EU Risk Management Plan (RMP)
for
YSELTY (linzagolix)

RMP Version Number:	1.1
Data Lock Point for this RMP:	05 NOV 2023
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Rationale for submitting an updated risk management plan (RMP):

- Extension of indication for linzagolix for treatment of endometriosis-associated pain (EAP).
- Information updated for YSELTY PASS Summary
- Removal of the completed Category 3 additional pharmacovigilance activity (P3)

Summary of significant changes in this RMP:

RMP Part/Module	Significant Change
PART I: Product Overview	Pharmacotherapeutic group and ATC code (H01CC04) included. Name and address updated for Marketing Authorisation Holder (MAH) Propose indication and Dosage Updated
PART II: Safety Specification	
MODULE SI: Epidemiology of the Indication(s) and Target Population	Endometriosis Epidemiology data updated
MODULE SII: Non-clinical Part of the Safety Specification	No changes made
MODULE SIII: Clinical Trial Exposure	Updated Endometriosis related clinical trial exposure
MODULE SIV: Populations not Studied in Clinical Trials	Endometriosis information updated
MODULE SV: Post-authorisation Experience	Information updated based on current product status.
MODULE SVI: Additional EU Requirements for the Safety Specification	No changes made
MODULE SVII: Identified and Potential Risks	Endometriosis information updated
MODULE SVIII: Summary of the Safety Concerns	No changes made
PART III: Pharmacovigilance Plan	Removed completed Category 3 additional pharmacovigilance activity Study PRIMROSE 3 (20-OBE2109-007) Information updated for YSELTY PASS Summary
PART IV: Plans for Post-Authorisation Efficacy Studies	No changes made
PART V: Risk Minimisation Measures	Removed completed Category 3 additional pharmacovigilance activity Study PRIMROSE 3 (20-OBE2109-007)
PART VI: Summary of the Risk Management Plan	Endometriosis information updated

RMP Part/Module	Significant Change
VII. PART VII: Annexes to the Risk Management Plan	Endometriosis information updated. Removed completed Category 3 additional pharmacovigilance activity Study PRIMROSE 3 (20-OBE2109-007) Information updated for YSELTY PASS Summary Annex 4 - update of TFUQs with current MAH name and updated contact details.

Other RMP Versions under Evaluation: None

Details of the Currently Approved RMP:
RMP version number: 1.0

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QPPV Name: Birger Fels

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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List of Abbreviations

Abbreviation	Definition
ABT	Add-Back Therapy
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AME	Absorption, metabolism and excretion
APA	Action potential amplitude
APD30 / APD90	Action potential duration at 30% and 90% repolarization
APD30-90	Difference between APD90 and APD30
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BMD	Bone mineral density
BMI	Body mass index
CDC	Centres for Disease Control and Prevention
CDP	Clinical development programme
CfB	Percent change from baseline
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	Confidence interval
CK	Creatine kinase
Cmax	Maximum concentration recorded
COC	Combined oral contraceptive
CSR	Clinical study report
CT	Computed tomography
CYP	Cytochrome P
DDI	Drug-drug interactions
DILI	Drug-induced liver injury
DLP	Data lock point
DMPA	Depot medroxyprogesterone acetate
DNA	Deoxyribonucleic acid

Abbreviation	Definition
DXA	Dual X-ray absorptiometry
DYS	Dysmenorrhea
E2/NETA	Oestradiol/Norethisterone acetate
EAP	Endometriosis-associated pain
ECG	Electrocardiogram
EEA	European economic area
eGFR	Estimated glomerular filtration rate
EIN	Endometrioid intraepithelial neoplasia
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESAF	Extension safety analysis set
ESRD	End stage renal disease
EU	European Union
ExFU	Follow-up extension
FD	Fixed dose
FDA	Food and Drug Administration (US)
FEAS	Follow-up extension analysis set
FIGO	International Federation of Gynaecology and Obstetrics
FPFV	Start of data collection
FRAX	Fracture risk assessment tool
FSH	Follicle-stimulating hormone
FU	Follow-up
GGT	Gamma-glutamyl transpeptidase
GLDH	Glutamate dehydrogenase
GLP	Good laboratory practice
GnRH	Gonadotropin-Releasing Hormone
Hb	Haemoglobin
HCP	Healthcare professional
HDL	High-density lipoprotein
HEK293	Human Embryonic Kidney 293
hERG	Human ether-a-go-go-related gene
HI	Hepatic impairment
HIFUS	High-intensity focused ultrasound

Abbreviation	Definition
HLT	High level term
HMB	Heavy menstrual bleeding
HRT	Hormone replacement therapy
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IF	Immunofluorescence
IMP	Investigational medicinal product
INN	International nonproprietary name
INR	International normalised ratio
IUD	Intra-Uterine Device
kg	Kilogram
LDL	Low density lipoprotein
LEEP	Loop electrosurgical excision procedure
LFT	Liver function tests
LH	Luteinising hormone
LPLV	End of data collection
LSM	Least squares mean
LTFU	Long term follow-up
MAA	Marketing Authorisation Application
MAD	Multiple ascending dose
MAH	Marketing Authorisation Holder
MBL	Menstrual blood loss
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
mL	Milliliter
MRgFUS	Magnetic resonance guided focused ultrasound surgery
NAFLD	Non-Alcoholic Fatty Liver Disease
NCE	New chemical entities
ng	Nanogram
NOAEL	No observed adverse effect level
NOV	November
NSAIDs	Non-steroidal anti-inflammatory drugs
PAP	Papanikolaou test

Abbreviation	Definition
PAS	Post Authorisation Studies
PASS	Post Authorisation Safety Study
PCOS	Polycystic ovarian syndrome
PK	Pharmacokinetics
PL	Package leaflet
PR	Parameters
PRAC	Pharmacovigilance Risk Assessment Committee
PSMF	Pharmacovigilance System Master File
PSUR	Periodic safety update reports
PT	Preferred Term
PTFU	Post-treatment follow-up
PV	Pharmacovigilance
QoL	Quality of life
QPPV	Qualified Person Responsible for Pharmacovigilance
QTc	QT interval corrected for heart rate
QTcF	Fridericia's correction formula
RA	Rheumatoid arthritis
RBC	Red blood cell
RI	Renal impairment
RMP	Risk Management Plan
SAD	Single ascending dose
SADRs	Serious adverse drug reaction
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SCS	Summary of clinical safety
SD	Standard deviation
SERMs	Selective oestrogen receptor modulators
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SOC	System organ class
SPRM	Selective progesterone receptor modulator
TD	Titrated dose

Abbreviation	Definition
TEAE	Treatment Emergent Adverse Event
TQT	Thorough QT
TSH	Thyroid stimulating hormone
UAE	Uterine Artery Embolisation
UBP-WRS	Uterine Bleeding and Pain Women's Research Study
UDS	Unscheduled DNA synthesis
UF	Uterine fibroids
UK	United Kingdom
ULN	Upper Limit of Normal
USA	United States of America
Vmax	Maximal upstroke velocity
WHI	Women's Health Initiative
WHO	World Health Organisation

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Linzagolix
Pharmacotherapeutic group(s) (ATC Code)	Anti-gonadotropin-releasing hormones (H01CC04)
Marketing Authorisation Holder (MAH)	Theramex Ireland Limited, 3rd Floor, Kilmore House, Park Lane, Spencer Dock, Dublin 1, D01 YE64, Ireland
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	YSELTY
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class:* Thienopyrimidine derivative
	Summary of mode of action: Linzagolix is a potent, selective, orally active, Gonadotropin-Releasing Hormone (GnRH) receptor antagonist that inhibits endogenous GnRH signalling by binding competitively to GnRH receptors in the pituitary gland, resulting in dose-dependent suppression of luteinising hormone (LH) and follicle-stimulating hormone (FSH), which leads to decreased serum concentrations of the ovarian sex hormones, oestradiol (E2) and progesterone. Reduction of E2 ultimately improves heavy menstrual bleeding (HMB) as well as other symptoms such as pain associated with uterine fibroids (UF).
	Important information about its composition: No relevant information

Hyperlink to the Product Information	Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	*Current:* YSELTY is indicated for the treatment of moderate to severe symptoms of UF in adult women of reproductive age.
	Proposed: YSELTY is indicated in adult women of reproductive age for: - treatment of moderate to severe symptoms of uterine fibroids, - treatment of endometriosis-associated pain.
Dosage in the EEA	*Current: Uterine Fibroids* YSELTY should preferably be started in the first week of the menstrual cycle and should be taken continuously once daily. The recommended dosage of YSELTY is: • 100 mg or, if needed, 200 mg once daily with concomitant hormonal add-back therapy (ABT, E2 1 mg and norethisterone acetate (NETA) 0.5 mg tablet once daily). • 100 mg once daily for women in whom ABT is not recommended or in women who prefer to avoid hormonal therapy. • 200 mg once daily for short term use (< 6 months) in clinical situations when reduction of uterine and fibroid volume is desired. Fibroid size may increase when the treatment is stopped. Due to the risk of bone mineral density (BMD) decrease with prolonged use, the 200 mg dose without concomitant ABT should not be prescribed for longer than 6 months. In patients with risk factors for osteoporosis or bone loss, a dual X-ray absorptiometry (DXA) is recommended prior to starting YSELTY treatment. YSELTY can be taken without interruption. A DXA scan is recommended after 1 year of treatment for all women, and there is a need for continued BMD monitoring thereafter.
	Proposed : YSELTY treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of uterine fibroids and/or endometriosis.

	The recommended dose of Yselty is: *For Uterine Fibroids:* *Above text remains unchanged* *For Endometriosis-associated pain*: • 200mg once daily with concomitant hormonal add-back therapy *Additional Posology and method of administration text common for both indications:* Pregnancy must be ruled out prior to initiating treatment with YSELTY. YSELTY should preferably be started in the first week of the menstrual cycle and should be taken continuously once daily.
Pharmaceutical form(s) and strengths	*Current:* • *Pharmaceutical form:* Film-coated tablets • *Strengths:* o YSELTY 100 mg film-coated tablets o YSELTY 200 mg film-coated tablets
	Proposed (if applicable): Not Applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

II.1. Indication

Uterine Fibroids:

Linzagolix, a new orally active, non-peptide GnRH receptor antagonist, is indicated in adult women of reproductive age for the treatment of moderate to severe symptoms of uterine fibroids.

Uterine fibroids are a hormone-dependent gynaecological condition, defined as benign smooth-muscle tumours of clonal origin that occur during women's reproductive years (Stewart, 2001).

When symptomatic, the main symptoms are HMB, abdominal and pelvic pain and pressure, bowel and bladder dysfunction including increased urinary frequency, abdominal protrusion. Fibroids are also associated with infertility and recurrent miscarriage. Anaemia may also occur as a consequence of fibroid-related heavy bleeding and in severe cases can lead to serious medical complications. Besides causing physical morbidity, UF are a frequent cause of significant long-term impairment of a wide range of aspects of Quality of Life (QoL) including self-image, interpersonal relationships and sexual function (Marsh, 2018; Borah, 2013).

Orally active GnRH antagonists have been shown to significantly reduce UF-related HMB as well as improvement in other fibroid-associated symptoms (Schlaff, 2020; Rocca, 2020).

Endometriosis:

YSELTY is indicated in adult women of reproductive age for the treatment of endometriosis-associated pain.

Endometriosis is an estrogen-dependent gynaecological condition, defined as the presence of endometrium-like tissue outside the uterus. Based on location and depth, lesions are further described as superficial peritoneal lesions, ovarian endometrioma, or deep endometriosis. It is one of the most common gynaecological diseases (Eskenazi 1997). Establishment and growth of such endometriotic tissue is oestrogen-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, Agarwal 2019).

Orally active GnRH antagonists with and without associated ABT have been shown to significantly reduce endometriosis associated pain (Taylor 2017, Giudice 2022).

II.2 Incidence

Uterine Fibroids:

Uterine fibroids are the most common tumours of the female reproductive tract in premenopausal women. For many women with fibroids, symptoms begin in the twenties and progress over time with increases in fibroid number and size and associated increases in heavy bleeding. Uterine fibroids occur in about 40% of women between 35 and 55 years (Parker, 2007). By the time they reach 50 years of age, nearly 70% of white women and more than 80% of black women will have had at least one fibroid; severe symptoms develop in 15 to 30% of these women with a decrease in symptoms seen after menopause (Bulun, 2013).

Endometriosis:

Endometriosis is one of the most common gynaecological diseases (Eskenazi 1997). The incidence of endometriosis cannot be accurately determined because of the uncertainties in making a definite diagnosis without laparoscopy. On the other hand, Jinhui mentioned that the incidence rate of endometriosis is about 5%–15% (Jinhui 2022).

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).

Establishment and growth of the ectopic endometriotic tissue is estrogen-dependent, thus the condition is predominantly found in women in their reproductive years and disappears spontaneously after menopause (Kitawaki 2002).

II.3. Prevalence

Uterine Fibroids:

Because of the progressive nature of UF, the prevalence of the condition increases with age until menopause (Drayer, 2015). The prevalence of UF varied widely across the studies from 4.5% to 68.6% depending on country/region, study methodology/diagnostic methods or population (Stewart, 2017). In 2009, a research study was conducted interviewing 21,479 women across 8 countries (the Uterine Bleeding and Pain Women's Research Study; UBP-WRS). The self-reported prevalence of uterine fibroids ranged from 4.5% (UK) to 9.8% (Italy), reaching 9.4% (UK) to 17.8% (Italy) in the age group of 40-49 years (Zimmermann 2012). Black race was the only factor that was recurrently reported to increase UF risk, by two–threefold compared with white race (Stewart, 2017). Based on an epidemiologic study of 1364 women, an estimate of the overall incidence of uterine myomas in white women by age 35 years is nearly 40% and by age 50 years approaches 70%; in comparison, for black women, these figures are approximately 60% and 80%, respectively (Baird, 2003).

Endometriosis:

The exact prevalence of endometriosis is not known, but a recent study estimated that the prevalence of endometriosis in North America, Australia, and Europe is ~1–5% in women of reproductive age (Barnard 2023). In women presenting with pelvic pain and/or infertility, its frequency may reach 50% (de Sanctis V, 2018).

II.4. Demographic of the population and risk factors of the disease/condition

Uterine Fibroids:

The two major risk factors for UF are increasing age and black race. As described above, the prevalence of fibroids increases with age until menopause.

Other risk factors include reproductive status, including early age at menarche, time since last birth and delay of childbirth (Stewart, 2017). Family history is also described as a risk factor; however, this effect could be partly due to more frequent screening in relatives of women with UF. It may also be attributable to genetic factors that play a role in the development of the condition. An association has been reported between alcohol, caffeine intake, and dietary habits (Stewart, 2017).

Endometriosis:

Endometriosis can affect individuals from various ethnicities, socioeconomic backgrounds, and geographical locations. Various factors contribute to the heightened risk of developing endometriosis. A family history of the condition, an early onset of menstruation before the age of 11 years, a shorter time between periods, and prolonged menstrual flow, all play significant roles. Furthermore, defects in the uterus or fallopian tubes can also increase the likelihood to develop endometriosis (Cleveland Clinic health library, endometriosis, 2022).

II.5. The main existing treatment option(s)

Uterine Fibroids:

The principal objective in treating UF is symptom-relief. Because of the lack of availability of effective medical therapies that can be used long-term, current treatment options for women with moderate to severe symptoms of UF are mainly surgical.

For women who wish to preserve fertility, there are a number of procedures that can be considered, including myomectomy by laparoscopy, hysteroscopy or laparotomy, Uterine Artery Embolisation (UAE) and ultrasonic ablation. UAE is less invasive and requires a shorter hospital stay, however is associated with potential impairment of fertility. Endometrial ablation may be indicated if the dominant symptom is bleeding, and uterine anatomy is not distorted or substantially enlarged by fibroids.

Recurrence of symptoms following conservative surgical treatment of UF is common; for example, at least 25% of women who have undergone myomectomy require additional treatment. Because of this, combined with the lack of effective long-term medical therapy, many women with UF ultimately undergo hysterectomy, which ends fertility and can result in long-term adverse outcomes, including urinary incontinence and sexual dysfunction. Surgical procedures, in

particular myomectomy and hysterectomy, are associated with potential serious complications, including high blood loss, pelvic abscess, abdominal ileus or bowel obstruction, and vaginal cuff complications (Lonky, 2017). Considering the risks and the high potential for recurrence, the need for effective alternatives to surgical intervention is very real, especially for women seeking to preserve their fertility.

GnRH receptor agonists (e.g., leuprorelin) have been shown to be effective in reducing fibroid-related bleeding, correcting anaemia when given concomitantly with iron therapy, reducing abdominal symptoms and reducing fibroid as well as uterine volume (Lethaby, 2001; Stovall, 1995). The use of GnRH receptor agonists has been relatively limited due to their sub-optimal side effect profile caused by full suppression of oestrogen, resulting in florid symptoms of menopause such as hot flushes, depression, mood swings, loss of libido, nervousness, and vaginitis. In addition, because GnRH receptor agonists continuously overstimulate the GnRH receptor, there is an initial overproduction of LH and FSH which leads to increased levels of oestrogen and associated increase in symptoms (i.e., the flare effect). Furthermore, GnRH agonists have a negative impact on bone mineralisation with an estimated loss of 3% in lumbar spine Bone Mineral Density (BMD) after 3 months of treatment, which increases to approximately 6% after 12 months of continuous use which may not be fully reversible. Due to effects on BMD, the use of GnRH agonists is limited to up to 6 months (PROSTAP® SR DCS 3.75 mg Prescribing Information) for the pre-operative treatment of symptomatic myomas, although there is no harmonised label in Europe.

Drugs that modulate progesterone action on the uterus have also been developed for management of UF. Ulipristal acetate (Esmya®), a selective progesterone receptor modulator (SPRM), was approved in Europe in 2012 for intermittent treatment of HMB associated with UF in women who are not eligible for surgery. Esmya has been associated with cases of serious drug-induced liver injury (DILI). Due to this DILI, EMA's human medicines committee (CHMP) recommended restricting use of medicines containing ulipristal acetate 5 mg (Esmya and generic medicines) as a result of cases of serious liver injury. The medicines can now only be used to treat UF in premenopausal women for whom surgical procedures (including UF embolisation) are not appropriate or have not been effective.

Other medical treatments, including oral contraceptives and non-steroidal anti-inflammatory drugs are often used for treatment of UF symptoms but there is limited evidence for their long-term efficacy in reducing heavy bleeding due to UF. The levonorgestrel-releasing Intra-Uterine Device (IUD) effectively decreases menstrual bleeding but its effectiveness may be limited in women with a distorted endometrial cavity due to submucosal fibroids; moreover, it is contraindicated in women with severe distortion of the uterine cavity. Rates of IUD expulsion are also higher in women with fibroids (Zapata, 2010).

The concept of partial suppression of oestrogen for the treatment of endometriosis, first described by Barbieri (Barbieri, 1992), has led to the development of a new drug class, the oral GnRH receptor antagonists. GnRH receptor antagonists such as linzagolix have a validated mechanism of action, binding competitively and reversibly to pituitary gland GnRH receptors and inhibiting receptor activation by endogenous GnRH (Struthers, 2009). The onset of action is immediate and leads to rapid, dose-dependent suppression of the gonadotropins, LH and FSH, which then leads to dose-dependent reduction in serum E2 and progesterone levels which deprive fibroids of two

major growth stimulants (Maruol, 2004); this results in reduced bleeding as well as improvement in other fibroid-associated symptoms.

Linzagolix offers the flexibility of having been developed at both a high dose (200 mg) and a low dose (100 mg), both with and without the use of concomitant ABT in the fibroid indication.

Endometriosis:

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, down-regulation 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 2015). 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).

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.

Development of Oral GnRH receptor antagonists

In 1992, the Barbieri estrogen threshold hypothesis was introduced based on multiple observations that suggested that endometriosis and uterine fibroids are estrogen-sensitive, and that E2 concentrations in the range of 10-20 pg/mL typically result in atrophy of endometriotic lesions, vasomotor symptoms, and loss of trabecular bone. Barbieri also observed that E2 concentrations greater than 60 pg/mL were often associated with growth of lesions. The hypothesis suggested that estrogen concentrations in a “therapeutic window,” i.e., an optimal range, could partially prevent bone loss while reducing disease symptoms. By using hormonal add- back therapy in combination with full suppression GnRH analogue doses, this window could potentially be achieved with an optimal benefit/risk ratio, treating symptoms while limiting BMD loss (Barbieri 1992). This concept was further supported with a semi-mechanistic model that showed that E2 concentrations >20 pg/mL are expected to minimize BMD loss while achieving symptom relief when E2 concentrations are in the <60 pg/mL range (Riggs 2012).

In the following years, a new class of GnRH analogue, the oral GnRH receptor antagonists, was developed. 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. Elagolix (ORILISSA® prescribing information) was approved by the US FDA with a low, partial suppression dose (150 mg once daily) and a high, full suppression dose (200 mg twice daily) for the treatment of endometriosis-association pain (Taylor 2017) and as a treatment for heavy uterine bleeding due to uterine fibroids at a dose of 300 mg twice daily associated with hormonal ABT (E2 1 mg + NETA 0.5 mg) for bone protection and prevention of hot flushes.

Similarly, relugolix has been developped in a fixed combination with E2 1 mg/ NETA 0.5 mg, and approved in Europe and US for the treatment of endometriosis in adult women of reproductive age (RYEQO SmPC, MYFEMBREE® prescribing information).

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.

II.6. Natural history of the indicated condition

Uterine Fibroids:

Despite fibroids being the most common uterine tumour, their life cycle remains poorly understood. Fibroids are characterized by two histologic features—proliferation of myocytes and production of an extracellular collagenous matrix. Flake, 2013 suggested that fibroids pursue a self-limited life cycle, whereby accumulation of collagen results in decreased microvessel density, followed by myocyte injury and atrophy, with eventual senescence and involution through ischemic cellular degeneration and inanition.

It is generally thought that UF grow in a linear pattern, starting in puberty and continuing through life until the hormonal milieu changes dramatically at menopause when shrinkage is typically observed. In contrast, Ghosh, 2018 suggested that fibroid growth is variable and can range from 18 to 120% per year. Fibroids may also undergo spontaneous regression, growth and shrinkage spurts despite a stable premenopausal hormonal environment. There is conflicting evidence regarding factors that affect fibroid growth. Many studies have investigated the impact of size at

presentation; however, there is no agreement as to whether smaller or larger fibroids grow faster. With regard to the position of fibroids in relation to the uterine cavity, submucous fibroids were least likely to increase in size.

There are no current therapies for primary prevention of UF.

Endometriosis:

The natural history of endometriosis is not yet fully understood (Mettler, 2017). Several theories have arisen to explain the pathogenesis of endometriosis reaching from endometrial tissue and cell reflux over extra uterine stem cells originating from bone marrow and differentiating into endometriotic tissue to epigenic regulation of steroid hormone action in the endometrium and dysregulation in women with endometriosis (Burney and Guidice, 2012).

Establishment and growth of endometriotic tissue is oestrogen-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. However, the requirement for surgical diagnosis has been challenged as it acts as a barrier to diagnosis for patients and women with endometriosis experience important delays to diagnosis and appropriate treatment. Diagnostic delay leads to chronic untreated pain which may contribute to dysregulations of the peripheral and central nervous system and an increased risk of developing abnormal pain referral patterns and a chronic pain presentation (Cromeens, 2021). 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 an earlier initiation of treatment without prior surgery (Taylor 2018).

II.7. Important co-morbidities

Uterine Fibroids:

Considering that women typically present with UF between the ages of 35 and 55 years, the patient population is most often generally healthy. In a retrospective cohort study to report the co-morbidities of patients undergoing UAE for symptomatic UF important co-morbidities were obesity; and hypertension (Charles, 2013), likely related to the propensity of fibroids to occur in black women who are at higher risk for these conditions.

Endometriosis:

Endometriosis is most commonly a disease seen in women in between 30 and 45 years of age and is strongly associated with gynaecologic [adenomyosis, uterine fibroids, polycystic ovarian syndrome (PCOS) and systemic (autoimmune, inflammatory, psychiatric and neurological disorders)] comorbidities that impair women quality of life and global health through multiple mechanisms, influencing everyday life and work activities (Capezzuoli, 2022).

Depression and anxiety are more prevalent among patients with endometriosis compared with the general population. Comorbid depression and anxiety have been associated with worse endometriosis symptoms, poor prognosis, and lower quality of life. When accounting for age, body mass index, socioeconomic status, age at menarche, length of menstrual cycle, irritable bowel syndrome, contraceptive medications, and several pain-related phenotypes, eating disorders were associated with higher odds of endometriosis than depression and anxiety. Many patients with endometriosis experience constant pain regardless of their menstrual cycle phase. This severe chronic pain increases the risk of depression and other psychiatric comorbidities. In a clinical study, depression was detected in 86% of the patients with endometriosis and chronic pelvic pain compared with 38% of the patients without chronic pelvic pain (Koller, 2023).

Endometriosis was significantly associated with a higher burden of infertility, chronic comorbidities, utilization of healthcare services, pain medications, and antidepressants, and overall higher direct medical costs. The excess burden among young women aged 15–24 years reflects substantially higher utilization of gynaecologists visits and oral contraceptives. The women with a diagnosis of endometriosis have a significantly higher burden of infertility and chronic comorbidities, increased healthcare resource utilization and excess costs (Eisenberg, 2022).

Part II: Module SII - Non-clinical part of the safety specification

Linzagolix (also known as linzagolix choline, OBE2109, KLH-2109 or KLH-2109 choline) was discovered and initially developed by Kissei Pharmaceutical Co., Ltd (Japan). The pharmacology, pharmacokinetics and toxicology studies were conducted largely through studies performed in house by Kissei Pharmaceutical or through contract laboratories.

The non-clinical program conducted by Kissei established the pharmacodynamic properties of linzagolix and provided safety pharmacology information (*in vitro*, rat and monkey) and toxicology data from single-dose studies (rat, dog and monkey), repeated-dose studies (up to 3 months in mouse, 6 months in rat, 1 month in dog and 9 months in monkey), genotoxic, carcinogenic and reproductive toxicity studies. These studies were supported by a pharmacokinetic program which determined plasma levels of linzagolix and the human metabolite, KP017 (*O*-demethylated linzagolix). KP017 was considered a key human metabolite during early stages of development and was thus further characterised and analysed. A later performed clinical absorption, metabolism and excretion (AME) study revealed KP017 to be a minor human metabolite. Consistent with the earlier stages of development, the analysis of KP017 was maintained throughout development.

During the pharmacokinetic studies, using radiolabelled [^{14}C] linzagolix (conducted *in vitro* and in mouse, rat and monkey), since no metabolite exceeded 10% of total drug-related exposure in humans, no stand-alone toxicology metabolite studies were performed. To obtain a better understanding of possible drug-drug interactions (DDI), *in vitro* studies were performed to investigate the potential of linzagolix to induce or inhibit cytochrome P450 enzymes, to interact with drug transporters, and also to address potential interactions with calcium/iron ions, or the plasma protein binding of linzagolix and other plasma protein bound drugs. In addition, *in vitro* and *in vivo* mechanistic toxicology studies were performed in hepatocytes, bile, mice, dogs and monkeys to address specific findings, such as elevated plasma transaminases without histological correlates in the liver and abnormal gall bladder content. Furthermore, mechanistic studies were conducted in rats to characterise the effects of linzagolix on dopamine at the hypothalamus, and prolactin, E2 and P4 levels in the blood.

Pivotal safety pharmacology, general toxicology, genotoxicity, carcinogenicity, phototoxicity and reproductive toxicology studies with linzagolix were all performed according to Good Laboratory Practice (GLP).

The non-clinical program of studies was generally conducted in animals of both genders, except for a limited number of specific cases where only female animals were used. As linzagolix is indicated only for use in women, this is considered justified. No toxicity studies in juvenile animals were performed since the disease does not occur in sexually immature women. In accordance with the Guideline on the non-clinical investigation of the dependence potential of medicinal products (EMA, 2006), the non-clinical program did not include dedicated *in vivo* studies assessing the dependence potential of linzagolix. In line with the Guidance on immunotoxicity studies for human pharmaceuticals S8 (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2006), no dedicated immunotoxicity studies were required.

Table 2: Non-Clinical Studies

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
Safety Pharmacology		
Linzagolix was evaluated in a core battery of ICH S7 compliant safety pharmacology study. Cardiovascular System: The effect of linzagolix on the cardiovascular system *in vitro* was studied using human embryonic kidney 293 (HEK293) cells expressing hERG (human ether-a-go-go-related gene) channels and papillary muscles extracted from Hartley guinea pigs. Linzagolix did not affect potassium current through hERG channels up to 100 µmol/L and did not affect action potential parameters (Action potential duration 30 (APD30), APD90, APD30-90, Action Potential Amplitude (APA), resting membrane potential and maximal upstroke velocity (Vmax)) of papillary muscles up to 100 µmol/L. *In vitro* study was also conducted using Chinese hamster ovary (CHO) or HEK293 cell lines stably expressing the full-length ion channels hKv1.5, hNaV1.5 peak and late current, hCaV1.2 (L-type), hKv4.3 (Ito), hKir2.1 and hKCNQ1/E1 (Iks). Linzagolix did not affect ion currents through hKv1.5, hNaV1.5 peak and late current, hCaV1.2 (L-type), hKv4.3 (Ito), hKir2.1 and hKCNQ1/E1 (Iks) channels up to 100 µmol/L. Effect of linzagolix action on cardiovascular system *in vivo* was studied using female cynomolgus monkeys. Linzagolix did not affect blood pressure, heart rate, or electrocardiogram (ECG) parameters (PR interval, RR interval, QRS interval, QT interval, and QTcF interval) in monkeys following administration of single oral doses up to 1000 mg/kg. Overall linzagolix had no effect on the cardiovascular system *in vitro* and *in vivo*. (Initial MAA/UF/Module 2.4, section 2.4.2.3) Central Nervous System:	*Relevance to Human Usage:* No	None

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
The effect of linzagolix action on the central nervous system *in vivo* was studied using female Sprague Dawley rats (modified Irwin's method) and female cynomolgus monkeys. Linzagolix had no effect on general behaviour, locomotor activity, or body temperature in rats up to single oral doses of 2000 mg/kg and had no effect on body temperature in female monkeys following administration of single oral doses up to 1000 mg/kg. (Initial MAA/UF/Module 2.4, section 2.4.2.3) Respiratory System: The effect of linzagolix action on the respiratory system *in vivo* was studied using female cynomolgus monkeys. Linzagolix did not affect the respiratory system parameters in monkeys with administration of single oral doses up to 1000 mg/kg. (Initial MAA/UF/Module 2.4, section 2.4.2.3) Overall, linzagolix had no effect on the cardiovascular, central nervous or respiratory systems.		
Single and Repeat Dose Toxicity		
Single-dose Toxicity		
Single dose administration of 2000 mg/kg of linzagolix to rats and monkeys did not induce any signs of toxicity. The minimum lethal dose was concluded to be higher than 2000 mg/kg in both species. A non-GLP compliant single-dose dog study had a minimum lethal dose in excess of 1000 mg/kg (highest tested dose). (Initial MAA/UF/Module 2.4, section 2.4.4.1)	*Relevance to Human Usage:* No	None
Repeat Dose Toxicity		

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
Twelve oral repeat-dose toxicity studies were performed in mice, rats, dogs and monkeys to investigate the sub-acute and chronic toxicity of linzagolix. Three non-GLP compliant studies were dose-range finding studies intended to supply information about the systemic toxicity of linzagolix and the doses to be selected for subsequent formal GLP-compliant toxicity studies (Initial MAA/UF/Module 2.4, section 2.4.4.2). The pivotal repeated-dose toxicity studies are considered to be the 4- and 13-week oral toxicity testing on mice, 4-, 13- and 26-week oral toxicity testing on rats, the 4-week oral toxicity testing on dogs and the 4-, 13- and 39-week oral toxicity testing on monkeys. These studies used dose levels between 40- 1500 mg/kg/day in mice, 20-2000 mg/kg/day in rats and, 10 -1000 mg/kg/day in dogs, or monkeys. With the exception of one dead and one moribund mouse treated at 1500 mg/kg/day, and one dead mouse at 750 mg/kg/day (suspected misgavage) in the 13-week study, pivotal toxicology studies in the mouse, rat, dog and monkey did not identify any evidence of overt toxicity following repeated oral administration of linzagolix but expected exaggerated pharmacological findings typically associated with disruption of the hypothalamus-pituitary-gonadal axis. Key findings comprised changes in reproductive organs such as atrophy of testes, ovaries, prostate, seminal vesicle, epididymites, mammary gland, oviducts, uterus and/or vagina in all species along with the atrophy in mammary glands and decreased pituitary glands weights in mice and rats. Interrupted menses or prolongations of the menstrual cycle were seen in monkeys. At high linzagolix doses, associated findings were altered body weights (decreased body weight in males of all species (and female dogs) and increased body weights in female mice and rats) as well as decreases in red blood cell (RBC) parameters in mice and rats. The latter was accompanied by increased extramedullary haemopoiesis, spleen weights and reticulocyte counts. Other observations were follicular dilatation of the thyroid gland in rats and increased liver enzymes in dog and monkey. Increased liver enzymes correlated with increased liver weights in the 4-week dog and the 39-week monkey	*Relevance to Human Usage:* Yes GnRH modulates LH and FSH secretion from the pituitary and thus it is expected that administration of toxicological dose of a GnRH antagonist would result in atrophy of reproductive organs – as was observed in mouse, rat, dog, and monkey studies – with resulting decreased pituitary weights in mice and rats and the absence or prolongation of menses in monkeys. Similar findings were previously described during repeated dose toxicity studies with GnRH antagonists in rats and monkey (Sundaram, 1990; Chester, 1991). These studies also describe alterations in body weights which were comparable to the observations with linzagolix and could be explained by a decrease in sex steroid hormones (Mooradian, 1987; Mirand, 1966). Red blood cell parameters were decreased in mice and rats and were accompanied by adaptive changes such as increased circulating reticulocyte counts, bone marrow polychromatic erythroblasts, extramedullary haemopoiesis and increased spleen weights. These changes were considered to be a down-stream consequence of the altered hypothalamus-pituitary activity and the suppression of sex steroid hormone release by linzagolix. Sex steroid hormones were reported to enhance erythropoiesis (Mooradian, 1987; Mirand, 1966) and similar changes were observed in published GnRH antagonist studies (Sundaram, 1990; Chester, 1991). Alterations in RBC parameters were considered to be of low safety concern.	Yes (as potential clinical consequence of elevated liver enzymes) *Liver Toxicity:* Important Potential Risk

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
study and were associated with increased serum lipid parameters in the dog (Initial MAA/UF/Module 2.4, section 2.4.4.2). Toxicologically relevant findings of linzagolix comprised histological tubular changes in the kidneys of mice and rats, associated in the latter with increases in serum creatinine, urine volume and urinary excretion of sodium and chloride, and dark granules in the gallbladders of mice and dogs (Initial MAA/UF/Module 2.4, section 2.4.4.2). Studies including non-dose recovery periods showed at least partial recovery from all pharmacological and/or toxicological effects of linzagolix. Overall, the toxicological profile of linzagolix emerging from repeated-dose toxicity studies appears largely to be a consequence of its pharmacological activity as a GnRH antagonist. During pivotal toxicology studies, dose levels of 200 and 10 mg/kg/day linzagolix were shown to be the No-adverse effect level (NOAEL) in the main toxicology species rat and monkey, respectively, and gave exposures (Area Under the Curve (AUC) total / AUC free) of 2700000 / 15000 and 310000 / 11000 ng•h/mL. Therapeutic indices for a clinical dose of 200 mg/day were 6.7 / 4.6 and 0.8 / 3.6, respectively. Therefore, based on overall non-clinical toxicology profile, there is a low safety concern for the treatment of women with UF at doses up to 200 mg/day (Initial MAA/UF/Module 2.4, section 2.4.4.2).	The thyroid gland was identified as a target organ in rats, showing increased incidences of dilated thyroid follicles. These follicle changes were considered to be related to decreased thyroid stimulating hormone (TSH)-mediated endocytosis of colloid (Capen, 1991). In previous studies it was shown that gonadectomy decreases serum TSH concentrations, TSH receptor concentrations in the thyroid glands and TSH binding to thyrocytes in rats (Banu, 2001), and induces microscopic enlargement of the thyroid follicles in female rats (Sosić-Jurjević, 2006). Therefore, these changes were probably secondary to the pharmacological effects of linzagolix in the rat and of low safety concern. In dogs and monkeys, increased serum liver enzyme activity in the absence of histopathological correlates, increased serum lipid parameters and associated increased liver weights were specifically addressed in a set of mechanistic toxicology studies (Initial MAA/UF/Module 2.4, section 2.4.4.7). These studies concluded that linzagolix was not cytotoxic for hepatocytes and that increases in serum alanine aminotransferase (ALT) and glutamate dehydrogenase (GLDH) were likely to be attributable to induction of ALT and GLDH in the liver by the pharmacological effects of linzagolix. The findings were considered to be of low concern due to therapeutic indices of 0.8 (3.6 for $AUC_{unbound}$) and 5.5 ($AUC_{unbound}$ /plasma protein binding not available in dogs) at the NOAEL of the monkey (10mg/kg/day @ 39-week) and dog (100 mg/kg/day @ 4-week) studies, respectively, the absence of histological liver findings and the confirmation of reversibility following treatment free recovery periods.	

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
	The mechanisms of renal changes in rats and mice remained unclear. These findings were, however, considered to be of low safety concern given the therapeutic indices of 5.2 (10.1 for $AUC_{unbound}$) and 6.7 (4.6 for $AUC_{unbound}$) at the NOAEL exposure for mice (40 mg/kg/day @ 13-week) and rats (200 mg/kg/day @ 26-week). Mechanistic investigations were carried out on the dark granules that were observed in the gallbladder in the 4-week study in dogs and the biliary sand that was observed in the gallbladder in the 13-week study in mice (Initial MAA/UF/Module 2.4, section 2.4.4.7). Abnormal contents formed in the gallbladders of dogs and mice resulted from precipitation as a result of a concentration of linzagolix that exceeded its solubility in the bile which was linked to the pharmacokinetics of linzagolix. The mean solubility of linzagolix in human (female) bile was 6410 µg/mL. Assuming similar linzagolix bile to blood ratios as for dogs and mice, the maximum linzagolix bile concentration in Caucasian women would be 3.9 – 5.5% or 2.9 – 4.1% of the saturation concentration, respectively (Study 32061). Thus, the probability of developing abnormal gallbladder content in humans is low.	
Genotoxicity		
The genotoxicity of linzagolix was investigated via a standard combined genotoxicity study, with an unscheduled DNA synthesis (UDS) study as an additional study. Linzagolix was found to be negative in all genetic toxicity studies with the exception of the chromosomal aberration test. In the chromosomal aberration test, linzagolix demonstrated clastogenicity at the high concentrations demonstrating clear cellular toxicity, both, in the presence and absence of a metabolic activation system (rat liver S9 mix). Because this effect on chromosomal aberration is a change observed only at concentrations indicating pronounced cytotoxicity and	*Relevance to Human Usage:* No	None

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
the results were negative in both the *in vivo* micronucleus *in vivo* UDS studies, it was considered not significant in terms of toxicological relevance (Initial MAA/UF/Module 2.4, section 2.4.4.3).		
Carcinogenicity		
Carcinogenic potential of linzagolix was assessed in the 6-months transgenic Tg rasH2 mice assay and a 2-year study in the Wistar rat at doses up to 500 mg/kg/day. Linzagolix had no effect on the survival rate and did not induce tumours. Marginal increases in the frequency of mammary gland and endometrial adenocarcinoma in Wistar rats were assessed and considered to be incidental. Non-carcinogenic histopathological findings in the ovary and uterus (mouse) or ovary and female mammary gland (rat) were considered to be related to the pharmacological action of linzagolix (Initial MAA/UF/Module 2.4, section 2.4.4.4).	*Relevance to Human Usage:* Yes The higher incidence of mammary gland adenocarcinoma was observed in female rats (at the mid dose, 50 mg/kg/day), and was not dose dependent (mammary gland adenocarcinoma incidence was lower at the high dose, 500 mg/kg/day). In addition, the incidences of lobular hyperplasia, a precursor of adenocarcinoma, in females at the mid and high dose groups were lower than the corresponding rates in the control groups. Therefore, the higher incidence of mammary gland adenocarcinoma was considered to be likely incidental and not related to linzagolix treatment. Observed endometrial adenocarcinoma incidences were slightly above published historical background incidences of carcinogenicity studies (16.7% vs 14%) in Wistar rats and within the range of incidences reported in a longevity study of this strain (up to 39%). The test article is not genotoxic or tumorigenic in Tg RasH2 mice, its pharmacological mode of action does not favour the formation of endometrial adenocarcinoma and no pre-neoplastic lesions were observed. Based on the above facts, the reported endometrial adenocarcinomas in the high dose group are thus considered to be likely incidental. The mechanism mediating the increase in endometrial adenocarcinoma and mammary gland adenocarcinoma is unclear; it does not appear to be related either to genotoxicity/carcinogenicity, or to the primary pharmacological activity of linzagolix. However, the data	Yes *Uterine endometrial and mammary gland adenocarcinoma:* Important Potential Risk

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
	available are not sufficient to conclude on the potential clinical relevance of these non-clinical findings. Therefore, "*Uterine endometrial and mammary gland adenocarcinoma*" was included as important potential risk.	
Reproductive and Developmental Toxicity		
<u>*Fertility and Early Embryonic Development:*</u> In the female fertility study (0.16, 0.8, 4, 20, 100 mg/kg/day) and early embryonic development toxicity study (100, 300, 1000 mg/kg/day), administration of 20 and 100 mg/kg/day to female rats for 4 weeks or longer before mating resulted in effects on the oestrous cycles and the number of implantations, which were attributable to the pharmacological effect of linzagolix. These findings were reversible at the highest tested dose of 100 mg/kg/day suggesting that linzagolix has no irreversible effects on the reproductive function. When linzagolix was administered to female rats during early pregnancy, doses up to 300 mg/kg/day did not affect the early embryonic development; a dose of 1000 mg/kg/day did, however, result in small conceptuses (Initial MAA/UF/Module 2.4, section 2.4.4.5.1). <u>*Embryo-foetal Development:*</u> Embryo-foetal development studies showed that oral doses of 300 mg/kg/day were associated with increased incidences of embryo-foetal mortality and total litter loss in pregnant rats; doses of 30 mg/kg/day resulted in abolished pregnancy in rabbits. These effects were considered to be related to the pharmacological effects of linzagolix. However, among foetuses in these studies, there was no significant effect on bodyweight or evidence of a teratogenic effect. A NOAEL of 100 and 3 mg/kg/day was established for developmental toxicity in rats	<u>*Relevance to Human Usage:*</u> Yes Due to its mechanism of action, linzagolix prevented conception and reduced implantation in rats and resulted in embryo-foetal mortality, total litter loss or abolished pregnancy in rat and rabbit embryo-foetal studies. There were no teratogenic effects and no adverse effect on the pre- and postnatal development of the offspring. Linzagolix is contraindicated during pregnancy and in women of childbearing potential at risk of pregnancy and not using contraception. Women of childbearing potential should use effective non-hormonal contraception.	Yes <u>*Embryo-foetal toxicity:*</u> Important potential risk

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
and rabbits, respectively (Initial MAA/UF/Module 2.4, section 2.4.4.5.2). *Pre/Post-natal Development:* Treatment with linzagolix at 300 mg/kg/day resulted in an effect on maternal function and prenatal embryo/foetal development which comprised total litter loss in three dams, and a decrease in the gestation index. There were no effects on clinical observation, food consumption, necropsy findings, gestation length, the number of implantation sites, the number of offspring at birth, the number of live births, the number of stillborns, the sex ratio, the birth index, the viability index on Day 4 after birth, the weaning index of F0 animals, and the postnatal body weights. There were neither abnormal clinical signs nor distinct macroscopic abnormalities for the F1 animals attributable to treatment with linzagolix. For physical development (differentiations), sensory functions, learning and behaviour, oestrous cycles, and reproductive function of the F1 animals, no significant effects were found. In addition, no notable clinical signs or changes in the body weights and food consumption in F1 dams were observed during the gestation period. No offspring had any external abnormality. Overall, the NOAEL for reproductive function and prenatal embryo/foetal development was 100 mg/kg/day, and 300 mg/kg/day for maternal toxicity and postnatal development of the offspring (F1) (Initial MAA/UF/Module 2.4, section 2.4.4.5.3).		
Other Toxicology Studies		
Phototoxicity		
Phototoxicity was assessed *in vitro* and *in vivo*. *In vitro*, linzagolix was observed to have phototoxic effects, which could not be confirmed in an *in vivo* assay. The *in vivo* assessment in rats at doses of 10, 100, 1000 mg/kg showed that linzagolix administration did not result in any	*Relevance to Human Usage:* No	None

Type of Non-Clinical Study	Relevance to Human Usage	Safety Concern
reactions indicative of phototoxicity (Initial MAA/UF/Module 2.4, section 2.4.4.8).	There was no incidence of photosensitivity reactions observed as TEAEs (Treatment Emergent Adverse Events) with linzagolix during the clinical development programme (CDP).	

Part II: Module SIII - Clinical trial exposure

Linzagolix is an orally active, non-peptide gonadotropin releasing hormone (GnRH) receptor antagonist. Linzagolix (also known as linzagolix choline, OBE2109 and KLH-2109) was discovered and initially developed by Kissei Pharmaceutical Co., Ltd. (Kissei, Japan) for the treatment of endometriosis. In 2015, ObsEva SA acquired the license to develop, register and commercialise linzagolix worldwide excluding some Asian countries.

ObsEva carried out a development program of linzagolix in two indications: for the management of heavy menstrual bleeding (HMB) associated with uterine fibroids (UF) and endometriosis-associated pain (EAP).

On 20 Nov 2020, ObsEva Ireland Ltd submitted a marketing authorisation application to the European Medicines Agency (EMA) for YSELTY® (linzagolix) through the centralised procedure (Procedure No. EMEA/H/C/005442/0000). On 14 June 2022, the European Commission granted Marketing Authorisation for YSELTY for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age (Marketing Authorisation number EU/1/21/1606/001-002). On June 2022, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisation for YSELTY in Great Britain through the European Commission Decision Reliance Procedure.

Since November 2022, Theramex Ireland Ltd (Theramex) is the new YSELTY Marketing Authorisation Holder (MAH) in both territories.

Theramex is submitting the current Type II Variation Application to support an extension of indication for the regimen of 200 mg linzagolix once daily with concomitant hormonal add-back therapy (ABT) in the indication of endometriosis-associated pain.

The safety of linzagolix has been evaluated in 27 clinical trials, 19 of which were included in the initial Marketing Authorisation Application (MAA) related to the treatment of uterine fibroids, and 8 additional trials (one phase 1, two phase 2, four Phase 3 and one observational study) which, though not part of the initial MAA. The application for extending the indication is primarily built on the results from the 4 completed, Phase 3 clinical studies.

The safety of linzagolix has been evaluated in 6 Phase 3 trials:

- 2 trials in subjects with UF (PRIMROSE 1 and 2) each of which included a 6-month placebo controlled treatment period and treatment extension period up to Month 12. Safety data from these trials formed the basis of safety evaluation in the initial MAA.
- 4 trials in subjects with moderate-to-severe EAP which included 2 trials with 6-month treatment period (EDELWEISS 3 and EDELWEISS 2) and 2 trials offering optional treatment extension up to Month 12 (EDELWEISS 6 and EDELWEISS 5, respectively). Study EDELWEISS 2 and its extension, Edelweiss 5, were prematurely terminated due to recruitment issues and thus mainly contribute to the pooled datasets.

As of 05 November 2023, a total of 2882 subjects have received at least one dose of linzagolix. Over 1450 patients have been exposed to linzagolix in Phase 3 clinical trials in the UF and EAP indications (Table 3). 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. Of the 744 patients who were

exposed to the 200 mg+ABT dosing regimen, 492 were patients with UF treated in the PRIMROSE trials and 252 were patients with endometriosis treated in the EDELWEISS trials.

Table 3: Phase 3 studies with linzagolix contributing to the safety evaluation of the linzagolix 200 mg+ABT dosing regimen

TRIAL	Total exposed to any linzagolix dosing regimen[a]	Total exposed to linzagolix 200 mg +/- ABT	Total exposed to linzagolix 200 mg+ABT	Status of the study
Indication: Endometriosis-associated pain				
EDELWEISS 2 & its extension EDELWEISS 5	64	33[b]	33[b]	Terminated
EDELWEISS 3 & its extension EDELWEISS 6	437	219[b]	219[b]	Completed
Indication: Uterine fibroids				
Pooled dataset: PRIMROSE 1 &PRIMROSE 2	951	541[c]	492[c]	Completed
Total	**1452**	**793**	**744**	

ABT = add-back therapy
a Excludes subjects randomised to placebo who were never switched to active treatment.
b Includes subjects from the placebo group who switched to 200 mg+ABT regimen in the extension studies.
c Includes subjects treated with 200 mg alone or placebo during the first 24 weeks who were then switched to the 200 mg+ABT regimen from Week 24 to Week 52.
Source: Module 2.7.4.1.2

Within the Risk Management Plan (RMP) document, safety data are presented by Phase of the clinical development program: Phase 3 studies, followed by Phase 2 studies and Phase 1 studies. The emphasis is placed on the Phase 3 trials conducted in the target indication of UF and EAP with supportive safety data from Phase 2 studies in women with endometriosis and Phase 1 studies in healthy women volunteers.

Safety Analysis Sets:

Phase 3 studies (EAP):

Study periods

In this document, the emphasis is on the safety data from two Phase 3 trials (EDELWEISS 3 and EDELWEISS 2) and their extensions (EDELWEISS 6 and EDELWEISS 5, respectively). The results are presented for two study periods:

- Period 1 (from Day 1 of treatment to Month 6) include a side-by-side data presentation from the EDELWEISS 3 and EDELWEISS 2 studies.
- Period 2 (from Month 6 to Month 12) include a side-by-side data presentation from the extension studies EDELWEISS 6 and EDELWEISS 5. As only very limited data are available from Month 12 visit in the prematurely terminated EDELWEISS 5 trial, data from this study is included in the cumulative evaluation of treatment-emergent adverse events (TEAEs) from

Month 6 to Month 12 but not for assessments made at a single timepoint at Month 12, such as DXA scans or blood draws for laboratory assessments.

- Follow-up: include side-by-side presentation from the 6-month drug-free follow-up after 6 months of treatment in studies EDELWEISS 3 and EDELWEISS 2 for subjects who did not enter the extension studies, and after 12 months of treatment in extension study EDELWEISS 6. Note that limited data were available from the follow-up period of extension study EDELWEISS 5.

The analysis populations for the evaluation of safety in the Phase 3 EDELWEISS studies are as follows:

- **Safety Analysis Set (SAF)**: All randomised subjects who received at least one dose of double-blind study drug irrespective of the treatment received. Subjects were analysed according to the treatment received. The SAFs from EDELWEISS 3 and EDELWEISS 2 trials were used to examine safety in Period 1 (from Day 1 to Month 6).
- **Follow-up Safety Set (FU SAF)**: All randomised subjects who entered the drug free follow-up period. Subjects were analysed according to the treatment received (during the preceding treatment period). Subjects eligible to enter follow-up included those who either (1) completed at least 3 months of treatment prior to discontinuing, or (2) completed the full 6 months of treatment and did not enter the separate extension study. The FU SAF was used to examine safety during the drug-free post-treatment follow-up (PTFU) in EDELWEISS 3 and EDELWEISS 2 trials.
- **Extension Safety Analysis Set (ESAF)**: All subjects randomised into the extension study who received at least one dose of study drug irrespective of the treatment received. Subjects were analysed according to treatment received. The ESAFs from EDELWEISS 6 and, when feasible, EDELWEISS 5 were used to examine safety in treatment Period 2 (from Month 6 to Month 12).
- **Follow-up Extension Safety Analysis Set (ExFU SAF):** All subjects randomised into the extension study who received at least one dose of study drug irrespective of the treatment received, and who entered the Post-Treatment Follow-Up Period. Subjects were analysed according to treatment received. The ExFU SAF was used to examine safety during the drug-free post-extension-treatment follow-up (ExFU) in EDELWEISS 6 and, when feasible, EDELWEISS 5 trials.

Phase 3 studies (UF):

The following analysis populations were considered for the evaluation of safety in the Phase 3 PRIMROSE studies:

- The (Week 24) Pooled Safety Analysis Set (N=1037) was defined as all randomised subjects in the two Phase 3 studies PRIMROSE 1 and PRIMROSE 2, who received at least one dose of double-blind study drug irrespective of the treatment received. Subjects were analysed according to the treatment received.
- The (Week 52) Pooled Safety Analysis Set (N=757) was defined as all subjects from the pooled safety analysis set who received at least one dose of double-blind study drug after

Week 24 irrespective of the treatment received during the 2nd treatment period. Subjects were analysed according to treatment received.

Pooled Safety analysis sets (Up to Week 52)

	Placebo (N=209) n (%)	Linzagolix 100 mg (N=199) n (%)	Linzagolix 100 mg + ABT (N=211) n (%)	Linzagolix 200 mg (N=210) n (%)	Linzagolix 200 mg + ABT (N=208) n (%)	Total (N=1037) n (%)
Pooled Safety Analysis Set	209 (100)	199 (100)	211 (100)	210 (100)	208 (100)	1037 (100)
Pooled Week 52 Safety Analysis Set	154 (73.7)	141 (70.9)	146 (69.2)	162 (77.1)	154 (74.0)	757 (73.0)

ABT=add back therapy
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-3

- Follow-up Safety Analysis Set (N=234 in the PRIMROSE 1 study and N=339 in the PRIMROSE 2 study) included all subjects from the safety analysis set who entered the follow-up period. Subjects were analysed according to treatment received.

Follow-up Safety Analysis Set (PRIMROSE 1)

	Placebo Placebo (N=53) n (%)	Placebo Linzagolix 200 mg+ABT N=51 n (%)	Linzagolix 100 mg (N=100) n (%)	Linzagolix 100 mg + ABT (N=109) n (%)	Linzagolix 200 mg Linzagolix 200 mg+ABT (N=106) n (%)	Linzagolix 200 mg + ABT (N=107) n (%)	Total (N=526) n (%)
Follow-up Safety Analysis Set	22 (41.5)	19 (37.3)	50 (50.0)	42 (38.5)	45 (42.5)	56 (52.3)	234 (44.5)

ABT=add back therapy
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-4

Follow-up Safety Analysis Set (PRIMROSE 2)

	Placebo (N=105) n (%)	Linzagolix 100 mg (N=99) n (%)	Linzagolix 100 mg + ABT (N=102) n (%)	Linzagolix 200 mg (N=104) n (%)	Linzagolix 200 mg + ABT (N=101) n (%)	Total (N=511) n (%)
Follow-up Safety Analysis Set	75 (71.4)	60 (60.6)	68 (66.7)	63 (60.6)	73 (72.3)	339 (63.4)

ABT: add-back therapy.
One subject from 200 mg was treated in Period 2 but did not switch to 200 mg +ABT as planned. This subject is included in the Week 52 Safety Analysis Set and the follow-up analysis set.
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-5

Data pooling across Phase 3 clinical program

Pooled analysis sets from the EDELWEISS *and* PRIMROSE *Phase 3 trials*

Pooled safety analyses were performed in order to obtain more precise estimates and to increase the sensitivity to detect uncommon events for the 200 mg+ABT dose. The specifications for the pooled analyses were described in the SCS Statistical Analysis Plan (SAP), issued on 10 October 2023 and included in Module 5.3.5.3 of this dossier.

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).

Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 was used for adverse event (AE) coding in each Phase 3 trial, and thus for the pooled analyses.

The following analysis populations were considered for the evaluation of safety across the Phase 3 linzagolix trials in subjects with endometriosis (EDELWEISS trials) and subjects with uterine fibroids (PRIMROSE trials):

- **Pooled Safety Analysis Set in Period 1** (SAFP1; N=797): All randomized subjects from Period 1 Pooling who received at least one dose of placebo or linzagolix 200mg with ABT in Period 1. Subjects will be analysed according to the treatment received.
- **Pooled Safety Analysis Set in Period 2** (SAFP2; N=662): All randomized subjects from Period 2 Pooling who received at least one dose of Placebo or Linzagolix 200mg with ABT in Period 2. Subjects will be analysed according to the treatment received.

Comparisons to studies previously submitted as part of the initial MAA

Comparisons to the pooled dataset of 1037 subjects treated in the PRIMROSE 1 and PRIMROSE 2 studies, which was submitted in the initial MAA in the uterine fibroid indication, are made with the endometriosis population in the EDELWEISS Phase 3 trials, where relevant.

Phase 2 studies:

- Safety analyses in individual studies were based on the Safety Set, defined as all patients who took at least one dose of study treatment. Subjects were analysed according to the treatment received.
- In the EDELWEISS study, safety of subjects treated for at least 24 weeks was evaluated based on the Safety set (N=327) and those treated for up to 52 weeks in the Treatment Extension Analysis Set (N=176). The safety of subjects entering the drug-free follow-up period of 24 weeks was evaluated for the Follow-up Safety Set (N=65; those entering follow-up after 24 weeks of treatment) and the Follow-up Extension Analysis Set (N=104; for those entering follow-up after 52 weeks of treatment).

Phase 1 studies:

Safety analyses in individual studies were based on the Safety Set, defined as all patients who took at least one dose of study treatment. Subjects were analysed according to the treatment received.

Demographics:

Demographic and other baseline characteristics are presented below for each phase of the clinical developmental program, as the subject populations varied: women with endometriosis and uterine fibroids in Phase 3 trials, women with endometriosis in Phase 2 trials, and healthy women volunteers in the Phase 1 trials.

Phase 3 studies (EAP):

EDELWEISS 3 and EDELWEISS 2

Subjects enrolled in the Phase 3 studies were representative of the target population of adult patients with endometriosis. The pivotal EDELWEISS 3 trial was conducted in Europe (Austria, Bulgaria, Czech Republic, France, Hungary, Poland, Romania, Spain, and Ukraine) and the US, with most of the subjects (460/486; 95%) randomised at European study sites. Thus, the subject population enrolled in the EDELWEISS 3 trial closely reflects the characteristics of a European endometriosis patient population. The prematurely terminated EDELWEISS 2 study (N=84), was conducted in the US and Canada.

The demographic and other baseline characteristics were comparable across treatment groups in the EDELWEISS 3 and EDELWEISS 2 trials (Table 4). In both trials, subjects were predominantly white (98.6% vs 82.1%, respectively) with 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/m^2 vs 28.10 (6.79) kg/m^2, respectively (EDELWEISS 3 CSR, Table 14.1.6.1, EDELWEISS 2 CSR, Table 14.1.6).

Extension studies EDELWEISS 6 and EDELWEISS 5

Given that 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 and the Extension Safety Analysis Sets in the extension study and thus are not presented in this document (see EDELWEISS 6 CSR, Section 11.2; EDELWEISS 5 CSR, Section 11.2). Notably, most of the eligible subjects in the EDELWEISS 3 parent study opted to continue treatment in the extension study (356/484). Due to early termination of EDELWEISS 2 and EDELWEISS 5 studies, only 30/84 subjects were enrolled in the extension study EDELWEISS 5 at the time of study termination.

Eligibility criteria for entry into extension studies (see Module 2.7.3.1.3.2) 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 due to this exclusion criterion.

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. Median DXA readings ranged from 1.054 to 1.262 g/cm^2 for the lumbar spine, from 0.853 to 1.005 g/cm^2 for the femoral neck, and from 0.960 to 1.033 g/cm^2 for the total hip. Median Z-scores ranged from 0.025 to 0.685 for the lumbar spine, from -0.240 to 0.405 for the femoral neck, and from 0.030 to 0.725 for the total hip. There were no subjects with minimum Z-scores lower than -2.0 at baseline in the Extension Safety Analysis Sets.

Phase 3 studies (UF):

PRIMROSE 1 and 2

In the Phase 3 trials, the mean age, weight and body mass index (BMI) of the subjects were similar for subjects in all groups. For the overall population of 1037 subjects, the mean (± Standard Deviation (SD)) age was 42.2 (5.6) years (range 20 to 58 years), mean (± SD) weight was 81.29 (19.13) kg (range 42.0 to 143.7 kg), and the mean (± SD) BMI was 29.87 (6.85) kg/m^2 (range 16.8 to 58.6 kg/m^2). The median BMI of 28.9 kg/m^2 (and Q1 of 24.6 kg/m^2 near the upper range of normal BMI) suggest that almost three quarters of the population was overweight to morbidly obese (maximum of 58.6 kg/m^2) per CDC BMI categories. There were differences between the two PRIMROSE studies in terms of race, baseline weight and BMI (Initial MAA/UF/Table 2.7.4-18).

PRIMROSE 1 was conducted exclusively in USA, while PRIMROSE 2 enrolled patients in Europe (91%) and the USA (9%). As such, the racial composition of the two studies differed: Black subjects represented 63.1% of the patient population in PRIMROSE 1 but only 4.9% in PRIMROSE 2. Subjects in PRIMROSE 1 had a higher mean weight (88.4 kg vs 74.0 kg) and mean BMI (32.7 kg/m^2 vs 27.0 kg/m^2) compared to those in PRIMROSE 2. A higher percentage of PRIMROSE 1 subjects were anaemic (Haemoglobin (Hb)<12 g/dL) compared to the PRIMROSE 2 population (73.6% vs 56.2%), had moderate to severe anaemia (Hb<10 g/dL) (31.9% vs 18.4%), and correspondingly lower mean Hb level (10.7 g/dL vs. 11.5 g/dL) despite having a lower mean menstrual blood loss (MBL) (198.5 mL vs. 216.5 mL) at baseline compared to those in the PRIMROSE 2 study.Baseline demographic parameters were generally consistent between the Pooled Safety Analysis Set and for the 757 subjects that were included in the Week 52 Pooled Safety Analysis (Initial MAA/UF/Module 2.7.4, table 2.7.4-19). Overall, 68.6% of White subjects remained at Week 52 compared to 63.5% at Week 24.

Data pooling across Phase 3 clinical program

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

The demographic characteristics were comparable between the placebo and LGX 200 mg+ABT treatment groups in the Pooled SAF for Period 1 (N=797). Subjects were predominantly white (79.9%) with a mean (SD) age 38.6 (7.3) years. The mean (SD) weight was 74.24 (18.33) kg and the mean (SD) BMI was 27.27 (6.70) kg/m^2(Table 4).

Table 4: Demographic characteristics of the study populations in the Pooled analysis of the Phase 3 trials EDELWEISS 3, EDELWEISS 2 SAFs, E3/E2/P1/P2 Pooled SAF for Period 1

	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)**
Age (years)								
n (missing)	162 (0)	160 (0)	162 (0)	27 (0)	28 (0)	29 (0)	398 (0)	399 (0)
Mean (SD)	34.9 (6.8)	35.1 (6.4)	34.6 (6.8)	32.1 (6.9)	32.6 (7.2)	33.4 (6.4)	38.7 (7.3)	38.6 (7.3)
Median	35.0	35.5	35.0	31.0	32.5	34.0	40.0	40.0
Q1; Q3	31.0; 40.0	31.0; 40.0	30.0; 40.0	26.0; 37.0	28.0; 36.0	29.0; 37.0	34.0; 45.0	34.0; 44.0
Min; Max	18; 49	19; 49	18; 49	21; 46	20; 47	19; 45	18; 54	18; 53
Race (n,%)								
n (missing)	162 (0)	160 (0)	162 (0)	27 (0)	28 (0)	29 (0)	398 (0)	399 (0)
American Indian or Alaska Native	0	0	1 (0.6)	1 (3.7)	0	0	2 (0.5)	2 (0.5)
Asian	0	1 (0.6)	0	1 (3.7)	1 (3.6)	0	1 (0.3)	3 (0.8)
Black or African American	2 (1.2)	1 (0.6)	1 (0.6)	5 (18.5)	4 (14.3)	1 (3.4)	78 (19.6)	71 (17.8)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	1 (0.3)

	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)**
White	160 (98.8)	158 (98.8)	159 (98.1)	20 (74.1)	22 (78.6)	27 (93.1)	317 (79.6)	320 (80.2)
Other	0	0	0	0	1 (3.6)	0	0	0
Multiple	0	0	1 (0.6)	0	0	1 (3.4)	0	2 (0.5)
Ethnicity (n,%)								
n (missing)	162 (0)	160 (0)	162 (0)	27 (0)	28 (0)	29 (0)	398 (0)	399 (0)
Hispanic or latino	1 (0.6)	5 (3.1)	7 (4.3)	9 (33.3)	7 (25.0)	12 (41.4)	37 (9.3)	42 (10.5)
Not hispanic or latino	161 (99.4)	155 (96.9)	155 (95.7)	18 (66.7)	20 (71.4)	17 (58.6)	360 (90.5)	356 (89.2)
Not reported	0	0	0	0	1 (3.6)	0	1 (0.3)	1 (0.3)
Weight (kg)								
n (missing)	162 (0)	160 (0)	161 (1)	27 (0)	28 (0)	29 (0)	398 (0)	398 (1)
Mean (SD)	65.81 (11.96)	67.73 (14.45)	65.75 (14.75)	71.280 (16.050)	78.130 (16.904)	76.540 (20.207)	74.08 (17.55)	74.41 (19.10)
Median	63.40	64.00	61.00	69.950	75.750	72.120	70.00	70.00
Q1; Q3	58.00; 70.00	58.25; 74.20	56.00; 73.00	60.240; 83.400	68.475; 88.905	65.320; 84.820	60.24; 83.92	60.00; 85.40
Min; Max	46.1; 110.0	46.0; 117.5	47.0; 143.9	43.09; 103.42	48.99; 113.40	48.08; 135.00	43.1; 140.6	47.0; 143.9
BMI (kg/m^2)								
n (missing)	162 (0)	160 (0)	161 (1)	27 (0)	28 (0)	29 (0)	398 (0)	398 (1)

	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)**
Mean (SD)	24.14 (4.44)	24.60 (5.23)	24.09 (5.17)	26.61 (5.84)	29.08 (5.57)	28.54 (8.48)	27.09 (6.33)	27.45 (7.05)
Median	23.00	23.35	22.90	26.00	28.50	26.30	25.77	25.95
Q1; Q3	21.00; 26.40	20.50; 27.10	20.40; 26.30	22.30; 30.60	26.10; 31.40	24.00; 30.10	22.35; 30.60	21.61; 30.76
Min; Max	18.0; 40.9	17.4; 41.7	17.6; 52.8	15.3; 37.9	19.1; 44.3	19.4; 58.4	15.3; 53.2	16.8; 58.4

ABT = add-back therapy; E = EDELWEISS study in endometriosis; LGX = linzagolix; P = PRIMROSE study in uterine fibroids; SD = standard deviation

Source: EDELWEISS 3 CSR, Table 14.1.6.1; EDELWEISS 2 CSR, Table 14.1.6; SCS Supplement Table 14.1.2.1.

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

In the Pooled SAF for Period 2 (N=662), the demographic characteristics were comparable between the treatment groups (Table 5) and similar to those in the parent studies in the Pooled SAF for Period 1 (Table 4). Subjects were predominantly white (77.5%) with a mean (SD) age 40.2 (7.1) years. The mean (SD) weight was 76.24 (18.24) kg and the mean (SD) BMI was 27.95 (6.64) kg/m^2.

Table 5: Demographic and baseline characteristics for the study populations in the Pooled analysis of the EDELWEISS 6, EDELWEISS 5, PRIMROSE 1, and PRIMROSE 2 Pooled SAF for Period 2

	E6/E5/P1/P2					
	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)**
Age (years)						
n (missing)	31 (0)	184 (0)	161 (0)	286 (0)	631 (0)	662 (0)
Mean (SD)	41.7 (7.3)	40.2 (7.3)	42.0 (5.9)	39.0 (7.4)	40.1 (7.1)	40.2 (7.1)
Median	41.0	42.0	43.0	40.0	41.0	41.0
Q1; Q3	37.0; 48.0	36.0; 46.0	39.0; 46.0	35.0; 44.0	36.0; 46.0	36.0; 46.0
Min; Max	22; 53	18; 54	20; 53	18; 53	18; 54	18; 54
Race (n,%)						
n (missing)	31 (0)	184 (0)	161 (0)	286 (0)	631 (0)	662 (0)
American Indian or Alaska Native	1 (3.2)	0	0	0	0	1 (0.2)
Asian	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Black or African American	19 (61.3)	27 (14.7)	53 (32.9)	45 (15.7)	125 (19.8)	144 (21.8)
Native Hawaiian or Other Pacific Islander	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
White	11 (35.5)	157 (85.3)	107 (66.5)	238 (83.2)	502 (79.6)	513 (77.5)

	E6/E5/P1/P2					
	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)**
Other	0	0	1 (0.6)	0	1 (0.2)	1 (0.2)
Multiple	0	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Ethnicity (n,%)						
n (missing)	31 (0)	184 (0)	161 (0)	286 (0)	631 (0)	662 (0)
Hispanic or latino	6 (19.4)	11 (6.0)	18 (11.2)	29 (10.1)	58 (9.2)	64 (9.7)
Not hispanic or latino	25 (80.6)	172 (93.5)	142 (88.2)	256 (89.5)	570 (90.3)	595 (89.9)
Not reported	0	1 (0.5)	1 (0.6)	1 (0.3)	3 (0.5)	3 (0.5)
Weight (kg)						
n (missing)	31 (0)	184 (0)	161 (0)	285 (1)	630 (1)	661 (1)
Mean (SD)	89.24 (19.65)	74.14 (16.34)	80.75 (17.64)	73.63 (18.59)	75.60 (17.94)	76.24 (18.24)
Median	88.45	71.00	80.97	69.85	71.63	72.00
Q1; Q3	73.48; 101.06	61.96; 82.05	67.00; 92.08	60.00; 85.00	61.60; 87.00	62.00; 87.32
Min; Max	53.7; 128.1	46.1; 123.0	42.0; 135.7	47.0; 138.9	42.0; 138.9	42.0; 138.9
BMI (kg/m^2)						
n (missing)	31 (0)	184 (0)	161 (0)	285 (1)	630 (1)	661 (1)
Mean (SD)	32.86 (7.15)	26.95 (5.85)	29.67 (6.32)	27.08 (6.83)	27.71 (6.52)	27.95 (6.64)
Median	31.47	26.04	29.20	25.70	26.61	26.95
Q1; Q3	28.19; 37.08	22.70; 30.19	24.24; 33.57	21.56; 30.50	22.77; 31.28	22.90; 31.50
Min; Max	19.4; 47.4	18.0; 47.0	18.2; 49.8	16.8; 56.0	16.8; 56.0	16.8; 56.0

ABT = add-back therapy; E = EDELWEISS study in endometriosis; LGX = linzagolix; P = PRIMROSE study in uterine fibroids; SD = standard deviation

Source: SCS Supplement Table 14.1.2.2.

Phase 2 studies:

Subjects enrolled in the Phase 2 studies were women with endometriosis; a quarter of these women (234/934; 25.0%) had concomitant UF. In general, patients with endometriosis in the Phase 2 studies tended to be younger than the women with UF enrolled in the Phase 3 studies. The details of the demographic characteristics in each individual Phase 2 study are reported in Initial MAA/UF/Module 2.7.4, section 2.7.4.3.2.

Phase 1 studies:

All Phase 1 trials were conducted in healthy female volunteers. The details of the demographic characteristics in each individual Phase 1 study are reported in Initial MAA/UF/Module 2.7.4, section 2.7.4.3.3.

Overall, the study groups within the studies were balanced in terms of demographic characteristics.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 6: Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criterion	**The subject has a clinically significant abnormal ECG or ECG with a QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 470 ms at screening or Day 1 (prior to first dose).**
Reason for exclusion	Patients with a clinically significant abnormal ECG or ECG with a QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 470 ms at screening or Day 1 (prior to first dose) were excluded from clinical trial participation due to a marginal QT prolongation in the QTc study and as their inclusion could have affected the safety assessment of linzagolix.
Is it considered to be included as missing information?	No
Rationale	The cardiovascular safety of linzagolix was addressed with a comprehensive set of studies. Linzagolix at concentrations of up to 100 µmol/L (corresponding to 166-fold the clinical exposure) had no effects on ion channels hERG, hNaV1.5 peak and late current, hCaV1.2 (L-type), hKv4.3 (Ito), hKir2.1, hKCNQ1/E1 (Iks) and hKv1.5 or a papillary muscle (guinea pig) assay. There were no effects in female cynomolgus monkeys at up to 1000 mg/kg. A thorough QT (TQT) trial showed borderline QTcF prolongation (beyond the 10 ms threshold) at 1 timepoint (3h) of 10.23 and 11.81 ms (upper limit of the CI 90%) at linzagolix therapeutic (200 mg) and supratherapeutic dose (700 mg), respectively. The 200 mg and 700 mg doses were found to prolong QTcF with least squares mean (LSMs) of 8.34 msec (90% CI 6.44 - 10.23) and 9.92 msec (90% CI 8.03 - 11.81), respectively. Linear concentration-effect modelling for linzagolix and metabolite KP017 was below the 10 ms threshold at the supratherapeutic C_{max} (Maximum Concentration Recorded), but hysteresis was identified for linzagolix. Thus, a J-Tpeak evaluation of the ECG data was undertaken. Observed J-Tpeak values were below the trigger value of 10 ms and not dose-dependent: values at 200 mg plateaued from 1.5 to 5.5 hours post-dose and values at 700 mg were equal (3h) or lower (all other occasions), despite 2.5-fold higher exposures at this dose. Given the absence of values beyond the trigger value and the apparently exposure independent

	and self-limiting nature of effects, it is considered that the evaluation of J-Tpeak prolongation is negative and the observed QTc prolongation is not clinically relevant. Overall linzagolix had no clinically relevant effect on the cardiovascular system *in vitro* as well as *in vivo*. (Initial MAA/UF/Module 2.4, section 2.4.2.3). However, although a trend for QT interval prolongation has not been demonstrated in clinical studies, there remains a concern about the potential for increases in QT interval because the clinical relevance of the observed QT effect is unknown in patients with risk factors for QT interval prolongation or concomitant use of medicinal products known to prolong the QT interval, both of which were exclusion criteria in the pivotal Phase 3 PRIMROSE studies. In the Phase 3 endometriosis trials, the maximum on-treatment value was 491 ms (Month 2) in the LGX 200 mg+ABT group up to Month 12 of treatment. The maximum QTcF value was 477 ms at Month 6 and 460 ms at Month 12 in the LGX 200 mg+ABT group. There were no PTs of torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures reported in the Phase 3 program. Available results support no evidence of an increased risk of QT interval prolongation with linzagolix treatment (Module 2.5, section 2.5.6.3.1). However, the QT interval prolongation is considered as an important potential risk (See Part II Module SVII.3.1).

Exclusion criterion	**The subject has a significant finding at breast examination at the screening visit, which would preclude inclusion and need follow-up treatment.**
Reason for exclusion	Subjects with a significant finding at breast examination with need for follow-up were excluded in line with the contraindication for the provided ABT, i.e. known, past or suspected breast cancer (reference to ACTIVELLE® E2 1mg/NETA 0.5mg label).
Is it considered to be included as missing information?	No
Rationale	As linzagolix dose-dependently suppresses E2, which is a major growth stimulant for breast cancer, no impact on prior breast cancer is expected. Since subjects could be randomised to linzagolix in combination with ABT, women with labelled contraindications to ABT were excluded

	from the trials. ABT with oestrogen-progestogen combined treatment increases the density of mammographic images which may adversely affect the radiological detection of breast cancer, and thus interfere with the appropriate follow-up of breast cancer. For this reason, if a potential subject had a significant finding on breast examination that requires follow-up, she was excluded from the trial to avoid exposure to ABT.

Exclusion criterion	**The subject has a haemoglobin level < 6 g/dL.** **The subject has a documented severe coagulation disorder (e.g. haemophilia or Von Willebrand disease).**
Reason for exclusion	Subjects with a haemoglobin level < 6 g/dL have risk of serious adverse consequences related to anaemia; inclusion in a clinical trial would not be appropriate. In addition, severely low haemoglobin could interfere with evaluation of linzagolix safety and efficacy. Subjects with severe coagulation disorder were excluded from the PRIMROSE studies as these can be an interfering factor for a proper evaluation of linzagolix efficacy and safety in reduction of bleeding associated with uterine fibroids.
Is it considered to be included as missing information?	No
Rationale	General risk consideration in experimental treatment.

Exclusion criterion	**The subject is pregnant or breastfeeding or is planning a pregnancy within the duration of the treatment period of the study.**
Reason for exclusion	Based on nonclinical data (see section Part II: Module SII - Non-clinical part of the safety), due to its mechanism of action, linzagolix was found to prevent conception and reduced implantation in rats and resulted in embryo-foetal mortality, total litter loss or abolished pregnancy in rat and rabbit embryo-foetal studies. Tissue distribution of radiolabelled linzagolix was widespread; and radioactivity was also detected in foetal tissues and milk. Although there were no teratogenic effects and no adverse effect on the pre- and postnatal development of the offspring, as a precaution linzagolix is contraindicated during pregnancy. As it is unknown whether linzagolix or its metabolites are excreted in human milk, a risk to newborns /infants cannot be excluded and consequently linzagolix is contraindicated during breastfeeding.
Is it considered to be included as missing information?	No
Rationale	Embryo-foetal toxicity is considered as important potential risk whereas pregnancy and breastfeeding are contraindications of YSELTY treatment.

Exclusion criterion	**The subject has a history of uterus surgery:** • **hysterectomy** • **total ovariectomy** • **myomectomy** • **endometrial ablation** • **UAE** • **magnetic resonance guided focused ultrasound surgery (MRgFUS)/ high-intensity focused ultrasound (HIFUS) in the past 6 months or** • **adenomyomectomy**
Reason for exclusion	The history of any uterine surgery may interfere with the assessment of the primary and key secondary endpoints, as all the excluded interventions have an impact on uterine bleeding amount and pattern, and thus would interfere with a proper assessment of the efficacy of linzagolix in the uterine fibroid indication. A subject with total ovariectomy is menopausal and will not have any menstrual bleeding, and thus does not qualify for the study.
Is it considered to be included as missing information?	No
Rationale	In clinical practice, women having undergone the above uterine surgeries are unlikely to opt for medications to treat the condition and therefore will not be a target population for linzagolix. Therefore, this exclusion criterion is not considered missing information.

Exclusion criterion	**The subject has only subserosal myoma(s) (International Federation of Gynaecology and Obstetrics (FIGO) classification type 7)**
Reason for exclusion	HMB in subjects with only subserosal fibroids is unlikely to be causally related to UF. Consequently, those patients were excluded from PRIMROSE studies.
Is it considered to be included as missing information?	No
Rationale	Uterine bleeding of unknown aetiology or for reasons other than UF is a contraindication of YSELTY treatment.

Exclusion criterion	**The subject has a large uterine polyp (> 2 cm), or another clinically significant gynaecological condition identified on screening transvaginal ultrasound or endometrial biopsy which might interfere with the study efficacy and safety objectives. Subjects who have had a uterine polypectomy in the 6 months before screening with no recurrence may be included.**
Reason for exclusion	Large uterine polyps can cause HMB which may impact the assessment of the primary and secondary efficacy endpoints. Consequently, those patients were excluded from PRIMROSE studies.
Is it considered to be included as missing information?	No
Rationale	Uterine bleeding of unknown aetiology or for reasons other than UF is a contraindication of YSELTY treatment.

Exclusion criteria	**The subject has had a significant finding on Papanikolaou test (PAP) smear within the past 12 months or at the screening visit, which will require surgical intervention (e.g., Loop electrosurgical excision procedure (LEEP) or cervical conization).** **OR** **The subject has a history of or current uterine, cervical, ovarian, breast cancer or any oestrogen-dependent neoplasia.** **OR** **The subject has a history of endometrium atypical hyperplasia or adenocarcinoma prior to screening or similar lesions in the screening biopsy.**
Reason for exclusion	a) Known, past or suspected oestrogen-dependent malignant tumours are contraindicated in the labelling of the provided ABT. b) A subject with an endometrial biopsy finding of atypical hyperplasia is at high risk to develop endometrial cancer. Untreated hyperplasia is contraindicated in the label of the provided ABT. Under treatment with the provided ABT, breakthrough bleeding and spotting may occur during the first months of treatment which interferes with the diagnosis of endometrial carcinoma. c) Subjects having a significant finding in the PAP smear which will require surgical intervention have an identified risk for cervical cancer. The presence of any malignancy may interfere with trial results.

Is it considered to be included as missing information?	No
Rationale	Known, past or suspected oestrogen-dependent malignant tumours as well as untreated endometrial hyperplasia are contraindications in the labelling of the provided ABT. The above exclusion criterion was included as a general risk consideration in experimental treatment.

Exclusion criterion	**The subject has significantly calcified myomas and/or calcified uterus, which in the opinion of the investigator would affect treatment response.**
Reason for exclusion	A significantly calcified myoma may not respond to linzagolix treatment and may interfere with the trial results. Consequently, those patients were excluded from PRIMROSE studies.
Is it considered to be included as missing information?	No
Rationale	The above exclusion criterion was included as a general risk consideration in experimental treatment.

Exclusion criterion	**The subject has an in-situ copper IUD or an IUD with progestogen. Subjects can be included one month after IUD removal.**
Reason for exclusion	The use of in-situ copper or progestin IUDs is known to decrease menstrual blood loss and to have effects on levels of haemoglobin, haematocrit and ferritin (Zapata, 2010). As these would interfere with the primary outcome of the studies, current IUD use was an exclusion criterion in the PRIMROSE and EDELWEISS studies.
Is it considered to be included as missing information?	No
Rationale	The above exclusion criterion was included as a general risk consideration in experimental treatment.

Exclusion criteria	**The subject is likely to require treatment during the study OR has received treatment within the specified period prior to screening with any of the medications:** • **GnRH antagonists,** • **GnRH agonist injections/3-month depot injections,** • **Combined contraceptives and progestins,** • **Depot contraceptives,** • **SPRMs and Selective Oestrogen Receptor Modulators (SERMs),** • **Systemic glucocorticoid treatments for acute diseases (not depot),** • **Acetylsalicylic acid,** • **Mefenamic acid,** • **Anticoagulants such as coumarins and/or antifibrinolytic drugs such as tranexamic acid,** • **Strong CYP 3A4 inducers or inhibitors that (might potentially) interact with the ABT metabolism,** • **Systemic glucocorticoid therapy for treatment of chronic diseases (e.g., systemic lupus erythematosus (SLE), rheumatoid arthritis (RA)),** • **Any experimental drug in the 12 weeks before dosing**
Reason for exclusion	Concomitant administration of the above-mentioned treatments may interfere with clinical assessment of the hormonal treatment, due to their mechanism of action and pharmacological activity.
Is it considered to be included as missing information?	No
Rationale	The above exclusion criteria were included as a general risk consideration in experimental treatment.

Exclusion criterion	**The subject is at significant risk of osteoporosis or has a history of or known osteoporosis or other metabolic bone disease.**
Reason for exclusion	BMD decrease with linzagolix was one of the expected side effects. Women with a known history or significant risk of osteoporosis or other metabolic bone disease were excluded from the study given the risk for further BMD decrease with treatment.
Is it considered to be included as missing information?	No
Rationale	There is a risk of BMD decrease associated with linzagolix treatment. The current SmPC contraindicates use of YSELTY in patients with known osteoporosis because of the risk of further BMD decrease. Also, a warning to healthcare professionals (HCP) regarding bone loss is made in section 4.4 of SmPC.

Exclusion criterion	**The subject has ALT, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) or total bilirubin serum levels ≥ 2 times the upper limit of normal at screening.**
Reason for exclusion	Linzagolix in nonclinical studies (in dogs and monkeys), showed an increase in serum liver enzyme activity, and increase in serum lipid parameters with associated increase of liver weight (Initial MAA/UF/ Module 2.4, section 2.4.4.7). To harmonise the patient population and properly assess the possible increase in liver enzymes, patients with increased serum levels of ALT, AST, GGT or total bilirubin at baseline were excluded from studies.
Is it considered to be included as missing information?	No
Rationale	The above exclusion criterion were included as a general risk consideration in experimental treatment as several of the GnRH analogues have been reported to cause transient aminotransferase elevations during therapy, but none have been so far convincingly implicated in reports of clinically significant liver injury. Irrespective, 'Liver Toxicity' is considered as an important potential risk for linzagolix.

Exclusion criterion	**The subject has a history of or known current (within twelve months) problems with alcohol or drug abuse (including painkiller abuse).**
Reason for exclusion	The concurrent condition may interfere with patient compliance and thus with trial results.
Is it considered to be included as missing information?	No
Rationale	General risk consideration in experimental treatment.

Exclusion criterion	**The subject has a contra-indication to E2 1mg / NETA 0.5 mg ABT including:** **Active deep vein thrombosis, pulmonary embolism, or history of these conditions** **Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction) and known hypersensitivity to the ingredients**
Reason for exclusion	As E2 / NETA ABT is one of the medications that the subjects may receive as per protocol, women for whom ABT is contraindicated were excluded from the study.
Is it considered to be included as missing information?	No
Rationale	General risk consideration in experimental treatment.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The CDP is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 7: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the CDP. **Uterine Fibroids**: Of the 1769 subjects enrolled in the Phase 2 and 3 studies, with treatment duration ranging from 8 weeks to 52 weeks, 16 pregnancies (0.9%) were reported (2 of them in Phase 3 studies). Two of the 16 pregnancies occurred during the post-treatment follow-up (PTFU) period of 24 weeks. The summary of the pregnancies and their outcomes are detailed in Part II Module SVII.3.1 Presentation of important identified risks and important potential risks. Of the 2 pregnancies reported in the Phase 3 UF studies, 1 (in subject 29916) occurred after the subject completed the first 24-week treatment period and voluntarily discontinued from the study (0 day of exposure to linzagolix). The second pregnancy occurred (in subject 81407) during treatment with linzagolix 100 mg (exposure approximately 40 days). **Endometriosis**: Of the 568 subjects enrolled in the Phase 3 trials in women with endometriosis, 4 pregnancies (0.7%) were reported. One of the 4 pregnancies occurred during the post-treatment follow-up period. No pregnancies were reported in subjects treated with LGX 200 mg+ABT. In the EDELWEISS 3 study, discontinuations due to pregnancies were reported in 3 subjects: • 1 subject (0.6%) in the LGX 75 mg group between Day 1 and Month 3; • 2 subjects between Month 3 and Month 6: 1 in the placebo (0.6%; Subject 411034) and 1 subject in LGX 75 mg (0.6%) group (EDELWEISS 3 CSR, Table 14.1.2.3) In the EDELWEISS 6 study, no discontinuations due to pregnancies were reported during the treatment period (EDELWEISS 6 CSR, Table 14.1.3). One subject (1.7%) in the placebo/LGX 75 mg group discontinued due to pregnancy during the post-treatment follow-up period. The pregnancy occurred more than 1 month after the end of treatment (EDELWEISS 6 CSR, Section 12.2.2.3). In the EDELWEISS 2 and EDELWEISS 5 study, no pregnancies were reported.

Breastfeeding women	Not included in the CDP.
Patients with relevant comorbidities:	
• *Patients with hepatic impairment*	Both urinary and faecal routes of elimination were important in the elimination of linzagolix and its metabolites. Thirty-nine percent (39%) of linzagolix-related compounds were eliminated in faeces (KLH1103). In a dedicated hepatic impairment (HI) study (18-OBE2109-009), the pharmacokinetics (PK) of a single 200 mg oral dose of linzagolix was investigated in adult women with normal hepatic function (N = 6), mild stable chronic HI (N = 6, Child-Pugh A), moderate stable chronic HI (N = 6, Child-Pugh B), or severe stable chronic HI (N = 6, Child-Pugh C). Headaches and vomiting were reported in subjects with moderate or severe HI; all were mild to moderate in intensity. There were no clinically significant trends noted in the physical examination, vital signs, laboratory, or ECG data among subjects with HI (CSR 18- OBE2109-009). Overall, HI (mild, moderate, and severe) had no relevant effect on total plasma linzagolix PK following administration of 200 mg linzagolix. The unbound fraction of linzagolix was not affected by mild and moderate HI compared to healthy subjects. Following administration of 200 mg linzagolix to severe HI patients, $C_{max\ unbound}$ and $AUC_{unbound}$ were 2- to 3-fold higher compared to healthy matched control subjects (for more details, refer to Initial MAA/UF/Module 2.7.2 section 2.7.2.2.2.3.1) A single oral dose of 200 mg linzagolix appeared to be safe and well tolerated in female subjects with mild, moderate, and severe HI, with Child Pugh scores ranging from 5 to 15 with features of cirrhosis. (CSR 18-OBE2109-009).
• *Patients with renal impairment*	Both urinary and faecal routes of elimination were important in the elimination of linzagolix and its metabolites. Fifty-two percent (52%) was eliminated in urine (KLH1103). In a dedicated renal impairment (RI) study (18-OBE2109-010), the PK of a single 200 mg oral dose of linzagolix was characterised in adult women with normal renal function (eGFR (Estimated glomerular filtration rate) $\geq$ 90 mL /min/1.73m^2, N = 6), mild (eGFR $\geq$ 60 mL /min/1.73m^2, N = 6), moderate (eGFR $\geq$ 30 mL /min/1.73m^2, N = 6) or severe renal impairment (eGFR $\geq$ 15 mL /min/1.73m^2, N = 4), and end stage renal disease (ESRD), eGFR < 15 mL /min/1.73m^2, N = 6) requiring dialysis. One subject each (1/6, 17%) in the ESRD reported headache and vomiting, with the headache considered as treatment-related. No AEs were reported among subjects with moderate or severe RI. There were no clinically significant

	observations reported for clinical laboratory parameters, vital signs, or ECG measurements. Overall, RI (mild, moderate, severe and ESRD) had no relevant effect on total plasma linzagolix PK following administration of 200 mg linzagolix. The unbound exposure is generally increased with RI with around 2-fold mean exposure increases occurring with severe RI and ESRD compared to healthy subjects with normal renal function. (for more details, refer to Initial MAA/UF/Module 2.7.2 section 2.7.2.2.2.3.2). Mean unbound plasma linzagolix increase was minimal in mild RI patients and was increased by approximately 50% in moderate RI patients compared to healthy subjects with normal renal function. Of note, severe RI and ESRD subjects in the RI study were not exposed to higher mean unbound exposures of linzagolix than those previously tested in studies where supratherapeutic single (up to 700 mg) or repeated doses (up to 400 mg/day) of linzagolix were administered and found to be well tolerated (CSR 17-OBE2109-001 and CSR KLH1101). A single oral dose of 200 mg linzagolix appeared to be safe and well tolerated in female subjects with mild, moderate, severe renal impairment, or ESRD (CSR 18-OBE2109-010).
• *Patients with cardiovascular impairment*	Not included in the CDP
• *Immunocompromised patients*	Not included in the CDP
• *Patients with a disease severity different from inclusion criteria in clinical trials*	Not included in the CDP
Population with relevant different ethnic origin	See Part II SIII Table 4, providing demographic data.
Subpopulations carrying relevant genetic polymorphisms	Identification of genetic polymorphism was not relevant for the CDP.
Other	Not applicable

Part II: Module SV - Post-authorisation experience

Although linzagolix has been authorised throughout the EU (European Union) and United Kingdom (UK) for the treatment of uterine fibroids (UF), this section is not applicable because it has not yet been launched in any countries at the time of this extension of indication application.

Part II: Module SVI - Additional EU requirements for the safety specification

The potential for misuse for illegal purposes

There is no potential for misuse of linzagolix for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

1. Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
    - Nausea
    - Vomiting
    - Constipation
    - Headache
    - Arthralgia
    - Asthenia
    - Hyperhidrosis
    - Night sweats
    - Change in menstrual bleeding pattern
2. Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
    - Hypertension
    - Libido decreased
    - Hot Flush
    - Mood disorders
3. Known risks that require no further characterisation and are followed up via routine pharmacovigilance:

- **Lipid Disorder:**

Changes in serum lipids are known to occur with decreases in serum E2 and have been observed with other oral GnRH antagonists, elagolix and relugolix (Surrey 2018; Taylor, 2017, Al-Hendy 2021). All on-treatment changes with linzagolix were small and included both favourable (increase in HDL (high-density lipoprotein) and unfavourable (increase in LDL (low-density lipoprotein) and triglycerides) changes.

Phase 3 Studies (uterine fibroids):

Up to week 24:

In the pooled safety analysis of PRIMROSE 1 and PRIMROSE 2 studies at Week 24, the percentage of subjects with LDL cholesterol ≥160 mg/dL (≥4.14 mmol/L) was similar in the 100 mg, 200 mg, and 200 mg + ABT arms: 12.5% vs 13.3% vs 10.8%, respectively. LDL cholesterol increases ≥190 mg/L (≥ 4.9 mmol/L) were reported in all linzagolix groups at Week 24, more frequently in the linzagolix without concomitant ABT arms (4.9% for 100 mg and 5.7% for 200 mg) compared to the corresponding arms with ABT (0.7% and 3.2%, respectively). The percentage

of subjects with HDL cholesterol <40 mg/dL (<1.03 mmol/L) showed relatively little change from baseline up to Week 24.

In the PRIMROSE 1 and PRIMROSE 2 studies up to Week 24, the incidence of TEAEs associated with changes in lipid metabolism was low (5/1037; 0.5%): 2 subjects (2/1037; 0.2%) in the 200 mg+ABT group reported an increase in blood triglycerides (2/208; 1.0%), 1 subject (1/1037; 0.1%) in the 100 mg group reported an increase in cholesterol (1/199; 0.5%), 1 subject (1/1037; 0.1%) in the 100 mg group reported an increase in LDL cholesterol (1/199; 0.5%), and 1 subject (1/1037; 0.1%) in the 200 mg group reported hyperlipidaemia (1/210; 0.5%) (Initial MAA/UF/Module 2.7.4, section 2.7.4.4.6.7).

Between Week 24 and Week 52:

Considering both treatment periods, initial dose-related increases from baseline were observed in cholesterol levels (mainly LDL cholesterol) in the groups receiving linzagolix, notably those not receiving ABT; these stabilised or lessened during the second treatment period. HDL cholesterol did not show any clinically relevant change from baseline in any treatment group; however, there was a mostly consistent pattern of decrease in the groups receiving ABT and increase in the other groups receiving linzagolix. Increases from baseline in triglyceride levels were observed in all groups; these increases were dose-related and were greater in the linzagolix groups without concomitant ABT during the first treatment period but were similar across groups during the second treatment period.

Among the 757 subjects who received linzagolix treatment between Week 24 and Week 52 in the Week 52 Pooled Safety Analysis Set, 2 subjects (2/757; 0.3%) reported TEAEs associated with lipid metabolism: 1 subject (0.6%) in the 200mg/200mg+ABT group reported an increase in HDL and 1 subject (0.7%) in the 100 mg+ABT group reported dyslipidaemia (Initial MAA/UF/Module 2.7.4, section 2.7.4.4.6.7).

During the follow-up period in the PRIMROSE 1 study:

The percentage of subjects with LDL cholesterol ≥160 mg /dL (≥4.14 mmol/L) was higher than baseline at Week 52 (22 subjects, 9.6%) but returned to baseline at Week 64 for 11 subjects (5.4%). LDL remained ≥190 mg/dL (≥4.91 mmol/L) up to Week 64 for the 2 subjects that had LDL values ≥190 mg/dL (≥4.91 mmol/L) at baseline. The overall percentage of subjects with HDL cholesterol <40 mg /dL (<1.03 mmol/L) decreased slightly from Baseline to Week 52 (36 subjects, 15.6%) and increased following the end of treatment, reaching 19.1% (39 subjects) at Week 64

During the follow-up period in the PRIMROSE 2 study:

The percentage of subjects with LDL cholesterol ≥160 mg /dL (≥4.14 mmol/L) was higher than baseline at Week 52 (39 subjects, 11.7%) but returned to baseline at Week 64 (21 subjects, 6.7%). Similarly, at Week 52, the percentage of subjects with LDL cholesterol ≥190 mg /dL (≥4.91 mmol/L) increased from baseline (0 and 8 subjects, 2.4%, respectively) and returned toward baseline at Week 64 (3 subjects, 1%). The overall percentage of subjects with HDL cholesterol <40 mg /dL (<1.03 mmol/L) increased from Baseline to Week 52 (24 subjects, 7.1%) and remained similar following the end of treatment, reaching 7.3% (23 subjects) at Week 64.

Phase 3 Studies (Endometriosis):

In the Phase 3 linzagolix studies, fasting lipids (HDL, LDL and total cholesterol, and triglycerides) were assessed from blood samples taken at Day 1, (Month 1 only in endometriosis studies), and every 3 months during treatment up to Month 12, then at a Month 3 follow-up visit. There were small percentage increases in LDL cholesterol, total cholesterol, and triglycerides at Month 3, which generally did not increase further at Month 6.

In the endometriosis Phase 3 trials, these increases were approximately 3% for LDL, 2% for total cholesterol, and 19% for triglycerides for the LGX 200 mg+ABT group (Module 2.7.4.3.2.1; Table 2.7.4-32). Except for triglycerides, the increases observed in the endometriosis EDELWEISS 3 trial were lower in magnitude than those observed in the PRIMROSE trials in subjects with uterine fibroids (LDL: 11%; total cholesterol: 6%; triglycerides: 12%).

At Month 12, there was an approximately 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 subjects continuing treatment in the EDELWEISS 6 endometriosis trial. Again, these increases in LDL and total cholesterol were lower in the endometriosis subjects compared to those observed in the PRIMROSE trials in subjects with UF: 14% (vs 10% at M6) for LDL cholesterol and 7% (vs 6% at M6) for total cholesterol.

On-treatment increases in LDL occurred with comparable frequently in the linzagolix groups and placebo. At Month 6, the percentage of subjects with LDL ≥160 mg/dL was slightly higher in the placebo group (9.0%) compared to the linzagolix groups (75 mg: 7.6%; 200 mg+ABT: 5.2%) in the EDELWEISS 3 study (overall baseline 9.9%). LDL levels ≥190 mg/L (4.91 mmol/L) were reported in 1 subject each in both linzagolix groups at Month 6. At Month 12, LDL levels ≥190 mg/dL were observed in 3 subjects each in the LGX 75 mg and LGX 200 mg+ABT groups (i.e., subjects who received up to 12 months of treatment). Data for subjects who switched from placebo at Month 6 are shown in Module 2.7.4.3.2.2.

The observed changes in serum lipids are consistent with expectations given the linzagolix mechanism of action, and appear to be similar to those observed with other oral GnRH receptor antagonists and of no apparent clinical impact (for more details, refer to Module 2.7.4, section 2.7.4.3.2.1).

Phase 2 Studies:

There were no clinically significant changes in the total cholesterol, triglycerides, HDL or LDL cholesterol in studies KLH1201, KLH1202, KLH1203, or KLH1204. In study 15-OBE2109-001 (EDELWEISS), mean serum LDL cholesterol, HDL cholesterol, ratio of LDL cholesterol to HDL cholesterol and triglyceride levels were similar in all groups at baseline. There were small increases in LDL cholesterol, HDL cholesterol, LDL/HDL ratio and triglycerides at 12 weeks which were maintained at 24 weeks. All on-treatment changes were small and included both favourable (increase in HDL) and unfavourable (increase in LDL and triglycerides) changes. There were no further appreciable increases in the lipid levels during treatment extension beyond those observed at Week 24. The lipid profile returned to pre-treatment levels within 3 months of the post-treatment follow-up period.

Phase 1 Studies:

Lipid levels were not evaluated in the Phase 1 studies 17-OBE2109-004, 17-OBE2109-006, 18-OBE2109-006, and 18-OBE2109-007. For other Phase 1 studies there were no changes or clinically insignificant elevations in lipid parameters.

Overall, increases in lipid levels were observed with linzagolix treatment. These increases were generally of no clinical relevance. However, in women with pre-existing elevated lipid profiles monitoring of lipid levels is recommended in the SmPC and will be monitored through routine pharmacovigilance.

- **Vaginal/uterine haemorrhage**

Phase 3 Studies (uterine fibroids):
In the pooled safety analysis of PRIMROSE 1 and PRIMROSE 2 studies, 43 subjects (4.1%) reported 46 uterine bleeding TEAEs, with a similar incidence in the placebo group (5 subjects; 2.4%) and linzagolix 100 mg (4 subjects; 2.0%) and 200 mg (6 subjects; 2.9%) groups. Subjects in the linzagolix with ABT groups had a slightly higher incidence of bleeding events: 7.6% (16 subjects) in the 100 mg + ABT group and 5.8% (12 subjects) in the 200 mg + ABT group (Initial MAA/UF/Module 2.7.4, table 2.7.4-154). The majority of these events were vaginal haemorrhage (20 subjects; 1.9%), metrorrhagia (12 subjects; 1.2%), and menorrhagia (9 subjects; 0.9%). The incidence of vaginal haemorrhage and menorrhagia were reported with a similar frequency in the placebo, 100 mg, and 200 mg + ABT groups. Metrorrhagia was reported only in the linzagolix groups, generally with a low incidence (<2.5%). Uterine haemorrhage was reported by 2 subjects (0.9%) in the 100 mg + ABT group and 1 subject (0.5%) in the 200 mg + ABT groups.

Between Week 24 and Week 52, 35 (4.6%) subjects reported a uterine bleeding event. Of these, 13 (1.7%) reported a PT of vaginal haemorrhage: with >50%, 7 (4.3%) in the 200 mg/200 mg+ABT group. The majority of the bleeding TEAEs were reported in the subjects who had switched from placebo to linzagolix 200 mg+ABT or from linzagolix 200mg to 200mg+ABT at Week 24 (Initial MAA/UF/Module 2.7.4, table 2.7.4-155).

During the Follow-up Period of the PRIMROSE 1 study, 1 (2.0%) subject in the linzagolix 100 mg group reported polymenorrhoea as a TEAE. During the Follow-up Period of the PRIMROSE 2 study, the following uterine bleeding events were reported as TEAEs: uterine haemorrhage in 3 subjects, menorrhagia in 2 subjects, and menometrorrhagia in 1 subject.

Phase 3 Studies (endometriosis):

The safety profile of linzagolix did not differ importantly in the Phase 3 endometriosis studies. A pooling of the 200mg + ABT dose was performed to increase the likelihood to detect any safety signals. Only pooled data for the 200 mg + ABT dose are consequently presented.

Pooled Phase 3 Studies
The pooled Phase 3 clinical database of the PRIMROSE and EDELWEISS studies was searched for the following PTs: vaginal haemorrhage, genital haemorrhage, uterine haemorrhage, menorrhagia, metrorrhagia, and menometrorrhagia. 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).

Phase 2 Studies:

Bleeding events were reported less frequently in Phase 2 EDELWEISS trial in women with endometriosis compared to Phase 3 trials in women with uterine fibroids; however, these events were more frequently reported in the Phase 2 trials conducted in Japan at all dose levels, likely due to different scoring of non-menstrual bleeding in the Japanese trials (i.e., all non-menstrual bleeding noted in the eDiary was considered as abnormal bleeding in Phase 2 Japanese trials).

Phase 1 Studies:

There were no reports of uterine bleeding in studies KLH1101, KLH1103, 16-OBE2109-005, 16-OBE2109-011, 17-OBE2109-001, 18-OBE2109-007, 18-OBE2109-009, 18-OBE2109-010 and 17-OBE2109-008.

For other studies following uterine bleeding events were reported as TEAE: metrorrhagia (reported in 15% subjects in 17-OBE2109-004; and 5.6% of subjects in 18-OBE2109-006 study) and menometrorrhagia (reported in 8.3% subjects in 17-OBE2109-006).This safety concern is considered as an identified risk with low public health impact because of very low incidence of vaginal/uterine haemorrhage. Vaginal haemorrhage is listed in section 4.8 of the SmPC.

4. Known risks that do not impact the risk-benefit profile:

- Pelvic pain
- Vulvovaginal dryness

5. Other reasons for considering the risks not important:

- None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

The risks that were considered important for inclusion in the list of safety concerns in the initial RMP are:

Table 8: Justification for risk-benefit impact of important identified risks

Important identified risk	Justification for risk-benefit impact
Bone mineral density decrease	An expected side effect of treatment with medications that lower serum E2 is dose- and duration-dependent BMD decrease due to increased bone resorption. These changes in BMD are most pronounced in the setting of full E2 suppression.

Important identified risk	Justification for risk-benefit impact
	Linzagolix 200 mg (without concomitant ABT): The 200 mg dose (without concomitant ABT) was associated with BMD decrease as expected with full E2 suppression. Due to the degree of observed BMD decrease at 24 weeks (-3.7% change from baseline at Week 24 at lumbar spine) the label limits use of linzagolix 200 mg (without concomitant ABT) to up to 6 months of treatment which is in line with the observed BMD decrease with the GnRH agonist leuproline acetate (SmPC of PROSTAP®). Data from GnRH agonists and the Phase 2 EDELWEISS linzagolix study in endometriosis show evidence of recovery after short-term (6 months) full E2 suppression. BMD decrease after short term use of GnRH agonists generally shows partial to complete recovery within a few months after treatment completion. In addition to the 6-month limitation on duration of treatment for the linzagolix 200 mg dose (without concomitant ABT), the SmPC also includes a contraindication in section 4.3 for women with known osteoporosis and a warning in section 4.4 regarding use in women with risk factors for decrease in BMD. Consequently, the observed decrease in BMD for up to 24 weeks of treatment in subjects treated with 200 mg (without concomitant ABT) has minimal impact on the overall risk-benefit balance of YSELTY. *Linzagolix 200 mg (with concomitant ABT) and linzagolix 100 mg (with and without concomitant ABT):* Only moderate reductions of serum E2 were observed with the 100 mg dose, 100 mg +ABT dose, and with 200 mg + ABT linzagolix dose (on-treatment medians ranging from 27.00 to 48.00 pg/mL) after 52 weeks of treatment. Although overall the BMD changes in both groups were below those described in the Prostap SmPC as acceptable (i.e., <5%) and were considered not clinically meaningful, the magnitude of BMD decrease was observed to be different for linzagolix 100 mg, 100 mg + ABT and 200 mg + ABT groups (-2.36, -1.61 and -0.93 percent change from baseline at Week 52 at lumbar spine, for the

Important identified risk	Justification for risk-benefit impact
	100 mg, 200 mg + ABT dose and 100 mg + ABT dose, respectively). BMD decrease was more pronounced for linzagolix 100 mg group as compared to linzagolix 200 mg + ABT group and linzagolix 100 mg + ABT group (at week 24 and 52). This suggests that the changes in BMD with the 100 mg and 200 mg linzagolix dose were clearly seen to be mitigated by the concomitant use of hormonal ABT. When the 10-year fracture probability was assessed with the FRAX® tool (web version 4.2) in all PRIMROSE patients assuming continuing linear rates of BMD loss over up to 5 years of duration, the analysis suggests that the treatment could be given for at least 5 years without significant concerns about bone health. With regard to the 100mg dose, the mean FRAX probabilities remain well below intervention thresholds whereas the 200mg with concomitant ABT demonstrate even lower probabilities of future fracture risk (Study 20-OBE2109-006). To compare the effects of linzagolix on percent change in BMD over 52 weeks treatment a comparison against a group receiving placebo for 52 weeks is of interest: mean percent changes in lumbar spine BMD over 52 weeks indicated a change of -0.83% for the placebo group which was just slightly less in comparison to the group which received linzagolix 100mg, 100 mg + ABT and 200 + ABT. Also, overall, there was evidence of recovery in BMD 24 weeks following treatment discontinuation at week 52 in all three groups (for more details see Initial MAA/UF/Module 2.7.4, section 2.7.4.6.3.2). Post treatment follow-up data from the Phase 2 EDELWEISS linzagolix study in endometriosis and the post treatment follow-up of patients having completed PRIMROSE 1 and PRIMROSE 2 studies, the PRIMROSE 3 study, also show evidence of recovery after end of treatment. In the PRIMROSE 3 study, across the linzagolix treatment groups, the proportion of subjects with partially or completely recovered BMD status at 24 months after treatment cessation ranged from 50.0% to 80.0%.

Important identified risk	Justification for risk-benefit impact
	Due to the decline in BMD on treatment and/or the lack of full recovery post treatment with linzagolix 200 mg with concomitant ABT and linzagolix 100 mg with or without ABT, the impact on long-term bone health and future fracture risk in the target population is uncertain. Consequently, the SmPC has been updated and includes a contraindication in section 4.3 for women with known osteoporosis and a warning in section 4.4 regarding use in women with risk factors for decrease in BMD. Further, a DXA scan is recommended after 1 year of treatment for all women to verify that the patient does not have an unwanted degree of BMD loss. Thereafter, depending on the prescribed dose of YSELTY, BMD assessment is recommended annually (YSELTY 100 mg) or at a frequency determined by the treating physician based on the woman's individual risk and previous BMD assessment (YSELTY 100 mg with concomitant ABT and YSELTY 200 mg with concomitant ABT). The benefits and risks of YSELTY in patients with a history of a low trauma fracture or other risk factors for osteoporosis or bone loss (such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, and low body weight), including those taking medications that may affect BMD (e.g., systemic corticosteroids, anticonvulsants), should be considered prior to initiating treatment. It is recommended to perform a DXA scan before commencing treatment with YSELTY in these patients. YSELTY should not be initiated if the risk associated with BMD loss exceeds the potential benefit of the treatment. BMD decrease was less pronounced in the Phase 3 endometriosis studies. 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 3 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).

Important identified risk	Justification for risk-benefit impact
	Overall, the BMD results with the LGX 200 mg+ABT dosing regimen show that: 1) BMD changes in the younger patient population in the endometriosis studies were less pronounced at the lumbar spine compared to those observed in patients with uterine fibroids, 2) the spine was most sensitive to BMD loss, 3) comparable BMD changes were observed at Month 6 at the femoral neck and total hip in both patient populations. Notably, the BMD changes observed with linzagolix 200 mg+ABT are similar to those published with other oral GnRH receptor antagonists at the lumbar spine and total hip. Therefore, the observed BMD decrease with linzagolix 100 mg with or without concomitant ABT and linzagolix 200 mg with concomitant ABT was assessed to have minimal impact on the risk-benefit balance of YSELTY. In order to collect further information on BMD decrease in real-life setting and for prolonged use of linzagolix, a Post Authorisation Safety Study (PASS) is proposed as an additional pharmacovigilance activity. (details of the study is presented in Part III.2 Additional pharmacovigilance activities).

Table 9: Justification for risk-benefit impact of important potential risks

Important potential risk	Justification for risk-benefit impact
Uterine endometrial and mammary gland adenocarcinoma	During a 104-week carcinogenicity study conducted in Wistar rats, higher incidence of uterine endometrial in the high-dose group of 500 mg/kg/day and of mammary gland adenocarcinoma in the middle dose group of 50 mg/kg/day was observed, however this higher incidence of uterine endometrial and mammary gland adenocarcinoma was judged to be incidental.

Important potential risk	Justification for risk-benefit impact
	It is accepted that the mechanism mediating this apparent treatment related effect is unclear and does not appear to be related either to genotoxicity, or the primary pharmacological activity of linzagolix. However, the data available are not sufficient to conclude on the potential clinical relevance of these findings. And therefore, only as a precaution "*Uterine endometrial and mammary gland adenocarcinoma*" is listed as important potential risk. A statement is included in the SmPC section 5.3: In a 2-year carcinogenicity study in rats, an increased incidence of uterine endometrial adenocarcinoma was observed in the mid- (50 mg/kg) and high-dose (500 mg/kg) groups (corresponding to respectively 6.8 and 9.6 times the maximum recommended human dose based on AUC) and a marginal increase in the frequency of mammary gland adenocarcinoma was observed at the mid-dose (50 mg/kg) only (6.8 times the maximum recommended human dose based on AUC). The clinical relevance of these findings remains unknown. During clinical studies, only 1 incidence of endometrial adenocarcinoma (n= 1 of 146 (0.7%)) was observed so far between Week 24 and Week 52 in the PRIMROSE 1 and PRIMROSE 2 studies in the 100 mg + ABT group. A pre-existing endometrial lesion was detected upon blinded review of the screening biopsy, this event was considered not related to linzagolix but to ABT treatment. Similarly, 2 cases of breast cancer were detected in the 200 mg and the 200 mg + ABT group after only 20 and 19 weeks of exposure to linzagolix, respectively. These cases were considered to be not related to linzagolix due to the short exposure to study drug. One additional SAE of breast cancer was reported in Study KLH1201 in the 50 mg group. The breast cancer was first suspected within 4 weeks of treatment start following a mammography. This event was considered not related to linzagolix. No cases of breast cancer or endometrial adenocarcinoma were reported in the EDELWEISS 2/3/5 and 6 studies. Risks of ABT also include breast and endometrial cancer. The use of ABT is contraindicated in women with known, past or suspected

Important potential risk	Justification for risk-benefit impact
	breast cancer and oestrogen-dependent malignancy, and untreated endometrial hyperplasia. In the linzagolix program to date, there is no indication that these conditions, if present during treatment, are aggravated by linzagolix. In order to collect further information on uterine endometrial and mammary gland adenocarcinoma in real-life setting, a PASS is proposed as an additional pharmacovigilance activity (details of this study is presented in Part III.2 Additional pharmacovigilance activities), in addition to post-marketing follow-up questionnaires as routine pharmacovigilance activities beyond adverse reactions reporting and signal detection (see Part III.1 Routine pharmacovigilance activities and Annex 4 - Specific adverse drug reaction follow-up forms). Impact on the risk-benefit balance of the product is assessed to be negligible. This was included as important potential risk only as a precaution as the data available are not sufficient to conclude on the potential clinical relevance of these findings.
QT Interval Prolongation	The results of the TQT study 17-OBE2109-001 indicated that linzagolix may prolong the QT/QTc interval. Therefore, QT prolongation and TEAEs in the System Organ Class (SOC) Cardiac disorders were explored following results of this study. Overall, the results of ECG readings did not raise any safety concerns. There were no QTcF prolongations >500 ms in the Phase 2 or Phase 3 trials, except for 1 Japanese subject in Phase 2 study KLH1204 with a pre-existing QT prolongation, reported QT interval prolongation (QTc 519 ms) 29 days after the initial linzagolix dose of 50 mg. This subject was ketogenic at the moment of QTc interval increase which may have contributed to the QTc prolongation. In accordance with ICH guidance *E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs* (EMEA 2005), the rates of the following TEAEs were compared in the treated and control subjects: torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures. Except for one event of syncope, none of the other PTs were reported to date in the

Important potential risk	Justification for risk-benefit impact
	linzagolix clinical development program; 1 subject in the 100 mg group reported 1 event of syncope which was not associated with QTcF prolongation (QTcF values ≤453 ms at all assessments). In the Phase 3 endometriosis trials, the maximum on-treatment value was 491 ms (Month 2) in the LGX 200 mg+ABT group up to Month 12 of treatment. The maximum QTcF value was 477 ms at Month 6 and 460 ms at Month 12 in the LGX 200 mg+ABT group. There were no PTs of torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures reported in the Phase 3 program. Overall available results support no evidence of an increased risk of QT prolongation with linzagolix treatment (Module 2.7.4.4.4). The SmPC carries a warning in section 4.4 to exercise caution when prescribing linzagolix in patients with known cardiovascular disease or family history of QT interval prolongation, hypokalaemia, and in concomitant use with other medicinal products that prolong the QT interval. Caution should also be exercised when linzagolix is prescribed in patients with co-existing disorders leading to increased linzagolix plasma levels. In order to gather more information on the reported events of cardiac disorders indicative for a potential QT prolongation in real-life setting, a PASS is proposed as an additional pharmacovigilance activity (details of this study is presented in Part III.2 Additional pharmacovigilance activities) in addition to post-marketing follow-up questionnaires as routine pharmacovigilance activities beyond adverse reactions reporting and signal detection (see Part III.1 Routine pharmacovigilance activities and Annex 4 - Specific adverse drug reaction follow-up forms). The QT interval prolongation is considered as an important potential risk due to the positive TQT study. However, due to the absence of concerning QT interval prolongations and the infrequent cardiac safety TEAEs observed with linzagolix and considering the addition to the Warning in section 4.4 of the SmPC, the impact on the risk-benefit balance of the product is minimal.

Important potential risk	Justification for risk-benefit impact
Embryo-foetal toxicity	Due to its mechanism of action, linzagolix prevented conception and reduced implantation resulted in embryo-foetal mortality, total litter loss or abolished pregnancy in nonclinical animal studies. There were no teratogenic effects and no adverse effect on the pre- and postnatal development of the offspring (see section Part II: Module SII - Non-clinical part of the safety). Patients being treated with linzagolix may be at risk of pregnancy since ovulation may occur during treatment. Although subjects in the EDELWEISS and PRIMROSE trials were instructed to use barrier methods of contraception, on-treatment pregnancies occurred. With limited exposure of pregnant women to linzagolix, effects on human pregnancy are unknown. Post-marketing follow-up with a questionnaire in order to gather more information on the reported cases of pregnancies will be implemented (see Part III.1 Routine pharmacovigilance activities and Annex 4 - Specific adverse drug reaction follow-up forms along with regular pregnancy checks and pregnancy follow-ups during the proposed PASS (details of this study are presented in Part III.2 Additional pharmacovigilance activities). Considering that pregnancy was one of the exclusion criterion in CDP and that a contraindication in pregnant women is mentioned in the current SmPC and that the need for contraception is stated, this important potential risk has minimal impact on the risk-benefit balance of the product.
Liver Toxicity	Elevations in liver function tests (LFTs) have been observed with other oral GnRH antagonists such as elagolix and relugolix (Schlaff, 2020; Osuga, 2019, Carr, 2018 and MYFEMBREE® (relugolix, estradiol, and norethindrone acetate prescribing information) and may be a class effect of GnRH analogues. Hence, in linzagolix multiple dose studies, liver enzymes were closely monitored. The current incidence of liver enzyme increases in the pivotal Phase 3 studies in the target indication is low. In PRIMROSE studies, ALT and/or AST serum level increases of >3x Upper Limit of Normal (ULN) up to Week 24 were observed

Important potential risk	Justification for risk-benefit impact
	in fewer than 1% (0.88%; 7/794) in linzagolix groups and 0.48% in placebo (1/209). None were associated with a serum bilirubin increase > 2ULN and/or INR (International normalised ratio) increase > 1.5 ULN, i.e., no cases met criteria for Hy's law. In the pooled safety analysis of PRIMROSE 1 and PRIMROSE 2 studies (N=1037) up to Week 24, 50 subjects (4.8%) reported 72 TEAEs of increases in liver function tests. Most were considered as related to linzagolix, and very few led to permanent discontinuation of drug, but none were considered serious. Between Week 24 and Week 52 in the pooled safety analysis, increases in LFTs were reported infrequently as TEAEs (ALT increase in 0.7% (5/757), GGT increase in 0.5% (4/757), and AST increase in 0.4% (3/757). Only few LFT abnormalities were reported as TEAEs at week 76 for both the studies. Transient fluctuations of LFTs are common, including in clinical trials, and furthermore, similar frequent and isolated elevations of serum transaminases are seen with other drugs (e.g., aspirin). Importantly, patients treated with linzagolix were asymptomatic and none had LFT elevations that met Hy's law criteria. Irrespective of the above, clinical consequences of elevated liver enzymes are included as a safety concern and liver toxicity has been included as important potential risk. In EDELWEISS studies, ALT increases ≥3×ULN were infrequent during the first six months of treatment and observed in 1 subject (1/191; 0.5%) in the LGX 200 mg+ABT group (peak at 5.4×ULN with AST 3×ULN), 1 subject in the LGX 75 mg group (peak at 4.0×ULN with AST 2.3×ULN), and 1 subject on placebo. For the subject in the LGX 200 mg+ABT group, concomitant intake of amoxicillin was implicated as a possible cause of the ALT and AST increases. In the period from Month 6 to Month 12, 1 subject (placebo/LGX 75 mg group) had ALT increase with a peak of 4.3×ULN at Month 10, declining to 2.7×ULN at Month 11 (while on treatment), and increasing again at Month 12 to 3.7×ULN. AST was mildly increased up to 2.1×ULN. One further subject (LGX 200 mg+ABT group) had increased ALT at Month 11 (ALT 3.7 ×ULN with AST

Important potential risk	Justification for risk-benefit impact
	2.4×ULN) and Month 12 (ALT 3.1×ULN with AST 2.2×ULN). No clinical symptoms (e.g., fever, fatigue, jaundice) were present. A retest performed a month later (at Month 1 ExFU) showed ALT and AST levels within the normal range. In summary, in the Pooled SAF (pooled for PRIMROSE and EDELWEISS Phase 3 studies) for Period 1, among the 399 subjects exposed to LGX 200 mg+ABT, 3 subjects (0.8%) had ALT values ≥3×ULN. AST values ≥3×ULN were also reported with a frequency of 0.8% (3 subjects), with 2 subjects having concomitant ALT increase and 1 subject having a concomitant CK increase, which suggested a muscular origin for the AST increase. These subjects are described in detail in Section 2.7.4.3.2.1. Between Month 6 and Month 12, among the 631 subjects treated with LGX 200 mg+ABT in the Pooled SAF for Period 2, 6 subjects (1.0%) had ALT values ≥3×ULN. These included 1 subject (peak ALT 3.7 ×ULN with AST 2.4×ULN) in the EDELWEISS 6 study, and 5 subjects from the PRIMROSE studies in patients with uterine fibroids. During this period, 5 subjects (0.8%) had AST values ≥3×ULN, all of which were reported in the PRIMROSE studies and examined in the initial MAA. Importantly, none of the above subjects reported any symptoms or had temporally associated elevations of total bilirubin >2×ULN or INR >1.5. The observed hepatic enzyme elevations are similar to those observed with other GnRH analogues, consistent with a class effect signal. A warning is included in the SmPC section 4.4 advising HCPs to instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice. As women with abnormal hepatic function parameters were excluded from studies with YSELTY, caution should be applied when administering linzagolix to these patients and regular monitoring should be performed. Additionally, post-marketing follow-up will be implemented using a targeted follow-up questionnaire for any reported cases of liver enzyme increase (see Annex 4). In combination with routine PV

Important potential risk	Justification for risk-benefit impact
	activities, this additional PV activity will increase the likelihood that any potential harm to patients will be rapidly detected and prevented. Along with this, monitoring of any liver associated adverse events will also be implemented during the proposed PASS in the post-market setting (details of this study are presented in Part III.2 Additional pharmacovigilance activities). With the above warnings in the SmPC and additional routine PV activity, the impact on the risk-benefit balance of the product was considered to be minimal due to the low rates of LFT elevations and the absence of Hy's law cases.

Table 10: Justification for risk-benefit impact of missing information

Missing Information	Justification for risk-benefit impact
Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT	As described earlier, GnRH antagonists such as linzagolix reduce serum E2 in a dose-dependent manner. These declines can result in dose-dependent decrease in BMD due to increased bone resorption, which is most pronounced with high doses with which close to full E2 suppression is reached. The aim of lower doses and the use of hormonal ABT with higher doses is to achieve E2 levels within a range that limits BMD decrease. Due to the decline in BMD on treatment and/or the lack of full recovery post treatment with linzagolix 200 mg with concomitant ABT and linzagolix 100 mg with and without ABT, the impact on long-term bone health and future fracture risk in the target population is uncertain. Considering that: 1. the BMD changes data available until week 52 demonstrate that BMD changes slowed after week 24; 2. the BMD changes for linzagolix 100 mg dose, linzagolix 100 mg + ABT dose and linzagolix 200 mg + ABT were considered clinically not meaningful; 3. post-treatment follow-up data provide evidence of partial to complete BMD recovery for a majority of patients

Missing Information	Justification for risk-benefit impact
	4. the FRAX analyses based on the PRIMROSE study showed minimal evidence of future fracture risk the consequence of this missing information is minimal. However, the data that will be collected from real-life situation post-market will be very valuable. In order to collect further information on BMD decrease in real-life setting and for prolonged use of linzagolix, a PASS is proposed as an additional pharmacovigilance activity (details of this study are presented in Part III.2 Additional pharmacovigilance activities).

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The safety profile observed with the LGX 200 mg+ABT regimen in the Phase 3 endometriosis trials was consistent with the safety profile previously established in the Phase 3 trials in patients with uterine fibroids. During this RMP update, no important identified or potential risk or missing information is re-classified or removed.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Table 11: Important identified risk – Bone mineral density decrease

Bone mineral density decrease	
MedDRA Search Terms	PTs: Bone mineral density loss, bone loss, osteopenia, and osteoporosis
Potential mechanisms	The mechanisms for BMD decrease during GnRH receptor antagonist treatment are well understood GnRH antagonists bind competitively to the GnRH receptor in the pituitary and inhibit production of gonadotropins (FSH and LH) which in turn limits the production of E2 leading to a chemical castration that resembles menopause in women (Maggi, 2016).
Evidence source and strength of evidence	GnRH antagonists such as linzagolix reduce serum E2 in a dose-dependent manner. These declines can result in dose-dependent BMD decrease due to increased bone resorption, which is most pronounced with high doses with which close to full E2 suppression is reached. The aim of lower doses and

Bone mineral density decrease	
	the use of hormonal ABT with higher doses is to achieve E2 levels within a range that limits BMD decrease. *Linzagolix 200 mg (without concomitant ABT):* Median levels of serum E2 for the 200 mg dose showed close to full suppression (<20 pg/mL), which was maintained at similar levels up to Week 24. BMD decrease related to linzagolix treatment was limited at 24 weeks. The protective effect of ABT was clearly observed with long term treatment (more than 6 months) at higher dose (200 mg). Individual categorical analysis shows that very few subjects experienced >8% BMD decrease, most of these subjects were in the 200 mg dose arm. BMD decrease after short term use of GnRH agonists generally shows partial to complete recovery within a few months after treatment completion. There was also evidence of recovery after short-term (6 months) full E2 suppression in the Phase 2 EDELWEISS linzagolix study in endometriosis which is in line with data from other GnRH agonists. *Linzagolix 200 mg (with concomitant ABT) and linzagolix 100 mg (with and without concomitant ABT):* Only moderate reductions of serum E2 were observed with the 100 mg dose, 100 mg+ABT and with 200 mg+ABT regimens (on-treatment medians ranging from 27.00 to 48.00 pg/mL) after 52 weeks of treatment. This results in BMD changes which were generally not clinically meaningful. Although overall the BMD changes in all groups were clinically not meaningful, the magnitude of BMD decrease was observed to be different for linzagolix 100 mg group, 100 mg+ABT and linzagolix 200 mg+ABT group (-2.36, -0.93 and -1.61 percent change from baseline at Week 52 at lumbar spine for the 100 mg, 100 mg+ABT and 200 mg+ABT dose, respectively). BMD decrease was more pronounced for linzagolix 100 mg group as compared to linzagolix 200 mg+ABT group and linzagolix 100 mg+ABT group (at week 24 and 52). This suggests that the changes in BMD with the 100 mg and 200 mg linzagolix dose were clearly seen to be mitigated by the concomitant use of hormonal ABT. When the 10-year fracture probability was assessed with the FRAX® tool (web version 4.2) in all PRIMROSE patients assuming continuing linear rates of BMD loss over up to 5 years of duration, the analysis suggests that the treatment could be given for at least 5 years without significant concerns

Bone mineral density decrease	
	about bone health. With regard to the 100mg dose, the mean FRAX probabilities remain well below intervention thresholds whereas the 200mg with concomitant ABT demonstrate even lower probabilities of future fracture risk (Study 20-OBE2109-006). Also, overall, there was evidence of recovery in BMD 24 weeks following treatment discontinuation at Week 52 in both groups. In the Phase 3 trials, bone mineral density loss at Month 6 was minimal at the 200 mg+ABT dose in endometriosis patients, lower than previously reported for UF patients, and similar to other oral GnRH receptor antagonists. Importantly, the rate of BMD change slowed or stabilized between Month 6 and Month 12, suggesting a non-linear pattern of BMD loss. There is no evidence of immediate fracture risk associated with linzagolix treatment.
Characterisation of the risk	To assess the effects of linzagolix with and without concomitant ABT, changes from baseline in BMD at three key anatomic sites (lumbar spine, total hip, and femoral neck) were assessed using DXA during treatment (Weeks 24 and 52) and at the end of the 6-month post-treatment follow-up. BMD was assessed at both group and individual levels: by mean percent change from baseline (including lower 95% CI) 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]) (Cummings, 2002). 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). **<u>Phase 3 studies (UF):</u>** ***Mean change from baseline:*** *Up to 24 Weeks in the Pooled Safety Analysis of the PRIMROSE 1 and PRIMROSE 2 studies:* As expected, changes in BMD were most prominent at the lumbar spine; mean (lower 95% CI) percent change from baseline (CfB) was 0.46% (0.06%), -2.0% (-2.5%), -0.96% (-1.5%), -3.7% (-4.2%) and -1.3% (-1.6%) for the placebo, 100 mg, 100 mg+ABT, 200 mg, and 200 mg+ABT groups,

Bone mineral density decrease

respectively demonstrating the more pronounced BMD decrease with the 200 mg dose as well as the protective effect of ABT on BMD.

Changes at the total hip and femoral neck were less pronounced at all doses but followed the same pattern. The minimal changes in the placebo group of -0.14% (-0.73%) (femoral neck) to 0.44% (-0.11%) (total hip) and 0.46% (0.06%) (lumbar spine) were expected for a study population with a mean age of around 42 years.

Percent change from baseline in BMD at Week 24 in the pooled analysis of the PRIMROSE 1 and PRIMROSE 2 studies (Pooled Safety Analysis)

	Placebo (N=209)	**Linzagolix 100 mg (N=199)**	**Linzagolix 10mg+ABT (N=211)**	**Linzagolix 200 mg (N=210)**	**Linzagolix 200 mg +ABT (N=208)**
Lumbar spine (g/cm^2)					
Baseline					
n (missing)	190 (19)	185 (14)	193 (18)	196 (14)	186 (22)
Mean (SD)	1.103 (0.133)	1.095 (0.124)	1.101 (0.134)	1.093 (0.124)	1.092 (0.121)
% CfB at Week 24					
n (missing)	130 (79)	121 (78)	122 (89)	138 (72)	127 (81)
Mean (SD)	**0.456 (2.285)**	**-1.985 (2.694)**	**-0.963 (2.696)**	**-3.697 (2.859)**	**-1.129 (2.690)**
95% CI for the mean	0.060; 0.853	-2.470; -1.500	-1.446 ; -0.480	-4.178; -3.215	-1.601; -0.657
Total hip (g/cm^2)					
Baseline					
n (missing)	193 (16)	190 (9)	196 (15)	196 (14)	191 (17)
Mean (SD)	0.990 (0.143)	0.994 (0.139)	0.998 (0.130)	0.986 (0.135)	0.995 (0.139)
% CfB at Week 24					
n (missing)	136 (73)	123 (76)	124 (87)	138 (72)	130 (78)

Bone mineral density decrease

Mean (SD)	**0.437 (3.227)**	**-0.711 (2.864)**	**0.005 (2.471)**	**-1.564 (2.702)**	**-0.133 (2.924)**
95% CI for the mean	-0.110; 0.985	-1.223; -0.200	-0.435 ; 0.444	-2.019; -1.110	-0.641; 0.374
Femoral neck (g/cm^2)					
Baseline					
n (missing)	193 (16)	190 (9)	196 (15)	196 (14)	191 (17)
Mean (SD)	0.917 (0.138)	0.910 (0.134)	0.905 (0.124)	0.905 (0.124)	0.907 (0.126)
% CfB at Week 24					
n (missing)	136 (73)	123 (76)	124 (87)	138 (21)	130 (78)
Mean (SD)	**-0.139 (3.493)**	**-1.026 (3.599)**	**-0.440 (3.247)**	**-1.884 (3.627)**	**-0.631 (3.409)**
95% CI for the mean	-0.732; 0.453	-1.668; -0.383	-1.018 ; 0.137	-2.494; -1.273	-1.222; -0.039

ABT = add-back therapy; BMD = bone mineral density; CfB = change from baseline; CI = confidence interval; SD = standard deviation
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-212

Up to 52 weeks in the pooled safety analysis of the PRIMROSE 1 and PRIMROSE 2 studies:

Of note, in the PRIMROSE 1 study, half of the patients in the placebo arm continued on placebo for 52 weeks. The other half and all placebo group patients in PRIMROSE 2 study were switched to 200 mg + ABT after week 24. At Week 52, the mean (lower 95% CI) %CfB for BMD in the lumbar spine in the placebo group was -0.83% (-2.1%) and in general, stabilized in the linzagolix groups compared to the first treatment period. The linzagolix 200mg/200 mg+ABT group had the greatest mean %CfB of -2.7% (-3.3%), followed by linzagolix 100 mg group with %CfB of -2.4% (-3.1%), and linzagolix 200 mg+ABT with %CfB of -1.6% (-2.2%), and linzagolix 100mg+ABT group with %CfB of -0.9% (-1.4%). Similar patterns were observed for the femoral neck and hip.

Percent change from baseline in BMD at Week 52 in the pooled analysis of the PRIMROSE 1 and PRIMROSE 2 studies (Pooled Week 52 Safety Analysis)

Bone mineral density decrease

	Placebo Placebo (N=31)	Linzagolix 100 mg (N=141)	Linzagolix 100 mg+ABT (N=146)	Linzagolix 200 mg Linzagolix 200 mg+ABT (N=161)	Linzagolix 200 mg +ABT (N=154)
Lumbar spine (g/cm^2)					
Baseline					
n (missing)	31 (0)	138 (3)	137 (9)	154 (7)	141 (13)
Mean (SD)	1.138 (0.131)	1.093 (0.120)	1.104 (0.132)	1.098 (0.119)	1.084 (0.120)
% CfB at Week 24					
n (missing)	25 (6)	117 (24)	117 (29)	133 (28)	125 (29)
Mean (SD)	**0.184 (2.140)**	**-2.052 (2.708)**	**-0.900 (2.671)**	**-3.717 (2.879)**	**-1.103 (2.703)**
95% CI for the mean	-0.699; 1.067	-2.548; -1.556	-1.389; -0.411	-4.211; -3.223	-1.582; -0.625
% CfB at Week 52					
n (missing)	19 (12)	93 (48)	84 (62)	91 (70)	97 (57)
Mean (SD)	**-0.831 (2.588)**	**-2.362 (3.559)**	-0.933 (2.135)	**-2.676 (2.857)**	**-1.608 (3.052)**
95% CI for the mean	-2.079 ; 0.417	-3.095 ; -1.629	-1.397 ; -0.470	-3.271; -2.081	-2.223; -0.993
Total hip (g/cm^2)					
Baseline					
n (missing)	31 (0)	140 (1)	139 (7)	153 (8)	145 (9)
Mean (SD)	1.029 (0.134)	0.994 (0.137)	0.999 (0.131)	0.991 (0.125)	0.986 (0.128)
% CfB at Week 24					
n (missing_	27 (4)	119 (22)	119 (27)	133 (28)	128 (26)
Mean (SD)	**0.371 (4.264)**	**-0.737 (2.901)**	**-0.026 (2.505)**	**-1.582 (2.734)**	**-0.139 (2.946)**
95% CI for the mean	-1.315; 2.058	-1.263; -0.210	-0.480 ; 0.429	-2.051; -1.113	-0.654; 0.376
% CfB at Week 52					
n (missing)	19 (12)	94 (47)	88 (58)	91 (70)	99 (55)
Mean (SD)	**-0.863 (2.352)**	**-1.328 (3.421)**	**-0.095 (2.908)**	**-1.556 (2.980)**	**0.103 (2.736)**
95% CI for the mean	-1.996 ; 0.271	-2.029 ; -0.628	-0.711 ; 0.522	-2.177; -0.936	-0.443; 0.649
Femoral neck (g/cm^2)					
Baseline					
n (missing)	31 (0)	140 (1)	139 (7)	153 (8)	145 (9)
Mean (SD)	0.948 (0.138)	0.905 (0.122)	0.906 (0.124)	0.910 (0.119)	0.895 (0.115)
% CfB at Week 24					
n (missing)	27 (4)	119 (22)	119 (27)	133 (28)	128 (26)
Mean (SD)	**-0.548 (3.854)**	**-1.014 (3.649)**	**-0.426 (3.279)**	**-1.827 (3.665)**	**-0.580 (3.405)**
95 % CI for the mean	-2.073; 0.977	-1.677; -0.352	-1.022 ; 0.169	-2.455; -1.198	-1.175; 0.016
% CfB at Week 52					
n (missing)	19 (12)	94 (47)	88 (58)	91 (70)	99 (55)
Mean (SD)	**-1.856 (3.587)**	**-1.663 (4.728)**	**-0.533 (3.556)**	**-1.799 (4.111)**	**-0.317 (3.597)**

Bone mineral density decrease

95% CI for the mean	-3.584 ; -0.127	-2.631 ; -0.694	-1.287 ; 0.220	-2.655; -0.943	-1.034; 0.401

ABT=add back therapy
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-213

Up to week 76 in the PRIMROSE 1 study:

After the end of treatment in the lumbar spine, between Week 52 and Week 76, increases towards baseline were noted across treatment groups.

At Week 52, the mean (lower 95% CI) % CfB in BMD for the lumbar spine for linzagolix 100mg group was -2.27% (-3.76%); for linzagolix 100mg+ABT group was 0.15% (-0.63%); for linzagolix 200mg/200mg+ABT group was -2.07% (-3.05%); and for linzagolix 200mg+ABT group it was -0.90% (-1.89%). In the placebo group, the mean (lower 95% CI) % CfB was -0.73% (-2.04%). At Week 76, the mean (lower 95% CI) %CfB in BMD for the lumbar spine for linzagolix 100mg group was -1.41% (-2.91%); for linzagolix 100mg+ABT group was -0.98% (-2.35%); for linzagolix 200mg/200mg+ABT group was -0.73% (-1.80%); and for linzagolix 200mg+ABT group it was -0.52% (-1.58%). In the placebo group, the mean (lower 95% CI) %CfB was 0.33% (-1.20%) (Initial MAA/UF/Module 2.7.4, table 2.7.4-216).

The general pattern of BMD changes in the total hip and femoral neck was similar to those observed in the lumbar spine, with evidence of ABT use at initiation of treatment mitigating the BMD decreases from baseline.

Up to Week 76 in the PRIMROSE 2 study:

After the end of treatment in the lumbar spine, between Week 52 and Week 76, increases towards baseline were noted across treatment groups.

At Week 52, the mean % CfB (lower 95% CI) in BMD for the lumbar spine for linzagolix 100mg group was -2.46% (-3.24%); for linzagolix 100mg+ABT group was -1.48% (-2.02%); for linzagolix 200mg/200mg+ABT group was -2.98% (-3.73%); and for linzagolix 200mg+ABT group it was -2.15% (-2.93%). At Week 76, the mean % CfB (lower 95% CI) in BMD for the lumbar spine for linzagolix 100mg group was -2.28% (-3.07%); for linzagolix 100mg+ABT group was -0.66% (-1.44%); for linzagolix 200mg/200mg+ABT group was -1.51% (-2.45%); and for linzagolix 200mg+ABT group it was -1.33% (-2.03%) (Initial MAA/UF/Module 2.7.4, table 2.7.4-219). As expected, the same patterns of

Bone mineral density decrease

BMD decrease were observed in the two other anatomic sites but less prominent than for the lumbar spine.

Categorical analysis of percent change in BMD:

Up to Week 24 in the pooled safety analysis:

Consistent with the mean % CfB data, BMD changes >3% were more frequent among subjects treated with linzagolix without concomitant ABT, particularly at the 200 mg dose, compared to the corresponding dose groups with ABT. At the total hip and femoral neck, BMD changes >3% were dose dependent as well in the linzagolix groups without concomitant ABT. In the 100 mg and 200 mg groups at Week 24, BMD changes of >8% from baseline at any site were observed in 8 subjects (6.5%) and 9 subjects (6.4%), respectively, compared to 2 subjects (1.5%) in the placebo group, 1 subject in the 100mg+ABT groups and 3 subjects (2.3%) in the 200mg+ABT group.

Proportion of subjects with BMD change >3% and >8% at Week 24 in the pooled analysis of the PRIMROSE 1 and PRIMROSE 2 studies (Pooled Safety Analysis)

	Placebo (N=209)	**Linzagolix 100 mg (N=199)**	**Linzagolix 100 mg+ABT (N=211)**	**Linzagolix 200 mg (N=210)**	**Linzagolix 200 mg +ABT (N=208)**
Subjects % (n) with BMD loss > 3%					
Spine	3.9 (5)	36.4 (44)	19.6 (24)	55.0 (86)	26.0 (33)
Total Hip	10.3 (14)	15.4 (19)	11.3 (14)	26.7 (37)	8.5(11)
Femoral Neck	16.9 (23)	25.2 (31)	22.4 (25)	37.0 (51)	22.3 (29)
Patients (%) with worst value at any bone site >3%	24.1 (33)	53.2 (66)	34.4 (43)	71.4 (100)	42.2 (55)
Subjects % (n) with BMD loss >8%					
Spine	0.8 (1)	2.5 (3)	0	4.3 (6)	0.8 (1)
Total Hip	1.5 (2)	0.8 (1)	0.8 (1)	1.4 (2)	0
Femoral Neck	0	3.3 (4)	0	2.2 (3)	0.8 (1)
Subjects (%, n) with worst value at any bone site >8%	1.5 (2)	6.5 (8)	0.8 (1)	6.4 (9)	2.3 (3)

ABT = add-back therapy; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-220

Bone mineral density decrease

Up to Week 52 in the pooled safety analysis of the PRIMROSE 1 and PRIMROSE 2 studies:

Consistent with the mean % CfB data, BMD changes >3% were more frequent among subjects treated with linzagolix without concomitant ABT, particularly at the 200 mg dose, compared to the corresponding dose groups with ABT. At the total hip and femoral neck, BMD changes >3% were dose dependent as well in the linzagolix groups without concomitant ABT. In the 100 mg group at Week 52 BMD changes of >8% from baseline at any site were observed in 12 subjects (12.6%) compared to 2 (10.5%) subjects in the placebo group. Groups that received ABT ranged from 0 subject in the 100mg+ABT group to 9 (9.8%) subjects in the 200mg/200mg+ABT group.

Proportion of subjects with BMD change >3% and >8% at Week 52 in the pooled analysis of the PRIMROSE 1 and PRIMROSE 2 studies (Pooled Week 52 Safety Analysis)

	Placebo Placebo (N=31)	**Linzagolix 100 mg (N=141)**	**Linzagolix 100 mg+ABT (N=146)**	**Linzagolix 200 mg Linzagolix 200 mg+ABT (N=161)**	**Linzagolix 200 mg +ABT (N=154)**
Subjects % (n) with BMD loss > 3%					
Spine	15.8 (3)	37.7 (35)	15.5 (13)	44.0 (40)	26.8 (26)
Total Hip	21.1 (4)	25.6 (24)	10.1 (9)	33.0 (30)	12.1 (12)
Femoral Neck	26.4 (5)	34.0 (32)	19.3 (17)	36.3 (33)	17.1 (17)
Patients (%) with worst value at any bone site >3%	47.3 (9)	57.9 (55)	36.4 (32)	65.3 (60)	39.4 (39)
Subjects % (n) with BMD loss >8%					
Spine	5.3 (1)	6.5 (6)	0	3.3 (3)	1.0 (1)
Total Hip	0	5.3 (5)	0	2.2 (2)	0
Femoral Neck	5.3 (1)	8.5 (8)	0	4.4 (4)	3.0 (3)
Subjects (%, n) with worst value at any bone site >8%	(10.5) 2	12.6 (12)	0	9.8 (9)	4.0 (4)

ABT = add-back therapy; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-222

Up to Week 76 in the PRIMROSE 1 study:

At Week 76, BMD decreases of more than 8% from baseline were observed in a total of 3 subjects for the lumbar spine of which 2 (6.5%) subjects were in the 100mg group.

Bone mineral density decrease	
	Up to Week 76 in the PRIMROSE 2 study: At Week 76, BMD decreases of more than 8% from baseline were observed in a total of 3 subjects (1.3%) for the femoral neck and 2 subjects (0.9%) for the total hip; no subject showed a decrease of more than 8% for the lumbar spine. ***Z-Scores:*** Z-Scores (a comparison of the patient's BMD to an age-matched population) are another important clinical measure of bone health. A Z-score of -2 or lower is considered below the expected range for age. In the Pooled Safety Analysis Set the median baseline Z-scores were ≥0 in all treatment groups (with medians ranged from 0.30 to 0.60 for the lumbar spine, from 0.50 to 0.70 for the total hip, and from 0.20 to 0.40 for the femoral neck) confirming the good bone health of the treated population in both PRIMROSE 1 and PRIMROSE 2 studies. Up to week 24, median BMD Z-scores at Week 24 remained ≥0 for all linzagolix groups, with the exception of a median of -0.10 in the 200 mg group for the lumbar spine; medians at Week 24 ranged from -0.10 to 0.55 for the lumbar spine, from 0.50 to 0.60 for the total hip, and from 0.20 to 0.30 for the femoral neck. Up to week 52 in the pooled safety analysis and up to week 76 for PRIMROSE 1 and PRIMROSE 2 studies, median Z-scores were >0 in all treatment groups at lumbar spine. Similar patterns were observed for the femoral neck and the hip (Initial MAA/UF/Module 2.7.4 section 2.7.4.6.3.2.3). ***Incidence of fractures (excluding motor vehicle accidents):*** All of the reported fractures occurred during the first 24 weeks of treatment (i.e., there were no fractures reported between Week 24 and Week 52). In total, 4 subjects experienced fractures: 2 in placebo subjects and 2 in linzagolix groups. The two fractures in the linzagolix groups were in the foot and toe, both due to accidents (Initial MAA/UF/Module 2.7.4 section 2.7.4.6.3.2.4). ***BMD decrease reported as TEAEs:*** *Up to 24 Weeks in the Pooled Safety Analysis of the PRIMROSE 1 and PRIMROSE 2 studies:* Overall, 12 subjects (12/1037; 1.1%) reported a AEs related to reduced BMD of which, 2 (1.0%) subjects were in the placebo group, 2 (1.0%) in

Bone mineral density decrease

the 100 mg group, 2 (1.0%) in the 200 mg group and 1 (0.5%) in the 200mg + ABT group. Remaining 5 (2.4%) subjects were in the 100 mg+ABT group. Of those:

Bone density decreased: 8 subjects (8/1037; 0.8%) reported a PT of 'bone density decreased' as a TEAE: 1 (0.5%) in the placebo group, 2 (1.0%) in the 100 mg group, 3 (1.4%) in the 100 mg+ABT group and 2 (1.0%) in the 200 mg group). The event reported in the placebo subject was considered as severe.

Osteopenia: A total of 3 (0.3%) subjects reported a PT of osteopenia as at TEAE: 1 (0.5%) subject was in the placebo group and 2 (0.9%) subjects in the 100 mg+ABT group.

Osteoporosis: A total of 2 (0.2%) subjects reported a PT of osteoporosis as a TEAE: 1 (0.5%) in the 100 mg+ABT group and 1 (0.5%) subject was in the 200mg+ABT group.

System Organ Class (SOC) Preferred Term (PT)	**Placebo (N=209)**	**Linzagolix 100 mg (N=199)**	**Linzagolix 100 mg+ABT (N=211)**	**Linzagolix 200 mg (N=210)**	**Linzagolix 200 mg +ABT (N=208)**
Subjects with at least one TEAE related to reduced BMD	2 (1.0)	2 (1.0)	5 (2.4)	2 (1.0)	1 (0.5)
Investigations	*1 (0.5)*	*2 (1.0)*	*3 (1.4)*	*2 (1.9)*	*0*
Bone density decreased	1 (0.5)	2 (1.0)	3 (1.4)	2 (1.9)	0
Musculoskeletal and connective tissue disorders	*1 (0.5)*	*0*	*2 (1.0)*	*0*	*1 (0.5)*
Osteopenia	1 (0.5)	0	2 (1.0)	0	0
Osteoporosis	0	0	1 (0.5)	0	1 (0.5)

Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-243

Up to 52 weeks in the pooled safety analysis of the PRIMROSE 1 and PRIMROSE 2 studies:

Overall, 21 subjects (21/757; 2.8%) reported a AEs related to reduced BMD of which 1 (3.2%) in the placebo group, 4 (2.8%) in the 100 mg group, 4 (2.7%) in the 100 mg+ABT group, and 7 (4.3%) in the 200 mg group and 2

Bone mineral density decrease

(1.3%) in the 200mg+ABT group (remaining 3 (2.4%) were in the placebo/200 mg+ABT group).

Bone density decreased: 15 subjects (15/757; 2.0%) reported a PT of 'bone density decreased' as a TEAE of which 1 (3.2%) in the placebo group, 4 (2.8%) in the 100 mg group, 2 (1.4%) in the 100 mg+ABT group, 5 (3.1%) in the 200 mg/200 mg+ABT group, and 1 (0.6%) in the 200 mg+ABT group (remaining were 2 (1.6%) in the placebo/200 mg+ABT group).

Bone loss: 3 (0.4%) subjects reported a PT of 'bone loss': 2 (1.4%) in the 100mg+ABTgroup and 1 (0.6%) subject was in the 200mg/200mg+ABT group during the second treatment period.

Osteoporosis: 2 (0.3%) subjects reported a PT of osteoporosis of which 1 (0.6%) subject was in the 200mg+ABT group (remaining subject was in the placebo/200 mg+ABT group).

System Organ Class (SOC) Preferred Term (PT)	**Placebo (N=31)**	**Linzagolix 100 mg (N=141)**	**Linzagolix 100 mg +ABT (N=146)**	**Linzagolix 200 mg/ Linzagolix 200 mg+ABT (N=161)**	**Linzagolix 200 mg +ABT (N=154)**
Subjects with at least one TEAE related to reduced BMD	1 (3.2)	4 (2.8)	4 (2.7)	6 (3.7)	2 (1.3)
Investigations	*1 (3.2)*	*4 (2.8)*	*2 (1.4)*	*5 (3.1)*	*1 (0.6)*
Bone density decreased	1 (3.2)	4 (2.8)	2 (1.4)	5 (3.1)	1 (0.6)
Musculoskeletal and connective tissue disorders	*0*	*0*	*2 (1.4)*	*1 (0.6)*	*1 (0.6)*
Bone loss	0	0	2 (1.4)	0	0
Osteopenia	0	0	0	0	1 (0.6)
Osteoporosis	0	0	0	1 (0.6)	0

ABT = add-back therapy
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-244

In the PRIMROSE 1 study during the Follow-up Period, 2 subjects (0.9%) reported a TEAE of bone density decreased of which 1 (2%) subject was in the 100 mg group. There were no reports of bone loss, osteopenia, or osteoporosis.

Bone mineral density decrease

In the PRIMROSE 2 study during the Follow-up period, bone density decreased was reported in 4 subjects (of which 2 subjects were in the 200 mg / 200 mg+ABT group and 1 subject in the 200 mg+ABT group). Bone loss was reported in 2 subjects (of which 1 subject in the 200 mg / 200 mg+ABT group). There were no reports of osteopenia or osteoporosis (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.3.2.6).

FRAX modelling

ObsEva performed an assessment of the 10-year fracture probability with the FRAX® tool (web version 4.2) in all PRIMROSE patients. The model assumes continuing linear rates of BMD loss over up to 5 years of duration with BMD and age being the only variables changing over time. The analysis suggests that the treatment could be given for at least 5 years without significant concerns about bone health. With regard to the 100mg dose, the mean FRAX probabilities remain well below intervention thresholds whereas the 200mg with concomitant ABT dose demonstrate even lower probabilities of future fracture risk. The use of the 200mg alone dose expectedly leads to the greatest increases in FRAX probabilities, but its use over short terms 1-2 years is comparable to that of the 200 mg with concomitant ABT dose over 5 years of exposure (Study 20-OBE2109-006).

Mean 10-year probability (%, calculated with BMD) for major osteoporotic fracture and hip fracture, plus 95%CI, at start of treatment and at annual intervals thereafter up to 5 years of exposure in the PRIMROSE 1 study population.

			Age*	T-score	FRAX MOF			FRAX Hip		
Dose	**BMD changes per year**	**Year**	**Mean**	**Mean**	**Mean**	**Lower 95% CI**	**Upper 95% CI**	**Mean**	**Lower 95% CI**	**Upper 95% CI**
		0	43.27	0.18	1.25	1.18	1.31	0.05	0.04	0.06
100mg	-1.7	1	43.94	0.05	1.33	1.26	1.41	0.06	0.05	0.07
	-1.7	2	44.66	-0.07	1.44	1.35	1.52	0.07	0.06	0.08
	-1.7	3	45.46	-0.20	1.56	1.46	1.65	0.09	0.07	0.10
	-1.7	4	46.27	-0.33	1.69	1.59	1.79	0.10	0.09	0.12

Bone mineral density decrease

	-1.7	5	47.12	-0.45	1.84	1.73	1.95	0.13	0.10	0.15
200mg +ABT	-0.3	1	43.94	0.16	1.32	1.24	1.39	0.05	0.04	0.06
	-0.3	2	44.66	0.14	1.40	1.32	1.48	0.06	0.05	0.07
	-0.3	3	45.46	0.11	1.49	1.40	1.57	0.06	0.05	0.07
	-0.3	4	46.27	0.09	1.58	1.49	1.68	0.07	0.05	0.08
	-0.3	5	47.12	0.07	1.69	1.59	1.79	0.07	0.06	0.08
200mg	-3.9	1	43.94	-0.11	1.37	1.29	1.44	0.07	0.06	0.08
	-3.9	2	44.66	-0.40	1.52	1.43	1.61	0.10	0.09	0.12
	-3.9	3	45.46	-0.69	1.71	1.60	1.81	0.15	0.13	0.18
	-3.9	4	46.27	-0.98	1.94	1.82	2.07	0.22	0.18	0.25
	-3.9	5	47.12	-1.27	2.24	2.09	2.39	0.31	0.27	0.36

In the PRIMROSE 3 study, the treatment groups were similar in terms of risk factors for BMD loss and fractions. Overall, interpretation of BMD data is limited due to the small number of subjects in each treatment group and the resulting high data variability. The observed small BMD changes from post-treatment baseline as well as from pre-treatment baseline to the Month 24 visit may not have any clinically relevant impact on the overall bone health of the linzagolix treated subjects since the Z-score of most subjects is within the expected range for age. Additionally, the observed changes in BMD values and Z-scores in the linzagolix treatment groups were mostly within the same range as in the placebo group i.e. there may be no long term consequences on BMD after the end of treatment with linzagolix.

Conclusions (UF):

As with all medications that reduce systemic E2 levels, linzagolix treatment was associated with dose-dependent changes in BMD, i.e., from partial suppression at lower doses to full suppression at higher doses. Overall, the observed changes were small, of limited clinical relevance (especially for linzagolix 100 mg (with and without concomitant ABT) and linzagolix 200 mg with concomitant ABT, and were largely prevented in women who received concomitant hormonal ABT.

Bone mineral density decrease	
	Mean percent BMD changes from baseline provide group level data which have less variability than individual BMD values. These showed that overall, BMD decrease related to linzagolix treatment is limited at 24 weeks and that the rate of decrease slows after 24 weeks during treatment. The protective effect of ABT was clearly observed with long term treatment of higher dose (200 mg). Individual categorical analyses show that very few subjects experienced >8% BMD decrease, and most of these subjects were in the 200 mg dose arm. During the treatment-free follow-up between week 52 and week 76, BMD increase towards baseline were observed with linzagolix treatment. There was also evidence of recovery after short-term (6 months) full E2 suppression with the 200 mg dose in the Phase 2 EDELWEISS linzagolix study in endometriosis which is in line with data from other GnRH agonists. Overall, the BMD results show that as expected: 1) dose dependent BMD changes were observed in all active treatment arms, 2) BMD changes were generally not clinically meaningful except in patients treated with the 200 mg full E2 suppression dose 3) the lumbar spine was most sensitive to BMD decrease, 4) BMD changes slowed after week 24, 5) changes in BMD were mitigated by the concomitant use of hormonal ABT, 6) there was evidence of partial recovery in BMD following treatment discontinuation in all treatment groups, 7) the FRAX analyses based on the PRIMROSE study results showed minimal evidence of future fracture risk **Phase 3 Studies (EAP):** ***Mean Percent Change from Baseline*** A summary of BMD assessments for the LGX 200 mg+ABT regimen in subjects with endometriosis (EDELWEISS trials) and uterine fibroids (PRIMROSE trials) is provided below. Month 6 data are presented for the EDELWEISS 3 SAF (N=162 for LGX 200 mg+ABT) and Month 12 data

Bone mineral density decrease

are presented for the EDELWEISS 6 ESAF (N=122 for LGX mg+ABT). The analogous populations from the PRIMROSE 1&2 trials in subjects with uterine fibroids were the Pooled SAF at Month 6 (N=208) and the Week 52 Pooled SAF at Month 12 (N=154).

At Month 6, the mean (lower 95% CI) percent change from baseline (% CfB) in the lumbar spine was -0.80% (-1.19%) in subjects with EAP and -1.13% (-1.60%) in subjects with UF. The rate of BMD loss slowed at the lumbar spine, with minimal additional changes in BMD at Month 12, suggesting the onset of plateauing of BMD changes. At Month 12, the mean % CfB was -1.10% (-1.79%) in subjects with EAP and -1.61% (-2.22%) in subjects with UF.

Summary of on-treatment BMD assessments for the LGX 200 mg+ABT regimen in the LGX Phase 3 program (EDELWEISS 3 SAF, EDELWEISS 6 ESAF; UF Pooled SAF and Week 52 Pooled SAF)

	EDELWEISS 3 (at M6), EDELWEISS 6 (at M12)		**Pooled PRIMROSE 1 & 2**	
	Placebo	**LGX 200 mg+ABT**	**Placebo**	**LGX 200 mg+ABT**
N at Month 6	**162**	**162**	**209**	**208**
N at Month 12	**0**	**122**	**31**	**154**
Lumbar spine				
Month 6 LSM* or mean %CfB (95% CI)	0.78 (0.39; 1.17)	-0.80 (-1.19; -0.42)	0.46 (0.06; 0.85)	-1.13 (-1.60; -0.66)
Month 12 mean %CfB (95% CI)	–	-1.10 (-1.79; -0.41)	-0.83 (-2.08; 0.42)	-1.61 (-2.22; -0.99)
With loss >8% at M6, n(%)	0	0	1 (0.8)	1 (0.8)
With loss >8% at M12, n(%)	–	2 (2.3)	1 (5.3)	1 (1.0)
Median Z-score at M6	0.40	0.14	0.55	0.35
Median Z-score at M12	–	0.09	0.70	0.50
Femoral neck				
Month 6 LSM* or mean %CfB (95% CI)	-0.32 (-0.80; 0.16)	-0.68 (-1.14; -0.22)	-0.14 (-0.73; 0.45)	-0.63 (-1.22; -0.04)
Month 12 mean %CfB (95% CI)	–	-0.70 (-1.35; -0.06)	-1.86 (-3.58; -0.13)	-0.32 (-1.03; 0.40)
With loss >8% at M6, n(%)	1 (0.8)	3 (2.3)	0	1 (0.8)

Bone mineral density decrease

With loss >8% at M12, n(%)	–	1 (1.2)	1 (5.3)	3 (3.0)
Median Z-score at M6	0.14	-0.02	0.20	0.30
Median Z-score at M12	–	-0.03	0.30	0.35
Total hip				
Month 6 LSM* or mean %CfB (95% CI)	0.30 (-0.03; 0.63)	-0.39 (-0.70; -0.07)	0.44 (-0.11; 0.99)	-0.13 (-0.64; 0.37)
Month 12 mean %CfB (95% CI)	–	-0.52 (-0.98; -0.06)	-0.86 (-2.00; 0.27)	0.10 (-0.44; 0.65)
With loss >8% at M6, n(%)	0	1 (0.8)	2 (1.5)	0
With loss >8% at M12, n(%)	–	1 (1.2)	0	0
Median Z-score at M6	0.40	0.09	0.50	0.50
Median Z-score at M12	–	0.03	0.50	0.60

ABT = add-back therapy; CI = confidence interval; LGX = linzagolix; LSM = least square mean; *EDELWEISS 3

Analysis of covariance with % change from baseline as response variable, baseline value, treatment as covariates.

(1) Bonferroni corrected p-value.

Source: EDELWEISS 3 CSR Table 14.4.1.4.1, Table 14.4.1.2.1, Table 14.4.1.3.1; EDELWEISS 6 CSR 14.4.1.1.1, Table 14.4.1.2.1, Table 14.4.1.3.1; UF MAA SCS Appendix Table 14.4.1.1.1.1, Table 14.4.1.1.1.2, Table 14.4.1.9.1, Table 14.4.1.9.2, Table 14.4.1.7.1, Table 14.4.1.7.2.

Comparable BMD loss was observed at Month 6 at the femoral neck and total hip in both patient populations. Whereas at the femoral neck, the BMD loss stabilized between Month 6 and Month 12 (-0.68% at M6 and -0.70% at M12), further mild loss was observed at the total hip (-0.39% at M6 and -0.52% at M12) in subjects with EAP.

BMD Categories

Few subjects had BMD loss > 8% from baseline in both patient populations; no more than 2 subjects at either time point at the lumbar spine, no more than 3 subjects at the femoral neck, and no more than 1 subject at the total hip.

Z-Scores

Aside from the prematurely terminated EDELWEISS 2 trial with small group sizes, median baseline Z-scores were ≥0 in all treatment groups at all anatomical sites in the EDELWEISS 3 and both PRIMROSE trials (SCS Table 2.7.4-44).

Bone mineral density decrease	
	In the Phase 3 EDELWEISS trials, there were no on-treatment Z-scores below -2.0. The lowest on-treatment Z-score was -1.9. Median scores at Month 6 and Month 12 were ≥0 at the lumbar spine and total hip, and <0 at the femoral neck (-0.02 at M6 and -0.03 at M12). **Conclusions (EAP):** Likely due to 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 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. 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 subjects with uterine fibroids in the Pooled Week 52 SAF treated with LGX 200 mg+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. The observed recovery after the end of treatment is in line with published data on pregnancy, lactation, DMPA use and GnRH agonist or antagonist use. It demonstrates that changes are modest, transient, and unlikely to increase fracture risk in premenopausal women (Module 2.7.4, Section 2.7.4.4.3.7). ***Phase 2 studies:*** Changes in BMD were not assessed in studies KLH1201, KLH1202, and KLH1203. Study 15-OBE2109-001 (EDELWEISS) – Endometriosis in European and US subjects: BMD was assessed at baseline, Weeks 12 (placebo then switched to 100 mg), 24 and 48; for subjects participating in the extension phase: at baseline, Weeks 12, 24 (200 mg then switched to 100 mg), 52 and 76 visits. The discussion focuses on the 100 mg and 200 mg doses.

Bone mineral density decrease	
	Mean Percent Change from Baseline: Baseline characteristics of the EDELWEISS population were different (younger age, lower BMI and majority white) from the PRIMROSE 1 and PRIMROSE 2 populations; however, BMD decreases after 24 weeks of treatment followed the same pattern for the three anatomic sites in all three trials, with the largest decreases seen in the 200 mg dose and minimal CfB in the 100 mg dose. BMD changes, after 52 weeks of treatment once again followed the same pattern for the three anatomic sites as for the PRIMROSE studies, with a slight but minimal increased loss (< -1.5%) for the 100 mg dose at the spine, total hip and femoral neck. Partial or complete recovery at Week 48 was observed for subjects who entered directly into the 24-week follow-up (n=65) after completing 24 weeks of treatment. The mean % CfB for subjects who completed the treatment extension (52 weeks of treatment), entered a 24-week post treatment follow-up, and were included in Follow-up Extension Analysis Set (FEAS, N=104). In the 100 mg group, complete recovery was observed at the femoral neck and lumbar spine, but not the total hip in the 8 subjects with DXA scans at Week 76. Subjects in the 200/100 mg group showed partial or complete recovery at all anatomic sites. Of note, in the 20 subjects in the placebo/100 mg group (i.e., received 40 weeks of treatment with linzagolix 100 mg between Week 12 and 52) who had Week 76 DXA, complete BMD recovery was observed in the femoral neck and total hip and partial recovery was seen in the lumbar spine. *Incidence of fractures (excluding motor vehicle accidents):* One subject (Subject 30133) in the 75 mg TD group reported radius fracture (subject slipped on ice) between Week 12 and 24. The event was considered unrelated to study drug. There were no other events of fractures in the main study or treatment extension. ***Z-scores:*** Similar to the PRIMROSE studies, after 24 weeks of treatment, median Z scores, interquartile ranges and total ranges for femoral neck, total hip and lumbar spine at baseline and Week 24 generally remained stable (> 0) over time (Initial MAA/UF/Module 2.7.4 section 2.7.4.6.3.3).

Bone mineral density decrease	
	Phase 1 studies: BMD decrease was not studied in the Phase 1 clinical program (Initial MAA/UF/Module 2.7.4 section 2.7.4.6.3.4).
Risk factors and risk groups	Major risk factors for decreased BMD include low body weight/BMI, chronic alcohol and/or tobacco use, family history of osteoporosis, hypogonadism, or chronic use of drugs that can reduce bone mass such as glucocorticoids and anticonvulsants. The use of linzagolix in these patients may further contribute to BMD decrease.
Preventability	The current SmPC: • In section 4.2 it is recommended that patients with risk factors for osteoporosis or bone loss, a dual X-ray absorptiometry (DXA) should be performed prior to starting YSELTY treatment. A DXA scan is also recommended after 1 year of treatment. • In section 4.3 use of YSELTY in patients with known osteoporosis is contraindicated • In section 4.4 a warning to HCP regarding BMD decrease is made and a recommendation to perform a DXA scan after 1 year of treatment for all women to verify that the patient does not have an unwanted degree of BMD loss. Thereafter, depending on the prescribed dose of YSELTY, BMD assessment is recommended annually (YSELTY 100 mg) or at a frequency determined by the treating physician based on the woman's individual risk and previous BMD assessment (YSELTY 100 mg with concomitant ABT and YSELTY 200 mg with concomitant ABT). The benefits and risks of YSELTY in patients with a history of a low trauma fracture or other risk factors for osteoporosis or bone loss (such as chronic alcohol and/or tobacco use, strong family history of osteoporosis, and low body weight), including those taking medications that may affect BMD (e.g., systemic corticosteroids, anticonvulsants), should be considered prior to initiating treatment. It is recommended to perform a DXA scan before commencing treatment with YSELTY in these patients. YSELTY should not be initiated if the risk associated with BMD loss exceeds the potential benefit of the treatment.

Bone mineral density decrease	
	In order to collect further information on BMD decrease in real-life setting, a PASS is proposed as an additional pharmacovigilance activity. Details of this study are presented in Part III.2 Additional pharmacovigilance activities.
Impact on the risk-benefit balance of the product	The decrease in BMD with linzagolix was dose-dependent. *Linzagolix 200 mg (without concomitant ABT):* The 200 mg dose was associated with BMD decrease as expected with full E2 suppression. Therefore, as per the label, 200 mg without concomitant ABT is limited to 6-month treatment duration. This is in line with GnRH-agonists which have a similar duration of treatment (PROSTAP SmPC). In the two pivotal studies, between week 52 and week 76 (i.e., 24 weeks after cessation of treatment), BMD increase towards baseline were observed with linzagolix treatment. Also, Phase 2 EDELWEISS linzagolix study in patients with endometriosis showed evidence of recovery after short-term full E2 suppression. In addition to the 6-month limitation on duration of treatment for the 200 mg dose, labelling will also include a contraindication for women with known osteoporosis and a warning regarding use in women with risk factors for BMD decrease. Consequently, the BMD decrease observed for up to 24 weeks of treatment with 200 mg YSELTY has minimal impact on the risk-benefit balance of YSELTY. *Linzagolix 200 mg (with concomitant ABT) and linzagolix 100 mg (with and without ABT):* The decrease in BMD with linzagolix was dose dependent. In line with literature, clinically not significant changes in BMD were observed with linzagolix 100 mg (with and without ABT) and 200 mg (with ABT). The protective effect of concomitant ABT therapy was evident for linzagolix 200 mg+ABT. Post treatment follow-up data from the Phase 3 PRIMROSE studies and the Phase 2 EDELWEISS linzagolix study in subjects with endometriosis show evidence of recovery after end of treatment. Also, based on the observed BMD decreases in the PRIMROSE studies, the FRAX analyses results showed minimal evidence of future fracture risk. Due to the decline in BMD on treatment and/or the lack of full recovery post treatment with linzagolix 200 mg with concomitant ABT and

Bone mineral density decrease	
	linzagolix 100 mg (with and without ABT), the impact on long-term bone health and future fracture risk in the target population is uncertain. Consequently, the SmPC has been revised to provide additional recommendations regarding BMD decrease. In endometriosis patients, bone mineral density loss at Month 6 was minimal at the 200 mg+ABT dose in the Phase 3 trials , lower than previously reported for UF patients, and similar to other oral GnRH receptor antagonists. Importantly, the rate of BMD change slowed or stabilized between Month 6 and Month 12, suggesting a non-linear pattern of BMD loss. The observed recovery after the end of treatment is in line with published data on pregnancy, lactation, DMPA use and GnRH agonist or antagonist use. (Watts et al, 2021) summarizes that, for all conditions, post-treatment data indicate at least partial BMD recovery after treatment cessation and that the observed reductions in BMD associated with pregnancy, lactation, or medications, including GnRH agonists or GnRH antagonists, are modest, transient, and unlikely to increase fracture risk in premenopausal women. The SmPC includes a contraindication for women with known osteoporosis and a warning regarding use in women with risk factors for decrease in BMD. In addition, it recommends regular assessment of BMD, recommends performing a DXA scan before commencing treatment for patients with prior history of a low trauma fracture or other risk factors for osteoporosis or bone loss and for patients taking medications that may affect BMD. It is also advised to make the assessment of the benefit risk balance of YSELTY treatment at regular intervals. Consequently, the observed BMD decrease for YSELTY 100 mg, 100 mg+ABT and 200 mg+ABT treatment has minimal impact on the risk-benefit balance of YSELTY.
Public health impact	A potential impact on public health is not anticipated.

Table 12: Important potential risk – Uterine endometrial and mammary gland adenocarcinoma

Uterine endometrial and mammary gland adenocarcinoma	
MedDRA Search Terms	PT: endometrial adenocarcinoma, breast cancer
Potential mechanisms	Uterine endometrial and mammary gland adenocarcinoma were observed only during the nonclinical studies of linzagolix. The mechanism mediating the increase in uterine endometrial adenocarcinoma in the high-dose animal group as well as an increased incidence of mammary gland carcinoma in the mid-dose animal group is unclear and does not appear to be related either to genotoxicity, or the primary pharmacological activity of linzagolix.
Evidence source and strength of evidence	During a 104-week carcinogenicity study conducted in Wistar rats, higher incidence of uterine endometrial at high dose (500 mg/kg/day) and mammary gland adenocarcinoma at mid-dose (50 mg/kg/day) was observed; this higher incidence of uterine endometrial and mammary gland adenocarcinoma was judged to be incidental. The mechanism mediating this effect is unclear and does not appear to be related either to genotoxicity, or the primary pharmacological activity of linzagolix. The data available are not sufficient to conclude on the potential clinical relevance of these findings. Therefore, only as a precaution "*Uterine endometrial and mammary gland adenocarcinoma*" is listed as important potential risk. During clinical studies, only 1 incidence of endometrial adenocarcinoma was observed in the PRIMROSE 1 and PRIMROSE 2 studies in the 100 mg+ABT group. For this event, a pre-existing lesion was detected in the screening biopsy. This event was considered as not related to linzagolix but to ABT treatment. In addition, 2 events of breast cancer (1 in the linzagolix 200 mg group, and the other in linzagolix 200 mg+ABT group (both from PRIMROSE 1 and 2 studies) were diagnosed. One more SAE of breast cancer was reported in Study KLH1201 in the 50 mg group. All three events were considered unrelated to linzagolix. Risks of ABT also include breast and endometrial cancer. The use of ABT is contraindicated in women with known, past or suspected breast cancer and oestrogen-dependent malignancy, and untreated endometrial hyperplasia. In the linzagolix program to date, there is no indication that these conditions, if present during treatment, are aggravated by linzagolix.

Uterine endometrial and mammary gland adenocarcinoma	
	In LGX 200 mg+ABT regimen in the Phase 3 endometriosis trials, no cancer SAEs were reported.
Characterisation of the risk	*Non-clinical:* The carcinogenic potential of linzagolix was evaluated in Wistar rats (RccHan:WIST). Linzagolix was administered by oral gavage to groups consisting of 60 male and 60 female rats for 104 weeks at daily doses of 0, 5, 50 and 500 mg/kg/day in 0.5% methylcellulose solution. In this study gross pathology findings comprised an increased incidence of nodules in the uterus in females at 500 mg/kg/day. This correlated microscopically with endometrial adenocarcinoma in two females of the vehicle control group, in three females at 50 mg/kg/day and nine females at 500 mg/kg/day. Histopathological examination revealed no evidence of linzagolix treatment related tumour induction in any organ or tissue. However, increases were noted in endometrial or mammary gland adenocarcinoma without preneoplastic lesions or dose-relationship. The higher incidence of uterine endometrial and mammary gland adenocarcinoma at 50 and 500 mg/kg/day were judged to be incidental. The incidence of uterine endometrial adenocarcinoma in the high-dose group of 500 mg/kg/day (16.7%) was outside the range of the historical control data of the testing laboratory, but this range is particularly low because of the limited number of 104-week carcinogenicity studies carried out with Wistar rats in this facility. In addition to this: • The rat repeated-dose toxicity studies up to 26-week duration did not show any increase in proliferative changes in the endometrium (i.e., hyperplasia) that would be considered precursor lesions to endometrial adenocarcinoma. • All other non-clinical toxicity studies of linzagolix did not demonstrate any evidence of mechanistic effects that might be precursors to endometrial adenocarcinoma. • No genotoxicity has been observed.

Uterine endometrial and mammary gland adenocarcinoma	
	• In the studies of the determination of sexual hormones in sexually mature or aged rats (52258,52262) no treatment-related hormonal changes such as oestradiol increase consistent with the induction of endometrial adenocarcinoma were observed. It is however worth mentioning that the incidence of 16.7% is only marginally higher than a value of 14% reported in the literature for a carcinogenicity study (Deerberg, 1981) and lower than a value of 39% reported in a longevity study (Taylor, 2020). In the mammary gland, the incidence of adenocarcinoma in females at 50 mg/kg/day (28.3%, 17/60) was outside the range of the historical control data at the test facility (mean incidence: 13.2% variation range: 7% to 20%). However, the incidence was low at 500 mg/kg/day, and there was no dose correlation. Also, there were no increased incidences in atypical or lobuloalveolar hyperplasia or mammary fibroadenoma which could have arisen as a precursor lesion prior to advancing to adenocarcinoma. Taking all the above into consideration, the non-clinical data indicate that the observed occurrence of endometrial adenocarcinoma and mammary gland adenocarcinoma is incidental and not related to linzagolix treatment. *Clinical:* Only 1 incidence of endometrial adenocarcinoma (n= 1 of 146 (0.7%)) was reported between Week 24 and Week 52 in the PRIMROSE 1 and PRIMROSE 2 studies in the 100 mg+ABT group. This event of endometrial adenocarcinoma occurred in 42-year-old female who received linzagolix 100 mg+ABT for approximately 25 weeks at the time of this event. Endometrial biopsy at screening, which was the basis for including the subject in the study, had shown benign endometrium; however, a blinded re-read by a second pathologist, following the reporting of the event, resulted in a diagnosis of endometrioid intraepithelial neoplasia (EIN), which is a lesion that predisposes to endometrial adenocarcinoma. The Investigator considered the event unrelated to linzagolix and related to ABT. According to ABT label, there is a possibility that the evolution of the pre-existing condition of EIN/complex atypical hyperplasia has been accelerated by the ABT, evolving towards carcinoma. Two cases of breast cancer were detected in the linzagolix 200 mg group (in the pooled analysis of the PRIMROSE 1 and PRIMROSE 2 studies up

Uterine endometrial and mammary gland adenocarcinoma	
	to Week 24) and the 200 mg+ABT group (reported between Week 24 to Week 52 in the pooled analysis of the PRIMROSE 1 and PRIMROSE 2 studies). These events occurred after only 20 and 19 weeks of exposure to linzagolix, respectively. Both these events were severe and lead to discontinuation of study drug. These cases were considered to be not related to linzagolix due to the short exposure to study drug. One more SAE of breast cancer was reported in Study KLH1201 in the 50 mg group. It was initially suspected within 4 weeks after treatment start following a mammography. This event was considered not related to linzagolix. In LGX 200 mg+ABT regimen in the Phase 3 endometriosis trials, no breast cancer or endometrial adenocarcinoma related SAEs were reported. The Women's Health Initiative study (WHI, Chlebowski., 2020) found an increased risk of breast cancer in women taking combined (i.e., oestrogen-progestogen) hormone replacement therapy (HRT) that became apparent after about 3 (1-4) years. Additionally, an up to 2-fold increased risk of breast cancer was reported in women taking combined HRT for more than 5 years. Similarly, in the Million Woman Study (Beral V, 2019), after 5 years of combined HRT, 6 additional cases of breast cancer were observed per 1000 women using HRT. In summary, the non-clinical data indicated that the observed occurrence of endometrial adenocarcinoma is incidental and not related to linzagolix treatment. Also, it is accepted that the mechanism mediating this effect is unclear and does not appear to be related either to genotoxicity, or the primary pharmacological activity of linzagolix. However, the data available are not sufficient to conclude on the potential clinical relevance of these non-clinical findings.
Risk factors and risk groups	No risk factors were identified.
Preventability	In the SmPC section 5.3 the following statement included: In a 2-year carcinogenicity study in rats, an increased incidence of uterine endometrial adenocarcinoma was observed in the mid- (50 mg/kg) and high-dose (500 mg/kg) groups (corresponding to respectively 6.8 and 9.6 times the maximum recommended human dose based on AUC) and a marginal increase in the frequency of mammary gland adenocarcinoma was observed

Uterine endometrial and mammary gland adenocarcinoma	
	at the mid-dose (50 mg/kg) only (6.8 times the maximum recommended human dose based on AUC). The clinical relevance of these findings remains unknown. In order to collect further information on uterine endometrial and mammary gland adenocarcinoma in real-life setting, a PASS is proposed as an additional pharmacovigilance activity (details of this study are presented in Part III.2 Additional pharmacovigilance activities), in addition to post-marketing follow-up questionnaires as a routine pharmacovigilance activity (see Part III.1 Routine pharmacovigilance activities and Annex 4 - Specific adverse drug reaction follow-up forms).
Impact on the risk-benefit balance of the product	Impact on the risk-benefit balance of the product is negligible as uterine endometrial and mammary gland adenocarcinoma were infrequently observed in clinical studies and most likely not related to linzagolix. As this was observed in non-clinical studies, this was included as important potential risk only as a precaution.
Public health impact	A potential impact on public health is not anticipated.

Table 13: Important potential risk – QT Interval Prolongation

QT Interval Prolongation	
MedDRA Search Terms	SOC Cardiac disorders
Potential mechanisms	Blockage of the GnRH receptor by GnRH antagonists results in decreased secretion of LH and FSH and, consequently, decreased release of sexual steroid hormones. It is well known that testosterone deprivation in men to levels below the normal age-adjusted physiological range, irrespective of cause, is associated with prolongation of the QT interval, and is thus suggested to be a risk factor for cardiovascular-related morbidity and mortality (Olsson H, 2017). In women the effect of E2 deprivation on QTc is less well established.

QT Interval Prolongation	
Evidence source and strength of evidence	In Study 17-OBE2109-001 (TQTc study), a positive QTc prolongation signal was observed following single doses of both 700 mg and 200 mg linzagolix. The 700 mg and 200 mg doses, at 3 hours post-dose, were found to prolong QTcF with LSM of 9.92 msec (90% CI 8.03 - 11.81) and 8.34 msec (90% CI 6.44 - 10.23), respectively. Post-hoc analyses accounting for heteroscedasticity produced similar results, with upper bounds of the 90% 2-sided CI of 11.55 and 9.91 msec for 700 mg and 200 mg linzagolix doses, respectively. With the exception of the above finding, the results of ECG readings performed in Phase 3 did not raise any safety concerns. There were no QTcF prolongations >500 ms in the Phase 2 or Phase 3 trials (except 1 Japanese subject in Phase 2 study KLH1204 who presented QT interval prolongation (QTc 519 ms) 29 days after the initial linzagolix dose of 50 mg). QT interval prolongation and TEAEs in the SOC *Cardiac disorders* were explored in accordance with ICH guidance *E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (*EMEA 2005*).* The rates of the following TEAEs were compared in the treated and control subjects: torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures. Except for one event of syncope, none of the other PTs were reported to date in the linzagolix clinical development program; 1 subject in the 100 mg group reported 1 event of syncope which was not associated with QTcF prolongation (QTcF values ≤453 ms at all assessments).
Characterisation of the risk	**<u>Phase 3 studies (UF):</u>** Subjects with clinically significant abnormal ECG, or ECG with QTcF > 470 msec at screening or Day 1 (prior to first dose) were excluded from participating in the studies. Notably, ECG assessments were instituted after the Phase 1 TQT study 17-OBE2109-001 was completed in amendments to both PRIMROSE trials. Local 12-lead ECG readings of QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) were performed at screening, Day 1 (prior to first dose), Week 4, 12, 24, 36, and 52 visits, and also during follow-up at the Week 64 visit. Since both PRIMROSE studies were

QT Interval Prolongation	
	ongoing, subjects who had started the study prior to the amendments did not have an ECG assessment performed at Day 1. This resulted in relatively low numbers of subjects with available ECG data. In the Pooled Safety Analysis (N=1037), QTcF data were available for only 556 subjects (53.6%) at baseline, and for only 516 (49.8%) to 581 (56.0%) subjects overall at subsequent time points. (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.4.1.1). In the Week 52 Pooled Safety Analysis, QTcF data were available for only 390 subjects (51.5%) and for only 397 to 568 overall at subsequent time points (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.4.1.2) *Summary statistics for ECG parameters in the PRIMROSE 1 and PRIMROSE 2 studies* In the PRIMROSE 1 study, the mean (SD) QTcF for the population was 420.4 ms (18.5) at baseline, with similar mean baseline QTcF among treatment groups. During the treatment, minor decreases in mean QTcF were observed in all groups, including the placebo group, with no evidence of dose relationship; the highest on-treatment QTcF value was 489 ms. In the PRIMROSE 2 study, baseline QTcF values were comparable across treatment groups in the Safety Analysis Set. Changes from baseline were minimal in all groups at time points up to Week 24; no QTcF value of more than 479 ms was noted. *Up to Week 24: pooled safety analysis of the PRIMROSE 1 and PRIMROSE 2 studies*: At baseline, ≥480 ms but below 500 ms. There were no subjects with on-treatment 1 subject in the 200 mg group had an absolute QTcF interval prolongation QTcF interval prolongation ≥500 ms. While on treatment at Week 4, 1 subject in the 100 mg group had had an absolute QTcF interval prolongation ≥480 ms but below 500 ms. Otherwise, no subject had an on-treatment absolute QTcF interval prolongation ≥480 ms as measured at Weeks 4, 12, and 24. Increases of ≥60 ms relative to the highest pre-treatment value were seen in 1 subject at Week 4 (Subject 93106 in the 200 mg group; baseline QTcF of 355 ms) and in 1 subject at Week 12 (Subject 93102 in the 100 mg group; baseline QTcF of 407 ms).

QT Interval Prolongation

Several increases of ≥30 ms relative to the highest pre-treatment value were observed, including in the placebo group. Increases of ≥30 ms from the highest pre-treatment value did not appear to be dose-related and did not show a clear temporal pattern. It should be noted that of the 3 subjects who had persistent or recurrent increases, 2 subjects had relatively low baseline values: Subject 26607 (100 mg group) had a baseline value of 396 ms, and Subject 93106 (200 mg group) had a baseline value of 355 ms (this subject experienced one of the increases of ≥60 ms).

A search of the pooled safety database for events potentially associated with (or indicative of) torsade de pointes or QT prolongation was performed. There were no reported PTs of "torsade de pointes," "sudden death," "ventricular tachycardia," "ventricular fibrillation and flutter," or "seizures." One subject in the 100 mg group (Subject 22613) experienced 1 event of syncope; this subject's QTcF values were ≤453 ms at all assessments (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.4.1.1).

No ECG abnormalities were reported as TEAEs in the PRIMROSE 2 study during the first treatment period (Day 1 to Week 24). TEAEs in the SOC *Cardiac disorders* were reported with a similar frequency between the placebo and linzagolix groups. The most commonly reported TEAE in this SOC was palpitations, reported with a similar frequency between the placebo and 200 mg (with or without concomitant ABT) groups. Tachycardia was reported only at the 200 mg dose (with or without concomitant ABT).

TEAEs in the SOC Cardiac disorders, reported between Day 1 and Week 24 in the pooled analysis of the PRIMROSE 1 and PRIMROSE 2 studies (Pooled Safety Analysis)

System organ class/ Preferred term	Placebo (N=209)		Linzagolix 100 mg (N=199)		Linzagolix 100 mg+ABT (N=211)		Linzagolix 200 mg (N=210)		Linzagolix 200 mg +ABT (N=208)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Cardiac disorders	**3 (1.4)**	**5**	**3 (1.5)**	**3**	**3 (1.4)**	**3**	**3 (1.4)**	**3**	**2 (1.0)**	**2**
Palpitations	1 (0.5)	1	3 (1.5)	3	2 (0.9)	2	1 (0.5)	1	1 (0.5)	1
Tachycardia	0	0	0	0	0	0	2 (1.0)	2	1 (0.5)	1

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Acute myocardial infarction	1 (0.5)	1	0	0	0	0	0	0	0	0
Coronary artery disease	1 (0.5)	1	0	0	0	0	0	0	0	0
Ischaemic cardiomyopathy	1 (0.5)	1	0	0	0	0	0	0	0	0
Left atrial enlargement	0	0	0	0	1 (0.5)	1	0	0	0	0
Supraventricular tachycardia	1 (0.5)	1	0	0	0	0	0	0	0	0

ABT = add-back therapy; E = events
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-254

Between Week 24 and Week 52: pooled safety analysis PRIMROSE 1 and PRIMROSE 2 studies:

At baseline, QTcF values were comparable across treatment groups in the Week 52 Pooled Safety Analysis. Changes from baseline were minimal in all groups at time points up to Week 52.

In the PRIMROSE 1 study, no subjects had on-treatment QTcF values ≥500 ms. During treatment, at Week 36 and Week 52, 1 subject in the placebo group had a QTcF value ≥480 ms but below 500 ms; no other subjects had QTcF values ≥480 ms at Week 36 and Week 52. No QTc interval increases of ≥60 ms from the highest pre-treatment value were observed in any of the subjects up to Week 52. At Weeks 24, 36, and 52, QTc interval increases of ≥30 ms were observed in up to 2 subjects per group in the 200 mg/200 mg+ABT, 100 mg+ABT, and 1 subject each in the placebo and 200 mg+ABT group.

In the PRIMROSE 2 study, maximum values were ≤479 ms at all time points except Week 36, when a maximum QTcF value of 493 ms was noted in the 100 mg group.

A QTcF value ≥480 ms was recorded for 1 subject in the 100 mg group at Week 36; no QTcF values ≥500 ms were recorded in any treatment group up to Week 52.

Several increases of ≥30 ms relative to the highest pre-treatment value were observed after Week 24:

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	• Week 36: 8 subjects (placebo/200 mg+ABT: 2 subjects; 100 mg: 2 subjects; 100 mg+ABT, 2subjects;200 mg/200 mg+ABT: 1 subject; 200 mg+ABT: 1 subject), and • Week 52: 4 subjects (1 subject, placebo/200mg+AB, 1 subject, 100 mg+ABT, 1 subject; 200 mg/200 mg+ABT; 1 subject, 200mg+ABT). Increase of ≥60 ms relative to the highest pre-treatment value was seen in 1 subject (200 mg/200 mg+ABT group) at Week 52. Two (2) of the subjects with increases of ≥30 ms relative to the highest pre-treatment value had already experienced such increases during the first treatment period (Subjects 26607 and 93106, both of whom had low baseline values as noted above). The increase of ≥60 ms at Week 52 occurred in Subject 93106 (baseline value 355 ms). Considering both treatment periods in the PRIMROSE 1 and the PRIMROSE 2 studies, increases of ≥30 ms relative to the highest pre-treatment value were transient in approximately half of the subjects experiencing such increases. No ECG abnormalities were reported as TEAEs during the second treatment period (Week 24 to 52) for subjects in the Week 52 Pooled Safety Analysis (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.4.1.2). The incidence of TEAEs in SOC *Cardiac Disorder* were comparable across all treatment groups. Tachycardia was reported in 3 subjects; 1 subject treated at the 100 mg dose and 2 subjects treated with 100mg+ABT. Bradycardia was reported in 2 subjects; 1 subject treated with 200 mg/200mg+ABT and 1 subject with 200mg+ABT. **TEAEs in the SOC Cardiac disorders, reported between Week 24 and Week 52 in the pooled analysis of the PRIMROSE 1 and PRIMROSE 2 studies (Pooled Week 52 Safety Analysis)**

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System organ class/ Preferred term	Placebo Placebo (N=31)		Placebo/ Linzagolix 200 mg+ABT (N=123)		Linzagolix 100 mg (N=141)		Linzagolix 100 mg+ABT (N=146)		Linzagolix 200 mg/ Linzagolix 200 mg+ABT (N=161)		Linzagolix 200 mg +ABT (N=154)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Cardiac disorders	**0**	**0**	**1 (0.8)**	**1**	**1 (0.7)**	**2**	**3 (2.1)**	**4**	**1 (0.6)**	**1**	**1 (0.6)**	**1**
Tachycardia	0	0	0	0	1 (0.7)	1	2 (1.4)	3	0	0	0	0
Bradycardia	0	0	0	0	0	0	0	0	1 (0.6)	1	1 (0.6)	1
Palpitations	0	0	0	0	1 (0.7)	1	0	0	0	0	0	0
Right atrial enlargement	0	0	1 (0.8)	1	0	0	0	0	0	0	0	0
Sinus Tachycardia	0	0	0	0	0	0	1 (0.7)	1	0	0	0	

ABT = add-back therapy; E = events
Dictionary coding: MedDRA version 23.0
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-256

Up to Week 64 in the PRIMROSE 1 study:

In the Follow-up Safety Analysis Set, QTcF data were available for only 165 of the 234 subjects at baseline, and for only 197 subjects at Week 64.

At baseline, QTcF values were comparable across treatment groups in the Follow-up Safety Analysis Set. At Week 64, changes from baseline were minimal in all treatment groups, including placebo/ placebo group. Maximum values were ≤471 ms in all treatment groups except the placebo/ placebo group, in which a maximum QTcF value of 491 ms was noted.

No QTcF values ≥500 ms were recorded in any treatment group up to Week 64.

No increases of ≥30 ms relative to the highest pre-treatment value were observed at Week 64.

In the SOC *Cardiac Disorders* TEAEs were reported by 3 subjects: "palpitations" was reported by 1 subject in the 100mg+ABT group, and by 1 subject in the 200mg/200mg+ABT group; angina pectoris was reported by 1 subject in the 100mg group. There were no reported TEAEs of torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation

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and flutter, seizures, or syncope from Day 1 to Week 64 (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.4.1.3).

TEAEs in the SOC Cardiac disorders, reported between Week 52 and Week 64 in the PRIMROSE 1 study (Follow-up Safety Analysis Set)

System organ class/ Preferred term	Placebo Placebo (N=22)		Placebo/ Linzagolix 200 mg+ABT (N=19)		Linzagolix 100 mg (N=50)		Linzagolix 100 mg+ABT (N=42)		Linzagolix 200 mg/ Linzagolix 200 mg+ABT (N=45)		Linzagolix 200 mg +ABT (N=56)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Cardiac disorders	**0**	**0**	**0**	**0**	**1 (2.0)**	**1**	**1 (2.4)**	**1**	**1 (2.2)**	**1**	**0**	**0**
Palpitations	0	0	0	0	0	0	1 (2.4)	1	1 (2.2)	1	0	0
Angina pectoris	0	0	0	0	1 (2.0)	1	0	0	0	0	0	0

ABT = add-back therapy; E = events
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-258

Up to Week 64 in the PRIMROSE 2 study

In the Follow-up Safety Analysis Set, QTcF data were available for only 128 of the 339 subjects at baseline, and for only 307 subjects at Week 64. Changes from baseline were minimal in all treatment groups at Week 64. Maximum values were ≤471 ms in all treatment groups except the 200 mg / 200 mg + ABT group, in which a maximum QTcF value of 495 ms was noted.

No QTcF values ≥500 ms were recorded in any treatment group up to Week 64.

Increases of ≥30 ms relative to the highest pre-treatment value were observed at Week 64 in 5 subjects (placebo/200 mg +ABT: 2 subjects; 200 mg /200 mg +ABT: 2 subjects; 200 mg +ABT: 1 subject).

Increase of ≥60 ms relative to the highest pre-treatment value was seen in 1 subject (200 mg /200 mg +ABT group) at Week 64.

During the Follow-up Period of the PRIMROSE 2 study, no TEAEs in the SOC Cardiac Disorders were reported. There were no reported TEAEs of torsade de pointes, sudden death, ventricular tachycardia, ventricular

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	fibrillation and flutter, seizures, or syncope from Day 1 to Week 64 (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.4.1.4). **Phase 3 trials (EAP):** The results of 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. **From Day 1 to Month 6 of treatment in Phase 3 endometriosis trials** Local 12-lead ECG readings of QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) were performed at screening, Day 1 (pre- and post- first dose), then monthly during treatment. Subjects with clinically significant abnormal ECG, or ECG with QTcF > 450 msec at screening or Day 1 (prior to first dose) were excluded from participating in the studies. 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 clinical significant ECG findings were recorded in 1 subject in the LGX 75 mg group at Months 1, 5, and 6 of the treatment period (EDELWEISS 3 CSR, Table 14.4.9.2.1). Similarly, 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) (EDELWEISS 2 CSR, Table 14.4.9.1). 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.

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	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 450 ms in any of the treatment groups. Abnormal clinically significant ECG findings were recorded in 1 subject in the placebo group at Month 3; there were no abnormal clinically significant ECG findings in any of the LGX groups throughout the 6-month treatment period (EDELWEISS 2 CSR, Table 14.4.9.2). **From Month 6 to Month 12 of treatment in Phase 3 endometriosis trials** 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. In the EDELWEISS 6 trial, the highest maximum QTcF values of 480 ms, 478 ms, 484 ms, and 460 ms were recorded in the placebo/LGX 75 mg, placebo/LGX 200 mg+ABT, LGX 75 mg, and LGX 200 mg+ABT groups, respectively, between Month 6 and Month 12. At Month 12, maximum QTcF values exceeded 450 ms in the LGX treatment groups but values were below 480 ms (LGX 75 mg: 454 ms; LGX 200 mg+ABT: 460 ms) (EDELWEISS 6 CSR, Table 14.4.9.1.1). Abnormal clinically significant ECG findings were recorded up until Month 12 in the same subject in the LGX 75 mg group for whom abnormal clinically significant findings had already been recorded at Months 1, 5, and 6 of the EDELWEISS 3 treatment period (EDELWEISS 6 CSR, Table 14.4.9.2.1). In the prematurely terminated EDELWEISS 5 trial, few subjects had evaluable data past Month 9 and up to that point, no increases were noted in the mean QTcF values in any treatment group. The highest post-baseline maximum QTcF values of 423 ms, 430 ms, 429 ms, and 435 ms were recorded in the placebo/LGX 75 mg, placebo/LGX 200 mg+ABT, LGX 75 mg, and LGX 200 mg+ABT groups, respectively, during the extension study (EDELWEISS 5 CSR, Table 14.4.9.1). There were no abnormal clinically significant ECG findings in any groups throughout the extension study (EDELWEISS 5 CSR, Table 14.4.9.2).

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Phase 2 studies:

Study 15-OBE2109-001 (EDELWEISS) – Endometriosis in European and US subjects

Per Protocol Amendment 9 implemented in the US, 12-lead ECG readings of QTcF were performed at Week 52 and Week 64 for subjects still on treatment when this amendment was implemented. Among the 8 subjects who underwent an ECG, 7 subjects treated with linzagolix had QTcF readings below 450 msec. One subject in the placebo/100 mg group had a QTcF reading of 464 msec at Week 52, which fell in the category of 450-480 msec (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.4.2).

TEAEs in the SOC *Cardiac disorders* were reported between Day 1 and Week 24 by 7 subjects (2.1%), none in the 200 mg group.

TEAEs in the SOC Cardiac disorders reported between Day 1 and Week 24 in the EDELWEISS study (Safety Set)

System Organ Class Preferred term	Placebo/ Linzagolix 100 mg (N=55) n (%) E	Linzagolix 50 mg (N=49) n (%) E	Linzagolix 75 mg FD (N=58) n (%) E	Linzagolix 75 mg TD (N=56) n (%) E	Linzagolix 100 mg (N=52) n (%) E	Linzagolix 200 mg (N=57) n (%) E
Cardiac disorders	**0**	**3 (6.1) 5**	**1 (1.7) 1**	**1 (1.8) 1**	**2 (3.8) 2**	**0**
Angina pectoris	0	1 (2.0) 2	1 (1.7) 1	1 (1.8) 1	0	0
Tachycardia	0	1 (2.0) 1	0	0	1 (1.9) 1	0
Palpitations	0	1 (2.0) 2	0	0	0	0
Cardiac flutter	0	0	0	0	1 (1.9) 1	0

E = events; FD = fixed dose; TD = titrated dose
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-261

Between Week 24 and Week 52, 1 subject (3.4%) in the 75 mg TD group reported 1 event of tachycardia. There were no other TEAEs in the SOC *Cardiac disorders* reported among subjects in the Treatment Extension Analysis Set between Week 24 and 52.

Study KLH1201 – Endometriosis in Japanese subjects

12-lead ECGs were performed at baseline, during treatment (Weeks 1, 4, 8), and during post-treatment observation period (28 days post-treatment).

QT Interval Prolongation	
	No clinically significant findings were observed in this study in terms of ECG readings. TEAEs in the SOC *Cardiac disorders* were reported by 1 subject (8.3%) in the linzagolix 50 mg group; the reported PT was supraventricular extrasystoles. **Study KLH1202 – Endometriosis in Japanese subjects** 12-lead ECGs were performed at baseline, during treatment (Weeks 1, 4, 8, 12), and during post-treatment observation period (4 weeks post-treatment). No clinically significant findings were observed in this study in terms of ECG readings. TEAEs in the SOC *Cardiac disorders* were reported by 1 subject (3.4%) in the linzagolix 50 mg group who reported palpitations. **Study KLH1203 – Endometriosis in Japanese subjects** 12-lead ECGs were performed at baseline, during treatment (Weeks 1, 4, 8), and during post-treatment observation period (4 weeks post-treatment). No clinically significant findings were observed in this study in terms of ECG readings. There were no TEAEs in the SOC Cardiac disorders reported during this study. **Study KLH1204 – Endometriosis in Japanese subjects** 12-lead ECGs were performed at baseline, every 4 weeks while on treatment, and 4 weeks after the end of treatment. One subject in the linzagolix 50 mg group presented ECG QT prolongation (QTc 519 ms) 29 days after the initial linzagolix dose which resulted in treatment discontinuation. The subject's baseline QTc was 461 ms; her QTc normalized to baseline levels and ranged from 444 ms to 462 ms during post-treatment follow-up visits. At the time of QT increase, the subject had a concomitant CK increase, which was considered to originate from skeletal muscle rather than the myocardium due to the subject's strenuous physical exercise regimen. No other adverse events were observed for this subject; there were no significant findings on the follow-up coronary CT scan, echocardiograph, or Holter ECG performed approximately 2 months after treatment discontinuation.

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No other clinically significant changes in 12-lead ECG readings were observed in this study.

TEAEs in the SOC *Cardiac disorders* were reported by 3 (3/326; 0.9%) subjects in the linzagolix groups and 3 subjects (7.0%) in the leuprorelin group. None of the PTs in this SOC was reported by more than 1 subject in any of the linzagolix groups.

TEAEs in the SOC Cardiac disorders reported up to Week 24 in the KLH1204 study (Safety Set)

	N (%) of subjects				
	Linzagolix 25 mg (N=78)	**Linzagolix 50 mg (N=86)**	**Linzagolix 75 mg (N=77)**	**Linzagolix 100 mg (N=85)**	**Leuprorelin (N=43)**
Cardiac disorders	1 (1.3)	0	2 (2.6)	0	3 (7.0)
Palpitations	0	0	1 (1.3)	0	3 (7.0)
Sinus bradycardia	0	0	1 (1.3)	0	0
Ventricular extrasystoles	1 (1.3)	0	0	0	0

Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-262

Phase 1:

Study 17-OBE2109-001 – TQT/SAD

As described above, an early positive QTc prolongation signal was observed in both the therapeutic (200 mg) and supratherapeutic (700 mg) doses. The 700 mg and 200 mg linzagolix doses, at 3 hours post dose, were found to prolong QTcF in this study up to 9.92 msec (90% CI 8.03 - 11.81) and to 8.34 msec (90% CI 6.44 - 10.23), respectively. Additional post-hoc by-time point analyses accounting for heteroscedasticity also produced borderline results for linzagolix 700 mg of 9.92 msec (90% CI 8.28 - 11.55) and values of 8.27 msec (90% CI 6.64 – 9.91 msec) for linzagolix 200 mg, both at 3 hours post dose.

Assay sensitivity was confirmed with the moxifloxacin arm of the study. The lower bounds of the 97.5%, 2-sided CI were > 11 msec at hours 1 through 4 for QTcF LSM differences between moxifloxacin and placebo, well above the > 5 msec threshold; therefore, the assay was adequately sensitive to test for QT prolongation. The numerical data did not appear to show any proarrhythmia or morphological risk. From a clinical perspective,

QT Interval Prolongation	
	there does not seem to be significant concerns given the magnitude of the QTc prolongation observed in the individual data. Furthermore, the categorical data for QTc showed no values greater than 480 msec and no changes greater than 30 msec following the therapeutic and supratherapeutic doses. There were no AEs based on ECGs in this study and the Investigator considered all abnormal findings to be clinically insignificant (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.4.3). A comprehensive analysis on linzagolix effects on the QT interval is included in Initial MAA/UF/Module 2.7.2.2.3.1.4. Apart from this, there were no clinically significant findings in the ECG recordings in any other Phase 1 studies.
Risk factors and risk groups	Patients with known cardiovascular disease or family history of QT interval prolongation, hypokalaemia, or in patients consuming other concomitant medicinal products that prolong the QT interval, or in patients with co-existing disorders leading to increased linzagolix plasma levels.
Preventability	The current SmPC warns healthcare professionals in section 4.4 that linzagolix marginally increases the QT interval but demonstrated no evidence of clinically relevant risk of QT interval prolongation or Torsade de Pointes. Caution should be exercised when linzagolix is prescribed in patients with known cardiovascular disease or family history of QT prolongation, hypokalaemia, and in concomitant use with other medicinal products that prolong the QT interval. Caution should also be exercised when linzagolix is prescribed in patients with co-existing disorders leading to increased linzagolix plasma levels. In order to gather more information on the reported events of cardiac disorders indicative for a potential QT prolongation in real-life setting, a PASS is proposed as an additional pharmacovigilance activity (details of this study is presented in Part III.2 Additional pharmacovigilance activities) in addition to a post-marketing follow-up questionnaire as a routine pharmacovigilance activity (see Part III.1 Routine pharmacovigilance activities and Annex 4- Specific adverse drug reaction follow-up forms).

QT Interval Prolongation	
Impact on the risk-benefit balance of the product	The impact on the risk-benefit balance of the product is minimal as there has been no evidence of clinically relevant risk of QT interval prolongation, ventricular rhythm disorders or Torsade de Pointes.
Public health impact	A potential impact on public health is not anticipated.

Table 14: Important potential risk – Embryo-foetal toxicity

Embryo-foetal toxicity	
MedDRA Search Terms	N/A
Potential mechanisms	Due to its mechanism of action, linzagolix suppresses levels of E2 and progesterone, which may interfere with conception, implantation and pregnancy maintenance.
Evidence source and strength of evidence	Linzagolix reproductive and developmental toxicology was assessed in a female rat fertility study (0.16, 0.8, 4, 20, 100 mg/kg/day), an early embryonic development study in rats (100, 300, 1000 mg/kg/day), embryo-foetal development studies in rats (30, 100, 300 mg/kg/day) and rabbits (0.3, 3, 30 mg/kg/day), and pre- and postnatal developmental studies in rats (0, 30, 100, 300 mg/kg/day). Due to its mechanism of action, linzagolix prevented conception and reduced implantation in rats and resulted in embryo-foetal mortality, total litter loss or abolished pregnancy in rat and rabbit embryo-foetal studies. There were no teratogenic effects and no adverse effect on the pre- and postnatal development of the offspring. In the clinical studies of linzagolix, patients were regularly evaluated for pregnancy, and any pregnancy that occurred was followed up for any evidence of treatment-related issues, including the pregnancy outcome and neonatal condition. With limited exposure of pregnant women to linzagolix, effects on human pregnancy are not known.
Characterisation of the risk	***Non-clinical Data:***

Embryo-foetal toxicity	
	Reproductive toxicity studies in particular the fertility study in female rats were limited in dose by the expected anti-GnRH effects of linzagolix preventing conception. As expected for a GnRH receptor antagonist, linzagolix had effects on fertility; reduced pregnancy rates were observed at ≥ 20 mg/kg/day. the NOAEL was set to 4 mg/kg/day. Reversibility of findings was demonstrated after a 4-week treatment free period. Linzagolix had no adverse effects on early embryonic development at dosages up to 300 mg/kg/day in rats; however, small foetuses were observed at 1000 mg/kg/day. A tendency towards an increase in embryonic and foetal death accompanied by the presence of litters with no living embryos was observed in rats at 300 mg/kg/day linzagolix (NOAEL: 100 mg/kg/day), and almost no rabbits administered 30 mg/kg/day became pregnant (NOAEL: 3 mg/kg/day). There was no indication of teratogenicity or adverse effects on the development or reproductive function of the offspring in any of these studies. Administration of linzagolix to female rats during embryo-foetal development and lactation at a dose of 300 mg/kg/day resulted in total litter loss in individual animals but had no adverse effect on the pre- and postnatal development of the offspring (NOAEL: 300 mg/kg/day) (Initial MAA/UF/Module 2.4, section 2.4.4.5.1, 2.4.4.5.2, and 2.4.4.5.3). Overall, non-clinical studies showed expected pharmacological activity and no adverse reprotoxic effects. ***Clinical Data:*** **Uterine Fibroids:** Although pregnancy was considered as an exclusion criterion, ovulation can still occur during treatment with linzagolix. Of the 1769 subjects enrolled in the Phase 3 and Phase 2 studies, with treatment duration ranging from 8 weeks to 52 weeks, 16 pregnancies (0.9%) were reported of which 2 during the PTFU period. Pregnancies and their outcomes are being followed up in both Phase 3 trials as part of the sponsor's pharmacovigilance surveillance. **Phase 3 studies (UF):** Two pregnancies were reported in the PRIMROSE studies. One of the pregnancies (Subject 29916) occurred after the subject completed Treatment Period 1 and voluntarily discontinued from the study (0 days of

Embryo-foetal toxicity	
	exposure to linzagolix) and was lost to follow-up, thus no information is available regarding the pregnancy outcome. The second pregnancy occurred in a 29-year-old subject (Subject 81407) while on treatment with linzagolix 100 mg; the subject's estimated exposure during pregnancy was approximately 40 days. The pregnancy was diagnosed at Week 36 and was confirmed on ultrasound. Ultrasound revealed one live foetus with prominent extension of collar space, femoral hypoplasia and absence of two cardiac chambers, assessed as markers of chromosomal-associated congenital anomalies. The subject underwent an induced abortion with no complications. The investigator assessed the event as severe and considered the foetal malformation as not related to linzagolix. One additional subject (29505) was discontinued from the PRIMROSE 1 study based on a positive urine pregnancy test; however, the serum test was negative, and the subject was therefore considered as not having been pregnant. (Initial MAA/UF/Module 2.7.4, section 2.7.4.4.6.11.1) **Endometriosis-associated Pain:** **Phase 3 trials (EAP):** Of the 568 subjects enrolled in the Phase 3 trials in women with endometriosis, 4 pregnancies (0.7%) were reported. In the EDELWEISS 3 study, discontinuations due to pregnancies were reported in 3 subjects: • 1 subject (0.6%; Subject 602004) in the LGX 75 mg group between Day 1 and Month 3; • 2 subjects: 1 in the placebo (0.6%; Subject 411034) and 1 subject in LGX 75 mg (0.6%; Subject 160004) group between Month 3 and Month 6 (EDELWEISS 3 CSR, Table 14.1.2.3) In the EDELWEISS 6 study, no discontinuations due to pregnancies were reported during the treatment period (EDELWEISS 6 CSR, Table 14.1.3). One subject (1.7%; Subject 406018) in the placebo/LGX 75 mg group discontinued due to pregnancy during the post-treatment follow-up period. The pregnancy occurred more than 1 month after the end of treatment (EDELWEISS 6 CSR, Section 12.2.2.3).

Embryo-foetal toxicity	
	No pregnancies occurred in the EDELWEISS 2 and EDELWEISS 5 studies. ***Phase 2 studies:*** In the EDELWEISS Phase 2 study, 11 subjects became pregnant during the course of the study, with linzagolix exposure during the pregnancy ranging from 0 (i.e., subject in PTFU) to 49 days. There were no AEs or SAEs related to study drug that accompanied the pregnancy. All pregnant subjects were withdrawn from the study. Of the 11 singleton pregnancies, 6 resulted in full-term deliveries (mostly by Caesarean section) and healthy neonates, while 1 neonate was delivered by C-section pre-term (at 32 weeks) due to fluid-membrane rupture and umbilical cord prolapse. Three pregnancies ended early: 2 due to ectopic pregnancy and 1 due to a miscarriage. The outcome of one pregnancy is unknown as the subject was lost to follow-up. There were no congenital anomalies or birth defects in the newborns of any of the women exposed to linzagolix. In study KLH1202, a subject in the 100 mg group (Subject identifier KLH20606) was found to be pregnant at the Week 12 visit during the treatment period. She withdrew from the study and underwent an abortion. Examination at discontinuation of the post-treatment period demonstrated no safety concerns. Two subjects in the KLH1204 trial reported pregnancies. One subject in the 25 mg group tested pregnant in Period II (i.e., between Week 12 and 24). She discontinued the study and chose to terminate pregnancy at 8 weeks. No abnormalities attributable to the investigational product were found in the mother or foetus, concluding that there were no safety concerns. One subject in the placebo group re-randomised at Week 12 to 100 mg (P-100 mg group), tested pregnant at Week 4 in the post-treatment period and chose to terminate the pregnancy at 9 weeks. No abnormalities were found during or after abortion, with no abnormalities in the extracted content. (Initial MAA/UF/Module 2.7.4, section 2.7.4.4.6.11.2) ***Phase 1 studies:*** No pregnancies were reported in the Phase 1 studies (Initial MAA/UF/Module 2.7.4, section 2.7.4.4.6.11.3).

Embryo-foetal toxicity	
Risk factors and risk groups	A major risk factor for women of childbearing potential is non-use of contraception in the context of sexual activity during linzagolix treatment. Irregular bleeding may occur during treatment with linzagolix and may reduce the ability to recognize the occurrence of a pregnancy in a timely manner. Pregnancy testing should be performed if pregnancy is suspected, and linzagolix should be discontinued if pregnancy is confirmed.
Preventability	The current SmPC section 4.4 includes a warning regarding reduction in the ability to recognize the occurrence of a pregnancy in a timely manner during linzagolix treatment, due to potential irregularities in bleeding patterns. Also, sections 4.3 and 4.6 contraindicates use of YSELTY during pregnancy and in women of childbearing potential at risk of pregnancy and not using contraception. Advice to women of childbearing potential to use effective non- hormonal contraception is provided in section 4.6 of the current SmPC. Post-marketing follow-up with a questionnaire in order to gather information on any reported pregnancies and their outcomes will be implemented (see PartIII.1 Routine pharmacovigilance activities and Annex 4 - Specific adverse drug reaction follow-up forms) along with regular pregnancy checks and pregnancy follow-ups during the proposed PASS (details of this study are presented in Part III.2 Additional pharmacovigilance activities).
Impact on the risk-benefit balance of the product	Considering that YSELTY is contraindicated in pregnant women and also the need for contraception is clearly stated in the current SmPC, the impact of this important potential risk on the risk-benefit balance of the product is assessed as minimal.
Public health impact	A potential impact on public health is not anticipated.

Table 15: Important potential risk – Liver Toxicity

Liver Toxicity	
MedDRA Search Terms	Preferred Terms" (PTs): Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Blood lactate dehydrogenase increased, Hepatic enzyme increased, Liver function test increased, Transaminase increased
Potential mechanisms	Elevations of LFT are frequently observed in clinical trials for new chemical entities (NCE) and have more specifically been reported within the oral GnRH analogues. The mechanism by which GnRH agonist/antagonists might cause these increases is unknown. Most of them do not undergo hepatic metabolism and although linzagolix (like elagolix) is substrate of CYPs, there are no documented potentially significant drug-drug interactions. It has been suggested that some aminotransferase increases arising with GnRH analogue therapy when used for prostate cancer in men, may be caused by non-alcoholic fatty liver disease (NAFLD), because of weight gain or metabolic changes caused by the androgen deprivation state induced by the GnRH agonist. By analogy, it can be speculated that for most instances of elevations in aminotransferases the effect on the liver may be due to the hormonal activity of linzagolix and the add-back therapy in patients with risk factors of –NAFLD (albeit un-diagnosed), such as obesity and metabolic syndrome present at baseline. LFT increases may also be related to co-morbidities such as viral hepatitis, NAFLD or biliary duct conditions. Although increases in LFT are seen with GnRH agonist/antagonists including linzagolix, there have been no reports of cases meeting Hy's law criteria/ liver toxicity to date in subjects treated with linzagolix.

Evidence source and strength of evidence	Elevations in liver function tests (LFTs) are potentially a class effect with GnRH antagonists as it has also been reported with elagolix and relugolix treatment (Schlaff, 2020; Osuga, 2019, Carr, 2018 and MYFEMBREE® prescribing information). However, no reports of cases meeting Hy's law criteria/ of confirmed liver toxicity were reported to date in subjects treated with linzagolix. Supporting data from nonclinical studies in dogs and monkeys have shown that increases in serum liver enzymes could occur with linzagolix treatment. These studies concluded that linzagolix was not cytotoxic for hepatocytes and that increases in serum ALT and GLDH were likely to be attributable to induction of ALT and GLDH in the liver by the pharmacological effects of linzagolix. The findings were considered to be of low concern due to the therapeutic indices at the respective NOAELs, the absence of histological liver findings and the confirmation of reversibility following treatment free recovery periods. In linzagolix multiple dose studies, liver enzymes were closely monitored from Phase 1 to pivotal Phase 3 studies. Both Phase 3 uterine fibroid studies included regular testing of liver function parameters. Alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total and indirect bilirubin were assessed from blood samples taken at Screening, Day 1 and Weeks 4, 8, 12, 24, 28, 32, 36, 52, and during follow-up at the Week 64 visit. As observed with other GnRH antagonists, liver enzyme elevations occurred. The rate of elevations >3x ULN was low and none were associated with a bilirubin increase > 2 ULN and/or INR (International normalized ratio) increase > 1.5 ULN; i.e., no cases met criteria for Hy's law. In the pooled safety analysis of PRIMROSE 1 and PRIMROSE 2 studies (N=1037) up to Week 24, 50 subjects (4.8%) reported 72 events of increases in liver function tests. The majority of these events were increases in GGT (28 subjects; 2.7%), ALT (22 subjects; 2.1%), or AST (15 subjects; 1.4%). Most were considered as related to linzagolix and very few led to permanent discontinuation of drug, but none were considered serious. Between Week 24 and Week 52 in the pooled safety analysis of PRIMROSE 1 and PRIMROSE 2 studies, increases in LFTs were reported infrequently as TEAEs (ALT increase in 0.7% (5/757), GGT increase in 0.5% (4/757), and AST increase in 0.4% (3/757)). Only few LFT abnormalities were reported as TEAEs at week 64 for both the studies.

Characterisation of the risk	Over the multiple dose studies, occasional increases in transaminase values were observed under treatment, however these increases were generally reversible under treatment and 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 with concomitant total bilirubin ≥2×ULN or INR>1.5) at any time point during linzagolix treatment. **Phase 3 studies (UF):** *Increases in LFTs above 3×ULN in individual subjects:* In the pivotal Phase 3 studies up to Week 24, increases from baseline > 3xULN (Grade 2 or higher) were observed for ALT and AST in 8 subjects, all but one during linzagolix treatment, for an overall incidence in the linzagolix groups of 0.88% (7/794) and 0.48%; (1/209) for placebo. Grade 3 (>5×ULN) elevations were seen only in subjects receiving 200 mg (1 subject) or 200 mg+ABT (1 subject). There were no Grade 4 elevations in any treatment groups up to Week 24. Each of these 8 subjects was followed up thoroughly to investigate the origin of these increases and alternate diagnoses were identified for 3 of the 7 subjects treated with linzagolix (subjects 80327 (100 mg + ABT), 25028 (200 mg), and 18275 (200 mg + ABT)). These subjects had very mild elevations of ALT and had elevations in AST that were associated with increases in creatine kinase, indicating rather a muscular origin for the transaminase increases, thus no liver enzyme elevations. Subject 29453 had a history of fatty liver. Additionally, of the 7 subjects who had received linzagolix, 5 subjects (29453, 80833, 80842, 18275, and 25028) had a negative re-challenge on active treatment. Between Week 24 and Week 52 in the pooled safety analysis of the PRIMROSE 1 and PRIMROSE 2 studies, 8 subjects experienced Grade 2 or higher elevations of ALT and/or AST during linzagolix treatment and one subject after discontinuation from linzagolix. Grade 3 and Grade 4 elevations were seen only in subjects receiving 200 mg + ABT; of note, 58% of subjects in the second treatment period received this regimen after subjects in the placebo and 200 mg groups had been switched to 200 mg+ABT at Week 24. Again, alternate diagnoses were identified for 3 of the 8 subjects: 2 subjects (80601 (200 mg + ABT) and 80611 (200 mg + ABT)) had AST and creatine kinase elevations indicating rather a muscular origin of the transaminase

increase and 1 subject (80404; 200 mg/200 mg + ABT) was diagnosed with acute hepatitis C.

No subjects had AST or ALT values >3xULN during the Follow-up Period of PRIMROSE 1 and PRIMROSE 2 studies. (Initial MAA/UF/Module 2.7.4 section 2.7.4.4.6.5.1).

Liver abnormalities reported as TEAEs:

The pooled safety database of Phase 3 PRIMROSE 1 and PRIMROSE 2 studies up to Week 24 was searched for PTs pertaining to increases in the LFTs using the HLT Liver function analyses. Few subjects (4.8%) were reported to have LFT elevation events. The majority of these events were increases in GGT (28 subjects; 2.7%), ALT (22 subjects; 2.1%), or AST (15 subjects; 1.4%). The incidence of GGT increases was highest in the 100 mg group (8 subjects; 4.0%), while it was similar in the placebo arm (5 subjects; 2.4%) and all other linzagolix arms (4 to 6 subjects per group; 1.9% to 2.9%). Overall, the incidence of TEAEs related to ALT and/or AST increases in the linzagolix arms was below 3%. The incidence of ALT and/or AST increases was similar between the placebo and 100 mg + ABT groups, but slightly higher in the 100 mg, 200 mg, and 200 mg + ABT groups. Most LFT elevation TEAEs were considered related and very few led to permanent discontinuation of drug. None were considered serious.

Increases in LFTs reported as TEAEs up to Week 24 in the PRIMROSE 1 and PRIMROSE 2 studies (Pooled Safety Analysis)

Preferred term (PT)	Placebo (N=209)		Linzagolix 100 mg (N=199)		Linzagolix 100 mg+ABT (N=211)		Linzagolix 200 mg (N=210)		Linzagolix 200 mg+ABT (N=208)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Subjects with at least 1 liver function event	8 (3.8)	12	14 (7.0)	19	6 (2.8)	8	12 (5.7)	18	10 (4.8)	15
Investigations	**8 (3.8)**	**12**	**14 (7.0)**	**19**	**6 (2.8)**	**8**	**12 (5.7)**	**18**	**10 (4.8)**	**15**
GGT increased	5 (2.4)	5	8 (4.0)	8	4 (1.9)	4	6 (2.9)	6	5 (2.4)	5
ALT increased	3 (1.4)	3	5 (2.5)	6	3 (1.4)	3	6 (2.9)	6	5 (2.4)	5
AST increased	2 (1.0)	2	4 (2.0)	4	1 (0.5)	1	3 (1.4)	3	5 (2.4)	5
Hepatic enzyme increased	1 (0.5)	1	1 (0.5)	1	0	0	1 (0.5)	1	0	0
LFT increased	1 (0.5)	1	0	0	0	0	1 (0.5)	1	0	0
Transaminases increased	0	0	0	0	0	0	1 (0.5)	1	0	0

ABT = add-back therapy; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-125

Between Week 24 and Week 52 in the pooled safety database, increases in LFTs were reported infrequently as TEAEs. In the Week 52 Safety Analysis Set, the incidence of ALT increases was 0.7% (5/757), GGT increases was 0.5% (4/757), and of AST increases 0.4% (3/757). These increases occurred in linzagolix groups at both dose levels and all in combination with ABT, with the exception of the 200mg/200mg+ABT group for which no increases were reported. No increases were reported in the placebo group, but it is to be noted that only 31 subjects, and only in Primrose 1 study, received placebo in the period between Week 24 and Week 52.

In addition to the above for 1 subject (1.2%) in the 200 mg + ABT group, the Investigator reported a PT of drug-induced liver injury of moderate intensity following an increase in ALT (10.9×ULN) and AST (5.5×ULN) at Week 28 with no concomitant increase in bilirubin with ALT rising to 18.2×ULN and AST to 8.6×ULN despite treatment discontinuation. The event was considered to be possibly related to both linzagolix and ABT (Subject 50637; 200mg+ABT); a full narrative for this subject is included in the CSR PRIMROSE 2 (16-OBE2109-009) Section 14.3.3.

Increases in liver function tests reported as TEAEs between Week 24 and Week 52 in the pooled analysis of the PRIMROSE 1 and PRIMROSE 2 studies (Week 52 Pooled Safety Analysis)

System organ class/ Preferred term	Placebo Placebo (N=31)		Placebo/ Linzagolix 200 mg+ABT (N=123)		Linzagolix 100 mg (N=141)		Linzagolix 100 mg+ABT (N=146)		Linzagolix 200 mg/ Linzagolix 200 mg+ABT (N=161)		Linzagolix 200 mg +ABT (N=154)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Subjects with at least one liver function analyses	0	0	2 (1.6)	2	2 (1.4)	2	1 (0.7)	2	0	0	4 (2.6)	7
Investigations*	**0**	**0**	**2 (1.6)**	**2**	**2 (1.4)**	**2**	**1 (0.7)**	**2**	**0**	**0**	**4 (2.6)**	**7**
ALT increased	0	0	0	0	1 (0.7)	1	1 (0.7)	1	0	0	3 (1.9)	3

GGT increased	0	0	2 (1.6)	2	0	0	1 (0.7)	1	0	0	1 (0.6)	1
AST increased	0	0	0	0	0	0	0	0	0	0	3 (1.9)	3
Hepatic enzyme increased	0	0	0	0	1 (0.7)	1	0	0	0	0	0	0

ABT = add-back therapy; ALT = alanine aminotransferase; AST = aspartate aminotransferase; E = events; GGT = gamma-glutamyl transferase
*in addition, Subject 50637, PRIMROSE 2 (ALT 10.9×ULN), and AST 5.5×ULN, rising to, ALT 18.2×ULN, and AST 8.6×ULN despite treatment discontinuation, was reported as a TEAE of drug induced liver injury possibly related to both linzagolix and ABT
Source: Initial MAA/UF/Module 2.7.4, table 2.7.4-129.

During the follow-up period of the PRIMROSE 1 study:

Few liver function test abnormalities were reported as TEAEs; GGT increased in 3 subjects, ALT increased in 2 subjects, and AST increased in 1 subject.

During the follow-up period of the PRIMROSE 2 study

Liver abnormalities reported as TEAEs were infrequent: AST increased (2 subjects, 0.6%), blood ALP decreased (1 subject, 0.3%), GGT increased (1 subject, 0.3%), INR increased (1 subject, 0.3%).

Phase 3 trials (EAP):

In both Phase 3 EDELWEISS trials, increases in ALT and/or AST ≥3×ULN were infrequent during the first six months of treatment: 2 linzagolix-treated subjects in the EDELWEISS 3 trial, and 1 linzagolix-treated and 1 placebo-treated subject in the EDELWEISS 2 trial (EDELWEISS 3 CSR, Listing 16.2.8.3.2; EDELWEISS 2 CSR, Listing 16.2.8.3.2, Listing 16.2.8.3.1):

- 1 subject (200 mg+ABT group; EDELWEISS 3) had ALT 5.4 ×ULN with AST 3.0×ULN at Month 6 visit. At her unscheduled visit 3 days later, her ALT decreased to 2.5×ULN with AST within the normal range. The Investigator identified the subject's intake of amoxicillin 1 g twice daily for 5 days, which included the Month 6 visit day, as a possible reason for the increased ALT and AST. The subject continued on treatment until Month 12 with normal ALT and AST values throughout the rest of the treatment period;
- 1 subject (75 mg group; EDELWEISS 3) had AST increase of 3.1×ULN at Month 5 visit (combined with an associated CK increase and normal ALT values, indicating rather a muscular origin of the AST increase);
- 1 subject (75 mg group; EDELWEISS 2) had ALT 4.0×ULN with AST 2.3×ULN at an unscheduled visit (repeat of Month 2 visit).

	• 1 subject (placebo; EDELWEISS 2) had ALT 3.6×ULN at baseline and stopped treatment immediately after receiving her baseline results, then had ALT of 4.8×ULN at her Month 2 withdrawal visit. Between Month 6 and Month 12, increases in ALT and/or AST ≥3×ULN were infrequent as well and reported in 2 linzagolix-treated subjects in the EDELWEISS 6 trial and in none of the subjects in the EDELWEISS 5 trial. • 1 subject in the placebo/LGX 75 mg group had ALT increase of 3.4×ULN at Month 9 visit, with a peak of 4.3×ULN at Month 10 (retest showing 3.8×ULN), declining to 2.7×ULN at Month 11 (while on treatment), and increasing again at Month 12 to 3.7×ULN. AST was mildly increased up to 2.1×ULN. • 1 subject in the LGX 200 mg+ABT group had increased ALT at Month 11 (ALT 3.7 ×ULN with AST 2.4×ULN) and Month 12 (ALT 3.1×ULN with AST 2.2×ULN). No clinical symptoms (e.g., fever, fatigue, jaundice) were present. A retest performed a month later (at Month 1 ExFU) showed ALT and AST levels within the normal range. Overall, among the 399 subjects exposed to LGX 200 mg+ABT in the Pooled SAF for Period 1, 3 subjects (0.8%) had ALT values □3×ULN. These included 1 subject in the EDELWEISS 3 study discussed above, and 2 subjects from the PRIMROSE studies in patients with uterine fibroids. Notably, AST values ≥3×ULN were also reported with a frequency of 0.8% (3 subjects), with 2 subjects having concomitant ALT increase (discussed above) and 1 subject having a concomitant CK increase, which suggested a muscular origin for the AST increase. Among the 631 subjects treated with LGX 200 mg+ABT in the Pooled SAF for Period 2, 6 subjects (1.0%) had ALT values ≥3×ULN. These included 1 subject in the EDELWEISS 6 study mentioned above, and 5 subjects from the PRIMROSE studies in patients with uterine fibroids. During this period, 5 subjects (0.8%) had AST values ≥3×ULN, all of which were reported in the PRIMROSE studies and examined in the initial MAA. Importantly, none of these subjects had temporally associated elevations of total bilirubin >2×ULN or INR >1.5. The observed hepatic enzyme elevations are similar to those observed with other GnRH analogues, consistent with a class effect signal. ***Phase 2 studies:***

	In study 15-OBE2109-001, there were no marked trends or shifts from baseline in liver enzymes data during the study, following dosing with linzagolix or placebo. A further analysis of the individual subject data was performed for liver enzyme parameters for the assessment of values >2×ULN. During the first 24 weeks of treatment, 4 subjects (7.7%) in the 100 mg group and 1 subject (1.8%) in the 200 mg group had raised liver transaminase levels (i.e. ALT and/or AST) >2×ULN. There were 2 subjects (2/52; 3.8%) in the 100 mg group with increases of 3×ULN for both ALT and AST. Neither of these subjects (Subjects 40201 and 43202) showed an increase in total bilirubin of 2×ULN. There were no increases of 5×ULN for ALT or AST. Among the subjects who entered the PTFU immediately after 24 weeks of treatment, 1 subject (Subject 44110) at the 75-mg TD dose had a raised AST level (2.7 × ULN) at Week 36 with no concomitant increase in ALT or total bilirubin. As this subject had a concomitant increase of creatine kinase, suggesting muscle damage, this AST elevation was not considered clinically meaningful. The ALT, GGT, and alkaline phosphatase levels were within normal range during the PTFU period for all subjects. There were no subjects with AST and/or ALT values >2×ULN during the treatment extension (Week 24 to Week 52). There were also no increased liver transaminase levels reported during PTFU among the subjects previously treated for 52 weeks. In studies KLH1201, KLH1202, and KLH1203, a total of 152 Japanese subjects were randomised and treated (of those 128 were exposed linzagolix). There were no ALT or AST increases >2×ULN among the subjects in studies KLH1201 and KLH1203. There were 3 cases of ALT increase >2×ULN reported in Study KLH1202. In all these cases there was a spontaneous return to normal or close to normal values either during treatment or within 4 weeks post treatment. None of these increases were associated with any changes in bilirubin levels. In study KLH1204, a total of 5 subjects experienced ALT and/or AST increases >3×ULN (2 subjects at 50 mg, 1 subject at 75 mg, 2 subjects at 100 mg) with no apparent dose dependence; 2 of these 5 subjects had concurrent AST increase >3×ULN (1 subject at 50 mg dose, 1 subject at 75 mg dose) with no apparent dose dependence; 2 of these 5 subjects had concurrent AST increase >3×ULN (1 subject at 50 mg dose, 1 subject at 75 mg dose). These increases were not accompanied by a concurrent bilirubin increase. Subject KLH407201 in the 75 mg group presented ALT >3×ULN at Week 8, which decreased on treatment at Weeks 12 and 16, increased again to

	>5×ULN and >3×ULN at Week 24 subsequently returned to normal. Bilirubin values fluctuated around the limits of normal from the screening visit through follow up; no increases were observed with the increased transaminase levels. Hence, this case did not meet Hy's law. Few cases of ALT or AST increases were reported as AEs. In the 100 mg group, an increase in ALT was reported as a TEAE by 7.1% vs 0% in placebo, and an increase in AST by 5.9% vs 0%, respectively, during the first 12 weeks of treatment. Over the entire 24-week treatment period, the incidence of ALT increased was 9.4% and AST increased was 5.9% in the 100 mg group. (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.5.2) ***Phase 1 studies:*** During the MAD part of study KLH1101, 3 Japanese subjects had increases in ALT and AST parameters >2×ULN, with one of these subjects (Subject 6001) with an ALT increase >3×ULN while on the 400 mg dose. One subject in study 17-OBE2109-008, a 21-year-old white female, experienced the event of mild increased AST (1.8 × ULN) and ALT (1.7 x ULN) on Day 29, which increased to 2.7 × ULN and 1.4 × ULN, respectively on Day 35, and returned to normal on Day 38 while still on treatment. The investigator considered the event to be unrelated to linzagolix and E2/NETA. There were no clinically significant elevations in liver function enzymes in the remaining Phase 1 studies. (Initial MAA/UF/Module 2.7.4, section 2.7.4.6.5.3) ***Summary:*** In the UF CDP, liver enzyme increases have been observed in a small proportion of subjects; in the Phase 3 UF studies up to Week 24, the incidence of liver function TEAEs was 4.8% of subjects on active treatment, compared to 3.8% on placebo. In both Phase 3 EDELWEISS trials, 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 line with the previously submitted MAA in uterine fibroids, there were no clinically relevant changes in any other clinical chemistry parameters in the Phase 3 endometriosis clinical program. Transient fluctuations of LFTs are common, including in clinical trials, and similar frequent and isolated transaminase elevations are seen with other drugs (e.g., aspirin) and other GnRH-antagonists (Carr, 2018

	MYFEMBREE® prescribing information and RYEQO SmPC). Importantly, patients treated with linzagolix were asymptomatic and none had elevations that met Hy's law criteria and none had confirmed liver toxicity.
Risk factors and risk groups	No risk factors/groups have been identified.
Preventability	The current SmPC warns healthcare professionals regarding elevations in liver enzymes with linzagolix treatment and provides a recommendation to instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice. As women with abnormal hepatic function parameters were excluded from studies with YSELTY, caution should be applied when administering linzagolix to these patients and regular monitoring should be performed. Additionally, post-marketing follow-up will be implemented using a targeted follow-up questionnaire for any reported cases of liver enzyme increase which will help to identify any potential liver toxicity (see Annex 4). In combination with routine PV activities, this additional PV activity will increase the likelihood that any potential harm to patients will be rapidly detected and prevented (see Part III.1 Routine pharmacovigilance activities). Along with this, monitoring of liver associated adverse events will also be implemented as a component of the proposed PASS in the post-market setting (details of this study are presented in Part III.2 Additional pharmacovigilance activities).
Impact on the risk-benefit balance of the product	The impact on the risk-benefit balance of the product can be considered as minimal due to the low rates of LFT elevations and the absence of Hy's law cases/ of confirmed liver toxicity.
Public health impact	A potential impact on public health is not anticipated.

SVII.3.2 Presentation of the missing information

Table 16: Missing Information – Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT

Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT	
MedDRA Search Terms	N/A
Evidence source	As described earlier, GnRH antagonists such as linzagolix reduce serum E2 in a dose-dependent manner. These declines can result in dose-dependent BMD decrease due to increased bone resorption, which is most pronounced with high doses with which close to full E2 suppression is reached. The aim of lower doses and the use of hormonal ABT with higher doses is to achieve E2 levels within a range that limits BMD decrease. Due to the decline in BMD on treatment and/or the lack of full recovery post treatment with linzagolix 200 mg with concomitant ABT and linzagolix 100 mg with and without ABT, the impact on long-term bone health and future fracture risk in the target population is uncertain. The maximum duration of linzagolix exposure in the clinical development program was 52 weeks (equivalent to 12 months). Post-treatment follow-up (from week 52 to week 76) was conducted in Phase 3 studies (PRIMROSE 1 and 2, as well as EDELWEISS 6 and 5). The results of the BMD changes are presented in characterisation of the important identified risk of "*Bone mineral density decrease*". Although the BMD changes data available till week 52 (including post-treatment follow-up) demonstrated that BMD changes slowed after week 24, to date there is no data available for linzagolix treatment extending beyond 12 months. Therefore, the long-term effects of linzagolix on bone health and future fracture risk remains unknown at this point in time.
Anticipated risk/consequence of the missing information	Considering: a) the modest BMD effects observed up to 12 months for the 100 mg with and without ABT and the 200 mg + ABT, b) the evidence of post-treatment BMD recovery,

Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT	
	c) the FRAX analyses based on the PRIMROSE study results which show minimal evidence of future fracture, d) the addition to the SmPC of recommendations for baseline assessment of BMD in women with risk factors for BMD loss and the addition for regular BMD assessments under treatment, the consequences of this missing information are minimal. However, the data that will be collected from real-life situation post-market will be very valuable. In order to collect further information on BMD changes in real-life setting, a PASS is proposed as an additional pharmacovigilance activity (details of this study presented in Part III.2 Additional pharmacovigilance activities).

Part II: Module SVIII - Summary of the safety concerns

Table 17: 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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

Theramex has a pharmacovigilance system in place, which fulfils the European requirements and provides adequate evidence that linzagolix has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any potential risks occurring either in the Community or in a third country.

Theramex has put in place a Pharmacovigilance System Master File (PSMF) describing the set of activities required to fulfil the legal requirements for routine pharmacovigilance activities for the medicinal product(s) in Europe.

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include (but are not limited to):

- Collection, collation, assessment and reporting of spontaneous reports,
- Periodic literature surveillance,
- Signal detection activities.

Routine pharmacovigilance practice includes comprehensive post-marketing surveillance assessment of spontaneously reported events with expedited reporting in compliance with worldwide regulatory requirements, and submission of periodic safety update reports (PSURs) in accordance with applicable regulatory requirements.

Periodic safety evaluation of cumulative data will also be conducted to evaluate safety signals. If a safety signal is identified, further assessment and characterisation of the safety signal will be conducted, including evaluation of individual case reports and aggregate data analysis.

New safety information will be communicated to the regulatory authorities worldwide, in accordance with local regulations. Additional activities may include product label revisions and updates with new safety information, in discussion with regulatory authorities, and informational letters to the treating physicians.

Specific adverse reaction follow-up questionnaires for the safety concerns:

Targeted follow-up questionnaires for QT interval prolongation, uterine endometrial and mammary gland adenocarcinoma, follow-up of reported pregnancies, and for reported cases of elevated liver enzymes (to detect early any potential liver toxicity) have been developed and will be available to collect and evaluate specific data related to these safety concerns to gain further information in post-marketing setting (Annex 4 - Specific adverse drug reaction follow-up forms).

III.2 Additional pharmacovigilance activities

YSELTY PASS Summary:

Study short name and title:

YSELTY PASS: A multinational Post Authorisation Safety Study evaluating real-world treatment in patients receiving YSELTY® (linzagolix choline) for moderate to severe symptoms of uterine fibroids.

Rationale and study objectives:

The Phase 3 studies showed that linzagolix is effective in the management of symptoms associated with UF; treatment found to be overall well-tolerated, with few reported SAEs and with low discontinuations due to AEs. The studies also demonstrate adequate safety for approval of linzagolix; however, data in patients taking linzagolix in the real-world setting and for more than one year is needed to better understand certain safety parameters with long-term use.

The overall study objective is to generate long-term data on the safety of linzagolix in the routine clinical setting.

The primary objectives are 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 The exploratory objectives are to

- evaluate the incidence of osteoporosis or fractures suspected to be due to osteoporosis.
- evaluate liver enzyme levels above the upper limit of normal and correlated events collected as part of clinical practice.
- evaluate any routinely collected clinical data on mood disorders.
- evaluate the incidence of uterine endometrial and mammary gland adenocarcinoma.
- describe treatment patterns for YSELTY® dosing regimens with and without ABT.
- evaluate patient adherence to YSELTY® treatment.
- evaluate any routinely collected clinical data on cardiac disorders indicative for QT interval prolongation.
- 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.
- evaluate the incidence of adverse drug reactions (ADRs), serious adverse drug reactions (SADRs) and pregnancies (including pregnancy follow up).
- evaluate BMD change in patients with routinely collected DXA scans at 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®.

Study design:

This is a non-interventional, prospective, multicentre, multinational, cohort study that will be conducted in five European countries (France, Germany, Italy, Spain, and UK), whereas the selection and sequence of countries may vary depending on the launch dates of YSELTY®.

Study population:

Adult female patients of reproductive age with documented uterine fibroids and symptoms such as HMB who are therapy-naïve to YSELTY® and who meet the criteria defined in the SmPC for prescription in the respective country will be included in this study. Patients will be enrolled after the decision to treat with YSELTY® has been made, or as soon as possible after the start of YSELTY® treatment, however, not longer than 3 months after treatment initiation. At enrolment, the intention should be for long-term (>12 months) YSELTY® treatment (any dose), as judged by the physician. The decision to treat with YSELTY® will not be influenced by study inclusion.

Milestones:

Milestone	**Planned date**
Start of data collection (FPFV)	Q1/Q2 2025
End of data collection (LPLV)	Q3/Q4 2028
Progress reports	Progress reports will be prepared as required/requested, according to country-specific requirements (to assess the enrolment status) and will be provided in the Periodic Safety Update Reports (PSURs).
Interim report	Q3/Q4 2027
Registration in the EU PAS register	Before start of data collection.
Final report of study results	December 2029 One year after end of data collection.

Note: Should the extension of the indication be approved, the MAH is open to discuss the possible inclusion of endometriosis patients into the Yselty PASS to allow further and complete characterisation of the long-term safety of linzagolix treatment not only in the uterine fibroid patients, but also in the younger endometriosis population.

III.3 Summary table of additional pharmacovigilance activities

Table 18. Ongoing and planned additional pharmacovigilance activities

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)	Primary objectives: 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 Exploratory objectives: To evaluate the incidence of osteoporosis or fractures 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.	• Bone mineral density decrease • Endometrial adenocarcinoma and mammary gland adenocarcinoma • QT interval prolongation • Embryo-foetal toxicity • Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT	Protocol submission	November 2023
			Start of data collection	Q1/Q2 2025

	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 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®.	• Liver toxicity	Last patient last visit	Q3/Q4 2028
			Interim analysis	Q3/Q4 2027
			Study report	Dec 2029

Part IV: Plans for post-authorisation efficacy studies

There are no post-authorisation efficacy studies imposed as condition to the marketing authorisation or specific obligation of YSELTY®.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Important identified risk	
Bone mineral density decrease	Routine risk communication: • Listed as an adverse drug reaction in SmPC Section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Contraindication for patients with known osteoporosis in SmPC Section 4.3 and PL section 2 because of the risk of further BMD decrease. Recommendation in SmPC sections 4.2 and 4.4 and PL section 2 to assess baseline BMD and to carefully weigh risk-benefit before commencing YSELTY treatment in patients with a history of a low-trauma or fragility fracture, or other risk factors for osteoporosis or BMD decrease. YSELTY should not be initiated if the risk associated with BMD loss exceeds the potential benefit of the treatment. • Recommendation to perform a DXA scan after 1 year of treatment for all women and thereafter annually (for YSELTY 100 mg) or at a frequency determined by the treating physician based on the woman's individual risk and previous BMD assessment (for YSELTY 100 mg with concomitant ABT and YSELTY 200 mg with concomitant ABT) in section 4.4. • Treatment duration limitation to 6 months for YSELTY 200 without concomitant ABT in SmPC section 4.2 and PL section 3. Other routine risk minimisation measures beyond the Product Information:

	• Legal status: YSELTY will be available as a prescription-only medicine
Important potential risk	
Uterine endometrial and mammary gland adenocarcinoma	Routine risk communication: • Preclinical safety data presented in SmPC section 5.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Legal status: YSELTY will be available as a prescription-only medicine
QT Interval Prolongation	Routine risk communication: • Information presented in SmPC section 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning in SmPC section 4.4 that linzagolix marginally increases the QT interval but demonstrated no evidence of clinically relevant risk of QT prolongation or Torsade de Pointes. Recommendation to exercise caution when prescribing linzagolix in patients with known cardiovascular disease or family history of QT prolongation, hypokalaemia, and in concomitant use with other medicinal products that prolong the QT interval. Caution should also be exercised when linzagolix is prescribed in patients with co-existing disorders leading to increased linzagolix plasma levels Other routine risk minimisation measures beyond the Product Information: • Legal status: YSELTY will be available as a prescription-only medicine

Embryo-foetal toxicity	Routine risk communication: • Information presented in SmPC section 4.6 Fertility, pregnancy and lactation and PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Contraindication in pregnant women in SmPC Section 4.3 and 4.6 and PL section 2. • Warning that linzagolix does not consistently inhibit ovulation and women on treatment may be at risk of pregnancy in the event of unprotected intercourse in SmPC section 4.4. Women of childbearing potential should be advised to use effective non-hormonal contraception. • Warning on change in menstrual bleeding pattern and reduced ability to recognise pregnancy in SmPC section 4.4. Pregnancy testing should be performed if pregnancy is suspected, and treatment should be discontinued if pregnancy is confirmed. Other routine risk minimisation measures beyond the Product Information: • Legal status: YSELTY will be available as a prescription-only medicine
Liver Toxicity	Routine risk communication: • Listed as an adverse drug reaction in SmPC Section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning in SmPC Section 4.4 and PL section 2 to instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice. In case of abnormal hepatic function parameters, warning in section 4.4: Caution should be applied when administering linzagolix to these patients [i.e. patients with

	abnormal hepatic function parameters] and regular monitoring should be performed. Other routine risk minimisation measures beyond the Product Information: • Legal status: YSELTY will be available as a prescription-only medicine
Missing Information	
Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT	Routine risk communication: • Listed as an adverse drug reaction in SmPC Section 4.8 and PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Contraindication for patients with known osteoporosis in SmPC Section 4.3 and PL section 2 because of the risk of further BMD decrease. Recommendation in sections 4.2 and 4.4 and PL section 2 to assess baseline BMD and to carefully weigh risk-benefit before commencing YSELTY treatment in patients with a history of a low-trauma or fragility fracture, or other risk factors for osteoporosis or BMD decrease. • Recommendation to perform a DXA scan after 1 year of treatment for all women and thereafter annually (for YSELTY 100 mg) or at a frequency determined by the treating physician based on the woman's individual risk and previous BMD assessment (for YSELTY 100 mg with concomitant ABT and YSELTY 200 mg with concomitant ABT) in section 4.4. Other routine risk minimisation measures beyond the Product Information: • Legal status: YSELTY will be available as a prescription-only medicine

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product. No additional risk minimisation measures are proposed.

V.3 Summary of risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important identified risk		
Bone mineral density decrease	Routine risk minimisation measures: Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.2: Posology and method of administration • Section 4.3: Contraindications • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects PL section: • Section 2: What you need to know before you take YSELTY. • Section 3: How to take YSELTY. • Section 4: Possible side effects Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • YSELTY PASS
Important potential risk		

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Uterine endometrial and mammary gland adenocarcinoma	Routine risk minimisation measures: Inclusion in the Summary of Product Characteristics (SmPC): • Section 5.3: Preclinical safety data Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaires for uterine endometrial and mammary gland adenocarcinoma Additional pharmacovigilance activities: • YSELTY PASS
QT Interval Prolongation	Routine risk minimisation measures: Inclusion in the Summary of Product Characteristics (SmPC): • -Section 4.4: Special warnings and precautions for use. • Section 5.1: Pharmacodynamic properties • Section 5.2: Pharmacokinetic properties PL section: • Section 2: What you need to know before you take YSELTY Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire for QT interval prolongation Additional pharmacovigilance activities: • YSELTY PASS

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Embryo-foetal toxicity	Routine risk minimisation measures: Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.3: Contraindications • Section 4.4: Special warnings and precautions for use. • Section 4.6: Fertility, pregnancy and lactation PL section: • Section 2: What you need to know before you take YSELTY. Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire for exposure in pregnancy/pregnancy outcome Additional pharmacovigilance activities: • YSELTY PASS
Liver Toxicity	Routine risk minimisation measures: Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects PL section: • Section 2: What you need to know before you take YSELTY. • Section 4: Possible side effects Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire for cases of elevated liver enzymes Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	No risk minimisation measures	• YSELTY PASS
Missing Information		
Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT	<u>Routine risk minimisation measures:</u> Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.2: Posology and method of administration • Section 4.3: Contraindications • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects PL section: • Section 2: What you need to know before you take YSELTY. • Section 4: Possible side effects <u>Additional risk minimisation measures:</u> No risk minimisation measures	• <u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u> None <u>Additional pharmacovigilance activities:</u> • YSELTY PASS

Part VI: Summary of the risk management plan

Summary of risk management plan for YSELTY (linzagolix)

This is a summary of the risk management plan (RMP) for YSELTY. The RMP details important risks of YSELTY, how these risks can be minimised, and how more information will be obtained about YSELTY's risks and uncertainties (missing information).

YSELTY's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how YSELTY should be used.

This summary of the RMP for YSELTY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of YSELTY's RMP.

I. The medicine and what it is used for

YSELTY is authorised in adult women of reproductive age for:

- treatment of moderate to severe symptoms of uterine fibroids,
- treatment of endometriosis-associated pain

(see SmPC for the full indication).

It contains linzagolix as the active substance and it is given orally.

Further information about the evaluation of YSELTY's benefits can be found in YSELTY's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/yselty.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of YSELTY, together with measures to minimise such risks and the proposed studies for learning more about YSELTY's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of YSELTY is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of YSELTY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of YSELTY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Bone mineral density decrease
Important potential risks	• 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

II.B Summary of important risks

Important identified risk: Bone mineral density decrease	
	Gonadotropin-Releasing Hormone (GnRH) antagonists such as linzagolix reduce serum oestradiol (E2) in a dose-dependent manner. These declines can result in dose-dependent bone mineral density (BMD) decrease due to increased bone resorption, which is most pronounced with high doses with which close to full E2 suppression is reached. The aim of lower doses and the use of hormonal ABT with higher doses is to achieve E2 levels within a range that limits BMD decrease. *Linzagolix 200 mg (without concomitant add-back therapy (ABT)):* Median levels of serum E2 for the 200 mg dose showed close to full suppression (<20 pg/mL), which was maintained at similar levels up to Week 24. BMD decrease related to linzagolix treatment was limited at 24 weeks. The protective effect of ABT was clearly observed with long term treatment (more than 6 months) at higher dose (200 mg). Individual categorical analysis shows that very few subjects experienced >8% BMD decrease, most of these subjects were in the 200 mg dose arm.
Evidence for linking the risk to the medicine	BMD decrease after short term use of GnRH agonists generally shows partial to complete recovery within a few months after treatment completion. There was also evidence of recovery after short-term (6 months) full E2 suppression in the Phase 2 EDELWEISS linzagolix study in endometriosis which is in line with data from other GnRH agonists. *Linzagolix 200 mg (with concomitant ABT) and linzagolix 100 mg (with and without concomitant ABT):* Only moderate reductions of serum E2 were observed with the 100 mg dose, 100 mg+ABT and with 200 mg+ABT regimens (on-treatment medians ranging from 27.00 to 48.00 pg/mL) after 52 weeks of treatment. This results in BMD changes which were generally not clinically meaningful. Although overall the BMD changes in all groups were clinically not meaningful, the magnitude of BMD decrease was observed to be different for linzagolix 100 mg group, 100 mg+ABT and linzagolix 200 mg+ABT group (-2.36, -0.93 and -1.61 percent change from baseline at Week 52 at lumbar spine for the 100 mg, 100 mg+ABT and 200 mg+ABT dose, respectively). BMD decrease was more pronounced for linzagolix 100 mg group as compared to linzagolix 200 mg+ABT group and linzagolix 100

	mg+ABT group (at week 24 and 52). This suggests that the changes in BMD with the 100 mg and 200 mg linzagolix dose were clearly seen to be mitigated by the concomitant use of hormonal ABT. When the 10-year fracture probability was assessed with the FRAX® tool (web version 4.2) in all PRIMROSE patients assuming continuing linear rates of BMD loss over up to 5 years of duration, the analysis suggests that the treatment could be given for at least 5 years without significant concerns about bone health. With regard to the 100mg dose, the mean FRAX probabilities remain well below intervention thresholds whereas the 200mg with concomitant ABT demonstrate even lower probabilities of future fracture risk (Study 20-OBE2109-006). Also, overall, there was evidence of recovery in BMD 24 weeks following treatment discontinuation at Week 52 in both groups. In the Phase 3 trials, bone mineral density loss at Month 6 was minimal at the 200 mg+ABT dose in endometriosis patients, lower than previously reported for UF patients, and similar to other oral GnRH receptor antagonists. Importantly, the rate of BMD change slowed or stabilized between Month 6 and Month 12, suggesting a non-linear pattern of BMD loss. There is no evidence of immediate fracture risk associated with linzagolix treatment.
Risk factors and risk groups	Major risk factors for decreased BMD include low body weight/ body mass index (BMI), chronic alcohol and/or tobacco use, family history of osteoporosis, hypogonadism, or chronic use of drugs that can reduce bone mass such as glucocorticoids and anticonvulsants. The use of linzagolix in these patients may further contribute to BMD decrease.

Risk minimisation measures	*Routine risk minimisation measures*: <u>Inclusion in the Summary of Product Characteristics (SmPC):</u> • Section 4.2: Posology and method of administration • Section 4.3: Contraindications • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects <u>PL section:</u> • Section 2: What you need to know before you take YSELTY • Section 3: How to take YSELTY • Section 4: Possible side effects *Additional risk minimisation measures*: • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Uterine endometrial and mammary gland adenocarcinoma	
Evidence for linking the risk to the medicine	During a 104-week carcinogenicity study conducted in Wistar rats, higher incidence of uterine endometrial at high dose (500 mg/kg/day) and mammary gland adenocarcinoma at mid-dose (50 mg/kg/day) was observed; this higher incidence of uterine endometrial and mammary gland adenocarcinoma was judged to be incidental. The mechanism mediating this effect is unclear and does not appear to be related either to genotoxicity, or the primary pharmacological activity of linzagolix. The data available are not sufficient to conclude on the potential clinical relevance of these findings. Therefore, only as a precaution "*Uterine endometrial and mammary gland adenocarcinoma*" is listed as important potential risk.

	During clinical studies, only 1 incidence of endometrial adenocarcinoma was observed in the PRIMROSE 1 and PRIMROSE 2 studies in the 100 mg+ABT group. For this event, a pre-existing lesion was detected in the screening biopsy. This event was considered as not related to linzagolix but to ABT treatment. In addition, 2 events of breast cancer (1 in the linzagolix 200 mg group, and the other in linzagolix 200 mg+ABT group (both from PRIMROSE 1 and 2 studies) were diagnosed. One more SAE of breast cancer was reported in Study KLH1201 in the 50 mg group. All three events were considered unrelated to linzagolix. Risks of ABT also include breast and endometrial cancer. The use of ABT is contraindicated in women with known, past or suspected breast cancer and oestrogen-dependent malignancy, and untreated endometrial hyperplasia. In the linzagolix program to date, there is no indication that these conditions, if present during treatment, are aggravated by linzagolix. In LGX 200 mg+ABT regimen in the Phase 3 endometriosis trials, no cancer SAEs were reported.
Risk factors and risk groups	No risk factors/groups have been identified.
Risk minimisation measures	*Routine risk minimisation measures*: <u>Inclusion in the Summary of Product Characteristics (SmPC):</u> • Section 5.3: Preclinical safety data *Additional risk minimisation measures*: • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: QT Interval Prolongation	
Evidence for linking the risk to the medicine	In Study 17-OBE2109-001 (TQTc study), a positive QTc prolongation signal was observed following single doses of both 700 mg and 200 mg linzagolix. The 700 mg and 200 mg doses, at 3 hours post dose, were found to prolong QTcF with least squares mean (LSM) of 9.92 msec (90%

	confidence interval (CI) 8.03 - 11.81) and 8.34 msec (90% CI 6.44 - 10.23), respectively. Post-hoc analyses accounting for heteroscedasticity produced similar results, with upper bounds of the 90% 2-sided CI of 11.55 and 9.91 msec for 700 mg and 200 mg linzagolix doses, respectively. With the exception of the above finding, the results of ECG readings performed in Phase 3 did not raise any safety concerns. There were no QTcF prolongations >500 ms in the Phase 2 or Phase 3 trials (except 1 Japanese subject in Phase 2 study KLH1204 who presented QT interval prolongation (QTc 519 ms) 29 days after the initial linzagolix dose of 50 mg). QT interval prolongation and TEAEs in the SOC *Cardiac disorders* were explored in accordance with ICH guidance *E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (EMEA 2005).* The rates of the following TEAEs were compared in the treated and control subjects: torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope, and seizures. Except for one event of syncope, none of the other PTs were reported to date in the linzagolix clinical development program; 1 subject in the 100 mg group reported 1 event of syncope which was not associated with QTcF prolongation (QTcF values ≤453 ms at all assessments). The results of 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.
Risk factors and risk groups	Patients with known cardiovascular disease or family history of QT interval prolongation, hypokalaemia, or in patients consuming other concomitant medicinal products that prolong the QT interval, or in patients with co-existing disorders leading to increased linzagolix plasma levels.

Risk minimisation measures	*Routine risk minimisation measures*: Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.4: Special warnings and precautions for use. • Section 5.1: Pharmacodynamic properties • Section 5.2: Pharmacokinetic properties PL section: • Section 2: What you need to know before you take YSELTY *Additional risk minimisation measures*: • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	Linzagolix reproductive and developmental toxicology was assessed in a female rat fertility study (0.16, 0.8, 4, 20, 100 mg/kg/day), an early embryonic development study in rats (100, 300, 1000 mg/kg/day), embryo-foetal development studies in rats (30, 100, 300 mg/kg/day) and rabbits (0.3, 3, 30 mg/kg/day), and pre- and postnatal developmental studies in rats (0, 30, 100, 300 mg/kg/day). Due to its mechanism of action, linzagolix prevented conception and reduced implantation in rats and resulted in embryo-foetal mortality, total litter loss or abolished pregnancy in rat and rabbit embryo-foetal studies. There were no teratogenic effects and no adverse effect on the pre- and postnatal development of the offspring. In the clinical studies of linzagolix, patients were regularly evaluated for pregnancy, and any pregnancy that occurred was followed up for any evidence of treatment-related issues, including the pregnancy outcome and neonatal condition.

	In the Phase 3 trials in women with endometriosis, 4 pregnancies (0.7%) were reported. One of the 4 pregnancies occurred during the post-treatment follow-up period. With limited exposure of pregnant women to linzagolix, effects on human pregnancy are not known.
Risk factors and risk groups	A major risk factor for women of childbearing potential is non-use of contraception in the context of sexual activity during linzagolix treatment. Irregular bleeding may occur during treatment with linzagolix and may reduce the ability to recognize the occurrence of a pregnancy in a timely manner. Pregnancy testing should be performed if pregnancy is suspected, and linzagolix should be discontinued if pregnancy is confirmed.
Risk minimisation measures	*Routine risk minimisation measures*: Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.3: Contraindications • Section 4.4: Special warnings and precautions for use. • Section 4.6: Fertility, pregnancy and lactation <u>PL section:</u> • Section 2: What you need to know before you take YSELTY *Additional risk minimisation measures*: • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Liver Toxicity	
	Elevations in liver function tests (LFTs) are potentially a class effect with GnRH antagonists as it has also been reported with elagolix and relugolix treatment (Schlaff, 2020; Osuga, 2019, Carr, 2018 and MYFEMBREE® prescribing information). However, no reports of cases meeting Hy's law criteria/ of confirmed liver toxicity were reported to date in subjects treated with linzagolix. Supporting data from nonclinical studies in dogs and monkeys have shown that increases in serum liver enzymes could occur with linzagolix treatment. These studies concluded that linzagolix was not cytotoxic for hepatocytes and that increases in serum alanine transaminase (ALT) and glutamate dehydrogenase (GLDH) were likely to be attributable to induction of ALT and GLDH in the liver by the pharmacological effects of linzagolix. The findings were considered to be of low concern due to the therapeutic indices at the respective no-observed-adverse-effect levels (NOAELs), the absence of histological liver findings and the confirmation of reversibility following treatment free recovery periods.
Evidence for linking the risk to the medicine	**Phase 3 trials (UF):** In linzagolix multiple dose studies, liver enzymes were closely monitored from Phase 1 to pivotal Phase 3 studies. Both Phase 3 uterine fibroid studies included regular testing of liver function parameters. Alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total and indirect bilirubin were assessed from blood samples taken at Screening, Day 1 and Weeks 4, 8, 12, 24, 28, 32, 36, 52, and during follow-up at the Week 64 visit. As observed with other GnRH antagonists, liver enzyme elevations occurred. The rate of elevations >3x ULN was low and none were associated with a bilirubin increase > 2 ULN and/or INR (International normalized ratio) increase > 1.5 ULN; i.e., no cases met criteria for Hy's law. In the pooled safety analysis of PRIMROSE 1 and PRIMROSE 2 studies (N=1037) up to Week 24, 50 subjects (4.8%) reported 72 events of increases in liver function tests. The majority of these events were increases in GGT (28 subjects; 2.7%), ALT (22 subjects; 2.1%), or AST (15 subjects; 1.4%). Most were considered as related to linzagolix and very few led to permanent discontinuation of drug, but none were considered serious. Between Week 24 and Week 52 in the pooled safety analysis of PRIMROSE 1 and

	PRIMROSE 2 studies, increases in LFTs were reported infrequently as TEAEs (ALT increase in 0.7% (5/757), GGT increase in 0.5% (4/757), and AST increase in 0.4% (3/757)). Only few LFT abnormalities were reported as TEAEs at week 64 for both the studies.
Risk factors and risk groups	No risk factors/groups have been identified.
Risk minimisation measures	*Routine risk minimisation measures*: Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects PL section: • Section 2: What you need to know before you take YSELTY • Section 4: Possible side effects *Additional risk minimisation measures*: • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Bone mineral density decrease with continued treatment >12 months for linzagolix 200mg with concomitant ABT and linzagolix 100mg with and without ABT	
Risk minimisation measures	*Routine risk minimisation measures*: Inclusion in the Summary of Product Characteristics (SmPC): • Section 4.2: Posology and method of administration • Section 4.3: Contraindications • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects PL section: • Section 2: What you need to know before you take YSELTY • Section 4: Possible side effects *Additional risk minimisation measures*: • No risk minimisation measures
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* • YSELTY PASS See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of linzagolix.

II.C.2 Other studies in post-authorisation development plan

YSELTY PASS Study

Purpose of the study:

To generate and evaluate data in patients taking YSELTY® in the real-world setting and for more than one year is needed to better understand certain safety parameters associated with long-term use. The overall study aim is to assess the long-term safety of YSELTY® when used in real life clinical practice.

Part VIII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Follow-up questionnaires as routine pharmacovigilance activities have been developed to collect and evaluate specific data related to the following safety concerns in the post-marketing period:

- Embryo-foetal toxicity
- QT interval prolongation
- Uterine endometrial and mammary gland adenocarcinoma
- Liver Toxicity

The following specific adverse drug reaction (ADR) follow-up forms are included in this Annex:

Questionnaire 1: Exposure in Pregnancy/Pregnancy Outcome Questionnaire

Questionnaire 2: Targeted follow-up questionnaire for QT interval prolongation

Questionnaire 3: Targeted follow-up questionnaire for uterine endometrial adenocarcinoma

Questionnaire 4: Targeted follow-up questionnaire for mammary gland adenocarcinoma

Questionnaire 5: Targeted follow-up questionnaire for elevated liver enzymes

Questionnaire 1: Exposure in Pregnancy/Pregnancy Outcome Questionnaire

YSELTY (Linzagolix)

Exposure in Pregnancy/ Pregnancy Outcome Questionnaire

Dear Doctor xxx/Ms xxx/M xxxx,

Theramex is committed to providing safe and effective treatments to patients.

You reported an occurrence of pregnancy in one of your patients while on Yselty® treatment.

In order to properly evaluate the effects of this product on pregnancy, we would be very grateful if you may complete and return to us the below questionnaire. Your feedback is of greatest value to allow an ongoing assessment of the safety profile of Yselty®.

Please complete this questionnaire according to your best knowledge. In case you do not have the information for one item available, please leave the box empty or cross it out.

For Office use only	
Case Number:	
Received by company:	*(dd/mm/yy)*

MATERNAL DETAILS			
Mother Initials		Date of last menstrual period prior to conception	*(dd/mm/yy)*
Age	*(in years)*	Ethnic Origin	☐ Caucasian
Date of Birth	*(dd/mm/yy)*		☐ Asian
Height	*(in cm)*		☐ Hispanic or Latino
Weight	*(in Kg)*		☐ Black
Date pregnancy confirmed	*(dd/mm/yy)*		☐ Other Specify……..

OBSTETRIC HISTORY	
Number of previous pregnancies:	
Live births:	Late Foetal Deaths:
Miscarriages:	Ectopic Pregnancies:

Elective Terminations:	Molar Pregnancies:
Were there any birth defects in any previous pregnancy? *(include any defect affecting appearance, organ function, and physical and mental development)*	☐Yes ☐No If yes, please provide details

MATERNAL MEDICAL HISTORY			
Rh:	☐ Pos	☐ Neg	
Smoking:	_____ cig/day		Duration of smoking:
Alcohol:	_____glass(es) /day		Duration of alcohol consumption:
Drug abuse:	☐ Yes	☐ No	Details:
Regular menstrual periods?	☐ Yes	☐ No	Details:
Sterility treatment?	☐ Yes	☐ No	Details:
Anterior immunisation? *(toxoplasmosis, rubella, other)*	☐ Yes	☐ No	Details:

Was there any relevant medical history? *(including high blood pressure, heart disease, thyroid disease, diabetes, psychiatric disorder, epilepsy, etc.)*	☐Yes ☐No If yes, please provide details

Was there any relevant family history? *(including malformations, brother/sister died young, psychomotor retardation, consanguinity, etc.)*	☐Yes ☐No If yes, please provide details

CURRENT PREGNANCY DETAILS

Presumed date of conception	*(dd/mm/yy)*	**Expected date of delivery**	*(dd/mm/yy)*
Gestational age at knowledge of pregnancy	*(dd/mm/yy)*	**Multiple pregnancies**	☐ Yes ☐ No
During course of this pregnancy			
Smoking:	_____cig/day	**Alcohol:**	_____glass(es) /day
Drug abuse:	Type of drug:		

What type of contraception was the patient using at the time of the conception?	☐No contraception ☐Barrier ☐Birth Control Pill ☐Implant ☐ IUD ☐ Other Specify _____

Describe any relevant diagnostic test results during pregnancy (amniocentesis, ultrasound, etc.) and provide test dates?	☐Yes ☐No If yes, please provide details ....

Is there evidence of a defect from a prenatal test?	☐Yes ☐No If yes, please provide details ....

Give details of any infections/illnesses during pregnancy (flu, diabetes, hypertension, etc.) and provide dates?	☐Yes ☐No If yes, please provide details ....

DRUG EXPOSURE DURING PREGNANCY

Yselty

Give details of any placental abnormality

OUTCOME OF THIS PREGNANCY		
Live-born infant	☐	weeks from LMP*: _____
Elective termination	☐	weeks from LMP*: _____
Spontaneous abortion	☐	weeks from LMP*: _____
Late Foetal Death / Stillborn	☐	weeks from LMP*: _____
Ectopic Pregnancy	☐	
Molar Pregnancy	☐	*LMP: Last Menstrual Period

NEONATE			
Date of birth	*(dd/mm/yy)*	Length at Birth	*(in cm)*
Birth Weight	*(Kg)*	Head Circumference at Birth	*(in cm)*
Sex	☐ Male ☐ Female	APGAR scores	1 minute _____ 5 minutes _____
Was resuscitation required? ☐ Yes ☐ No ☐ Not known			
Was admission into intensive care required for the neonate? ☐ Yes ☐ No ☐ Not known			

Does the neonate have any congenital anomalies? ☐Yes ☐No If yes, please provide details
.....
.....
.....
.....

Were there complications in the neonate other than congenital anomalies? *(e.g. signs linked to placenta insufficiency, neonatal illness, hospitalisation, need for specific therapies)*	☐Yes ☐No If yes, please provide details

Please provide any further information that you consider may be relevant *(add further page if required)*	

Reporting ☐Doctor ☐Pharmacist ☐other:	**Contact details (email and phone)**
Name:	
Address:	
Postcode: Signature	Date: *(dd/mm/yy)*

Thank you for your time to provide responses and sending the questionnaire back to Theramex at email safety.global@theramex.com

Questionnaire 2: Targeted follow-up questionnaire for QT interval prolongation

YSELTY (Linzagolix)

Follow-up Questionnaire for possible QT Interval Prolongation

Dear Doctor xxx/Ms xxx/M xxxx,

You have reported an adverse event of xxxxx (VERBATIM).

Theramex is committed to providing safe and effective treatments to patients.

In order to properly evaluate this adverse event and its severity, we would be very grateful if you may complete and return to us the below questionnaire. Your feedback is of greatest value to allow an ongoing assessment of the safety profile of Yselty®.

Please complete this questionnaire according to your best knowledge. In case you do not have the information for one item available, please leave the box empty or cross it out.

For Office use only	
Case Number:	
Received by company:	*(dd/mm/yy)*

PATIENT INFORMATION			
Patient Initials		Ethnic Origin	☐ Caucasian
Age	*(in years)*		☐ Asian
Date of Birth	*(dd/mm/yy)*		☐ Hispanic or Latino
Height	*(in cm)*		☐ Black
Weight	*(in Kg)*		☐ Other Specify……

SUSPECT PRODUCT INFORMATION
Yselty

Any other suspect product involved? ☐ Yes ☐ No If yes, provide details				
Name:	**Indication:**		**Batch N°:**	
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency**
Start *(dd/mm/yy)*	**Stop** *(dd/mm/yy)*			
Name:	**Indication:**		**Batch N°:**	
Dates (treatment duration if dates unknown)		**Route**	**Total Daily Dose**	**Dosing frequency**
Start *(dd/mm/yy)*	**Stop** *(dd/mm/yy)*			

CONCOMITANT MEDICAL CONDITION/ SPECIAL DIET INFORMATION
Did the patient have any medical condition in the 2 months preceding the reported event *(e.g. infection, disease, special diet, other?)*?
☐Yes ☐No If yes, provide details

CARDIAC CO-MORBIDITIES
Did the patient have any cardiac co-morbidities *(e.g. especially those co-morbidities which are known to prolong the pro-arrhythmic risk such as cardiac arrhythmia, congestive heart failure, long QT Syndrome, hypokalemia)*?
☐Yes ☐No If yes, provide details

CONCOMITANT MEDICATION/VITAMIN/DIETARY SUPPLEMENT INFORMATION Did the patient take any medications/vitamins/dietary supplements in the 2 months preceding the reported event?				
Medication/Vitamin/Supplement name	**Route/Dose**	**Indication**	**Start date**	**Stop date**

ADVERSE EVENT INFORMATION			
	Event 1	Event 2	Event 3
Description of the event experienced by patient			
Event Start date	*(dd/mm/yy)*	*(dd/mm/yy)*	*(dd/mm/yy)*
Event Stop date	*(dd/mm/yy)*	*(dd/mm/yy)*	*(dd/mm/yy)*
Outcome of event*			
Action taken with Yselty® in response to this event **			
Treatment(s) in response to the event			
Seriousness Criteria ***	☐Serious: ____ ☐ Non-serious	☐Serious: ____ ☐ Non-serious	☐Serious: ____ ☐ Non-serious
Did Yselty® cause the Adverse Event	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

* Event outcome: A = Not recovered/Not resolved/Unchanged, B = Recovered/Resolved, C = Improving/Recovering/Resolving, D = Recovering with sequelae, E = Fatal, F = Unknown

** Drug action taken with suspected product: A = treatment continued unchanged, B = treatment withdrawn, C = dose reduced, D = dose increased, E = treatment interrupted, F = Unknown

*** Serious criteria: The event is serious if - A = Death, B = Life Threatening, C = Inpatient hospitalisation or prolongation of existing hospitalisation. D = Persistent or significant disability/incapacity, E = Congenital anomaly/birth defect, F = Medical significant event

When experiencing the event, did the patient report any other symptoms *(e.g. heart palpitation, arrhythmia, blurred vision, syncope, seizures, or cardiac arrest?)*	☐Yes ☐No	If yes, please report start and stop date (or duration of symptoms) ....

Please provide details of recent ECG performed, if any: *(Please provide precise details or join anonymized copies of the ECG reports)*	Date	
	Which Population-Derived Correction Formulae used?	☐ Bazett's correction ☐ Fridericia's correction ☐ Others Specify……
	Absolute QTc interval prolongation	☐ QTc interval > 450 ms ☐ QTc interval > 480 ms ☐ QTc interval > 500 ms
	Additional ECG findings	☐ Ventricular tachycardia ☐ Flutter ☐ Ventricular fibrillation ☐ Torsade de pointes ☐ Others Specify……

Does the patient have any former QT prolongation finding?	☐Yes ☐No	If yes, please provide details ....

	☐Yes ☐No	If yes, please provide details

Did the patient have electrolyte abnormalities? (e.g., hypokalemia, hypomagnesemia, hypocalcaemia)	

Did the patient have renal or hepatic impairment?	☐Yes ☐No If yes, please provide details

Any possible drug interactions? (e.g. use of diuretics, digitalis treatment or concurrent use of more than one drug that can prolong QT interval)	☐Yes ☐No If yes, please provide details

Any known ion-channel polymorphism?	☐Yes ☐No If yes, please provide details

Does the patient have occult congenital long QT syndrome (LQTS) or silent mutations in LQTS genes?	☐Yes ☐No If yes, please provide details

Did the patient have any other existing risk factors for QT prolongation?	☐Yes ☐No If yes, please provide details

Is a follow-up ECG planned?	☐ Yes ☐ No If yes, could you please provide the date?

Please provide any further information that you consider may be relevant (add further page if required)

Reporting ☐Doctor ☐Pharmacist ☐other: Name: ..... Address: .... Signatur	**Contact details (email and phone)**
	Date: ..... *(dd/mm/y*

Thank you for your time to provide responses and sending the questionnaire back to Theramex at email safety.global@theramex.com

Questionnaire 3: Targeted follow-up questionnaire for uterine endometrial adenocarcinoma

YSELTY (Linzagolix)

Follow-up Questionnaire for Uterine Endometrial Adenocarcinoma

Dear Doctor xxx/Ms xxx/M xxxx,

You have reported an adverse event of xxxxx (VERBATIM).

Theramex is committed to providing safe and effective treatments to patients. In order to properly evaluate this adverse event and its severity, we would be very grateful if you may complete and return to us the below questionnaire. Your feedback is of greatest value to allow an ongoing assessment of the safety profile of Yselty®.

Please complete this questionnaire according to your best knowledge. In case you do not have the information for one item available, please leave the box empty or cross it out.

For Office use only	
Case Number:	
Received by company:	*(dd/mm/yy)*

PATIENT INFORMATION			
Patient Initials		Ethnic Origin	☐ Caucasian
Age	*(in years)*		☐ Asian
Date of Birth	*(dd/mm/yy)*		☐ Hispanic or Latino
Height	*(in cm)*		☐ Black
Weight	*(in Kg)*		☐ Other Specify……
Patient's alcohol consumption details		Alcohol: ☐ Yes ☐ No	If yes, _____glas

SUSPECT PRODUCT INFORMATION

Yselty

Name:	Indication:	Batch N°:		
Dates (treatment duration if dates unknown)		Route	Total Daily Dose	Dosing frequency
Start *(dd/mm/yy)*	Stop *(dd/mm/yy)*			
Name:	Indication:	Batch N°:		
Dates (treatment duration if dates unknown)		Route	Total Daily Dose	Dosing frequency
Start *(dd/mm/yy)*	Stop *(dd/mm/yy)*			

MEDICAL HISTORY/ PAST MEDICAL DRUGS Could you please provide details of patient's relevant medical history/ past medical drugs (especially following)?	
Any history of polycystic ovary syndrome (PCOS)?	☐ Yes ☐ No If yes, provide details
Did patient experience any other cancer(s) in the past?	☐ Yes ☐ No If yes, provide cancer type: Did patient receive any therapy(ies) for this cancer? ☐ Yes ☐ No If yes, provide details
Did the patient use any intrauterine device (IUD) in the past?	☐ Yes ☐ No If yes, provide details
Does the patient have any medical history of diabetes, endometrial hyperplasia, or hypertension?	☐ Yes ☐ No If yes, provide details
Does the patient have any family history of endometrial, ovarian, breast and/or colorectal cancers?	☐ Yes ☐ No If yes, provide details

Was the patient previously treated with any hormonal therapy?	☐ Yes ☐ No If yes, provide details
Information on any other relevant medical history/ past medical drugs	☐ Yes ☐ No If yes, provide details

CONCOMITANT MEDICATION INFORMATION Did the patient take any medications in the 2 months preceding the reported event?				
Medication	Route/Dose	Indication	Start date	Stop date

OBSTETRIC HISTORY			
Number of previous pregnancies: _____			
Live births:	_____	Still Births:	_____
Miscarriages:	_____	Ectopic Pregnancies:	_____
Elective Terminations:	_____	Molar Pregnancies:	_____

Could you provide information on patient's reproductive status?	Age at menarche: Age at menopause (if applicable): ☐ Tick this box if patient has not reached menopause

Could you provide information on patient's physical activity? ☐ Yes ☐ No If yes, please provide frequency ☐ Daily ☐ 1-2 times a week ☐ 3-4 times a week

ADVERSE EVENT INFORMATION		
Description of the event experienced by patient		
Event Start date	*(dd/mm/yy)*	
Event Stop date	*(dd/mm/yy)*	
Outcome of event*		
Action taken with Yselty® in response to this event **		
Treatment(s) in response to the event		
Seriousness Criteria ***	☐Serious: ____	☐ Non-serious
Did Yselty® cause the Adverse Event (AE)	☐ Certain ☐ Probable /Likely ☐ Possible	☐ Unlikely ☐ Conditional / Unclassified ☐ Unassessable / Unclassifiable
If add-back therapy (ABT) was given, did the ABT cause the AE	☐ Certain ☐ Probable /Likely ☐ Possible	☐ Unlikely ☐ Conditional / Unclassified ☐ Unassessable / Unclassifiable

* Event outcome: A = Not recovered/Not resolved/Unchanged, B = Recovered/Resolved, C = Improving/Recovering/Resolving, D = Recovering with sequelae, E = Fatal, F = Unknown

** Drug action taken with suspected product: A = treatment continued/unchanged, B = treatment withdrawn, C = dose reduced, D = dose increased, E = treatment interrupted, F = Unknown, G = Not Applicable

*** Serious criteria: The event is serious if - A = Death, B = Life Threatening, C = Inpatient hospitalisation or prolongation of existing hospitalisation. D = Persistent or significant disability/incapacity, E = Congenital anomaly/birth defect, F = Medical significant event

Could you provide Stage of uterine endometrial adenocarcinoma at the time of diagnosis? Stage - ……
Please use below FIGO staging guide:
Stage I: The cancer is found only in the uterus or womb, and it has not spread to other parts of the body.
Stage IA: The cancer is found only in the endometrium or less than one-half of the myometrium.
Stage IB: The tumor has spread to one-half or more of the myometrium.

Stage II: The tumor has spread from the uterus to the cervical stroma but not to other parts of the body.

Stage III: The cancer has spread beyond the uterus, but it is still only in the pelvic area.

Stage IIIA: The cancer has spread to the serosa of the uterus and/or the tissue of the fallopian tubes and ovaries but not to other parts of the body.

Stage IIIB: The tumor has spread to the vagina or next to the uterus.

Stage IIIC1: The cancer has spread to the regional pelvic lymph nodes. Lymph nodes are small, bean-shaped organs that help fight infection.

Stage IIIC2: The cancer has spread to the para-aortic lymph nodes with or without spread to the regional pelvic lymph nodes.

Stage IV: The cancer has metastasized to the rectum, bladder, and/or distant organs.

Stage IVA: The cancer has spread to the mucosa of the rectum or bladder.

Stage IVB: The cancer has spread to lymph nodes in the groin area, and/or it has spread to distant organs, such as the bones or lungs.

Could you provide the Grading of uterine endometrial adenocarcinoma at the time of diagnosis? *Please use below grading guide:* Grade 1 or well differentiated: The cells are slower-growing and look more like normal tissue. Grade 2 or moderately differentiated: The cells are growing at a speed of and look like cells somewhere between grades 1 and 3. Grade 3 or poorly differentiated: The cancer cells look very different from normal cells and will probably grow and spread faster.	Grade - …….

Could you provide information on how the uterine endometrial adenocarcinoma was diagnosed?	Please provide details here …… ……

Is the patient currently undergoing any medical or radiologic treatment for uterine endometrial adenocarcinoma?	☐Yes ☐No If yes, please provide details …… ……

Was any surgery performed?	☐Yes ☐No If yes, please provide details …… ……

Please provide any further information that you consider may be relevant (add further page if required)

In order to closely monitor the event, we would like follow-up with you until the patient recovers. Could you please confirm if this is acceptable to you? ☐ Yes ☐ No

Reporting ☐Doctor ☐Pharmacist ☐other: Name: Address: Postcode: Signature	Contact details (email and phone) Date: *(dd/mm/yy)*

Thank you for your time to provide responses and sending the questionnaire back to Theramex at email safety.global@theramex.com

Questionnaire 4: Targeted follow-up questionnaire for mammary gland adenocarcinoma

YSELTY (Linzagolix)

Follow-up Questionnaire for Mammary Gland Adenocarcinoma

Dear Doctor xxx/Ms xxx/M xxxx,

You have reported an adverse event of xxxxx (VERBATIM).

Theramex is committed to providing safe and effective treatments to patients. In order to properly evaluate this adverse event and its severity, we would be very grateful if you may complete and return to us the below questionnaire. Your feedback is of greatest value to allow an ongoing assessment of the safety profile of Yselty®.

Please complete this questionnaire according to your best knowledge. In case you do not have the information for one item available, please leave the box empty or cross it out.

For Office use only	
Case Number:	
Received by company:	*(dd/mm/yy)*

PATIENT INFORMATION			
Patient Initials		Ethnic Origin	☐ Caucasian
Age	*(in years)*		☐ Asian
Date of Birth	*(dd/mm/yy)*		☐ Hispanic or Latino
Height	*(in cm)*		☐ Black
Weight	*(in Kg)*		☐ Other Specify……
Patient's alcohol consumption details		Alcohol: ☐ Yes ☐ No	If yes, _____glas

SUSPECT PRODUCT INFORMATION
Yselty

Dates (treatment duration if dates unknown)		Route	Total Daily Dose	Dosing frequency
Start *(dd/mm/yy)*	Stop *(dd/mm/yy)*			

Any other suspect product involved? ☐ Yes ☐ No If yes, provide details				
Name:		Indication:		Batch N°:
Dates (treatment duration if dates unknown)		Route	Total Daily Dose	Dosing frequency
Start *(dd/mm/yy)*	Stop *(dd/mm/yy)*			
Name:		Indication:		Batch N°:
Dates (treatment duration if dates unknown)		Route	Total Daily Dose	Dosing frequency
Start *(dd/mm/yy)*	Stop *(dd/mm/yy)*			

MEDICAL HISTORY/ PAST MEDICAL DRUGS Could you please provide details of patient's relevant medical history/ past medical drugs (especially following)?	
Any history of polycystic ovary syndrome (PCOS)?	☐ Yes ☐ No If yes, provide details
Did patient experience any other cancer(s) in the past?	☐ Yes ☐ No If yes, provide cancer type: Did patient receive any therapy(ies) for this cancer? ☐ Yes ☐ No If yes, provide details
Does the patient have any family history of endometrial, ovarian, breast and/or colorectal cancers?	☐ Yes ☐ No If yes, provide details

Was the patient previously treated with any hormonal therapy?	☐ Yes ☐ No If yes, provide details
Information on any other relevant medical history/ past medical drugs	☐ Yes ☐ No If yes, provide details

CONCOMITANT MEDICATION INFORMATION Did the patient take any medications in the 2 months preceding the reported event?				
Medication	Route/Dose	Indication	Start date	Stop date

OBSTETRIC HISTORY			
Number of previous pregnancies: _____			
Live births:	_____	Still Births:	_____
Miscarriages:	_____	Ectopic Pregnancies:	_____
Elective Terminations:	_____	Molar Pregnancies:	_____
Previous breast-feeding details: ☐ Yes ☐ No		Comments (if any):	

Could you provide information on patient's reproductive status?	Age at menarche: Age at menopause (if applicable):

☐ Tick this box if patient has not reached menopause

Could you provide information on patient's physical activity?	☐ Yes ☐ No	If yes, please provide frequency ☐ Daily ☐ 1-2 times a week ☐ 3-4 times a week

ADVERSE EVENT INFORMATION		
Description of the event experienced by patient		
Event Start date	*(dd/mm/yy)*	
Event Stop date	*(dd/mm/yy)*	
Outcome of event*		
Action taken with Yselty® in response to this event **		
Treatment(s) in response to the event		
Seriousness Criteria ***	☐Serious: ____	☐ Non-serious
Did Yselty® cause the Adverse Event (AE)	☐ Certain ☐ Probable /Likely ☐ Possible	☐ Unlikely ☐ Conditional / Unclassified ☐ Unassessable / Unclassifiable
If add-back therapy (ABT) was given, did the ABT cause the AE	☐ Certain ☐ Probable /Likely ☐ Possible	☐ Unlikely ☐ Conditional / Unclassified ☐ Unassessable / Unclassifiable

* Event outcome: A = Not recovered/Not resolved/Unchanged, B = Recovered/Resolved, C = Improving/Recovering/Resolving, D = Recovering with sequelae, E = Fatal, F = Unknown

** Drug action taken with suspected product: A = treatment continued/unchanged, B = treatment withdrawn, C = dose reduced, D = dose increased, E = treatment interrupted, F = Unknown, G = Not Applicable

*** Serious criteria: The event is serious if - A = Death, B = Life Threatening, C = Inpatient hospitalisation or prolongation of existing hospitalisation. D = Persistent or significant disability/incapacity, E = Congenital anomaly/birth defect, F = Medical significant event

Could you provide Stage of mammary gland adenocarcinoma at the time of diagnosis? Stage - …….
Please use below TNM staging guide:
Stage 0: The cancer is only in the ducts of the breast tissue and has not spread to the surrounding tissue of the breast (Tis, N0, M0).
Stage IA: The tumour is small, invasive, and has not spread to the lymph nodes (T1, N0, M0).
Stage IB: Cancer has spread to the lymph nodes and the cancer in the lymph node is larger than 0.2 mm but less than 2 mm in size. There is either no evidence of a tumour in the breast or the tumour in the breast is 20 mm or smaller (T0 or T1, N1mi, M0).
Stage IIA: Any 1 of these conditions:
There is no evidence of a tumour in the breast, but the cancer has spread to 1 to 3 axillary lymph nodes. It has not spread to distant parts of the body (T0, N1, M0).
The tumour is 20 mm or smaller and has spread to 1 to 3 axillary lymph nodes (T1, N1, M0).
The tumour is larger than 20 mm but not larger than 50 mm and has not spread to the axillary lymph nodes (T2, N0, M0).
Stage IIB: Either of these conditions:
The tumour is larger than 20 mm but not larger than 50 mm and has spread to 1 to 3 axillary lymph nodes (T2, N1, M0).
The tumour is larger than 50 mm but has not spread to the axillary lymph nodes (T3, N0, M0).
Stage IIIA: The cancer of any size has spread to 4 to 9 axillary lymph nodes or to internal mammary lymph nodes. It has not spread to other parts of the body (T0, T1, T2, or T3; N2; M0). Stage IIIA may also be a tumour larger than 50 mm that has spread to 1 to 3 axillary lymph nodes (T3, N1, M0).
Stage IIIB: The tumour has spread to the chest wall or caused swelling or ulceration of the breast, or it is diagnosed as inflammatory breast cancer. It may or may not have spread to up to 9 axillary or internal mammary lymph nodes. It has not spread to other parts of the body (T4; N0, N1, or N2; M0).
Stage IIIC: A tumour of any size that has spread to 10 or more axillary lymph nodes, the internal mammary lymph nodes, and/or the lymph nodes under the collarbone. It has not spread to other parts of the body (any T, N3, M0).
Stage IV (metastatic): The tumour can be any size and has spread to other organs, such as the bones, lungs, brain, liver, distant lymph nodes, or chest wall (any T, any N, M1).
Recurrent: Recurrent cancer is cancer that has come back after treatment and can be described as local, regional, and/or distant.
For details of TNM staging please visit https://www.cancer.net/cancer-types/breast-cancer/stages

Could you provide the Grading of mammary gland adenocarcinoma at the time of diagnosis? Grade - …….
Please use below grading guide:
Grade 1 or well differentiated: The cells are slower-growing and look more like normal tissue.
Grade 2 or moderately differentiated: The cells are growing at a speed of and look like cells somewhere between grades 1 and 3.
Grade 3 or poorly differentiated: The cancer cells look very different from normal cells and will probably grow and spread faster.

Could you provide information on how the mammary gland adenocarcinoma was diagnosed? Please provide details here …… ……

☐Yes ☐No If yes, please provide details

Is the patient currently undergoing any medical or radiologic treatment for mammary gland adenocarcinoma?

Was any surgery performed? ☐Yes ☐No If yes, please provide details

Please provide any further information that you consider may be relevant (add further page if required)

In order to closely monitor the event, we would like follow-up with you until the patient recovers. Could you please confirm if this is acceptable to you? ☐ Yes ☐ No

Reporting ☐Doctor ☐Pharmacist ☐other: Name: Address: Postcode: Signature	Contact details (email and phone) Date: *(dd/mm/yy)*

Thank you for your time to provide responses and sending the questionnaire back to Theramex at email safety.global@theramex.com

Questionnaire 5: Targeted follow-up questionnaire for elevated liver enzymes

YSELTY (Linzagolix)

Follow-up Questionnaire for elevated liver enzymes

Dear Doctor xxx/Ms xxx/M xxxx,

You have reported an adverse event of xxxxx (VERBATIM).

Theramex is committed to providing safe and effective treatments to patients.

In order to properly evaluate this adverse event and its severity, we would be very grateful if you may complete and return to us the below questionnaire. Your feedback is of greatest value to allow an ongoing assessment of the safety profile of Yselty®.

Please complete this questionnaire according to your best knowledge. In case you do not have the information for one item available, please leave the box empty or cross it out.

For Office use only	
Case Number:	
Received by company:	*(dd/mm/yy)*

PATIENT INFORMATION			
Patient Initials		Ethnic Origin	☐ Caucasian
Age	*(in years)*		☐ Asian
Date of Birth	*(dd/mm/yy)*		☐ Hispanic or Latino
Height	*(in cm)*		☐ Black
Weight	*(in Kg)*		☐ Other Specify……

SUSPECT PRODUCT INFORMATION
Yselty

Any other suspect product involved? ☐ Yes ☐ No If yes, provide details			
Name:	Indication:		Batch N°:
Dates (treatment duration if dates unknown)	Route	Total Daily Dose	Dosing frequency
Start *(dd/mm/yy)* Stop *(dd/mm/yy)*			
Name:	Indication:		Batch N°:
Dates (treatment duration if dates unknown)	Route	Total Daily Dose	Dosing frequency
Start *(dd/mm/yy)* Stop *(dd/mm/yy)*			

CONCOMITANT MEDICAL CONDITION/ SPECIAL DIET INFORMATION
Did the patient have any medical condition in the 2 months preceding the reported event *(e.g. infection, disease, special diet, other?)*?
☐Yes ☐No If yes, provide details

CONCOMITANT MEDICATION/VITAMIN/DIETARY SUPPLEMENT INFORMATION				
Did the patient take any medications/vitamins/dietary supplements in the 2 months preceding the reported event?				
Medication/Vitamin/Supplement name	Route/Dose	Indication	Start date	Stop date

ADVERSE EVENT INFORMATION

When experiencing the event, did the patient report any other symptoms *(Fatigue, Rash, Fever, Jaundice, Dark urine, other ?)*	☐Yes ☐No	If yes, please report start and stop date (or duration of symptoms) ....

	Event 1	Event 2	Event 3
Description of the event experienced by patient			
Event Start date	*(dd/mm/yy)*	*(dd/mm/yy)*	*(dd/mm/yy)*
Event Stop date	*(dd/mm/yy)*	*(dd/mm/yy)*	*(dd/mm/yy)*
Outcome of event*			
Action taken with Yselty® in response to this event **			
Treatment(s) in response to the event			
Seriousness Criteria ***	☐Serious: ____ ☐ Non-serious	☐Serious: ____ ☐ Non-serious	☐Serious: ____ ☐ Non-serious
Did Yselty® cause the Adverse Event	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

* Event outcome: A = Not recovered/Not resolved/Unchanged, B = Recovered/Resolved, C = Improving/Recovering/Resolving, D = Recovering with sequelae, E = Fatal, F = Unknown

** Drug action taken with suspected product: A = treatment continued unchanged, B = treatment withdrawn, C = dose reduced, D = dose increased, E = treatment interrupted, F = Unknown

*** Serious criteria: The event is serious if - A = Death, B = Life Threatening, C = Inpatient hospitalisation or prolongation of existing hospitalisation. D = Persistent or significant disability/incapacity, E = Congenital anomaly/birth defect, F = Medical significant event

Please provide details of recent liver enzyme function tests: *(Please precise or join anonymized copies of the laboratory reports)*	Date	GGT *(U/L)*	AST/SGOT *(U/L)*	ALT/SGPT *(IU/L)*	Alkaline phosphatase *(IU/L)*	Bilirubin *(umol/L)*

Please provide any other important abnormal laboratory values at the time	☐Yes ☐No	If yes, please provide details .....

of the event, any follow-up laboratory reports and if available, laboratory reports prior to the event: *(Please precise or join anonymized copies of the laboratory reports)*	

Was there any prior history of elevated liver enzymes? have these results been:	☐ Stable ☐ Increasing ☐ Decreasing ☐ Fluctuating ☐ Unknown

Has the patient been exposed to any liver toxic substances?	☐Yes	☐No	If yes, please provide details

Does patient consume alcohol/recreational drugs?	☐Yes	☐No	If yes, please report the patient's average alcohol/drug intake/week

Does the patient have any other risk factors for liver disease? *(history of liver disease, previous drug induced liver injury or drug allergy?)*	☐Yes	☐No	If yes, please provide details

Has any imaging of the liver, biliary vesicle and bile duct been performed?	☐Yes	☐No	If yes, please provide details

(type and results ?)	

Did the patient undergo liver biopsy? *(Result?)*	☐Yes ☐No If yes, please provide details

Has a hepatitis panel be performed?	☐Yes ☐No If yes, please provide results (Hepatitis Panel (A, B, C, E))

Did the patient undergo any testing for viral infections	CMV *(Cytomegalovirus)*	☐ Yes ☐ No	If yes, provide details
	HIV	☐ Yes ☐ No	If yes, provide details
	EBV *(Epstein Barr Virus)*	☐ Yes ☐ No	If yes, provide details
	Other	☐ Yes ☐ No	If yes, provide details

Are there any other parameters or investigations to report, such as ANA and SmAB, AMA and anti-LKM, MRCP or ERCP results? *ANA, antinuclear antibody; SmAb, smooth muscle antibody, AMA, antimitochondrial antibody; LKM,*	☐Yes ☐No If yes, please provide details

liver-kidney microsomal; MRCP, magnetic resonance cholangiopancreatography ERCP, endoscopic retrograde cholangiopancreatography

Please provide any further information that you consider may be relevant (add further page if required)

Reporting ☐Doctor ☐Pharmacist ☐other: Name: Address: Postcode: Signature	Contact details (email and phone) Date: *(dd/mm/yy)*

Thank you for your time to provide responses and sending the questionnaire back to Theramex at email safety.global@theramex.com

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not Applicable