELWEISS 2 trial, 5 subjects (6.0%) had at least 1 TEAE leading to permanent IMP discontinuation. The rate of treatment discontinuation due to TEAEs was similar between placebo (7%) and LGX groups (4-7%). There was no pattern to the TEAEs leading to treatment discontinuations: subjects in the LGX 200 mg+ABT group discontinued due to vaginal haemorrhage, subject in the LGX 75 mg group discontinued due to a headache, and subjects in the placebo group discontinued due to chest discomfort and COVID-19.

In the EDELWEISS 3 trial, 18 subjects (3.7%) had at least 1 TEAE leading to permanent IMP discontinuation. The rate of treatment discontinuation due to TEAEs was similar between the placebo (2.5%) and LGX 200 mg+ABT (3.1%) groups, while slightly higher in the LGX 75 mg group (5.6%). There was no pattern to the TEAEs leading to treatment discontinuations. Aside from nausea (3 subjects), headache (3 subjects), and mood swings (2 subjects), all other TEAEs leading to treatment discontinuation were reported in one subject each. Nausea led to treatment discontinuation in both the

placebo (1 subject) and LGX groups (200 mg+ABT: 2 subjects), while headache and mood swings led to discontinuation only in LGX groups.

In the E3/E2/P1/P2 Pooled SAF for Period 1 (N=797), 5.8% of subjects reported TEAEs that led to permanent discontinuation of the study drugs, with an identical frequency in both treatment groups (5.8%). The following TEAEs led to discontinuation of study drugs in at least 2 subjects (0.5%) in any group: nausea (0.8% in the LGX 200 mg+ABT group vs 0.3% in the placebo group), headache (0.5% vs 0.8%, respectively), hot flush (0.5% in each group), hypertension (0.5% vs 0%), migraine (0% vs 0.5%), menstruation irregular (0.5% vs 0%), vaginal haemorrhage (0.5% vs 0%), GGT increased (0% vs 0.8%), and bone density decreased (0% vs 0.5%). All other TEAEs led to permanent discontinuation of the study drug in no more than 1 subject per group.

EDELWEISS 5 and EDELWEISS 6

There were no TEAEs leading to treatment discontinuation during the EDELWEISS 5 study.

In the EDELWEISS 6 trial, 9 subjects (2.5%) had at least 1 TEAE leading to permanent IMP discontinuation from Month 6 to Month 12. The rate of treatment discontinuation due to TEAEs was comparable across treatment groups (Placebo/LGX 75 mg: 3.4%; Placebo/LGX 200 mg+ABT: 3.5%; LGX 75 mg: 2.5%; LGX 200 mg+ABT: 1.6%).

Bone density decreased was reported in 4 subjects in total (1 in the Placebo/LGX 75 mg group and 3 in the LGX 75 mg group). All other TEAEs leading to treatment discontinuation were reported in one subject each.

Pooled dataset (EDELWEISS 6, EDELWEISS 5, PRIMROSE 1, PRIMROSE 2)

In the E6/E5/P1/P2 Pooled SAF for Period 2 (N=662), 4.4% of subjects reported TEAEs that led to the permanent discontinuation of study drugs. In the Total LGX 200 mg+ABT group (n=631), TEAEs that led to permanent discontinuation of study drugs in at least 2 subjects (0.3%) were: bone density decreased (0.8%), menorrhagia (0.3%), pelvic pain (0.3%), vaginal haemorrhage (0.3%), uterine leiomyoma (0.3%), and headache (0.3%).

Laboratory findings

Haematology

EDELWEISS 2 and EDELWEISS 3

In the EDELWEISS 2 trial, no clinically significant abnormalities in haematology or coagulation parameters were observed during treatment administration in any of the study groups. Few subjects had clinically significant abnormal haematology or coagulation values prior to treatment administration.

In the EDELWEISS 3 trial, 8 subjects had clinically significant abnormal haematology values only at the screening or baseline visits, both of which took place prior to treatment administration.

Clinically significant abnormalities in haematology parameters were observed with equal frequency among treatment groups during treatment administration:

- 10 subjects (10/162; 6.2%) in the placebo group, 2 of whom had also abnormal readings at baseline

- 8 subjects (8/160; 5.0%) in the LGX 75 mg group, half of whom had also abnormal readings at baseline.
- 3 subjects (3/162; 1.9%) in the LGX 200 mg+ABT group, 2 of whom had also abnormal readings at baseline.

Clinically significant abnormalities in coagulation parameters were observed during treatment administration with a similar frequency in the placebo group (1 subject), LGX 75 mg group (1 subject), and LGX 200 mg+ABT group (2 subjects). All of these abnormalities were due to prolonged aPTT. In addition, 1 subject in the LGX 200 mg+ABT group had a prolonged aPTT and prothrombin time at the Baseline/Day 1 visit only.

EDELWEISS 5 and EDELWEISS 6

In the EDELWEISS 5 trial, 1 subject in the LGX 75 mg group had a low on-treatment platelet level (78×109/L) at Month 10. This subject had normal platelet levels at baseline. After the trough platelet levels at Month 10, platelet values rebounded to >200×109/L for the rest of the extension treatment period at Month 12, and remained within a normal reference range during the extension follow-up.

In the EDELWEISS 6 trial (extension of EDELWEISS 3), on-treatment clinically significant abnormalities in haematology parameters were observed in 5 subjects in the placebo/LGX 75 mg group, 3 subjects in the placebo/LGX 200 mg+ABT group, 7 subjects in the LGX 75 mg group, and 1 subject in the LGX 200 mg+ABT group.

Clinically significant abnormal values in haematology parameters were noted during post treatment follow-up in 7 subjects (2 in each of the placebo/LGX groups, and 3 in the LGX 75 mg group). The most frequently reported on-treatment abnormality was related to decreases in haemoglobin.

Biochemistry:

EDELWEISS 2 and EDELWEISS 3

Liver Function Tests

Small decreases in group values were observed for both ALT and AST in the LGX 200 mg+ABT group, while small increases were noted in the LGX 75 mg group.

In both Phase 3 EDELWEISS trials, increases in ALT and/or AST ≥3×ULN were infrequent: 2 linzagolix-treated subjects in the EDELWEISS 3 trial, and 1 linzagolix-treated and 1 placebo treated subject in the EDELWEISS 2 trial.

Creatine Kinase

There were no on-treatment clinically significant elevations in CK in the EDELWEISS 2 trial

In the EDELWEISS 3 trial, 8 subjects (1.7%) had on-treatment elevations in CK ≥10×ULN between Day 1 and Month 6.

In 6 of the 8 subjects with CK elevation >10×ULN, the underlying reason for the transient increases in CK was strenuous physical exercise. In the remaining 2 subjects, the reasons for the transient CK increases were unknown despite queries to the sites (likely because the CK levels normalized upon retest).

Lipids

Changes in lipid parameters are a known side-effect of GnRH antagonists. All on-treatment changes were small and included both favorable (increase in the HDL/LDL ratio) and unfavorable (increase in LDL and triglycerides) changes.

At Month 6, there was an approximately 5-7% increase in HDL/LDL cholesterol ratio, 3-5% increase in LDL cholesterol, 2-5% increase in total cholesterol, and 19-24% increase in triglycerides in the LGX 200 mg+ABT group in the Phase 3 trials. This lipid profile compares favourably to that observed in Phase 3 trials in subjects with uterine fibroids in terms of LDL and total cholesterol but not triglycerides; the corresponding increases in the PRIMROSE trials were 11% for LDL cholesterol, 6% for total cholesterol, and 12% for triglycerides for the LGX 200+ABT arm at Month 6 (Week 24).

Shifts from normal at baseline in LDL values were infrequent, with the highest increase up to grade 2 in both Phase 3 EDELWEISS trials. Worsening by 2 categories (all from grade 0 to grade 2) was observed in 1 subject in each treatment group. Worsening by 1 category was observed with a similar frequency in the LGX groups (75 mg: 3 subjects; 200 mg+ABT: 2 subjects) compared to placebo (5 subjects), with most of the shifts in the LGX groups from grade 0 to grade 1.

There was no worsening in triglyceride levels from baseline to Month 6 by 4, 3, or 2 categories. Worsening by 1 category was observed with a higher frequency in the LGX groups (75 mg: 19 subjects; 200 mg+ABT: 14 subjects) compared to placebo (8 subjects), most accounted for by shifts from grade 0 to grade 1 in all treatment groups. There were no shifts to grade 3 or 4 in any of the treatment groups in both Phase 3 EDELWEISS trials.

EDELWEISS 5 and EDELWEISS 6

Between Month 6 and Month 12 there were no clinically relevant changes over time in group values for any clinical chemistry parameters in the EDELWEISS 6 and EDELWEISS 5 extension studies.

There were no unexpected clinically significant shifts from baseline in any clinical chemistry parameters following treatment with LGX 75 mg or LGX 200 mg+ABT during the extension study.

Liver enzymes

Small fluctuations in group values were observed for both ALT and AST in all treatment groups between Month 6 and Month 12.

Increases in ALT and/or AST ≥3×ULN were infrequent and reported in 2 linzagolix-treated subjects in the EDELWEISS 6 trial and in none of the subjects in the EDELWEISS 5 trial.

1 additional subject (508039) in the LGX 75 mg group, had ALT 3.2×ULN (and GGT of 2.5×ULN, with no associated bilirubin increase) during the drug-free post-treatment follow-up, without having any previous ALT increases ≥3×ULN while on treatment. There were no other subjects with ALT or AST increases ≥3×ULN during the ExFU.

The potential for elevated liver enzymes is captured in section 4.8 of the SmPC.

Creatine kinase

There were no clinically significant elevations in CK in the EDELWEISS 5 trial.

In the EDELWEISS 6 trial, 2 subjects had on-treatment elevations in CK ≥10×ULN, 1 subject in each of the LGX 200 mg+ABT and LGX 75 mg groups. In both subjects, intense physical exercise was reported as a possible reason for the CK increase and CK levels normalised.

Lipids

All on-treatment changes were small and included both favourable (increase in the HDL/LDL ratio) and unfavourable (increase in LDL and triglycerides) changes.

At Month 12, there was an approximately 8% (vs 5% at M6) increase in HDL/LDL cholesterol ratio, 5% (vs 3% at M6) increase in LDL cholesterol, 4% (vs 2% at M6) increase in total cholesterol, and 24% (vs 17% at M6) increase in triglycerides in the LGX 200 mg+ABT group in the EDELWEISS 6 trial.

Shifts from normal at baseline in LDL values were infrequent, with the highest increase up to grade 3 in the EDELWEISS 6 trial. Worsening by 2 categories (most from grade 0 to grade 2) was observed in 1 subject in the placebo/LGX 75 mg group, 4 subjects in the LGX 75 mg group and 2 subjects in the LGX 200 mg+ABT group. Worsening by 1 category was observed with a similar frequency in the LGX groups that received treatment with linzagolix for up to 12 months (75 mg: 12 subjects; 200 mg+ABT: 14 subjects), with most of the shifts in the LGX groups from grade 0 to grade 1.

At Month 12, LDL levels ≥190 mg/dL (4.91 mmol/L) were observed in 2 subjects (4.2%) in the placebo/LGX 75 mg group, 1 subject (2.1%) in the placebo/LGX 200 mg+ABT group, 3 subjects (3.4%) in the LGX 75 mg group, and 3 subjects (3.0%) in the LGX 200 mg+ABT group.

There was no worsening in triglyceride levels from baseline to Month 6 by 4, 3, or 2 categories. Worsening by 1 category was observed in all treatment groups (placebo/LGX 75 mg: 5.2%; placebo/LGX 200 mg+ABT: 10.5%; LGX 75 mg: 5.0%; LGX 200 mg+ABT: 9.8%), with most of the shifts from grade 0 to grade 1. There were no shifts to grade 3 or 4 in any of the treatment groups in both Phase 3 EDELWEISS trials. The Applicant has discussed and provided justifications for changes in triglycerides and the risk of lipid parameter changes with linzagolix use is captured in section 4.4 of the SmPC.

Physical examination:

Vital signs

In both EDELWEISS 2, EDELWEISS 3, EDELWEISS 5 and EDELWEISS 6 trials, blood pressure and heart rate were monitored at each monthly visit during the treatment period. At the population level, small fluctuations in the systolic and diastolic blood pressure, as well as heart rate were observed throughout the treatment period, both in the placebo and LGX groups. There was no consistent directionality in these small fluctuations with the mean and median remaining close to those observed at baseline.

Weight

In the EDELWEISS 3 trial, baseline weight was generally maintained at Month 6 of the treatment period, with the mean (SD) change from baseline of +0.419 (2.686) kg in the placebo group, +0.050 (3.243) kg in the LGX 75 mg group, and +0.320 (2.787) kg in the LGX 200 mg+ABT group. Similar small increase in weight was observed in the LGX 200 mg+ABT group in the EDELWEISS 2 trial (+0.341 [3.179] kg) with larger changes observed in both the placebo (+1.939 [4.450] kg) and the LGX 75 mg (+1.682 [4.107] kg) groups in the prematurely terminated trial.

In the EDELWEISS 6 trial, the baseline weight was generally maintained at Month 12 of the treatment period, with the mean (SD) change from baseline of +0.201 (3.726) kg in the placebo/LGX 75 mg group, +0.850 (3.349) kg in the placebo/LGX 200 mg+ABT group, +0.290 (4.151) kg in the LGX 75

mg group, and +0.462 (4.741) kg in the LGX 200 mg+ABT group. There were few subjects in the EDELWEISS 5 trial to meaningfully evaluate any possible changes in weight.

ECG

In the EDELWEISS 2 trial, baseline mean (SD) QTcF values were comparable between treatment groups: placebo 418.7 (17.1), LGX 75 mg 415.3 (21.1), and LGX 200 mg+ABT 414.5 (15.9). There were no increases in the mean QTcF values in any treatment groups throughout the treatment period; small decreases in the mean QTcF values occurred in the placebo and both LGX groups. During the treatment period, the highest maximum QTcF values of 453 ms, 470 ms, and 454 ms were recorded in the placebo, LGX 75 mg, and LGX 200 mg+ABT groups, respectively. At Month 6, there were no maximum QTcF values above 450ms in any of the treatment groups. Abnormal CS ECG findings were recorded in 1 subject in the placebo group at Month 3; there were no abnormal CS ECG findings in any of the LGX groups throughout the 6-month treatment period.

In the EDELWEISS 3 trial, baseline QTcF values were similar between treatment groups with mean (SD) as follows: placebo: 414.9 (15.2) ms, LGX 75 mg: 414.7 (17.0) ms, and LGX 200 mg+ABT: 412.7 (16.1) ms (EDELWEISS 3 CSR, Table 14.4.9.1.1). There were no increases in the mean QTcF values in any treatment groups throughout the treatment period; small decreases in the mean QTcF values occurred in the placebo and both LGX groups. The highest maximum QTcF values of 485 ms, 484 ms, and 491 ms were recorded in the placebo, LGX 75 mg, and LGX 200 mg+ABT groups, respectively, during the treatment period. At Month 6, maximum QTcF values exceeded 450 ms in all treatment groups but were all below 480 ms (placebo: 473 ms; LGX 75 mg: 456 ms; LGX 200 mg+ABT: 477 ms). Abnormal CS ECG findings were recorded in 1 subject in the LGX 75 mg group at Months 1, 5, and 6 of the treatment period.

In EDELWEISS 5 and EDELWEISS 6, ECG readings were evaluated on a monthly basis during the treatment. As observed in the parent studies, there were no increases in the mean QTcF values in any treatment groups throughout the treatment period while small decreases in the mean QTcF values occurred in all treatment groups in the extension studies.

Gynaecological examination

A gynaecological exam was performed at Screening, and every 3 months during the treatment period.

At baseline, 3 subjects (all in the LGX 200 mg+ABT group [1.9%]) had abnormal clinically significant (CS) findings.

Most subjects (>80% in each group) had normal gynaecological examination findings at baseline.

Most subjects (placebo: 83%; LGX 75 mg: 86-89%; LGX 200 mg+ABT: 88-92%) had normal findings at both Month 3 and Month 6.

There were no abnormal CS findings at Month 3 in any treatment group. At Month 6, 3 subjects (2 in the placebo group [1.4%] and 1 in the LGX 75 mg group [0.7%]) had abnormal CS gynaecological examination findings. The CS findings were unspecified abnormalities for all 3 subjects.

At Month 6 and Month 9, 1 subject in the LGX 75 mg group had abnormal CS gynaecological examination findings, which were unspecified abnormalities.

Endometrial biopsy

Endometrial biopsies were performed at Screening, unless the subject had a normal endometrial biopsy performed within the previous 6 months, and for which slides were available for assessment through retrospective central laboratory reading. During treatment, endometrial biopsy was performed at Month 6 if endometrium thickness on TVUS was >5 mm.

At Month 6, endometrial biopsies were performed on 99/484 (20.5%) subjects, 95 of whom had assessable results. All assessable endometrial biopsies (95/95) were normal.

All endometrial biopsies were classified as being benign endometrium without hyperplasia or atypia at both Screening and Month 6.

At Month 6, endometrial biopsies were performed on 81/356 of the subjects, most of whom (78/81) had assessable results. No subjects had abnormal findings on the endometrial biopsy at Month 6. At Month 12, endometrial biopsies were performed on 69/356 subjects, 63 of whom had assessable results. All assessable endometrial biopsies (63/63) were normal.

All endometrial biopsies were classified as being benign endometrium without hyperplasia or atypia at both Month 6 and Month 12.

Transvaginal ultrasound

In both studies, there was a trend toward a decrease in uterine dimensions and endometrial thickness at Month 3 and maintained at Month 6. At Month 6, the median change from baseline in uterine volume was -6.80 cm3 and -19.80 cm3 in the LGX 75 mg group in the EDELWEISS 3 and EDELWEISS 2 trials, respectively, and -13.00 cm3 and -17.70 cm3 in the LGX 200 mg+ABT group, respectively, vs -1.15 cm3 and -7.40 cm3 in the placebo group, respectively.

Similarly, reductions in endometrial thickness observed in the LGX groups at Month 3 were maintained at Month 6. At Month 6, the median change from baseline in endometrial thickness was -2.10 mm and -1.10 mm in the LGX 75 mg group in the EDELWEISS 3 and EDELWEISS 2 trials, respectively, and -4.15 mm and -3.80 mm in the LGX 200 mg+ABT group, respectively, vs -2.55 mm and +0.70 mm in the placebo group, respectively.

A similar pattern was observed in EDELWEISS 5 and 6.

Breast Examination

There were no abnormal clinically significant breast examination findings in any of the subjects in the Phase 3 endometriosis studies between Day 1 and Month 6 or between Month 6 and Month 12.

BMD- Mean change from baseline

The aim of using hormonal ABT with the 200 mg linzagolix dose was to achieve E2 levels within a range that prevents clinically significant BMD loss.

Partial suppression of estradiol was observed with both linzagolix regimens, with the on-treatment median E2 levels <36 pg/mL in the LGX 200 mg+ABT group and <45 pg/mL in the LGX 75 mg group, compared to placebo (87-101 pg/mL).

Changes from baseline BMD were measured at three key anatomic sites (lumbar spine, total hip, and femoral neck) using DXA during treatment and at the end of post-treatment follow-up in the Phase 3 EDELWEISS studies.

BMD was assessed at both group and individual levels: by mean percent change from baseline and by categories of BMD change based on individual subject data (<3% [within the variability of DXA], 3 to 7-8% [probable change], >7-8% [significant change]). Z-score data were also assessed as they provide important information on BMD of the study population compared to a reference group of

women of the same age (Z-score = number of standard deviations below or above BMD of a reference group of same age and gender). Z-scores correspond to percentiles, which represent the percent of women in the population with a lower BMD; a person with average BMD has a Z-score of zero and is at the 50th percentile).

In the pivotal Phase 3 EDELWEISS 3 and EDELWEISS 2 trials, data included in the BMD analyses are according to the following visit windows:

- Baseline: DXA assessments up to Baseline visit + 10 days
- Month 6: DXA assessments in the interval of Day 169 ± 28 days.
- Month 6 PTFU: DXA assessments in the interval of Day 337 ± 28 days (i.e., 168 days post Month 6 theoretical visit date on Day 169 or after treatment discontinuation).

In the extension Phase EDELWEISS 6 and EDELWEISS 5 trials, data included in the BMD analyses are according to the following visit windows:

- Month 9: DXA assessments in the interval of Day 253 ± 28 days.
- Month 12: DXA assessments in the interval of Day 337 ± 28 days
- Month 6 ExFU: DXA assessments in the interval of Day 505 ± 28 days (i.e., 168 days after Month 12 theoretical visit date on Day 337 or after treatment discontinuation).

Subjects with DXA results of the lumbar spine (L1–L4), femoral neck, or total hip BMD showed a z-score ≤ –1.5 at Screening, were not eligible to participate in the Phase 3 EDELWEISS trials.

While on treatment, subjects who experienced more than 8% BMD loss or had a z-score ≤ - 2.5 at any site (femoral neck, hip or spine) were discontinued from study treatment and entered the follow-up period (i.e., they were not eligible to enter the extension study).

At the end of the 6-month follow-up period, subjects with a BMD decrease from baseline of >1.5% for lumbar spine and/or >2.5% for total hip had an additional DXA scan 6 months later.

Subjects who discontinued treatment prior to Month 3 of the Treatment Period did not to enter the follow-up period.

EDELWEISS 2 and EDELWEISS 3

As expected, reductions in BMD were most prominent at the lumbar spine. In the EDELWEISS 3 trial, the mean percent change from baseline at Month 6, calculated using ANCOVA (analysis of covariance) as least square mean (LSM), was -0.80% in the LGX 200 mg+ABT group and -0.88% in the LGX 75 mg group. For the recommended dosing regimen of LGX 200 mg+ABT, the LSM at Month 6 was -0.68% at the femoral neck and -0.39% at the total hip.

Given the younger patient population in the EDELWEISS studies (endometriosis) compared to the PRIMROSE studies (uterine fibroids), the effect of the LGX 200 mg+ABT was less pronounced at the lumbar spine in the EDELWEISS studies (-0.80%) compared to the results with the same dosing regimen in the PRIMROSE studies (mean percent change from baseline of -1.13% at lumbar spine) with comparable results in both patient populations at the femoral neck and total hip (pooled PRIMROSE trials: mean % change from baseline was -0.63% at the femoral neck, and - 0.13% at the total hip after 24 weeks of treatment).

EDELWEISS 5 and EDELWEISS 6

There were too few subjects continuing treatment in the prematurely terminated EDELWEISS 5 trial for any meaningful conclusions.

After Month 6, the rate of BMD change slowed in both linzagolix groups, suggesting the plateauing BMD loss. Minimal further changes were observed at Month 12 in the Extension SAF in the LGX 200 mg+ABT group: -1.10% (vs -0.83% at M6) at the lumbar spine, -0.70% (vs -0.49% at M6) at the femoral neck, and -0.52% (vs -0.30% at M6) at the total hip. A similar pattern was observed among subjects continuing treatment with the LGX 75 mg dose.

Post treatment follow up

Of the 51 subjects in FU SAF, 19 subjects had DXA scan data at Month 6 follow-up visit (placebo: 6; LGX 75 mg: 5; LGX 200 mg+ABT: 8). With small number of subjects per group, which increases variability of the results, the data presented for this population should be interpreted with caution.

The mean percent change from baseline 6 months post-EOT at the lumbar spine was -0.83% (vs +0.60% at Month 6) in the placebo group, -0.15% (vs -0.04% at Month 6) in the LGX 75 mg group, and -0.22% (vs –0.29% at Month 6) in the LGX 200 mg+ABT group. The respective changes at the femoral neck were: -1.10% (vs -0.92% at Month 6), -1.96% (vs -0.50% at Month 6), and -0.25% (vs –0.81% at Month 6). The respective changes at the total hip were: -0.72% (vs +0.19% at Month 6), -0.93% (vs +0.10% at Month 6), and -0.68% (vs –0.66% at Month 6).

EDELWEISS 2 PTFU

Of the 3 subjects in the FU SAF, only 2 subjects had a DXA scan at the end of follow-up. Thus, no meaningful interpretation of the post-treatment BMD changes can be made.

EDELWEISS 6 Extension follow-up

Of the 329 subjects in the ExFU SAF, 129 subjects had a DXA scan at Month 6 ExFU visit. BMD changes are shown below in the ExFU SAF at Month 6 ExFU vs Month 12 in the ESAF. Signs of BMD recovery was observed in all groups at the lumbar spine but not at femoral neck, while negligible changes were observed at the total hip between EOT and Month 6 ExFU.

In subjects who received LGX 75 mg or LGX 200 mg+ABT for up to 12 months, any losses in BMD incurred while on treatment showed signs of recovery at the lumbar spine in both dose groups 6 months after the end of treatment. In the Follow-up SAF, at Month 6 ExFU, the mean percent change from baseline at the lumbar spine was -0.61% (vs -1.06% at M12) in the LGX 200 mg+ABT group, and +0.11% (vs -1.09% at M12) in the LGX 75 mg group.

Virtually no changes between Month 12 and Month 6 ExFU were observed at the total hip, though approximately only half of the subjects had data available at Month 6 ExFU. At Month 6 ExFU, the mean percent change from baseline at the total hip was -0.57% (vs -0.55% at M12) in the LGX 200 mg+ABT group and -0.42% (vs -0.36% at M12) in the LGX 75 mg group.

A worsening was observed at the femoral neck, with the mean percent change from baseline at Month 6 ExFU of -1.43% (vs -0.73% a t M 12) in the LGX 200 mg+ABT group and -1.50% (vs -0.55% at M12) in the LGX 75 mg group.

Similar trends were observed in the placebo/LGX groups (i.e., after subjects received up to 6 months of linzagolix treatment). At the lumbar spine, the mean percent change from baseline to Month 6 ExFU

was −0.27% (vs -0.72% at Month 12) in the placebo/LGX 75 mg group and +0.94% (vs -0.60% at Month 12) in the placebo/LGX 200 mg+ABT group. The mean BMD change at the femoral neck was -1.64% (vs -0.87% at Month 12) in the placebo/LGX 75 mg group and −0.73% (vs -0.97% at Month 12) in the placebo/LGX 200 mg+ABT group. At the total hip, the mean percent change from baseline to Month 6 ExFU was +0.18% (vs -0.50% at Month 12) in the placebo/LGX 75 mg group and +0.90% (vs +0.54% at Month 12) in the placebo/LGX 200 mg+ABT group.

EDELWEISS 5 Extension follow-up

Of the 12 subjects who entered follow-up, only 2 subjects had a DXA scan at the end of extension follow-up. Thus, no meaningful interpretation of the post treatment BMD changes can be made.

BMD- Categorical analysis of percent change

EDELWEISS 2 and EDELWEISS 3

Most subjects (approx. 83-86%) in each linzagolix group experienced either an increase, no change, or decrease ≤3%, which is within variability of DXA and suggests no meaningful changes in BMD.

In the EDELWEISS 3 and EDELWEISS 2 studies (N=568), significant (i.e., >7%) BMD decreases from baseline were infrequent and observed in the LGX 75 mg group at the lumbar spine (2 subjects out of 188, 1.1%) and at the femoral neck (2 subjects, 1.1%) (Table 2.7.4-42). Of note, 3 subjects (1.6%) in the placebo group had BMD decrease >7% at the femoral neck.

At the recommended dosing regimen of LGX 200 mg+ABT, the proportion of subjects considered to have experienced a significant BMD loss (i.e., decrease of >7%) was 2.6% (5 subjects out of 191) at the femoral neck, 0.5% (1 subject out of 191) at the total hip, and 0% at the lumbar spine.

EDELWEISS 5 and EDELWEISS 6

There were no subjects with decreases >7% at any of the bone sites in the EDELWEISS 5 trial.

In the EDELWEISS 6 Extension Safety Analysis Set, the majority of subjects had an increase, no change, or decrease ≤3%, which signifies no clinically relevant changes in the BMD and is within the variability of DXA.

Significant BMD decreases (i.e., >7%) were observed in 4 subjects (4.6%) at the lumbar spine, 2 subjects (2.4%) at the femoral neck, and 1 subject (1.2%) at the total hip in the LGX 200 mg+ABT group. In the LGX 75 mg group, significant BMD decreases were observed in 1 subject (1.3%) at the lumbar spine and 2 subjects (2.6%) at the femoral neck.

Post treatment follow up (PTFU)

EDELWEISS 3 PTFU

Of the 20 subjects with available data at Month 6 PTFU, there were no subjects with BMD decrease >5% at any bone sites in the EDELWEISS 3 trial.

EDELWEISS 2 PTFU

Of the 2 subjects with available data at Month 6 PTFU, there were no subjects with BMD decrease >5% trial at any bone sites in the EDELWEISS 2 trial.

EDELWEISS 6 ExFU

In the EDELWEISS 6 ExFU SAF, approximately 40% of subjects in the LGX 75 mg and LGX 200 mg+ABT groups had available DXA readings at Month 6 ExFU.

Of the 48 subjects with available data in the LGX 75 mg group, significant (i.e., decrease >7%) BMD change from baseline was observed in 4 subjects (8.3%) at the lumbar spine, 3 subjects (6.4%) at the femoral neck, and 1 subject (2.1%) at the total hip.

Of the 42 subjects with available data in the LGX 200 mg+ABT group, significant (i.e., decrease >7%) BMD change from baseline was observed in 3 subjects (7.1%) at the lumbar spine, 2 subjects

(4.8%) at the femoral neck, and 1 subject (2.4%) at the total hip.

EDELWEISS 5 ExFU

There were no subjects with BMD decrease >7% in the EDELWEISS 5 trial at Month 6 ExFU

BMD- Z-score

EDELWEISS 2 and EDELWEISS 3

Baseline Z-scores for BMD were generally comparable between the placebo and LGX 75 mg group in the EDELWEISS 3 trial, with slightly lower median values in the LGX 200 mg+ABT group. More variability across treatment groups in the baseline Z-scores was observed in the prematurely terminated EDELWEISS 2 trial, likely to the small sample sizes available. Aside from the EDELWEISS 2 LGX 200 +ABT group at the femoral neck (median -0.09), median baseline Z-scores were ≥0 in all other treatment groups in both trials. The median Z-scores ranged from 0.11 to 0.82 for the lumbar spine, from -0.09 to 0.46 for the femoral neck, and from 0.12 to 0.81 for the total hip in the EDELWEISS 3 and EDELWEISS 2 trials. The lowest Z-score in both trials was -1.5. This confirms the good bone health of the treated population in both EDELWEISS 3 and EDELWEISS 2 studies.

In the EDELWEISS 3 trial, median changes from baseline in Z-scores were comparable between the LGX 75 mg and LGX 200 mg+ABT groups, while more variability was observed in the EDELWEISS 2 trial. At Month 6, median absolute changes from baseline in Z-scores for the lumbar spine were -0.07 and -0.05 for 75 mg (EDELWEISS 3 and EDELWEISS 2, respectively), -0.07 and +0.03 for 200 mg+ABT, versus +0.09 and -0.075 for placebo. Smaller changes were observed at the femoral neck; median changes from baseline were -0.05 and -0.15 for 75 mg, -0.04 and 0 for 200 mg+ABT, versus +0.01 and -0.145 for placebo. The smallest effect was at the total hip; median changes from baseline were 0 and -0.06 for 75 mg, -0.02 and +0.035 for 200 mg+ABT, versus +0.02 and -0.025 for placebo.

Consistent with the small median BMD changes observed, median BMD Z-scores at Month 6 remained ≥0, with the exception of a median of -0.02 in the 200 mg+ABT group for the femoral neck. Medians at Month 6 ranged from -0.14 to 0.40 for the lumbar spine, from -0.02 to 0.34 for the femoral neck, and from 0.09 to 0.52 for the total hip.

There were no on-treatment Z-scores below -2.0. The lowest on-treatment Z-score was -1.9.

EDELWEISS 5 and EDELWEISS 6

There were too few subjects (i.e., 1-5 subjects per group) with DXA measurement at Month 12 in the prematurely terminated EDELWEISS 5 study to allow for any meaningful interpretation.

Of particular interest are the two groups in the EDELWEISS 6 trial that continued treatment with linzagolix from EDELWEISS 3 and thus were exposed to linzagolix for up to 12 months: LGX 75 mg and

LGX 200 mg+ABT. For subjects who switched from placebo, changes in Z-scores were in line with those described above for subjects initiating treatment. Median baseline Z-scores were ≥0 in all treatment groups in the EDELWEISS 6 Extension Analysis Set.

Median changes from baseline in Z-scores at Month 12 were comparable between the LGX 75 mg and LGX 200 mg+ABT groups. Changes in Z-scores observed during the second treatment period (Month 6 to Month 12) were smaller compared to those observed during the first treatment period (Day 1 to Month 12), suggesting slowing BMD changes. Median absolute changes from baseline to Month 12 in Z-scores for the lumbar spine were -0.115 (vs -0.70 at M6) for 75 mg, -0.095 (vs -.070 at M6) for 200 mg+ABT. Smaller changes were observed at the femoral neck; median changes from baseline were -0.06 (vs -0.02 at M6) for 75 mg, -0.02 (vs -0.04 at M6) for 200 mg+ABT. The smallest effect was at the total hip; median change from baseline was -0.01 for both dose groups (vs 0 and -0.005 at M6 for 75 mg and 200 mg+ABT, respectively).

Consistent with the small median BMD changes observed, median BMD Z-scores at Month 12 remained ≥0, with the exception of a median of -0.03 in the 200 mg+ABT group for the femoral neck. Medians at Month 12 for the 75 mg and 200 mg+ABT groups, respectively, were from 0.470 and 0.090 for the lumbar spine, 0.320 and -0.030 for the femoral neck, and 0.430 and 0.030 for the total hip.

There were no on-treatment Z-scores below -2.0 in any of the treatment groups. In the LGX 75 mg and LGX 200 mg, the lowest Z-score at Month 12 was -1.7. Among subjects switching from placebo, the lowest Z-score at Month 12 was -2.0 (placebo/LGX 200 mg+ABT group, at lumbar spine).

Post treatment follow-up

There were only 2 subjects with DXA measurement at Month 12 in the prematurely terminated EDELWEISS 5 study to allow for any meaningful interpretation.

Median baseline Z-scores were ≥0 in all treatment groups in the EDELWEISS 6 Follow-up SAF.

LGX 75 mg and LGX 200 mg+ABT groups

Subjects in the LGX 75 mg and LGX 200 mg+ABT were exposed to linzagolix for up to 12 months. At Month 6 ExFU, some recovery was observed in the LGX 75 mg group at the lumbar spine, and at both LGX 75 mg and LGX 200 mg+ABT groups at the total hip. There were no signs of recovery at the femoral neck in both dose groups. Median absolute changes from baseline to Month 6 ExFU in Z-scores for the lumbar spine were -0.065 (vs -0.105 at M12) for 75 mg, -0.095 (vs -0.090 at M12) for 200 mg+ABT. Median changes from baseline to Month 6 ExFU in Z-scores for the femoral neck were -0.080 (vs -0.060 at M12) for 75 mg, -0.040 (vs -0.020 at M12) for 200 mg+ABT. Median changes from baseline to Month 6 ExFU in Z-scores for the total hip were +0.020 (vs -0.010 at M12) for 75 mg, -0.005 (vs -0.010 at M12) for 200 mg+ABT.

Median absolute BMD Z-scores at Month 6 ExFU remained ≥0. Medians at Month 6 ExFU for the 75 mg and 200 mg+ABT groups, respectively, were from 0.390 and 0.040 for the lumbar spine, 0.090 and 0 for the femoral neck, and 0.320 and 0.215 for the total hip.

There were no on-treatment Z-scores below -2.0 in any of the treatment groups. In the LGX 75 mg and LGX 200 mg, the lowest Z-score at Month 6 ExFU was -1.4.

Placebo/LGX 75 mg and Placebo/LGX 200 mg+ABT

Subjects who switched from placebo to one of the linzagolix dosing regimens in the EDELWEISS 6 study were exposed to linzagolix for up to 6 months.

At Month 6 ExFU, some recovery was observed in the placebo/LGX 200 mg+ABT group at all bone sites, and in the placebo/LGX 75 mg group at the total hip (Table 2.7.4-46). Median absolute changes from baseline to Month 6 ExFU in Z-scores for the lumbar spine were -0.160 (vs -0.060 at M12) for placebo/LGX 75 mg, +0.030 (vs -0.020 at M12) for placebo/LGX 200 mg+ABT.

Median changes from baseline to Month 6 ExFU in Z-scores for the femoral neck were -0.085 (vs -0.040 at M12) for placebo/LGX 75 mg, -0.060 (vs -0.070 at M12) for placebo/LGX 200 mg+ABT. Median changes from baseline to Month 6 ExFU in Z-scores for the total hip were +0.055 (vs -0.050 at M12) for placebo/LGX 75 mg, +0.080 (vs +0.060 at M12) for placebo/LGX 200 mg+ABT.

Median absolute BMD Z-scores at Month 6 ExFU remained ≥0. Medians at Month 6 ExFU for the placebo/LGX 75 mg and placebo/LGX 200 mg+ABT groups, respectively, were from 0.795 and 0.180 for the lumbar spine, 0.140 and 0.444 for the femoral neck, and 0.510 and 0.760 for the total hip.

There were no Z-scores below -2.0 in any of the treatment groups at Month 6 ExFU. In the placebo/LGX 75 mg and placebo/LGX 200 mg, the lowest Z-score at Month 6 ExFU was -1.1.

Incidence of fractures

A total of 3 subjects (all dosed with 200 mg+ABT) reported fractures. Two fractures occurred while on treatment. One subject with a tibia fracture had a BMD loss of -2.6% at the femoral neck (but +0.4% at the total hip) on a DXA performed 3 months prior to the fracture (note; no other DXA readings were available for this subject). No bone loss was detected in the subject with the radius fracture. Both subjects completed treatment up to Month 12 in the EDELWEISS 6 study and were both followed up until Month 6 ExFU.

One subject experienced a foot fracture more than 30 days after the end of treatment (i.e., recorded as a post-treatment AE). On the DXA scan performed approximately 2.5 months prior to the fracture, which was the nearest reading available, the subject had a BMD change of -0.5% at the lumbar spine with no BMD loss at the femoral neck or total hip (note: no other DXA readings are available for this subject). The subject completed treatment up to Month 6 in the EDELWEISS 3 study and was followed up until Month 6 follow-up visit.

Bone Mineral Density changes at 2 years- PRIMROSE 1 and PRIMROSE 2

Subjects with uterine fibroids who completed at least 20 weeks of treatment in the Phase 3 PRIMROSE 1 or PRIMROSE 2 trials were eligible to participate in a 2-year follow-up study to evaluate long-term changes in BMD following linzagolix treatment. Of the 137 screened subjects, a total of 134 (97.8%) subjects were enrolled and 130 (94.9%) subjects were included in the safety analysis set. Of these, 109 (79.6%) subjects had a Month 24 visit.

The majority of subjects were white (64.6%) and a third of the population was black or African American (33.1%). At baseline, the mean (SD) age was 42.8 (5.7) years, and a mean (SD) BMI was 30.85 (7.60) kg/m2. Thus, this population was both older and had a higher mean BMI compared to the EDELWEISS 3 study population (mean age of 34.9 (6.6) years and mean BMI of 24.27 (4.95) kg/m2).

The mean (SD) overall treatment duration in the PRIMROSE 1 or PRIMROSE 2 studies was 50.95 (3.89) weeks (Min/Max: 23.9/53.1 weeks) and similar between the treatment groups.

At Week 52 (Month 12), the mean percent BMD decrease from baseline in the LGX 200 mg+ABT group (n=154) was greater in the pooled PRIMROSE 1+PRIMROSE 2 trials than the one observed in the EDELWEISS 6 LGX 200 mg+ABT group (n=122) at the lumbar spine but not at the femoral neck or

total hip: -1.608% (vs -1.10%) at the lumbar spine, -0.317% (vs -0.70%) at the femoral neck, and +0.103% (vs -0.52%) (PRIMROSE data from the initial MAA/UF/SCS/Section 2.7.4.6.3.2.1).

Among subjects in the LGX 200 mg+ABT group enrolled in the PRIMROSE 3 study (n=21), the mean percent changes from baseline at the end of treatment in the PRIMROSE 1 or PRIMROSE 2 trials were -1.539% at the lumbar spine, -0.577% at the femoral neck, and +0.430% at the total hip (PRIMROSE 3 CSR, Table 14.1.2). At the Month 24 follow-up in the PRIMROSE 3 study (i.e., up to 3 years from baseline), the mean percent changes from baseline were -1.985% at the lumbar spine, -2.378% at the femoral neck, and +0.729% at the total hip, suggesting further BMD loss after the end of treatment in the 18 subjects who had a Month 24 DXA scan (PRIMROSE 3 CSR, Table 14.4.1.1.2).

However, seemingly contradictory results were obtained in 21 subjects with available data at Month 24 who, in the PRIMROSE 1 or PRIMROSE 2 studies, received 200 mg up to Week 24 then 200 mg+ABT up to Week 52, and who showed complete recovery at all three bone sites. The mean percent change from baseline to Month 24 was +0.093% at the lumbar spine, +0.517% at the femoral neck, and +0.584% at the total hip in this group (PRIMROSE 3 CSR, Table 14.4.1.1.2). Notably, subjects (n=161) in this LGX 200 mg/200 mg+ABT group showed the most prominent BMD changes at all anatomical bone sites at the end of treatment at Week 52 (-2.676% at the lumbar spine, -1.799% at the femoral neck, and -1.556% at the total hip) which were closely reflected in the 30 subjects from this group who entered the PRIMROSE 3 trial (-2.742%6% at the lumbar spine, -1.857% at the femoral neck, and -1.603% at the total hip).

Two years after treatment cessation, the recovery status was defined as follows:

- A subject was considered completely recovered if study visit assessment was greater than or equal to the pre-treatment baseline BMD assessment.
- A subject was considered partially recovered if she was not completely recovered and study visit assessment was greater than or equal to the post-treatment baseline within analysis window.
- A subject continued to lose BMD if she was not completely recovered, and study visit assessment was less than the post treatment baseline within analysis window.

Two years after the end of treatment, 50% of the subjects in the LGX 200 mg+ABT group and 76% in the LGX 200 mg/200 mg+ABT group had either partial or complete recovery at the lumbar spine, which is known to be the most sensitive region to BMD changes in the context of E2 suppression. The respective percentages of subjects with partial or complete recovery were 39% and 80% at the femoral neck, and 67% and 70% at the total hip.

The mean (SD) percent changes in lumbar spine BMD from pre-treatment baseline to the Month 24 visit remained above -2% in all linzagolix treatment groups with the highest decrease of -1.985% (4.234) (95% CI: -4.090, 0.121) in the LGX 200 mg +ABT group. Consistent with the small mean percent changes in BMD, mean absolute changes in Z-scores from pre-treatment baseline to the Month 24 visit were also low and ranged in the lumbar spine from -0.06 (LGX 200 mg+ABT) to +0.19 (LGX 200/200 mg+ABT). In the placebo group, the mean percent BMD change as well as the mean absolute change in Z-score (mean [SD] percent change: -0.699 [2.701], Z-score: 0.00) were similar as compared to the changes observed in the linzagolix treatment groups. The results suggest that the observed BMD changes in the linzagolix treatment groups results from an age-related BMD decrease since a similar decrease was observed in an untreated population of comparable age. Additionally, Z-scores of most subjects were within the expected range for their age, i.e., minimum Z-scores were above -2 in most treatment groups.

BMD loss is a known side effect of GnRH antagonists due to reduction of serum estradiol.

Given the younger patient population in the EDELWEISS studies (endometriosis) compared to the PRIMROSE studies (uterine fibroids), the effect of the LGX 200 mg+ABT mean change from baseline was less pronounced at the lumbar spine in the EDELWEISS studies. The effect of the LGX 200 mg+ABT was less pronounced at the lumbar spine in the EDELWEISS 3 study (-0.80%) compared to the results with the same dosing regimen in the pooled PRIMROSE studies (mean percent change from baseline of -1.1% at lumbar spine). In both patient populations, comparable results were observed at the femoral neck (-0.63% in PRIMROSE trials vs -0.68% in EDELWEISS 3) and total hip (-0.13% in the PRIMROSE trials vs -0.39% in EDELWEISS 3) after 6 months of treatment.

In the presented clinical data, mean percent BMD changes from baseline provide group level data which have less variability than individual BMD values. These showed that overall, BMD loss related to linzagolix treatment is limited at 6 months and that the rate of loss slows after 6 months. Individual categorical analysis shows that very few subjects experienced >7% BMD loss. This data is included in section 4.8 of the SmPC as it is indicative of a potential trend in BMD loss in a patient.

After Month 6, the rate of BMD change slowed in both linzagolix groups, suggesting the plateauing BMD loss. Minimal further changes were observed at Month 12 in the Extension SAF in the LGX 200 mg+ABT group.

Only 19 subjects had DXA scan data 6 months after treatment stop in the EDELWEISS 3 study. BMD results for the intended dose after 6 months follow up were numerically similar to baseline values.

After stopping treatment in the EDELWEISS 6 study, 129 subjects had a DXA scan at Month 6 ExFU visit. BMD measurements in the ExFU SAF at 6 months were compared to Month 12 in the SAF. Signs of BMD recovery were observed at the lumbar spine in both LGC 75mg and LGX 200mg+ABT 6 month after the end of treatment. While negligible changes were observed at the total hip, a worsening was observed at the femoral neck with the mean percent change from baseline at Month 6 ExFU of -1.43% (vs -0.73% at M 12) in the LGX 200 mg+ABT group and -1.50% (vs -0.55% at M12) in the LGX 75 mg group.

It was acknowledged by the CHMP that the mean changes from baseline 6 months after stopping treatment were based on less subjects compared to earlier timepoints.

Safety in special populations

Bone Mineral Density by age, weight, and BMI in Phase 3 endometriosis trials

Baseline mean BMD measurements were similar at the lumbar spine, femoral neck, and total hip for the subjects < 35 years of age and those ≥ 35 years of age (Table 2.7.4-49). At the lumbar spine – the site most sensitive to BMD changes – subjects ≥ 35 years of age had slightly more pronounced losses compared to those < 35 years of age. The LSM (lower 95% CI) at Month 6 for the LGX 75 mg group was -1.11% (-1.61%) for subjects ≥ 35 years of age and -0.57% (-1.14%) for subjects < 35 years of age, and for the LGX 200 mg+ABT group -1.11% (-1.67%) and -0.49% (-1.01%), respectively. The LSM difference with placebo was significant for both LGX groups (p-value ≤0.001). In general, there were similar changes in BMD at the femoral neck (decrease of no more than0.4%, except for the LGX 200 mg+ABT group in the younger age group) and total hip (decrease of no more than 0.5%) at Month 6 in both age subgroups. The LSM difference with placebo was not significant at the femoral neck or total hip for both age groups, with the exception of the LGX75 mg group in subjects < 35 years of age (p-value=0.03).

At Month 6 of treatment, decreases >8% were infrequent in both the younger (< median age of 35years) and older (≥ median age of 35 years) subgroups (Table 2.7.4-50). In the older subgroup, 1 subject in the 75 mg group had a decrease >8% at the lumbar spine. There were no other subjects with a decrease >8%. In the younger subgroups, decreases >8% were observed only in the LGX 200 mg+ABT group and only at the femoral neck (4.5%) and total hip (1.5%).In the older subgroup, decreases >3% were similar between the placebo and LGX groups at the femoral neck (≤12.3%) and total hip (≤4.6%). However, at the lumbar spine, a larger proportion of subjects in the LGX groups – and similar between LGX groups (75 mg: 18.4%; 200 mg+ABT:21.5%) – had a BMD decrease >3% compared to placebo (3.0%).In the younger subgroup, decreases >3% were generally similar between placebo and LGX 200mg+ABT group at the lumbar spine (≤6%) and total hip (≤7.1%), but not at the femoral neck(placebo: 7.1%; LGX 200 mg+ABT: 14.9%). Among the younger subjects, 16.1% of those receiving LGX 75 mg had decreases >3% at the lumbar spine compared to 5.4% of those in the placebo group.

Table 33 BMD changes by age group and by category at Month 6 (EDELWEISS 3 SAF)

	Number (%) of subjects					
	< median age of 35 years			≥ median age of 35 years		
	Placebo (N=76)	LGX 75 mg (N=71)	LGX 200 mg + ABT (N=80)	Placebo (N=86)	LGX 75 mg (N=89)	LGX 200 mg + ABT (N=82)
Lumbar spine						
n (missing)	56 (20)	56 (15)	67 (13)	67 (19)	76 (13)	65 (17)
Decrease >3% (1)	3 (5.4)	9 (16.1)	4 (6.0)	2 (3.0)	14 (18.4)	14 (21.5)
Decrease >8%	0	0	0	0	1 (1.3)	0
Femoral neck						
n (missing)	56 (20)	54 (17)	67 (13)	65 (21)	76 (13)	65 (17)
Decrease >3% (1)	4 (7.1)	4 (7.4)	10 (14.9)	8 (12.3)	9 (11.8)	8 (12.3)
Decrease >8%	0	0	3 (4.5)	1 (1.5)	0	0
Total hip						
n (missing)	56 (20)	54 (17)	67 (13)	65 (21)	76 (13)	65 (17)
Decrease >3% (1)	4 (7.1)	6 (11.1)	4 (6.0)	3 (4.6)	2 (2.6)	3 (4.6)
Decrease >8%	0	0	1 (1.5)	0	0	0

ABT = add-back therapy; LGX = linzagolix
A record was counted as missing if it was present in the laboratory file but with no associated result. In case of repeated assessment due to BMD loss ≥ 5%, the initial scan value was used. Adjusted values were used for Anterior Posterior Lumbar Spine.
(1) Includes categories for decrease >3% and ≤5%, >5% and ≤7%, >7% and ≤8%, and >8%.

Population-level changes in Z-scores

Baseline values were calculated for subjects with available BMD results at both time-points (baseline and Month 6). There was no clear pattern in baseline mean or median z-scores between corresponding treatment groups among subjects <35 and ≥35 years of age. At Month 6, the minimum z-scores tended to be lower among subjects ≥35 years of age compared with the younger group at the lumbar spine: LGX 75 mg (-1.9 vs -1.5), LGX 200 mg+ABT (-1.5vs -1.4), placebo (-1.5 vs -1.2). Mean and median change from baseline values to Month 6 tended to be slightly greater in the older subgroup (and similar between the LGX dose groups) compared to the younger subjects at the lumbar spine. Generally, changes from baseline in the mean and median to Month 6 at the femoral neck and total hip appeared slightly smaller in magnitude, compared with those at the lumbar spine, in both age subgroups and across treatment groups. No clear pattern emerged.

By baseline weight

Population-level mean changes from baseline

Baseline mean BMD measurements were similar at the lumbar spine, femoral neck, and total hip for

the subjects with median weight of < 63 kg and those ≥ 63 kg (Table 2.7.4-52).In the LGX 75 mg group, subjects below 63 kg tended to have more bone loss compared to those weighing ≥ 63 kg at all bone sites at Month 6. This pattern was not observed in the LGX 200mg+ABT group at the lumbar spine or femoral neck. Notably, the LSM difference with placebo was significant for both LGX groups in both weight subgroups at the lumbar spine (p-value <0.001). The LSM difference with placebo was not significant for either LGX group in both weight subgroups. However, there was a significant difference for both LGX groups vs placebo among subjects weighing <63 kg (but not among those≥63 kg) at the total hip.

Percentage of subjects with decreases from baseline by category

Among subjects weighing <63 kg, BMD decreases >8% were observed in the LGX 75 mg group at the lumbar spine (1.7%), and in the LGX 200 mg+ABT group at the femoral neck (2.5%) and total hip (1.3%), compared with only 1 subject (2.0%) in the LGX 200 mg+ABT group among subjects weighing ≥63 kg.

At the lumbar spine, BMD decrease >3% was observed with a similar frequency in the placebo and LGX 200 mg+ABT group (8.5% vs 8.8%, respectively). A comparable proportion of subjects had decrease >3% in the LGX 75 mg group in both weight groups (20% of subjects weighing <63 kg compared with 15.3% of subjects weighing ≥63 kg) and LGX 200 mg+ABT group with weight ≥63 kg (21.6%).

At the femoral neck, a similar proportion of subjects in the corresponding LGX dose group had BMD decrease >3% in both weight subgroups (LGX 75 mg: 8.6% and 11.1%; LGX 200 mg+ABT: 13.8% and 13.7%).

At the total hip, the proportion of subjects with BMD decrease >3% was lower among the heavier subjects in each corresponding LGX group.

Table 34 BMD changes by weight group and by category at Month 6 (EDELWEISS 3 SAF)

	Number (%) of subjects					
	< median weight of 63 kg			≥ median weight of 63 kg		
	Placebo (N=76)	LGX 75 mg (N=71)	LGX 200 mg + ABT (N=92)	Placebo (N=86)	LGX 75 mg (N=89)	LGX 200 mg + ABT (N=69)
Lumbar spine						
n (missing)	59 (17)	60 (11)	80 (12)	64 (22)	72 (17)	51 (18)
Decrease >3% (1)	5 (8.5)	12 (20.0)	7 (8.8)	0	11 (15.3)	11 (21.6)
Decrease >8%	0	1 (1.7)	0	0	0	0
Femoral neck						
n (missing)	58 (18)	58 (13)	80 (12)	63 (23)	72 (17)	51 (18)
Decrease >3% (1)	3 (5.2)	5 (8.6)	11 (13.8)	9 (14.3)	8 (11.1)	7 (13.7)
Decrease >8%	0	0	2 (2.5)	1 (1.6)	0	1 (2.0)
Total hip						
n (missing)	58 (18)	58 (13)	80 (12)	63 (23)	72 (17)	51 (18)
Decrease >3% (1)	2 (3.4)	5 (8.6)	5 (6.3)	5 (7.9)	3 (4.2)	2 (3.9)
Decrease >8%	0	0	1 (1.3)	0	0	0

ABT = add-back therapy; LGX = linzagolix
A record was counted as missing if it was present in the laboratory file but with no associated result. In case of repeated assessment due to BMD loss ≥ 5%, the initial scan value was used. Adjusted values were used for Anterior Posterior Lumbar Spine.
(1) Includes categories for decrease >3% and ≤5%, >5% and ≤7%, >7% and ≤8%, and >8%.

Population-level changes in Z-scores

Baseline mean and median z-scores were higher among subjects weighing ≥63 kg compared with those weighing <63 kg at all bone sites and for each treatment group.

The mean and median change from baseline to Month 6 in z-scores tended to be slightly greater among subjects weighing <63 kg compared to those weighing ≥63 kg in each corresponding LGX treatment group at all bone sites.

By baseline BMI

Population-level mean changes from baseline

Baseline mean BMD measurements were similar at the lumbar spine, femoral neck, and total hip for the subjects with median BMI of < 23 and those ≥ 23 kg/m2. At Month 6, subjects with higher BMI tended to have less bone loss in the LGX 75 mg group (percent change from baseline: -0.64% vs -1.16%, for the higher and lower BMI, respectively), while similar magnitude of bone loss (-0.84% vs -0.77%, respectively) was observed in the LGX 200 mg+ABT group for both BMI subgroups at the lumbar spine. Changes from baseline in lumbar spine BMD were significantly higher in the LGX groups compared to placebo regardless of BMI.

Similar trend was observed at the total hip and femoral neck at Month 6, i.e., less bone loss in the higher BMI subgroup for the LGX 75 mg group and similar in magnitude change from baseline in BMD for the LGX 200 mg+ABT group regardless of BMI.

Percentage of subjects with decreases from baseline by category

Decreases >8% were observed in in the LGX 75 mg group at the lumbar spine (1.7%) and in the LGX 200 mg+ABT group at the femoral neck and total hip (1.4% each), all among the subjects with lower BMI (<median of 23 kg/m2). There were no decreases >8% among

the subjects with higher BMI (≥23 kg/m2).

Decreases >3% were more frequent among subjects with lower BMI compared to those with higher BMI in the LGX 75 mg group at all bone sites, with the highest number of subjects with BMD decreases >3% observed at the lumbar spine (22.0% vs 13.7%, respectively), followed by femoral neck (12.3% vs 8.2%, respectively), and total hip (10.5% vs 2.7%, respectively).

Conversely, decreases >3% were more frequent among subjects with higher BMI compared to those with lower BMI in the LGX 200 mg+ABT group at the lumbar spine (20.0% vs 8.5%, respectively), but with similar frequency between the BMI subgroups at the femoral neck (15.0% vs 12.7%, respectively), and total hip (5.0% vs 5.6%, respectively).

Table 35 BMD changes by BMI group and by category at Month 6 (EDELWEISS 3 SAF)

	Number (%) of subjects					
	< median BMI of 23			≥ median BMI of 23		
	Placebo (N=78)	LGX 75 mg (N=73)	LGX 200 mg + ABT (N=82)	Placebo (N=84)	LGX 75 mg (N=87)	LGX 200 mg + ABT (N=79)
Lumbar spine						
n (missing)	59 (19)	59 (14)	71 (11)	64 (20)	73 (14)	60 (19)

	Number (%) of subjects					
	< median BMI of 23			≥ median BMI of 23		
Decrease >3% (1)	5 (8.5)	13 (22.0)	6 (8.5)	0	10 (13.7)	12 (20.0)
Decrease >8%	0	1 (1.7)	0	0	0	0
Femoral neck						
n (missing)	58 (20)	57 (16)	71 (11)	63 (21)	73 (14)	60 (19)
Decrease >3% (1)	6 (10.3)	7 (12.3)	9 (12.7)	6 (9.5)	6 (8.2)	9 (15.0)
Decrease >8%	1 (1.7)	0	1 (1.4)	0	0	2 (3.3)
Total hip						
n (missing)	58 (20)	57 (16)	71 (11)	63 (21)	73 (14)	60 (19)
Decrease >3% (1)	5 (8.6)	6 (10.5)	4 (5.6)	2 (3.2)	2 (2.7)	3 (5.0)
Decrease >8%	0	0	1 (1.4)	0	0	0

ABT = add-back therapy; LGX = linzagolix
A record was counted as missing if it was present in the laboratory file but with no associated result. In case of repeated assessment due to BMD loss ≥ 5%, the initial scan value was used. Adjusted values were used for Anterior Posterior Lumbar Spine.
(1) Includes categories for decrease >3% and ≤5%, >5% and ≤7%, >7% and ≤8%, and >8%.

Population-level changes in Z-scores

Baseline mean and median z-scores were higher among subjects with a median BMI ≥23 kg/m2 compared with those with a BMI <23 kg/m2 at all bone sites and for each treatment group.

The mean and median change from baseline to Month 6 in z-scores tended to be slightly greater among subjects with BMI <23 kg/m2 compared to those with ≥23 kg/m2 in the LGX 75 mg group at all bone sites. Similar mean and median change from baseline to Month 6 in z-scores were observed in the LGX 200 mg+ABT group at all bone sites regardless of the baseline BMI category.

Subjects with adenomyosis

Study 16-OBE2109-015 was an exploratory single centre, open label, pilot study investigating the efficacy and safety of OBE2109 200 mg daily for 12 weeks followed by 100 mg daily for 12 weeks in uterine adenomyosis.

8 subjects with adenomyosis received linzagolix 200 mg (2x100 mg tablets) daily dose (without ABT) for 12 weeks of the initiation phase and 100 mg daily dose for another 12 weeks of the maintenance phase. Subjects were between 37 and 45 years of age, with a median of 43 years. Three subjects (37.7%) were black and 5 (62.5%) were white. The mean BMI (SD) was 27.14 (6.85) kg/m2. Subjects were highly compliant with treatment, with the mean (SD) number of 100-mg tablets was 169.5 (7.8) tablets in the initiation phase and 79.6 (4.9) tablets in the maintenance phase.

The primary endpoint of the study was the change from baseline in uterus volume at Week 24. At Week 24, the mean (SD) uterine volume was 203.9 (125.7) cm^3 compared with 333.0 (249.8) cm^3 at baseline, corresponding to a mean relative change of -32.4 % (33.3). The adjusted mean (standard error (SE)) for change from baseline at 24 weeks was -135.44 (33.00) cm^3 and was statistically significant (95% CI [-216.19; -54.69], p=0.0063).

All subjects reported TEAEs; none were severe or serious or led to treatment discontinuation. The most common TEAEs were hot flush (6/8), fatigue (3/8), anxiety (2/8), and loss of libido (2/8), with all other TEAEs reported by 1 subject each.

Median serum E2, was reduced from 50.5 pg/mL at baseline to 12.0 pg/mL at Week 4 then maintained up to the end of the initiation phase with the 200mg dose. During the maintenance phase, the switch to the 100mg dose led to an increase of median serum E2 to 37.5 pg/mL at

Week 24, and up to 99.5 pg/mL by the end of the follow-up period. This was in line with the time and dose dependent efficacy observed in the study.

At Week 24, the mean percent change from baseline was -2.391% at lumbar spine (L1-L4), -1.301% at the femoral neck, and -4.106% at the total hip, underscoring the need for coadministration with ABT, if used for more than 6 months.

Notably, aside from the unexpected high loss at the total hip (which may be confounded by the low number of subjects and associated variability), the results from this small study are in line with the results of the previously reported Phase 2b EDELWEISS 1 study, in which the mean percent change from baseline with the 200 mg dose at Week 24 was -2.602% at the lumbar spine, -1.992% at the femoral neck, and -1.690% at the total hip.

Lowest Z-scores at baseline were -1.6 at the lumbar spine and total hip, and -1.1 at the femoral neck, with the median baseline scores of -0.50 at the lumbar spine, -0.05 at the femoral neck, and -0.10 at the total hip. The median change from baseline in Z-scores was -0.15 at the lumbar spine, -0.05 at the femoral neck, and -0.25 at the total hip.

The mean endometrial thickness measured by TVUS decreased sharply from 10.6 (3.8) mm at baseline to 4.1 (1.8) mm at the end of the initiation phase (Week 12) while dosed with linzagolix 200 mg, with a less pronounced change from baseline at the end of the maintenance phase (Week 24) of 4.5 (4.4) mm while the subjects were on the 100 mg dose.

No emergent clinically significant abnormalities were reported in laboratory values, vital signs, ECGs, physical exams, or gynaecological exams.

Subjects with rectovaginal endometriosis nodes

In study 16-OBE2109-016, 3 subjects with rectovaginal node (type II or III) of at least 2 cm received linzagolix 200 mg (2x100 mg tablets) daily dose (without ABT) for 12 weeks of the initiation phase and 100 mg daily dose for another 12 weeks of the maintenance phase. Subjects were 38 to 39 years of age. One subject was black and 2 were white. The BMI was between 24.0 and 27.7 kg/m2.

Subjects were highly compliant with treatment: 160-166 of the 100-mg tablets in the initiation phase and 81-83 tablets in the maintenance phase. The primary endpoint of the study was the change from baseline in the volume of rectovaginal endometriosis nodes at Week 24. Two of the subjects had a decrease in rectovaginal node volume by 15.7% and 50%, while 1 subject had an increase by 15.8%.

All 3 subjects reported TEAEs, with the most common being headaches and migraines. One subject reported haemorrhagic ascites, severe in intensity but not considered as treatment related.

Treatment-related AEs included hot flush (2 subjects), with one of these subjects also reporting trouble sleeping due to hot flush, all mild in intensity. There were no TEAEs that were serious or led to treatment discontinuation.

In these 3 subjects, the changes in BMD were highest at the lumbar spine (between -2.888% to -5.603%), followed by total hip (between -2.218% and -3.340%), and femoral neck (between +0.098% to -2.709%).

Aside from 1 subject with CS abnormalities linked to anaemia, there were no other abnormalities in laboratory values. No emergent clinically significant abnormalities were reported in vital signs, ECGs, physical exams, endometrial biopsies, or gynaecological exams.

Safety related to drug-drug interactions and other interactions

Except for being a weak inhibitor of cytochrome P450 (CYP)2C8, no clinically relevant effects of linzagolix on the PK of other drugs was identified, including effects on metabolizing enzymes, drug transporter proteins, or calcium or iron preparations. Linzagolix is not expected to be a victim of clinically relevant interactions with drugs interfering with metabolizing enzymes, drug transporter proteins or drugs with plasma protein binding or calcium or iron preparations.

Clinical DDI study 22-OBE2109-001, conducted as part of a post-approval commitment, confirmed that linzagolix OATP1B1 inhibition is of no clinical relevance.

Section 4.5 of the SmPC already contains information regarding interaction with CYP2C8 substrate medicinal products.

2.5.1. Discussion on clinical safety

The safety profile seen in the populations in the EDELWEISS 3 and EDELWEISS 6 studies is similar to that of the PRIMROSE studies in uterine fibroids.

The safety profile of linzagolix in EAP is based on 4 clinical trials, 2 of 6 months treatment duration (EDELWEISS 3 and EDELWEISS 2) and 2 extension studies for up to 12 months of treatment (EDELWEISS 6 and EDELWEISS 5, respectively). Studies EDELWEISS 2 and its extension, EDELWEISS 5, were prematurely terminated due to recruitment problems following a change in the diagnostic approach to endometriosis.

To date, 2882 subjects have been exposed to different daily doses of linzagolix in completed clinical trials (12.5 mg, 25 mg, 50 mg, 75 mg, 100 mg, 200 mg, 400 mg and 700 mg). Of these, 744 patients have been treated with the dose proposed for the EAP indication: linzagolix 200 mg + ABT, either as an initial dosing regimen or upon switching after 6 months from either the placebo group or the 200 mg alone group.

In total 568 patients with endometriosis are included in the safety analysis set (SAF) for Period 1 (from Day 1 to Month 6). Of those, 386 patients with endometriosis are included in the extension safety analysis set (ESAF) for Period 2 (from Month 6 to Month 12). The total exposure to linzagolix 200mg+ABT in patients with endometriosis in all 4 EDELWEISS studies is 252 participants. The median treatment duration in EDELWEISS 3 and EDELWEISS 6 studies was 24 weeks for each treatment group.

The pooled safety sets concentrate on patients with endometriosis and uterine fibroids who were treated with linzagolix 200mg+ABT or placebo in either Period 1 (SAFP1) or Period 2 (SAFP2). SAFP1 contains 797 patients with a median treatment duration of 24 weeks while SAFP2 contains 662 patients with the median treatment duration of 26 weeks.

The EDELWEISS studies conducted in support of the endometriosis associated pain indication enrolled a younger population with lower mean weight than the uterine fibroid population. The lower mean weight and BMI is likely because EDELWEISS 3 and 6 were conducted in a European population whereas a significant proportion of patients enrolled to the uterine fibroid pivotal studies were North American. The subjects in the EDELWEISS studies were predominantly white which would be expected with this disease phenotype. From the uterine fibroid studies and this application, there is no evidence to suggest that race impacts on the safety of this product.

Overall, the EDELWEISS 3 population was relatively homogenous with participants having moderate to severe pain and increased analgesia requirements on bleeding days.

Regarding adverse events, the percentage of participants reporting at least one TEAE in EDELWEISS 3 study (E3) was higher in those receiving linzagolix 200mg+ABT compared to placebo but comparable to the pooled Phase 3 (E3/E2/P1/P2) set (56.8% vs 46.9% vs 55.9%, respectively). There were no new TEAEs identified in this population. A comparable rate of TEAE in LGX 200mg+ABT was previously reported in patients with uterine fibroids (55.3%). The pattern of TEAES was like that previously seen in that the rates of TEAEs, particularly those related to the known hypoestrogenic effects of GnRH antagonists, was highest during the first 12 weeks of treatment and attenuated over time. In EDELWEISS 6 ExFU, the only TEAEs reported by 2 subjects per group were bone density decreased (in the LGX 75 mg and LGX 200 mg+ABT groups), hot flush (LGX 200 mg+ABT group) and vaginal haemorrhage (LGX 200 mg+ABT group).

No TEAEs leading to death were reported in any of the studies.

Serious TEAEs were also infrequent and comparable across the treatment arms of interest (0 in placebo E3 vs 1.2% in LGX 200mg+ABT in E3 vs 1.5% in LGX 200mg+ABT in Phase 3 pooled set).

The percentage of TEAEs leading to permanent discontinuation of IMP was similar for placebo and LGX 200mg+ABT in the E3 study (2.5% vs 3.1%, respectively), and overall, less frequent compared to the pooled Phase 3 set (5.8% in placebo vs 5.8% in LGX 200mg+ABT).

Among participants continuing treatment with LGX 200mg + ABT after the initial 6 months in EDELWEISS 6 compared to the pooled phase 3 studies, the percentage of any TEAE, severe TEAE, serious TEAE, TEAE leading to permanent discontinuation and fatal TEAE were all comparable (40.2% vs 37.8%, 0.8% vs 2.1%, 0 vs 1%, 1.6% vs 1.4% and 0 vs 0).

The common TEAEs seen across EDELWEISS 2, 3, 5 and 6 were consistent with those in the uterine fibroid development programme with headache, hot flush, fatigue, anaemia, mood swings and arthralgia most seen. Hypoestrogenic effect of GnRH antagonists, such as hot flush, was reported more frequently in the LGX groups, as expected.

In the EDELWEISS 3 trial up to 6 months of treatment, the following PTs were recorded more frequently in LGX 200mg+ABT compared to placebo arm: abdominal distension (3.7% vs 1.9%), constipation (3.1% vs 1.2%), urinary tract infection (4.3% vs 0), vaginal infection (2.5% vs 0.6%), headache (10.5% vs 8%), vaginal haemorrhage (3.7% vs 0.6%), pelvic pain (2.5% vs 0.6%), vulvovaginal dryness (1.9% vs 0), mood swings (3.1% vs 1.9%), fatigue (6.8% vs 2.5%), hot flush (6.8% vs 2.5%).

Of the above listed TEAEs that occurred more frequently in the active arm, the majority are recognised as ADRs and listed in the SmPC. However, abdominal distension, urinary tract infection and vaginal infection are not included as ADRs. The Applicant has provided justification as to why these TEAEs are not to be regarded as ADRs. Of note, in EDELWEISS 3, anaemia was more frequently reported in the placebo group (6.2%) compared to the LGX groups (75 mg: 3.1%; 200 mg+ABT: 2.5%), which is supportive of the reduced number of bleeding days seen with treatment.

The severe TEAEs reported in the LGX 75 mg group included dysmenorrhea, COVID-19, vaginal infection, blood pressure increased, hot flush (all reported by 1 subject each), and headache (reported by 2 subjects). The severe TEAEs reported in the LGX 200 mg+ABT group included menstruation irregular, vulvovaginal dryness, and abdominal pain (each reported by 1 subject). The TEAEs fit with the symptoms of disease or potentially hypoestrogenic side effects. In EDELWEISS 3, the incidence of severe TEAEs was comparable across study groups: 1.2% (2 subjects) in the placebo group reported

severe TEAEs, 3.1% (5 subjects) in the LGX 75 mg group, and 1.9% (3 subjects) in the LGX 200 mg+ABT group.

In the EDELWEISS 3 study, 29.1% of the subjects in the Safety Analysis Set (SAF) reported TEAEs considered related to linzagolix. The percentage of subjects reporting TEAEs considered related to linzagolix was comparable between placebo (24.7%) and LGX 75 mg (28.1%) groups, while slightly higher in the LGX 200 mg+ABT group (34.6%). The common (i.e., in at least 2% of the SAF) linzagolix-related TEAEs included headache (5.8%), hot flush (5.6%), fatigue (3.3%), nausea (3.1%), mood swings (2.9%), and abdominal distension (2.5%).

During the first 6 months of treatment, related TEAEs reported by more than 1 participant in LGX 200mg+ABT arm (in EDELWEISS 3 or in the pooled population) and with a higher frequency compared to placebo include: abdominal distension, abdominal pain upper, headache, dizziness, mood swings, sleep disorder, libido decreased, vaginal haemorrhage, vulvovaginal dryness, metrorrhagia, amenorrhea, pelvic pain, uterine haemorrhage, hot flush, fatigue, asthenia and bone density decreased. The majority of these TEAEs are identified as ADRs. Upon CHMP request, the applicant provided adequate justification why abdominal distension, dizziness and sleep disorders were not identified as ADRs.

From month 6 to month 12, related TEAEs reported by more than 1 participant in LGX 200mg+ABT arm (in the pooled population) and with a higher frequency compared to placebo include: ALT increased, AST increased, hot flush, hyperhidrosis, headache, increased appetite and arthralgia.

In the EDELWEISS 3 trial, 22.9% of the subjects in the SAF reported TEAEs considered related to ABT. The percentage of subjects reporting TEAEs considered related to ABT was nearly identical in the placebo (20.4%) and LGX 75 mg (20.6%) groups, while slightly higher in the LGX 200 mg+ABT group (27.8%).

The pooled data for TEAEs potentially related to linzagolix or add back therapy did not identify any concerning trends or discernible patterns.

Narratives for the serious TEAEs have been provided. The MAH has concluded that the serious TEAEs are unrelated to linzagolix treatment. The serious TEAEs consisted of abdominal pain and peritonitis, vaginal haemorrhages, anxiety, pneumonia and cholelithiasis. It is accepted that there is no concerning trend regarding serious TEAEs.

At CHMP request, the applicant further discussed causality regarding cases of vaginal and genital haemorrhage and attributed these cases to the required add back therapy and not Linzagolix, which was accepted by the CHMP.

For most AEs related to GnRH antagonists, rates are higher in the treated population compared to placebo as would be expected. These AEs are captured in section 4.8 of the SmPC.

In the EDELWEISS 3 trial, 18 subjects (3.7%) had at least 1 TEAE leading to permanent IMP discontinuation. The rate of treatment discontinuation due to TEAEs was similar between the placebo (2.5%) and LGX 200 mg+ABT (3.1%) groups, while slightly higher in the LGX 75 mg group (5.6%). There was no pattern to the TEAEs leading to treatment discontinuations.

In EDELWEISS 6, bone density decreased was reported in 4 subjects in total (1 in the Placebo/LGX 75 mg group and 3 in the LGX 75 mg group). All other TEAEs leading to treatment discontinuation were reported in one subject each.

In the E6/E5/P1/P2 Pooled SAF for Period 2 (N=662), 4.4% of subjects reported TEAEs that led to the permanent discontinuation of study drugs. In the Total LGX 200 mg+ABT group (n=631), TEAEs that led to permanent discontinuation of study drugs in at least 2 subjects (0.3%) were: bone density

decreased (0.8%), menorrhagia (0.3%), pelvic pain (0.3%), vaginal haemorrhage (0.3%), uterine leiomyoma (0.3%), and headache (0.3%).

There was no adverse event of special interest highlighted prior to study commencement.

Hypertension, decreased libido, mood disorders, vaginal haemorrhage, change in menstrual bleeding, elevated liver enzymes and BMD decrease, which are known side effects of GnRH antagonists, were seen throughout the EDELWEISS development program. The rates were in keeping with those previously seen in the PRIMROSE studies and are captured in section 4.8 of the SmPC.

In the EDELWEISS 3 and EDELWEISS 2 trials, there were no meaningful changes over time in group values for any haematology parameters. There were no unexpected obvious trends or shifts from baseline in the haematology data during the study, following dosing with LGX 75 mg, LGX 200 mg+ABT, or placebo.

In EDELWEISS 3, most on-treatment abnormalities were related to decreases in haemoglobin, haematocrit, or erythrocytes, which is expected in this patient population prone to prolonged bleeding (median average number of days with uterine bleeding over the two selected screening menstrual cycles of 6.5 days).

In EDELWEISS 5 and 6, there were no meaningful changes over time in group values for any haematology parameters. There were no unexpected obvious trends or shifts from baseline in the haematology data during the study, following dosing with LGX 75 mg or LGX 200 mg+ABT.

There were no meaningful changes over time in group values for any clinical chemistry parameters in the Phase 3 EDELWEISS 3 and EDELWEISS 2 trials.

No subjects met the criteria for Hy's law.

The potential for elevated liver enzymes is captured in section 4.8 of the SmPC.

There were transient elevations of creatine kinase seen. These were not of clinical relevance.

Changes in lipid parameters are a known adverse effect of GnRH antagonists. At month 6 there was an increase in LDL and cholesterol of a smaller magnitude compared to patients in the PRIMROSE trials. However, a different pattern is observed with triglycerides. A significant increase (19-24%) in triglycerides was observed in the LGX 200 mg+ABT group in EDELWEISS trials during the first 6 months of treatment. The corresponding increase in triglycerides in PRIMROSE trials was 12%. The majority of shifts from baseline in triglyceride levels were from grade 0 to grade 1. During months 6 to 12 of treatment in EDELWEISS 6 trial, lipid parameters continued to rise, although at a slower rate. Month 12, there was an 24% (vs 17% at M6) increase in triglycerides in the LGX 200 mg+ABT group in the EDELWEISS 6 trial. Upon request, the Applicant discussed the rise in triglycerides. The amount of missing data regarding triglyceride levels increases with the duration of exposure, hampering interpretation. According to available data, almost all shifts from baseline in triglyceride levels at month 6 and month 12 were from grade 0 (≤150 mg/dL) to grade 1 (151 to 300 mg/dL) with all mean values below 125 mg/dL and all Q3 (third quartile) values below 145 mg/dL. The risk of lipid parameter changes with linzagolix use is captured in section 4.4 of the SmPC and further details provided in Section 5.1.

No concerning trends were noted regarding weight and vital signs.

ECG readings in the Phase 3 trials in subjects with endometriosis were in line with those observed previously in subjects with uterine fibroids and did not raise any safety concerns. There were no QTcF prolongations >500 ms in any of the Phase 3 trials, including extension trials, in subjects with endometriosis.

Gynaecological examinations did not raise any safety concerns.

Endometrial biopsy results did not raise any safety concerns. All endometrial biopsies were classified as being benign endometrium without hyperplasia or atypia at baseline, Month 6 and Month 12.

Transvaginal ultrasound results did not raise any safety concerns. Subjects receiving the 200 mg dose with ABT achieved the greatest reduction in endometrial thickness: -4 mm at Month 6 and -5 mm at Month 12, as observed previously in subjects with uterine fibroids.

Regarding bone mineral density, given the younger patient population in the EDELWEISS studies (endometriosis) compared to the PRIMROSE studies (uterine fibroids), the effect of the LGX 200 mg+ABT mean change from baseline was less pronounced at the lumbar spine in the EDELWEISS studies. The effect of the LGX 200 mg+ABT was less pronounced at the lumbar spine in the EDELWEISS 3 study (-0.80%) compared to the results with the same dosing regimen in the pooled PRIMROSE studies (mean percent change from baseline of -1.1% at lumbar spine). In both patient populations, comparable results were observed at the femoral neck (-0.63% in PRIMROSE trials vs -0.68% in EDELWEISS 3) and total hip (-0.13% in the PRIMROSE trials vs -0.39% in EDELWEISS 3) after 6 months of treatment.

In the presented clinical data, mean percent BMD changes from baseline provide group level data which have less variability than individual BMD values. These showed that overall, BMD loss related to linzagolix treatment is limited at 6 months and that the rate of loss slows after 6 months. Individual categorical analysis shows that very few subjects experienced >7% BMD loss. This data is included in section 4.8 of the SmPC. In the EDELWEISS 6 ExFU SAF, of the 42 subjects with available data in the LGX 200 mg+ABT group, a decrease >7% BMD change from baseline was observed in 3 subjects (7.1%) at the lumbar spine, 2 subjects (4.8%) at the femoral neck, and 1 subject (2.4%) at the total hip.

After Month 6, the rate of BMD change slowed in both linzagolix groups, suggesting the plateauing BMD loss. Minimal further changes were observed at Month 12 in the Extension SAF in the LGX 200 mg+ABT group: -1.10% (vs -0.83% at M6) at the lumbar spine, -0.70% (vs -0.49% at M6) at the femoral neck, and -0.52% (vs -0.30% at M6) at the total hip. Similar trends were observed in the subjects with uterine fibroids in the Pooled Week 52 SAF treated with LGX 200mg+ABT (n=154): -1.61% (vs -1.10% at M6) at the lumbar spine, -0.32% (vs -0.58% at M6) at the femoral neck, and +0.10% (vs -0.14% at M6) at the total hip.

After stopping treatment in the EDELWEISS 6 study, 129 subjects had a DXA scan at Month 6 ExFU visit. BMD measurements in the ExFU SAF at 6 months were compared to Month 12 in the SAF. Signs of BMD recovery were observed at the lumbar spine in both LGC 75mg and LGX 200mg+ABT 6 month after the end of treatment. While negligible changes were observed at the total hip, a worsening was observed at the femoral neck with the mean percent change from baseline at Month 6 ExFU of -1.43% (vs -0.73% at M 12) in the LGX 200 mg+ABT group and -1.50% (vs -0.55% at M12) in the LGX 75 mg group. The Applicant argued that these findings are consequential to a smaller amount of data and greater variability of femoral neck DXA scans, while no subject in 200mg+ABT group fell below the z-score of -2 at any timepoint at any site.

Only 19 subjects had DXA scan data 6 months after treatment stop in the EDELWEISS 3 study. BMD results for the intended dose after 6 months follow up were numerically similar to baseline values.

Missing BMD data has been accounted for by the applicant. The majority of the missing data is from patients recruited in Ukraine where long term follow up was not possible due to ongoing conflict in the region. Patterns of bone mineral density loss were analysed by age, weight and BMI. As expected,

those of a younger age were less susceptible to bone mineral density loss. With weight and BMI, those of higher weight and BMI had less bone mineral density loss.

Study 16-OBE2109-015 was an exploratory single centre, open label, pilot study investigating the efficacy and safety of OBE2109 200 mg daily for 12 weeks followed by 100 mg daily for 12 weeks in uterine adenomyosis. Numbers in this study were very low, with 8 adenomyosis and 3 retrovaginal node participants included. These small numbers make meaningful interpretation of the data difficult but suggest a response to treatment in the adenomyosis population with reduction in uterine volume seen. There were no significant adverse events reported in these participants. BMD loss of -4.106% at the total hip was seen at 24 weeks but is of uncertain significance given the low number of participants.

Overall, the safety profile is as expected. Bone mineral density loss will be followed in the Yselty PASS study.

2.5.2. Conclusions on clinical safety

The clinical safety profile seen in the EDELWEISS studies is generally similar to the safety profile of linzagolix in the authorised indication of uterine fibroids (at the same dosing regimen, LGX 200mg+ABT) and the known effects of GnRH antagonists.

The main concern has been related to bone mineral density loss. Given the younger population in the EDELWEISS studies, participants appear to have a better baseline BMD reading and less significant losses excluding at the femoral neck. The Yselty PASS study will examine long term bone mineral density loss.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application (version 1.1, signed 8 Feb 2024).

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.1 with the following content:

Safety concerns

There have been no changes to Module SVIII. No new safety concerns were identified (reference is made to the section 5.5.2 of this assessment report). The summary of safety concerns in the RMP remains unchanged as follows:

Table 35 Summary of safety concerns

Summary of Safety Concerns	
Important identified risk	• Bone mineral density decrease
Important potential risk	• Uterine endometrial and mammary gland adenocarcinoma • QT Interval Prolongation • Embryo-foetal toxicity • Liver Toxicity
Missing information	• Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT

Pharmacovigilance plan

The pharmacovigilance plan was updated to remove information on the completed clinical trial PRIMROSE 3 that was previously listed as a category 3 study. This is endorsed. The final study report of this trial was assessed in detail during the variation procedure EMEA/H/C/005442/II/0010.

In addition, the description of the agreed category 3 YSELTY PASS was updated to reflect the requested changes to the study protocol. This is endorsed as well. Of note, the study protocol is still under assessment (EMEA/H/C/005442/MEA/002.3) and further amendments might be necessary in future.

Table 36 The summary table of additional pharmacovigilance activities in the RMP

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
YSELTY PASS A multinational PASS evaluating real-world treatment in patients receiving YSELTY (linzagolix choline) for moderate to severe symptoms of uterine fibroids. (planned)	<u>Primary objectives:</u> To evaluate routinely collected data on long-term safety (>12 months) in relation to BMD with use of YSELTY 200 mg (with ABT) and 100 mg (with and without ABT) dosing regimens <u>Exploratory objectives:</u> To evaluate the incidence of osteoporosis or fractures	• Bone mineral density decrease • Endometrial adenocarcinoma and mammary gland adenocarcinoma • QT interval prolongation • Embryo-foetal toxicity • Bone mineral density decrease with continued treatment	Protocol submission	Nov 2023
			Start of data collection	Q1/Q2 2025

	suspected to be due to osteoporosis. To evaluate liver enzyme levels above the upper limit of normal and correlated events collected as part of clinical practice. To evaluate any routinely collected clinical data on mood disorders. To evaluate the incidence of uterine endometrial and mammary gland adenocarcinoma. To describe treatment patterns for YSELTY dosing regimens with and without ABT. To evaluate patient adherence to YSELTY treatment. To evaluate any routinely collected clinical data on cardiac disorders indicative for QT interval prolongation. To assess if physicians who prescribe YSELTY follow the summary of product characteristics (SmPC) recommendations including performance of annual dual-energy X-ray absorptiometry (DXA) scans and adherence to the requirement of not-prescribing the YSELTY 200 mg regimen without concomitant ABT. To evaluate the incidence of adverse drug reactions (ADRs), serious adverse drug reactions (SADRs) and pregnancies (including pregnancy follow up). To evaluate BMD change in patients with routinely collected DXA scans at	>12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT • Liver toxicity	Last patient last visit	Q3/Q4 2028
			Interim analysis	Q3/Q4 2027
			Study report	Dec 2029

	multiple timepoints to assess mean change of BMD z- and t-scores from baseline or 12-month assessment during long-term (>12 months) use of YSELTY.			

The primary objective of the planned YSELTY PASS is the evaluation of long-term safety of linzagolix in patients with uterine fibroids in relation to BMD. In general, participants in the EDELWEISS trials for endometriosis-associated pain appear to have a better baseline BMD reading and less significant BMD losses in comparison with participants in the PRIMROSE trials for uterine fibroids. With the present application, no post-marketing safety studies in patients with endometriosis-associated pain were proposed by the applicant, who was of the opinion that the current study design already encompasses all critical safety endpoints relevant to both patient populations. Since the 200 mg (+ABT) dose of linzagolix is expected to be the most frequently administered regimen in the current PASS, the applicant expects that the safety results for the primary and explorative objectives can largely be extrapolated to the endometriosis population. As the safety profile of linzagolix 200 mg (+ABT) in the younger endometriosis population has been shown to be comparable to the safety profile of the same recommended dose in the uterine fibroid population, it is agreed that the current study design will provide sufficient evidence to evaluate and confirm the safety profile of linzagolix and that the results of the study will be applicable to both indications. Of note, the effect of the linzagolix 200 mg (+ABT) dose with regard to BMD loss was less pronounced in the endometriosis population compared to the results with the same dosing regimen in the pooled population of the PRIMROSE trials for uterine fibroids. It was also noted that the planned study size already achieves sufficient precision for the primary objective and that the recruitment process will be closely monitored and regularly reported and the CHMP agreed that there is currently no immediate need for opening the current PASS to endometriosis patients. A study extension may be considered in future in case of emerging needs or recruitment issues. The proposed pharmacovigilance plan is considered sufficient for the time being.

Risk minimisation measures

There have been only formal changes to Part V. These changes are considered acceptable. No additional risk minimisation measures are considered necessary. Routine risk minimisation is sufficient for the time being.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Endometriosis is an estrogen-dependent gynaecological condition, defined as the presence of endometrium-like tissue outside the uterus. It is one of the most common gynaecological diseases (Eskenazi 1997). Establishment and growth of such endometriotic tissue is estrogen-dependent, thus the condition is predominantly found in women in their reproductive years and disappears spontaneously after menopause (Kitawaki 2002). A chronic, inflammatory reaction, induced by the ectopic endometrial cells, results in a variety of symptoms including dysmenorrhea, dyspareunia, chronic non-menstrual pelvic pain, dysuria and dyschezia, and infertility (Fauconnier 2005; Dunselman 2014).

Symptoms of endometriosis have an impact on the woman's quality of life (QoL), her physical and psychosocial functioning, including social life, absenteeism from school or work, intimacy and intimate partnerships, as well as mental health and emotional wellbeing (Culley 2013).

Traditionally, a definitive diagnosis was made based on surgical visualization and histologic confirmation. More recently, a paradigm shift has been observed and a ''clinically suspected endometriosis'' in patients who have undergone a thorough medical assessment is leading to the initiation of treatment without prior surgery (Taylor 2018).

3.1.2. Available therapies and unmet medical need

The principal objective in treating endometriosis is symptom-relief management. Treatment options for women with endometriosis-associated pain are diverse and consist of analgesic therapies, hormonal therapies, conservative or minimal invasive surgery, or a combination of these (Dunselman 2014). Approximately 30% of women with endometriosis develop chronic pelvic pain that is unresponsive to conventional treatments, including surgery (Horne 2022). Thus, despite these available treatment modalities, there is still a major need for better options for the treatment of endometriosis.

According to the 2022 Endometriosis guideline published by the European Society of Human Reproduction and Embryology (ESHRE), there is scarce evidence to support the use of simple analgesics, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), for management of pain symptoms related to endometriosis (ESHRE 2022).

First-line hormonal therapies such as combined oral contraceptives (COC) and progestins are effective in two-thirds of women suffering from endometriosis associated pain. These hormonal therapies aim at inhibiting ovulation, preventing cyclic endometrium growth, and suppressing menstruation by achieving a stable steroid hormone milieu, based on the concept that the response of the eutopic and ectopic endometrium is substantially similar (Vercellini 2008; Vercellini 2009).

The administration of COCs, although not approved for the treatment of EAP, results in anovulation, reduction of menstrual bleeding, decidualization of endometriotic lesions, downregulation of cell proliferation and enhanced apoptosis in the endometrium (Meresman, 2002).

However, over time many women on COCs no longer have adequate pain relief and require additional

medical therapy (Practice Committee of the American Society for Reproductive Medicine 2014). Only one randomized placebo-controlled clinical trial of combined hormonal contraceptives has been published demonstrating a statistically significant, though modest, 50% reduction in dysmenorrhea, but no beneficial effect on non-menstrual pelvic pain or dyspareunia (Harada 2008). Progestin monotherapy can be efficacious for the reduction of endometriosis-associated pain as it induces anovulation and a hypoestrogenic state by suppressing the release of pituitary gonadotropin. Progestins also have direct effects on the endometrium, causing decidualization of eutopic and ectopic endometrium leading to atrophy of the endometriotic implants (Schweppe 2001). However, progestin monotherapy is often associated with breakthrough bleeding, alterations in mood, weight gain, and breast tenderness (Vercellini 2003). In addition, progestins are not always effective and progestin resistance occurs in 30%–50% of women using progestin-based therapies for endometriosis (Flores 2018; Donnez 2021).

Other hormonal therapies with proven efficacy for the treatment of endometriosis-associated pain are often limited due to undesirable side effects. For example, depot GnRH agonists – available only as intramuscular or subcuteneous injections – stimulate the receptor leading to a flare in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which results in an increase in estradiol (E2) secretion. However, eventually they lead – through a constant stimulation of the GnRH receptor at the pituitary level – to its desensitization, to reduced LH and FSH output and ultimately to suppression of ovulation and a significant reduction in serum estrogen; thus, their use is associated with hypoestrogenic side-effects. Short-term side effects include menopausal symptoms such as hot flushes, vaginal dryness, loss of libido and emotional lability, and their long-term use is limited by substantial bone mineral density (BMD) reduction (Olive 2008). For example, leuprorelin has a negative impact on bone mineralization, with an estimated loss of 3% in lumbar spine BMD after 3 months of treatment, which increases to approximately 6% after 12 months of continuous use (Hornstein 1998; LUPRON DEPOT US label). To minimize or prevent the hypoestrogenic side effects of GnRH agonists, add-back hormone replacement therapy (estrogen or progestin or combination of both) is frequently used and is known to improve quality of life, BMD and adherence rates to treatment.

As a result, if treatment fails due the inability to tolerate the aforementioned medications or in case of progesterone resistance, additional medical interventions become necessary. This highlights the ongoing necessity for a reliable and durable oral treatment option that can effectively manage symptoms associated with endometriosis, while simultaneously minimizing the adverse effects it may induce.

GnRH antagonists are a promising new oral treatment option that allows dose-dependent control of E2 levels, reducing endometriosis implants and endometriosis-associated pain without or with limited hypo-estrogenic side-effects including hot flushes and BMD loss (Ezzati 2015).

Ryeqo, a GnRH antagonist, was granted a centralised marketing authorisation in the EU in 2023 for the following indication:

Ryeqo is indicated in adult women of reproductive age for:
- treatment of moderate to severe symptoms of uterine fibroids,
- symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis.

3.1.3. Main clinical studies

The efficacy of linzagolix (LGX) to reduce endometriosis-associated pain (EAP), both dysmenorrhoea (DYS) and non-menstrual pelvic pain (NMPP), is based on the results from a single double-blind, randomised, placebo-controlled Phase 3 trial, EDELWEISS 3 (Figure 2.5-1), and its extension study, EDELWEISS 6 (Figure 2.5-2). The single pivotal Phase 3 EDELWEISS 3 trial was intended to provide substantial evidence of effectiveness to support the extension indication: long-term treatment of endometriosis-associated pain.

EDELWEISS 3 was a prospective, randomized, placebo-controlled, parallel-group, multicentre, double-blind, double-dummy study of linzagolix administered once daily at a dose of 75 mg alone or at a dose of 200 mg in combination with add-back therapy (ABT) (E2 1 mg / NETA 0.5 mg) for up to 6 months for the management of moderate-to-severe EAP in women with surgically-confirmed endometriosis. The majority of subjects (94.2%) had previous medical or surgical treatment for their endometriosis. Subjects with endometriosis in the Phase 3 EDELWEISS 3 trial were enrolled from Europe and the US, providing sufficient diversity that justifies the application of study findings to the general population of women with EAP.

Eligibility was assessed during an approximately 3-month screening period, encompassing at least 2 full menstrual cycles. Subjects were randomised to one of three treatment groups in a 1:1:1 ratio for placebo, linzagolix 75 mg, and linzagolix 200 mg + ABT, with no stratification.

At Month 6 of the treatment period, bone mineral density (BMD) change was assessed via DXA measurement. Eligible subjects who completed the 6-month treatment period could enter a separate extension study (EDELWEISS 6) for 6 additional months of active treatment (no placebo control).

Subjects who declined to participate in – or did not qualify for – the extension study and who had received at least 3 months of treatment were to enter a 6-month drug-free post-treatment follow up (PTFU). Subjects who discontinued treatment prior to Month 3 of the treatment period were not to enter the follow-up period.

In the EDELWEISS 6 extension study, subjects who received placebo in the EDELWEISS 3 study were to be randomly switched to one of the two active treatments (75 mg alone or 200 mg + ABT). Subjects who received active treatment in the EDELWEISS 3 study were to continue with the same treatment.

After the end of treatment in the extension study (6-month treatment period: from Month 6 to Month 12), subjects entered a post-treatment extension Follow-Up Period (ExFU) of 6 months with no investigational medicinal product (IMP).

In the EDELWEISS 3 study, the two co-primary, efficacy endpoints were clinically meaningful reduction from baseline to the last 28 days preceding the Month 3 visit (the 4-week period preceding Month 3 visit) or, for subjects who discontinued randomized treatment prior to the Month 3 visit, to the last 28 days of randomized treatment, along with a stable or decreased use of analgesics for EAP, in the mean daily assessment of 1) DYS and of 2) NMPP measured on a Verbal Rating Scale (VRS) using an electronic diary (eDiary). The responders were defined based on the Month 3 MCT analysis.

Ranked, hierarchically tested secondary endpoints were:

1. Change from baseline to Month 6 in DYS (VRS).
2. Change from baseline to Month 6 in NMPP (VRS).
3. Change from baseline to Month 6 in dyschezia (Numeric Rating Scale - NRS).
4. Change from baseline to Month 6 in overall pelvic pain (NRS).

5. Change from baseline to Month 6 in the interference of pain with the ability to performdaily activities, measured using the pain dimension of the Endometriosis Health Profile-30 (EHP-30).
6. Change from baseline to Month 6 in dyspareunia (VRS).
7. No analgesics use for EAP during the preceding 4-week period at Month 6.
8. No opiate use for EAP during the preceding 4-week period at Month 6.

The responders were defined based on the Month 6 MCT analysis.

In the EDELWEISS 6, the two co-primary, composite, efficacy endpoints were clinically meaningful reduction from baseline to the last 28 days preceding the Month 12 visit (the 4-week period preceding Month 12 visit), along with a stable or decreased use of analgesics for EAP, in the mean daily assessment of 1) DYS and of 2) NMPP, both measured on a Verbal Rating Scale (VRS) using an eDiary. Analyses of these endpoints were performed using the Month 3 MCT (as for primary analysis in EDELWEISS 3) and Month 6 MCT (as for ranked secondary endpoint analyses in EDELWEISS 3).

3.2. Favourable effects

Treatment with LGX 200 mg dose administered with ABT demonstrated statistically significant reductions in both co-primary endpoints of DYS and NMPP at 3 months (or the last 28 days of randomized treatment if treatment was discontinued before 3 months) with a stable or decreased use of analgesics for EAP. From the logistic regression analysis, the estimated percentage of responders:

- for DYS was 72.9% (95% CI: 65.3, 79.4) compared with 23.5% (95% CI: 17.5, 30.7) in the placebo group with an Odds Ratio (OR) vs placebo of 8.80 (97.5% CI: 4.86, 15.91) and a Bonferroni-corrected p-value of treatment effect <0.001.
- for NMPP was 47.3% (95% CI: 39.5, 55.3) compared with 30.9% (95% CI: 24.1, 38.6) in the placebo group with an OR vs placebo of 2.01 (97.5% CI: 1.18, 3.42) and a Bonferroni-corrected p-value of treatment effect of 0.007.

The 75 mg dosing regimen met the co-primary endpoint for DYS but not for NMPP (Table 2.5-1). Thus, the discussion that follows centres primarily on the dosing regimen of LGX 200 mg+ABT which is intended for the long-term treatment of women with EAP.

Results for the ranked secondary endpoints showed statistically significant improvements over placebo for the LGX 200 mg+ABT dosing regimen for: DYS (VRS), NMPP (VRS), dyschezia (NRS), overall pelvic pain (NRS), and the ability to do daily activities measured using the pain dimension of EHP-30. The corresponding proportions of responders, using Month 6 MCT, were 77.2% (vs. 20.3% for placebo) for DYS, 56.3% (vs 38.0% for placebo) for NMPP, 51.9% (vs 43.7% for placebo) for dyschezia, 63.3% (vs 41.8% for placebo) for overall pelvic pain, and 62.6% (vs 34.8% for placebo) for EHP-30 pain dimension. Treatment effect for dyspareunia was not statistically significant, with the corresponding proportion of responders of 52.9% (vs 46.2% for placebo).

The estimated mean change from baseline in DYS (VRS) 6 was −1.83 (95% CI: −1.96, −1.70) vs and NMPP (VRS) −0.92 (95% CI: −1.03, −0.82) in LGX 200 mg+ABT group at Month. The LSM differences to placebo were −1.17 (97.5% CI: −1.38, −0.97), p-value <0.001 for DYS, and −0.26 (97.5% CI: −0.43, −0.09), p-value 0.002 for NMPP. Proportion of participants with a reduction of at least 1.25 in DYS (VRS) with stable or decreased use of analgesics for EAP at Month 6 was 77.2% in LGX 200 mg+ABT vs 20.3% in placebo group. Proportion of participants with a reduction of at least 0.85 in

NMPP (VRS) with stable or decreased use of analgesics for EAP at Month 6 was 56.3% in LGX 200 mg+ABT vs 38% in placebo group.

The estimated mean reduction in dyschezia score (NRS) was statistically significant for the LGX 200 mg+ABT group compared to placebo, with the LSM difference to placebo of −0.58 (97.5% CI: −1.05, −0.11), p-value 0.012. Proportion of participants with a reduction of at least 1.5 in dyschezia (NRS) at Month 6 was 59.1% in LGX 200 mg+ABT vs 43.7% in placebo group.

The statistically significant improvement in the OPP (NRS) for LGX 200 mg+ABT at Month 6 was reached, with the LSM difference to placebo of −1.19 (97.5% CI: −1.77, −0.62), p-value <0.001. Proportion of participants with a reduction of at least 2.7 in OPP (NRS) at Month 6 was 63.3% in LGX 200 mg+ABT vs 41.8% in placebo group.

The reduction in the EHP-30 Pain Dimension was shown to be statistically significant for the LGX 200 mg+ABT group at Month 6, with the LSM difference to placebo of -16.13 (97.5% CI: -21.24, -11.02), p-value <0.001. Proportion of participants with a reduction of at least 28 in EHP-30 Pain Dimension at Month 6 was 62.6% in LGX 200 mg+ABT vs 34.8% in placebo group.

Only 2.5% of subjects in the LGX 200 mg+ABT group did not use analgesics for EAP at baseline. The percentage of subjects not using analgesics for EAP rose to 45.3% at Month 6, with a statistically significant change from baseline (OR = 5.27; 97.5% CI: 2.83, 9.82; p<0.001). Most subjects did not use opiates for EAP at baseline (87.7%) and at Month 6 (93.7%). The co-primary endpoints at Month 12 were a clinically meaningful reduction in DYS and NMPP (analysed using both the Month 3 MCT and Month 6 MCT) with stable or decreased use of analgesics. (VRS) was 59.5% in the LGX 75 mg group and 67.6% in the LGX 200 mg+ABT group based on the month 3 MCT.

At Month 12, the proportion of subjects with a reduction of 1.25 or greater in DYS (VRS) and stable or decreased use of analgesics was 50.5% in the LGX 75 mg group and 88.3% in the LGX200 mg+ABT group. The proportion of subjects with a reduction of 0.85 or greater in NMPP(VRS) and stable or decreased use of analgesics was 55.9% in the LGX 75 mg group and 64.9% in the LGX 200 mg+ABT group based on month 6 MCT. At Month 12, the proportion of participants with a reduction of 1.10 or greater (Month 3 meaningful change threshold, MCT) in DYS (VRS) and stable or decreased use of analgesics was 91.0% in the LGX 200 mg+ABT group. At Month 12, the proportion of participants with a reduction of 0.80 or greater (Month 3 MCT) in NMPP (VRS) and stable or decreased use of analgesics was 67.6% in the LGX 200 mg+ABT group. Similar response pattern was observed when applying Month 6 MCT (DYS=-1.25; NMPP=-0.85). Secondary endpoint results are supportive of co-primary endpoints results and of the maintenance of the LGX treatment effect over 12 months.

3.3. Uncertainties and limitations about favourable effects

There is also uncertainty about the stage and extent of the endometriosis in patients in the pivotal clinical trial and the location of endometriotic lesions outside of the pelvis. The surgical confirmation could have occurred up to 10 years prior to screening. While all subjects exhibited pelvic endometriosis, the information regarding the presence at surgery of extra pelvic endometriotic lesions was not collected in the case report forms (CRF), as this information, derived from a surgical procedure that occurred up to 10 years prior to inclusion, was deemed to be of insufficient informative value for analysis.

3.4. Unfavourable effects

The common TEAEs seen across EDELWEISS 2, 3, 5 and 6 were consistent with those in the uterine fibroid development programme with headache, hot flush, fatigue, anaemia, mood swings and arthralgia most seen.

The common (i.e., in at least 2% of the SAF) linzagolix-related TEAEs included headache (5.8%), hot flush (5.6%), fatigue (3.3%), nausea (3.1%), mood swings (2.9%), and abdominal distension (2.5%). Headache, hot flush, fatigue, and mood swings were reported more frequently in the LGX groups compared with placebo.

Hypertension, decreased libido, mood disorders, vaginal haemorrhage, change in menstrual bleeding, elevated liver enzymes and BMD decrease, which are known side effects of GnRH antagonists, were seen throughout the EDELWEISS development program. The rates were in keeping with those previously seen in the PRIMROSE studies. These known AEs are captured in section 4.8 of the SmPC.

Abdominal distension, urinary tract infection and vaginal infection are not included as ADRs despite occurring with a higher frequency in LGX200mg + ABT compared to placebo in EDELWEISS 3 study. Abdominal distension, dizziness and sleep disorders are not considered ADRs despite being reported by more than 1 participant receiving LGX 200mg+ABT, occurring with a higher frequency compared to placebo and being considered related to linzagolix by investigators. Similarly, increased appetite was considered related to linzagolix in more than 1 participant receiving LGX 200mg+ABT arm and occurred with a higher frequency compared to placebo during months 6-12 of treatment.

A rise in triglycerides is observed in patients with endometriosis treated with lingazolix to greater extent than seen in the uterine fibroid population.

Bone mineral density decreases were seen in participants. However, given the younger patient population in the EDELWEISS studies (endometriosis) compared to the PRIMROSE studies (uterine fibroids), the effect of the LGX 200 mg+ABT mean change from baseline was less pronounced at the lumbar spine in the EDELWEISS studies. The effect of the LGX 200 mg+ABT was less pronounced at the lumbar spine in the EDELWEISS 3 study (-0.80%) compared to the results with the same dosing regimen in the pooled PRIMROSE studies (mean percent change from baseline of -1.1% at lumbar spine). In both patient populations, comparable results were observed at the femoral neck (-0.63% in PRIMROSE trials vs -0.68% in EDELWEISS 3) and total hip (-0.13% in the PRIMROSE trials vs -0.39% in EDELWEISS 3) after 6 months of treatment. From Month 6 onwards, the rate of BMD change slowed in both linzagolix groups, suggesting the plateauing BMD loss.

However, a worsening was observed at the femoral neck with the mean percent change from baseline at Month 6 ExFU of -1.43% (vs -0.73% at M 12) in the LGX 200 mg+ABT group and -1.50% (vs -0.55% at M12) in the LGX 75 mg group.

3.5. Uncertainties and limitations about unfavourable effects

The long-term impact of this treatment on bone mineral density will be further reviewed in the Yselty PASS study. This is particularly relevant given that participants with endometriosis associated pain tended to be younger than those in the uterine fibroid studies.

A notable rise in triglycerides is observed, which is of a greater magnitude compared to the rise observed in patients with uterine fibroids at the same dose. The MAH discussed these findings noting that the proposed information in Section 4.4 and 5.1 adequately addresses this issue.

BMD was measured after the end of treatment in EDELWEISS 6 study. A worsening was observed at the femoral neck with the mean percent change from baseline at Month 6 ExFU of -1.43% (vs -0.73% at M 12) in the LGX 200 mg+ABT group and -1.50% (vs -0.55% at M12) in the LGX 75 mg group. The MAH provided some possible explanations for these findings, including the variability of DEXA scans for femoral neck and small absolute numbers of measurements.

3.6. Effects Table

Table 37 Effects table

Effect	Description	Unit	LGX 200 mg + ABT	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
DYS	Percentage of responders at month 3	%	72.9	23.5	OR vs placebo (97.5% CI): 8.80 (4.86; 15.91)	(1)
	Percentage of responders at month 6	%	80.0	23.5	OR (97.5% CI): 12.98 (7.00; 24.06)	(1)
NMPP*	Percentage of responders at month 3	%	47.3	30.9	OR vs placebo (97.5% CI): 2.01 (1.18; 3.42)	(1)
	Percentage of responders at month 6	%	57.1	38.5	OR vs placebo (97.5% CI): 2.13 (1.26; 3.60)	(1)
DYS	Change from baseline	VRS	-0.66 (-0.79; -0.53)	-1.83 (-1.96; -1.70)	Diff with PBO (97.5% CI): -1.17 (-1.38; -0.97)	(1)
NMPP	Change from baseline in LSM (95% CI) at month 6	VRS	-0.66 (-0.77, -0.56)	-0.92 (-1.03, -0.82)	Diff with PBO (97.5% CI): -0.26 (-0.43; -0.09)	(1)
Dyschezia	Change from baseline in LSM (95% CI) at month 6	NRS	-1.41 (-1.71, -1.12)	-1.99 (-2.29, -1.70)	Diff with PBO (97.5% CI): -0.58 (-1.05; -0.11)	(1)
OPP	Change from baseline in LSM (95% CI) at month 6	NRS	-2.19 (-2.55, -1.84)	-3.39 (-3.74, -3.03)	Diff with PBO (97.5% CI): -1.19 (-1.77; -0.62)	(1)
EHP-30 pain dimension score	Change from baseline in LSM (95% CI) at month 6		-19.47 (-22.66, -16.28)	-35.60 (-38.73, -32.48)	Diff with PBO (97.5% CI): -16.13 (-21.24; -11.02)	(1)
Unfavourable Effects						
BMD	Mean percent change from baseline (95% CI) in lumbar spine BMD at week 24	% CfB in g/cm^2	0.77 (0.40, 1.14)	-0.79 (-1.15, -0.43)		(1)

Effect	Description	Unit	LGX 200 mg + ABT	Placebo	Uncertainties/ Strength of evidence	References
	Percent change from baseline in lumbar spine BMD at month 12	% CfB in g/cm^2	-	-1.10 (-1.79, -0.41)	Missing BMD measurements at month 12; no placebo comparison	(2)

Abbreviations: ABT = add-back therapy; BMD = Bone Mineral Density; CfB = change from baseline; DYS = dysmenorrhea; LGX = linzagolix; EHP-30 = Endometriosis Health Profile-30; LSM = least square mean; NMPP = non-menstrual pelvic pain; NRS = numeric rating scale; OPP = overall pelvic VRS = verbal rating scale; OR = Odds Ratio; CI = Confidence Interval.

Notes: (1) EDELWEISS 3; (2) EDELWEISS 6
* Reduction of 1.1 (resp. 0.8) for DYS (resp. NMPP) in mean pelvic pain score within last 28 days prior to Month 3 or discontinuation, and stable or decreased use of analgesics for endometriosis within the same calendar days. VRS and NRS scores were computed as mean of daily assessments on the last 28 days prior to Month 6 or discontinuation.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Endometriosis associated menstrual pain is a cause of significant morbidity. Linzagolix, in a phase 3 double blind multicentre trial has been shown to reduce both menstrual and non-menstrual pain associated with endometriosis. The study design does not allow for the positioning regarding the line of treatment. However, it is important to notice that almost all participants (94%) underwent prior surgical procedures for the treatment of endometriosis, and that almost half of participants (44%) received prior genito-urinary system and sex hormones ATC class of medicinal products. The reduction in pain is associated with a reduction in analgesia intake. Reduction in pain begins within a month of treatment and the product is effective by month 3. The effect on pain reduction lasted for patients on treatment up to 12 months. Although the co-primary endpoints analysis was done at 3 months, stable efficacy was shown in the following period up to 6 months of treatment. It is agreed that the early onset of the effect is important for the patients. Those co-primary endpoints are supported by results of five of eight hierarchically tested key secondary endpoints: DYS (VRS), NMPP (VRS), dyschezia (NRS), OPP (NRS) and EHP-30 Pain Dimension. The effect of linzagolix 200 mg+ABT was maintained over additional 6 months (treatment duration of 12 months in total) for the co-primary and the key secondary endpoints, studied in the controlled, double-blinded extension study. These clinical effects are significant however there are other products which are used to treat endometriosis some of which act in a similar manner, e.g. GnRH agonists. The efficacy and safety of Linzagolix when compared to other treatments in clinical use is not clear, whilst an indirect comparison of the linzagolix efficacy to the efficacy of the medicinal product of the same class, approved in the same indication is not possible as different pain scores were used. Nevertheless, the clinically meaningful threshold of at least approximately 20% improvement was observed among the linzagolix efficacy endpoints compared to placebo.

The safety profile seen in the EDELWEISS development program is in keeping with that seen in uterine fibroid patients. The issue of long-term bone mineral density loss will be addressed in a PASS study.

3.7.2. Balance of benefits and risks

Linzagolix has demonstrated clinically relevant treatment effects across a number of outcomes in the intended indication, i.e. symptomatic treatment of endometriosis in women with a history or previous medical or surgical treatment for their endometriosis. Given the chronic, inflammatory nature of endometriosis, the impact on long-term bone mineral density is an important identified risk in the summary of safety concerns and is being addressed in a PASS study.

The MAH has withdrawn their request for an additional year of market protection for a new indication.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7.4. Conclusions

The overall B/R of YSELTY is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of endometriosis-associated pain in adult women of reproductive age for YSELTY, based on final results from studies Edelweiss 3 (18-OBE2109-003) and Edelweiss 6 (19-OBE2109-006) as well as additional supporting studies. Edelweiss 3 is a pivotal phase 3, randomised, double-blind, placebo-controlled, safety and efficacy study to evaluate linzagolix with add-back therapy as a therapy for pain associated with endometriosis, while Edelweiss 6 is an open-label extension study including patients who completed Edelweiss 3 pivotal study regardless of their previous treatment assignment and met the eligibility criteria. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 1.1 of the RMP has also been submitted.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.