Post-Authorisation Safety Study Protocol

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

Non-Interventional Study

DAISY

Protocol Final Version Date: version 6.0

01 Apr 2025

Sponsor
Theramex Ireland Limited

PASS Information

Title	**DAISY** (Bone Mineral **D**ensity **A**ppraisal and other **I**mportant long-term **S**afety endpoints of **Y**selty) A multinational Post-Authorisation Safety Study evaluating real-world treatment in patients receiving Yselty® (linzagolix choline) for moderate to severe symptoms of uterine fibroids
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EU PAS register number	EUPAS
Active substance	linzagolix choline ATC code: H01CC04
Medicinal product	Yselty® (linzagolix choline)
Product reference	EU/1/21/1606/001 Yselty® 100 mg EU/1/21/1606/002 Yselty® 200 mg
Procedure number	EMEA/H/C/005442/0000
Marketing authorisation holder(s)	Theramex Ireland Limited
Joint PASS	No
Research question and objectives	The overall study aim is to assess the long-term safety of Yselty® when used in real life clinical practice. The primary objective is: • To evaluate routinely collected data on long-term safety (>12 months) in relation to bone mineral density (BMD) with use of Yselty® 200 mg (with add-back therapy

	[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 • To evaluate liver enzyme levels above upper limit of normal and correlated events collected as part of clinical practice • To evaluate any routinely collected clinical data on mood disorders • To evaluate the incidence of uterine endometrial and mammary gland adenocarcinoma • To describe treatment patterns for Yselty® dosing regimens with and without ABT • To evaluate patient adherence to Yselty® treatment • To evaluate any routinely collected clinical data on cardiac disorders indicative for QT interval prolongation • To assess if physicians who prescribe Yselty® follow the summary of product characteristics (SmPC) recommendations including performance of annual dual-energy X-ray absorptiometry (DXA) scans and adherence to the requirement of not prescribing the Yselty® 200 mg regimen without concomitant ABT • To evaluate the incidence of adverse drug reactions (ADRs), serious adverse drug reactions (SADRs) and pregnancies (including pregnancy follow-up) • To evaluate BMD change in patients with routinely collected DXA scans at 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®
Country(-ies) of study	Five European countries (Germany, Italy, Spain, Poland and UK)

Author	Marina Todorova, Senior Director Pharmacovigilance

MARKETING AUTHORISATION HOLDER(S)

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SIGNATURE PAGE

The study will be conducted in compliance with the PASS protocol, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements.

The following individuals are responsible for the content of this PASS protocol:

Clinical project manager	Date (dd Month yyyy)	Signature
Medical expert	Date (dd Month yyyy)	Signature
Biostatistician	Date (dd Month yyyy)	Signature

The following individuals also significantly contributed to the development of the PASS protocol:

Coordinating investigator	Date (dd Month yyyy)	Signature

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2 List of Abbreviations

ABT	Add-back therapy
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMD	Bone mineral density
CI	Confidence interval
COC	Combined oral contraceptives
CRO	Contract Research Organisation
DMP	Data Management Plan
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
E2	Oestradiol
EDC	Electronic data capture
EAIR	Exposure adjusted incidence rate
EMA	European Medicines Agency
EU	European Union
GGT	Gamma-glutamyl transferase
GnRH	Gonadotropin-releasing hormone
GVP	Good Pharmacovigilance Practice
HMB	Heavy menstrual bleeding
IEC	Independent Ethics Committee
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary of Regulatory Activities
PASS	Post-authorisation safety study
PSUR	Periodic Safety Update Reports
PT	Preferred term

RMP	Risk Management Plan
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDV	Source data verification
SMP	Safety Management Plan
SmPC	Summary of Product Characteristics
SOC	System organ class
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

3 Responsible Parties

Name:

Function: Study conduct responsible

Name:

Function: Study medical expert

Name:

Function: Study safety lead

Name:

Function: Study statistician

Name:

Function: Study data manager

Name:

Function: Coordinating investigator – Germany

Contact details on the coordinating investigators and other site personnel for each country and sites participating in the study are listed in a stand-alone document (see section 15.1) which is available upon request.

Administrative changes of responsible persons and/or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

4 Abstract

Title

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

V6.0, 01 Apr 2025, Marina Todorova PASS Lead linzagolix

Rationale and background

Uterine fibroids are benign, hormone-sensitive, smooth muscle tumours of the uterus that occur during women's reproductive years. Heavy menstrual bleeding (HMB) is one of the most disabling symptoms of uterine fibroids, and has been associated with physical, social, and financial implications. Current treatment options for women with HMB due to uterine fibroids are mainly surgical with many women with fibroids ultimately undergoing hysterectomy. For women who wish to preserve fertility, there are few conservative surgical and non-surgical options such myomectomy by hysteroscopy, myomectomy by laparotomy or laparoscopy, uterine artery embolization, and other interventions performed under radiological or ultrasound guidance, but unfortunately, recurrence of symptoms is common after these procedures.

Due to their easy availability, progestins and combined oral contraceptives (COCs) are the most frequent therapies for uterine fibroids, despite they are used off-label and despite a clear lack of evidence of their effectiveness. In addition, progestins and COCs are not able to reduce fibroid size. Oral gonadotropin-releasing hormone (GnRH) receptor antagonists dose-dependently reduce serum oestradiol (E2) to reduce disease symptoms. However, there are adverse consequences of prolonged hypoestrogenic state from GnRH suppression, including loss of bone mineral density (BMD). Hormonal add-back therapy (ABT) has been shown to lessen these consequences but has its own specific safety profile, and contraindications include smoking in women over 35 years of age, obesity, and uncontrolled hypertension. Yselty® (linzagolix choline), a GnRH antagonist, was developed with both a full suppression dose and a partial suppression dose to be used with or without ABT for the treatment of moderate to severe symptoms of uterine fibroids in the following dosing regimens: 100 mg once daily and 200 mg once daily. The 100 mg dose or, if needed, the 200 mg dose is to be taken with concomitant hormonal ABT from the initiation of treatment to prevent BMD loss. The 100 mg dose without ABT is recommended for use by women in whom ABT is contraindicated or not recommended and by women who prefer to avoid hormonal therapy. Due to the risk of BMD decrease with prolonged Yselty® use, the 200 mg dose without concomitant ABT should not be prescribed for longer than 6 months.

Two Phase 3 trials found treatment with Yselty® to be overall well-tolerated, with few reported serious adverse events (SAEs) and with low discontinuations due to adverse events (AEs). However, typical side effects of oestrogen suppression – such as flushes (and night

sweats etc.) and BMD loss – were observed in all linzagolix-based regimes. Real-world data on long-term safety of linzagolix in relation to typical oestrogen suppression-linked events are lacking, and the present non-interventional prospective cohort study is aimed to fill this important gap. Limited safety data for continued treatment with linzagolix are of particular interest because of the effect of linzagolix on BMD, as sustained BMD loss – even at a slow rate – may become significant over time.

Research question and objectives

Data in patients taking Yselty® in the real-world setting and for more than 1 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.

The primary objective is:

- **I.** 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:

- **II.a** To evaluate the incidence of osteoporosis or fractures suspected to be due to osteoporosis
- **II.b** To evaluate liver enzyme levels above the upper limit of normal and correlated events collected as part of clinical practice
- **II.c** To evaluate any routinely collected clinical data on mood disorders
- **II.d** To evaluate the incidence of uterine endometrial and mammary gland adenocarcinoma
- **II.e** To describe treatment patterns for Yselty® dosing regimens with and without ABT
- **II.f** To evaluate patient adherence to Yselty® treatment
- **II.g** To evaluate any routinely collected clinical data on cardiac disorders indicative for QT interval prolongation
- **II.h** 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
- **II.i** To evaluate the incidence of adverse drug reactions (ADRs), serious adverse drug reactions (SADRs) and pregnancies (including pregnancy follow-up)
- **II.j** 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®

Study design

This is a non-interventional, prospective, multicentre, multinational, cohort study that will be conducted in 5 European countries (Germany, Italy, Spain, Poland and UK), whereas the selection and sequence of countries may vary depending on the launch dates of Yselty®.

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. The decision to treat with Yselty® will not be influenced by study inclusion.

Patients with 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, chronic kidney disease, overactive parathyroid gland), including those taking medications that may affect BMD (e.g., systemic corticosteroids, anticonvulsants) will be considered as patients with high risk for osteoporosis or bone loss.

Variables

At the enrolment visit, demographic data, medical history and concomitant diseases, prior and concomitant medication, risk factors for osteoporosis, and Yselty® dosing regimen will be collected. At baseline, date of first Yselty® dose will be collected.

The variables to assess the primary endpoint, which will be collected at the enrolment visit (recommended only in patient at high risk of osteoporosis or bone loss) and at follow-up visit(s) are:

- BMD z-score measured in lumbar spine, total hip, or femoral neck
- Date of DXA scan, if performed
- Anatomic site of DXA scan, machine type, imaging parameters of DXA scan, and reference population used, if available

The variables to assess the exploratory endpoints will be collected at the enrolment visit and at follow-up visit(s).

Data sources

The physician is requested to collect historical data (demographic and clinical characteristics) by reviewing the patient medical records, if available, by interviewing the patient, or during the clinical examination. Likewise, the physician collects treatment-related data during visits that take place in routine clinical practice. Additionally, in accordance with the Risk Management Plan, targeted follow-up questionnaires will be used to collect information on uterine endometrial and mammary gland adenocarcinoma, QT interval prolongation, exposure in pregnancy/pregnancy outcome, and cases of elevated liver enzymes. Physicians who report an event indicative of these events will be sent the respective targeted follow-up questionnaire.

Study size

This is a descriptive study and is not intended to test a formal hypothesis. The sample size is based on feasibility and practical considerations rather than statistical. Approximately 1,000 women of reproductive age with documented uterine fibroids and symptoms such as HMB being treated with Yselty® long-term, according to the SmPC. This is a multinational study in 5 European countries and the number of study sites will vary per country, dependent on use of Yselty®.

Data analysis

Statistical analyses will be of an exploratory and descriptive nature. All variables will be analysed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by descriptive statistics (i.e., number of patients, mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables will be summarised by absolute value and changes from baseline per analysis time point, if applicable.

All issues concerning patient data validity, data consistency checks, and permissible data modifications will be described in detail in the Data Management Plan. All statistical issues including calculated variables and the proposed format and content of tables will be detailed in the Statistical Analysis Plan which will be finalised before study database lock.

Milestones

Milestone	Planned date
Start of data collection (FPFV)	Q1/Q2 2026
End of data collection (LPLV)	Q3/Q4 2029 The scheduled study duration per country includes a patient recruitment phase of up to 18 months and an individual prospective observational period for as long as feasible within the scheduled study timeframe. In case the observational period per country is prolonged, data collection will be prolonged as well.
Progress reports	Progress reports related to the state of PASS recruitment will be part of every PSUR. The PSUR will be submitted as per the EURD list requirements.
Interim report	First interim report is expected in Q3/Q4 2028. Further interim analyses will be provided every two years unless the final report is delivered until Q4 2029.
Registration in the EU PAS register	Before start of data collection.
Final report of study results	December 2030 One year after end of data collection.

5 Amendments and Updates

None.

6 Milestones

Milestone	Planned date
Start of data collection (FPFV)	Q1/Q2 2026
End of data collection (LPLV)	Q3/Q4 2029 The scheduled study duration per country includes a patient recruitment phase of up to 18 months and an individual prospective observational period for as long as feasible within the scheduled study timeframe. In case the observational period per country is prolonged, data collection will be prolonged as well.
Progress reports[(1)]	Progress reports related to the state of PASS recruitment will be part of every PSUR. The PSUR will be submitted as per the EURD list requirements.
Interim report	First interim report is expected in Q3/Q4 2028. Further interim analyses will be provided every two years unless the final report is delivered until Q4 2029.
Registration in the EU PAS register	Before start of data collection.
Final report of study results	December 2030 One year after end of data collection.

1 Only if agreed with authorities.

7 Rationale and Background

Uterine fibroids are benign, hormone-sensitive, smooth muscle tumours of the uterus that occur during women's reproductive years [1]. Uterine fibroids are the most common tumour of the female reproductive tract in premenopausal women, affecting approximately 40% of women between 35 and 55 years [2]. While many of these women will have no or mild symptoms, more severe symptoms requiring treatment develop in 15% to 30% of women affected with fibroids, and for these women the condition has serious consequences [3].

Heavy menstrual bleeding (HMB) is one of the most disabling symptoms of uterine fibroids, and has been associated with physical, social, and financial implications [4]. The principal objective in treating uterine fibroids is symptom relief, including reduction in HMB. Current treatment options for women with HMB due to uterine fibroids are mainly surgical [4] with many women with fibroids ultimately undergoing hysterectomy [5, 6]. For women who wish to preserve fertility, there are few conservative surgical and non-surgical options such myomectomy by hysteroscopy, myomectomy by laparotomy or laparoscopy, uterine artery embolization, and other interventions performed under radiological or ultrasound guidance [5], but unfortunately, recurrence of symptoms is common after these procedures [5, 7]. Considering the risks of surgical or radiological interventions and the high potential for recurrence with fertility-sparing procedures, the need for effective alternatives is high.

Current guidelines [7–9] recommend several medical therapies for uterine fibroids including the use of progestogens, levonorgestrel-releasing intrauterine devices, and combined oral contraceptives (COCs). Most recently, oral gonadotropin-releasing hormone (GnRH) receptor antagonists have entered the market for treatment of endometriosis.

Due to their easy availability, progestins and COCs are the most frequent therapies for uterine fibroids, despite they are used off-label and despite a clear lack of evidence of their effectiveness. In addition, progestins and COCs are not able to reduce fibroid size. GnRH receptor antagonists dose-dependently reduce serum oestradiol (E2) to reduce disease symptoms. However, there are adverse consequences of prolonged hypoestrogenic state from GnRH suppression, including loss of bone mineral density (BMD) [10]. Hormonal add-back therapy (ABT) has been shown to lessen these consequences but has its own specific safety profile, and contraindications include smoking in women over 35 years of age, obesity, and uncontrolled hypertension.

Yselty® (linzagolix choline), a GnRH antagonist, was developed with both a full suppression dose and a partial suppression dose to be used with or without ABT (E2 1 mg and norethisterone acetate 0.5 mg tablet once daily) for the treatment of moderate to severe symptoms of uterine fibroids, such as HMB, in the following dosing regimens:

(1) 100 mg once daily

(2) 200 mg once daily

The 100 mg dose or, if needed, the 200 mg dose is to be taken with concomitant hormonal ABT from the initiation of treatment to prevent BMD loss. The 100 mg dose without ABT is recommended for use by women in whom ABT is contraindicated or not recommended and by women who prefer to avoid hormonal therapy. Due to the risk of BMD decrease with prolonged Yselty® use, the 200 mg dose without concomitant ABT should not be prescribed for longer than 6 months.

In the two pivotal Phase 3 trials, PRIMROSE 1 (USA) and PRIMROSE 2 (mainly EU), both low (100 mg) and high (200 mg) doses of Yselty® were shown to be effective in the treatment of moderate to severe symptoms of uterine fibroids, such as HMB, and to have an acceptable benefit risk profile [11]. In both Phase 3 trials, the primary endpoint of subjects with menstrual blood loss of <80 ml and ≥50% reduction in menstrual loss from baseline over the last 28 days prior to week 24 was met. The highest percentage of responders was observed in subjects treated with 200 mg Yselty® plus ABT. The secondary endpoints (related to reduction and maintenance of reduction in menstrual blood loss, amenorrhoea, number of days of uterine bleeding, haemoglobin levels in anaemic subjects, pain, fibroid volume, quality of life, and persistence of efficacy) were supportive of the primary endpoint.

The two Phase 3 trials found treatment to be overall well-tolerated, with few reported serious adverse events (SAEs) and with low discontinuations due to adverse events (AEs). However, typical side effects of oestrogen suppression – such as flushes (and night sweats etc.) and BMD loss – were observed in all linzagolix-based regimes. Real-world data on long-term safety of linzagolix in relation to typical oestrogen suppression-linked events are lacking. Limited safety data for continued treatment with linzagolix are of particular interest because of the effect of linzagolix on BMD, as sustained BMD loss – even at a slow rate – may become significant over time.

The current study aims to complement existing data from the Phase 3 PRIMROSE studies on the long-term safety of Yselty® treatment regimens in this patient population under routine clinical practice. It is of key importance to evaluate the different Yselty® treatment regimens outside of the context of a trial so that safety outcomes can be determined across the potentially more diverse “real-world” patient populations that will be initiated on this treatment.

8 Research Question and Objectives

Data in patients taking Yselty® in the real-world setting and for more than 1 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.

The primary objective is:

- **I.** 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:

- **II.a** To evaluate the incidence of osteoporosis or fractures suspected to be due to osteoporosis
- **II.b** To evaluate liver enzyme levels above the upper limit of normal and correlated events collected as part of clinical practice
- **II.c** To evaluate any routinely collected clinical data on mood disorders
- **II.d** To evaluate the incidence of uterine endometrial and mammary gland adenocarcinoma
- **II.e** To describe treatment patterns for Yselty® dosing regimens with and without ABT
- **II.f** To evaluate patient adherence to Yselty® treatment
- **II.g** To evaluate any routinely collected clinical data on cardiac disorders indicative for QT interval prolongation
- **II.h** 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
- **II.i** To evaluate the incidence of adverse drug reactions (ADRs), serious adverse drug reactions (SADRs) and pregnancies (including pregnancy follow-up)
- **II.j** 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®.

9 Research Methods

9.1 Study Design

This is a non-interventional, prospective, multicentre, multinational, cohort study based on primary data collection. Approximately 1,000 patients with documented uterine fibroids and symptoms such as HMB and with long-term Yselty® treatment in accordance with the SmPC will be included.

The study will be conducted in 5 European countries (Germany, Italy, Spain, Poland, and the UK), whereas the selection and sequence of countries may vary depending on the launch dates of Yselty®. For each country included in the study, the study start will be defined as after Yselty® has been authorised and made commercially available in that country. It is planned that Germany will be the first country to launch. The scheduled total study duration per country includes a recruitment phase of up to 18 months and an individual prospective observational period per patient for as long as feasible within the scheduled study timeframe. In case the observational period per country is prolonged, the data collection will be prolonged as well. The number of follow-up visits as per routine clinical practice for an individual patient will be dependent on the individual prospective observational period and are expected to be approximately every 12 months for this patient population. Visits to assess response to treatment will be more frequent at the beginning, and further visits may be required (depending on the country) to renew prescriptions approximately every 3 months.

Treatment with Yselty® will follow the physician's prescription according to the recommendations given in the SmPC. All decisions on therapeutic or diagnostic procedures, treatments, management of the indication, or resource utilisation will be at the full discretion of the treating physician without interference by the sponsor/MAH (referred to as MAH in the rest of this document) or study protocol. All treatment decisions will follow the real life treatment behaviour.

The assessment of BMD by DXA scans will be done as per routine clinical practice. For patients who received ABT from the initiation of Yselty®, the study results regarding BMD assessment will be contextualised with the real-world data available from literature for Ryeqo® at the time of the reports.

Patterns in which patients switch dosing regimens over the observational period will be described (further information to be provided in the Statistical Analysis Plan [SAP]).

9.1.1 Strength of Study Design

The non-interventional design allows the observation of patients in a broad range of settings reflecting routine clinical practice. A prospective cohort design was chosen to reflect real-world characterization of patients with documented uterine fibroids and symptoms such as HMB treated long-term with Yselty®. The prospective nature of the study will allow for

the accurate measurement of exposure with the potential measurement of multiple outcomes as defined by the primary and exploratory endpoint measures.

9.1.2 Endpoints

The primary endpoint of objective **I.** is only assessed in patients with long-term treatment (>12 months) and is:

- Number and proportion of patients with a lumbar spine, total hip, or femoral neck BMD z-score below the threshold of -2 standard deviations.

The exploratory endpoints of this study are:

- For objective **II.a**:
  - Incidence rate of osteoporosis or fractures suspected to be due to osteoporosis; all suspected osteoporotic fractures (minimal- or non-traumatic) of long bones or spine where the physicians suspect an osteoporotic cause of the fracture
- For objective **II.b**:
  - Number and proportion of patients with elevated liver enzyme levels above the upper limit of normal
  - Incidence rate of adverse events[1] suggestive of liver injury or related to liver enzyme elevation[2,3]
- For objective **II.c**:
  - Incidence rate of adverse events[1] regarding mood disorders including mood swings, affect lability, emotional disorder, irritability, mood altered, anxiety, bipolar disorder, mania, depression, depressed mood
- For objective **II.d**:
  - Incidence rate of uterine endometrial adenocarcinoma events[2]
  - Incidence rate of mammary gland adenocarcinoma events[2]

[1]Additional analyses on ADRs will be performed.
[2] The RMP (see section 15.1) contains targeted follow-up questionnaires for these events. Physicians who report these events will be asked to fill the corresponding targeted follow-up questionnaire.
[2] The RMP (see section 15.1) contains targeted follow-up questionnaires for these events. Physicians who report these events will be asked to fill the corresponding targeted follow-up questionnaire.
[3] A list of MedDRA terms for hepatic events is available as a stand-alone document (see section 15.1).

- For objective **II.e**:
    - Number and proportion of patients starting each Yselty® dosing regimen, time spent on each dosing regimen, and changes in dosing regimens

- For objective **II.f**:
    - Patient adherence to prescribed treatment, including ABT

- For objective **II.g**:
    - Incidence rate of adverse events [4] for cardiac disorders (ventricular arrhythmias [e.g., ventricular tachycardia and ventricular fibrillation, flutter, torsade de points], cardiac arrest, and sudden cardiac death) suggestive of potential QT interval prolongation[5]

    - Incidence rate of adverse events regarding[4] electrocardiogram (ECG) findings indicative of QT interval prolongation, according to the physician's information

- For objective **II.h**:
    - Frequency of use of DXA scans in defined time periods:
        - Among patients with >1-year treatment, the number and proportion of Yselty® users who received at least 1 DXA scan between 10 months until 14 months
        - Among patients with >2-year treatment, the number and proportion of Yselty® users who received at least 2 DXA scans between 10 months until 26 months
        - Among patients with >3-year treatment, the number and proportion of Yselty® users who received at least 3 DXA scans between 10 months until 38 months
        - Among patients with ≥4-year treatment, the number and proportion of Yselty® users who received at least 4 DXA scans between 10 months until end of study
    - Frequency of DXA scans prior to treatment initiation in patients at high risk[6] for osteoporosis or bone loss

[4] Additional analyses on ADRs will be performed.
[5] The RMP (see 15.1) contains targeted follow-up questionnaires for these events. Physicians who report these events will be asked to fill the corresponding targeted follow-up questionnaire.
[5] The RMP (see 15.1) contains targeted follow-up questionnaires for these events. Physicians who report these events will be asked to fill the corresponding targeted follow-up questionnaire.
[6] High risk patients will be identified by their treating physician as described in section 9.2.1.

- Number and proportion of patients who received Yselty® at a dose of 200 mg for more than 6 months without concomitant prescriptions for ABT at suitable time periods (e.g., 3-month intervals)

- For objective **II.i**:
  - Incidence rate of ADRs
  - Incidence rate of SADRs

- For objective **II.j**:
  - Mean absolute and relative change in density (g/cm^2) and absolute value and relative change of BMD z-score and t-score from baseline (for patients with baseline DXA scan as per routine clinical practice – per SmPC only recommended for patients at high risk[7] for osteoporosis or bone loss)
  - Mean absolute and relative change in density (g/cm^2) and absolute value and relative change of BMD z-score and t-score from DXA scan at 12 months (for patients with multiple follow-up DXA scans as per routine clinical practice)

9.2 Setting

9.2.1 Study Population

Patients 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. 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. The decision to treat with Yselty® will not be influenced by study inclusion.

No further selection criteria except for inclusion and exclusion criteria outlined below should be applied. Based on examination of patient enrolment using progress reports on recruitment, a Steering Committee (see section 9.8.1) will provide recommendations regarding modifications to the study conduct that might be introduced to maximise recruitment.

Physicians should identify patients at high risk for osteoporosis or BMD loss according to the SmPC and relevant local guidelines. Such risk factors include 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, low body weight, chronic kidney

[7] High risk patients will be identified by their treating physician as described in section 9.2.1.

disease, and overactive parathyroid gland), including those taking medications that may affect BMD (e.g., systemic corticosteroids, anticonvulsants). A more extensive reference list of risk factors is provided available as a stand-alone document in section 15.1.

9.2.2 Inclusion Criteria

- Signed informed consent
- Females of reproductive age ≥18 years
- New users of Yselty® (not longer than 3 months after treatment initiation)
- Indication of moderate to severe symptoms of uterine fibroids

9.2.3 Exclusion Criteria

- Patients who have ever used another GnRH antagonist (e.g., relugolix, elagolix) before enrolment
- Contraindications as per the approved SmPC
- Enrolment in a prior clinical trial with Yselty®
- Patients participating in an investigational program with interventions outside of routine clinical practice

9.2.4 Withdrawal

In this observational study, withdrawal from the study is independent of the underlying therapy and will not affect the patient's medical care. Each patient can refuse to further participate or may withdraw from the study at any time and without giving a reason. If a patient wants to terminate the study participation, no further data will be collected. In case the patient does not agree that the so far collected study data can be further used, her data will be deleted from the study database and not be used for any study related analysis. This does not include safety data already captured in the MAH's safety database and data already included in interim analysis datasets and outputs, which will be kept. In case a patient would like to withdraw the consent given earlier, she should inform her doctor and the site should document the withdrawal in the electronic case report form (eCRF) as well as in the patient medical records.

Patients who discontinue prematurely will not be replaced.

9.2.5 Representativeness

The non-interventional, prospective cohort design was chosen to reflect real-world characterization of patients with documented uterine fibroids and symptoms such as HMB treated long-term with Yselty®.

The patients documented in this study shall be selected by eligibility. The eligibility criteria have been selected to allow for a broad representation of patients within the study.

No further selection criteria except for inclusion and exclusion criteria should be applied. Patients should be enrolled consecutively in order to avoid any selection bias and to increase the likelihood of representativeness. Non-eligible patients (e.g., no informed consent signed) will not be included. In case a patient is not eligible, the reason for non-enrolment, together with the dosing regimen must be documented in the patient screening log file to evaluate a possible selection bias. It is planned that a minimum of 10% of the total sample size (see section 9.5) will be recruited from each country to increase the likelihood of representativeness. There is no patient limitation per site.

9.2.6 Visits

The physician documents an initial visit, follow-up visit(s), and a final visit for each patient in the electronic data capture (EDC) system. Follow-up visit(s) are documented as they occur per routine practice or physician's decision. The study protocol does not define exact referral dates for those visits. The expected schedule of the conduct of this study as per routine clinical practice is shown in Table 1. More than 1 visit per year can be recorded in the eCRF.

Enrolment/Baseline

Once a patient is found eligible for inclusion, the physician will inform the patient about the study. This will include discussing the consent form and asking the patient to read and – when agreeing to participate – sign the informed consent. 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. Information will be collected by reviewing the patient medical records, if available, or during the clinical examination as shown in Table 1.

Follow-up visit(s) during treatment

Follow-up visits will be carried out during regular clinical practice visits until study completion. In this patient population, regular clinical practice visits are expected about every 12 months after Yselty® treatment start (see Table 1).

Follow-up visit(s) for patients who experienced BMD decrease or osteoporosis during the study

Patients who discontinued treatment with Yselty® but had BMD decrease or osteoporosis during the study should be observed in the study for up to 24 months after the last administration of Yselty®. Documentation of further visits by the physician during the further follow-up period will be limited to BMD assessments and relevant concomitant medications. For AE reporting please see section 11.3.

Final visit/End of observation period

The final data collection (last visit) is at the end of study (regular end of study or after further follow-up for patients with BMD decrease or osteoporosis) or at discontinuation of Yselty® therapy for patients without BMD decrease or osteoporosis (whatever is earlier). At this final observation point, the patient's condition and a treatment assessment will be documented as a follow-up visit with additional information on:

- Regular end of observation, or
- End of observation after further follow-up for patients who discontinued Yselty® treatment but had a BMD decrease or osteoporosis (see section above) during the study, or
- Discontinuation of follow-up with the reason for discontinuation (e.g., end of therapy with Yselty® and no BMD decrease or osteoporosis).

Table 1 Estimated schedule for the Yselty® PASS

	First Visit (Enrolment)	**Baseline** (Yselty® Treatment Start)[1]	**Observation Time Points**[2] (Months Since Yselty® Treatment Start)			
			12	**24**	**36**	**48**
Assessment of inclusion/exclusion criteria	X	–	–	–	–	–
Date of signed informed consent	X	–	–	–	–	–
Date of first Yselty® dose	–	X	–	–	–	–
Year of birth	X	–	–	–	–	–
Sex	X	–	–	–	–	–
Height/weight	X	–	–	–	–	–
Yselty® dosing regimen (100 mg without ABT, 100 mg with ABT, or 200 mg with ABT)	X	–	X	X	X	X
Medical history	X	–	–	–	–	–
Concomitant diseases	X	X				
Alcohol/nicotine/drug/stimulant consumption	X	–	X	X	X	X
Relevant prior medication	X	–	–	–	–	–
Relevant concomitant medication	X	–	X	X	X	X
BMD assessment, including absolute density values, z-score/t-score values, DXA scan date, anatomic site of DXA scan, machine type, imaging parameters, reference population used (if available)	X	–	X	X	X	X
Clinical evaluation (including weight, blood pressure, clinical assessment of fibroid)	X	–	X	X	X	X
Change in Yselty® dosing regimen, reasons for change	–	–	X	X	X	X
Reported adherence to prescribed treatment	–	–	X	X	X	X
Laboratory values[3] and date of laboratory assessment (if available)	X	–	X	X	X	X
Liver enzyme elevation events[4]	X	–	X	X	X	X
Bone fracture events[5]	X	–	X	X	X	X
Events of uterine endometrial adenocarcinoma and mammary gland adenocarcinoma	X	–	X	X	X	X

	First Visit (Enrolment)	Baseline (Yselty® Treatment Start)[1]	Observation Time Points[2] (Months Since Yselty® Treatment Start)			
			12	24	36	48
Mood disorder events[6]	X	–	X	X	X	X
Cardiac disorder events suggestive of potential QT interval prolongation	X	–	X	X	X	X
ECG findings indicative of QT interval prolongation, according to the physician's information	X	–	X	X	X	X
RMP targeted follow-up questionnaires on uterine endometrial and mammary gland adenocarcinoma, QT interval prolongation, exposure in pregnancy/pregnancy outcome, cases of elevated liver enzymes[7]			X	X	X	X
AEs, SAEs, ADRs, SADRs, special situations[8.9]	X	–	X	X	X	X
Premature discontinuation, including reasons[10]	–	–	X	X	X	X

1 Date of first visit (enrolment) and date of first Yselty® dose (baseline) may be the same, or the date of first Yselty® dose may be up to 3 months prior to first visit. For patients with first Yselty® treatment before enrolment, baseline data can be documented retrospectively at enrolment.

2 This is the expected visit schedule, however, visits are to be performed as per routine practice. Additional visits can also be recorded. In case the observational period per country is prolonged, data collection will be prolonged as well.

3 Laboratory values include 25-hydroxy vitamin D, if available, and liver enzyme levels or values indicative of liver injury such as ALT, AST, bilirubin, GGT, and ALP, if available.

4 A list of MedDRA terms for hepatic events is available as a stand-alone document (see section 15.1) and will be further specified in the SAP.

5 Including events of osteoporosis or fractures suspected to be due to osteoporosis; all suspected osteoporotic fractures (minimal- or non-traumatic) of long bones or spine where the physicians suspect an osteoporotic cause of the fracture.

6 Including events of mood swings, affect lability, emotional disorder, irritability, mood altered, anxiety, bipolar disorder, mania, depression, depressed mood.

7 The RMP (see section 15.1) contains a targeted follow-up questionnaire for events indicative of uterine endometrial and mammary gland adenocarcinoma, QT interval prolongation, exposure in pregnancy/pregnancy outcome, and cases of elevated liver enzymes. Physicians who report an event indicative of these events will be sent the appropriate targeted follow-up questionnaire.

8 In case of discontinuation, AEs, SAEs, ADRs, SADRs, and special situations have to be documented as outlined in section 11.3.

9 Special situations include drug interactions, medication abuse, medication misuse, medication overdose, medication errors, unexpected therapeutic or clinical benefit from product use, pregnancy or lactation exposure with the product, lack of efficacy, off-label use, and occupational exposure (see section 11.4).

10 Physicians should continue to document BMD measurements during the extended follow-up period for patients who experienced BMD decrease or osteoporosis during the study. Management of AE/ADR occurring after treatment discontinuation will be managed in accordance with section 11.3.

ABT=add-back therapy; ADR=adverse drug reaction; AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BMD=bone mineral density; DXA= Dual-energy X-ray absorptiometry; ECG=electrocardiogram; GGT=gamma-glutamyl transferase; MedDRA= Medical Dictionary of Regulatory Activities; RMP=Risk Management Plan; SADR=serious adverse drug reaction; SAE=serious adverse event; SAP=Statistical Analysis Plan.

9.3 Variables

9.3.1 Demographic Data and Other Baseline Characteristics

The following data will be recorded at first visit (enrolment)[8]:

- Date of patient consent
- Year of birth
- Sex
- Height, body weight
- Yselty® dosing regimen

The following data will be recorded at Yselty® treatment start (baseline)[8]:

- Date of first Yselty® dose

9.3.2 Comorbidities (Medical History, Concomitant Diseases)

Comorbidities are any relevant medical findings that were present before start of therapy with Yselty®, independent of whether or not they are still present. They have to be documented in the Medical History/Concomitant Diseases section of the eCRF at the enrolment visit. Specific medical history will be collected on initial diagnosis, history of disease, history of an indication for surgical treatment of fibroids, as well as in the categories of:

- Previous fracture
- Mood disorders, including family history
- Hepatic disorders
- Cardiac disorders
- Malignant carcinoma
- Other relevant risk factors for osteoporosis or bone loss (including alcohol abuse, smoking, obesity, strong family history of osteoporosis, type I diabetes mellitus, rheumatoid arthritis, Vitamin D absorption disorders, Paget disease, osteogenesis imperfecta in adults, chronic kidney disease, untreated long-standing hyperthyroidism, chronic malnutrition, or malabsorption and chronic liver disease and long-term use of systemic steroids)

For any comorbidity, the diagnosis and if the disease is still ongoing at time of enrolment visit have to be documented.

[8] Date of first visit (enrolment) and date of first Yselty® dose (baseline) may be the same, or the date of first Yselty® dose may be up to 3 months prior to the first visit.

A clinical evaluation, including body weight, blood pressure, and clinical assessment of the fibroid, will be performed at enrolment visit and at follow-up visits, as per routine clinical practice.

9.3.3 Prior and Concomitant Medication

Medication taken before study start (initiated and stopped before study start) are defined as prior medications. All medication taken in addition to the prescribed Yselty® dosing regimen for any indication (either initiated before study start or during the study) are defined as concomitant medications.

Information on prior treatment with ABT, prior treatments for fibroids (labelled and off-label), previous GnRH-agonist treatment, and previous systemic treatment (glucocorticoids, aromatase inhibitors, thiazolinediones, thyroxine, drugs targeting the immune system (such as calcineurin inhibitors and antiretroviral drugs), selective serotonin reuptake inhibitor anticonvulsants, loop diuretics, heparin, and proton pump inhibitors) is to be collected as part of the enrolment data collection. Additionally, all relevant concomitant medication taken at enrolment and during the study will be recorded. Relevant concomitant medication includes anything influencing BMD loss (list defined for previous systemic treatment). Medications which may impact on liver enzyme increase or QT prolongation will be specified in the SAP.

Information on medication (including changes) will be collected in the categories stated below:

- Trade name or international non-proprietary name
- Start date (at least year)
- Stop date or "continued"
- Daily dose, if applicable
- Indication (prespecified categories: treatment of concomitant disease/treatment of AE/other)

9.3.4 Exposure/Treatment

Information to be documented on Yselty® exposure/treatment[9] includes:

- Start date
- Stop date (if applicable)
- Dosing regimen (200 mg with ABT, 200 mg without ABT, 100 mg with ABT, 100 mg without ABT)

[9] Exposure/treatment variables will inform on the exploratory endpoint assessing the proportion of patients starting each Yselty® dosing regimen, time spent on each dosing regimen, and changes in dosing regimens.

- Reason for interruption or premature discontinuation of Yselty® treatment (AE, withdrawal of consent, lost to follow-up, treatment with Yselty® discontinued permanently [pregnancy, onset of menopause], administrative problems, death, other), if applicable
- Reason for interruption or premature discontinuation of ABT (AE, withdrawal of consent, lost to follow-up, treatment with ABT discontinued permanently, administrative problems, death, other), if applicable
- Reason for dosing regimen change, if applicable

9.3.5 Variables to Assess the Primary Endpoint

The variables for the primary endpoint **I.** are:

- BMD z-score measured in lumbar spine, total hip or femoral neck
- Date of DXA scan, if performed
- Anatomic site of DXA scan, machine type, imaging parameters of DXA scan, and reference population used, if available

9.3.6 Variables to Assess the Exploratory Endpoints

The variables for the exploratory endpoints are:

- For objective **II.a**:
  - Osteoporosis diagnoses
  - Bone fracture events (long bones, spine)
  - For fractures, the probability of an osteoporotic cause of the fracture judged by the physician
  - Laboratory values of 25-hydroxy vitamin D, if available
- For objective **II.b**:
  - Laboratory values of liver enzyme levels or values indicative of liver injury such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP), if available
  - Date of laboratory assessment of liver enzyme levels, if performed
  - Elevated liver enzyme events
  - Events indicative of liver injury
- For objective **II.c**:
  - Mood disorder events of mood swings, affect lability, emotional disorder, irritability, mood altered, anxiety, bipolar disorder, mania, depression, depressed mood

- For objective **II.d**:
    - Uterine endometrial adenocarcinoma events
    - Mammary gland adenocarcinoma events
- For objective **II.e**:
    - Yselty® dosing regimen and changes in dosing regimens (see section 9.3.4)
- For objective **II.f**:
    - Reported patient adherence to prescribed treatment, including use of ABT
- For objective **II.g**:
    - Cardiac disorder events (ventricular arrhythmias [e.g., ventricular tachycardia and ventricular fibrillation, flutter, torsade de points], cardiac arrest, and sudden cardiac death) suggestive of potential QT interval prolongation
    - ECG findings indicative of QT interval prolongation, according to the physician's information
- For objective **II.h**:
    - DXA scan in defined time periods; Yes/No (see section 9.1.2)
    - DXA scan prior to treatment initiation in patients with risk factors for fractures, osteoporosis, or bone loss; Yes/No
    - Prescription of 200 mg Yselty® without concomitant ABT in defined time periods; Yes/No (see section 9.1.2)
- For objective **II.i**:
    - ADRs
    - SADRs
- For objective **II.j**:

  For patients with multiple DXA scans (at baseline and/or follow-up[s]):
    - BMD z-score and BMD t-score measured in lumbar spine, total hip, or femoral neck
    - Absolute value of density (g/cm^2)
    - Date of DXA scan, if performed
    - Anatomic site of DXA scan, machine type, imaging parameters of DXA scan, and reference population used, if available

9.3.7 Other Variables

Other variables to be collected include:

- Alcohol/nicotine/drug/stimulant consumption
- AEs, SAEs, ADRs, SADRs, special situations[10]
- Risk Management Plan (RMP) targeted follow-up questionnaires (see section 9.4)

9.4 Data Sources

The physician is requested to collect historical data (demographic and clinical characteristics) by reviewing the patient medical records, if available, by interviewing the patient, or during the clinical examination. Likewise, the physician collects treatment-related data during visits that take place in routine clinical practice.

In accordance with the RMP, targeted follow-up questionnaires will be used to collect information on:

- Uterine endometrial and mammary gland adenocarcinoma
- QT interval prolongation
- Exposure in pregnancy/pregnancy outcome
- Cases of elevated liver enzymes

Physicians who report an event indicative of these events will be sent the respective targeted follow-up questionnaire.

9.5 Study Size

Approximately 1,000 women of reproductive age with documented uterine fibroids and symptoms such as HMB being treated with Yselty® long-term, according to the SmPC. This is a multinational study in 5 European countries (Germany, Italy, Spain, Poland and UK), whereas the selection and sequence of countries may change depending on the launch dates of Yselty®. The number of study sites will vary per country, dependent on use of Yselty®.

This is a descriptive study and is not intended to test a formal hypothesis. The sample size is based on feasibility and practical considerations rather than statistical. Sample size considerations are based on the primary endpoint, BMD z-score, which compares bone mineral density with a reference population of the same age and sex. The BMD z-score will

[10] Special situations include drug interactions, medication abuse, medication misuse, medication overdose, medication errors, unexpected therapeutic or clinical benefit from product use, pregnancy or lactation exposure with the product, lack of efficacy, off-label use, and occupational exposure (see section 11.4).

be measured at 3 sites for each patient, i.e., lumbar spine, total hip, and femoral neck and the lowest individual value is used to estimate the population proportion.

A single-group design was used to obtain a 2-sided 95% confidence interval (CI) for a single proportion. Given the standard normal distribution of BMD z-scores (z-distribution), the expected sample proportion of values < -2 (cutoff for low bone density) is assumed to be 2.5%, which corresponds to the lower 2.5% quantile of the z-distribution. With an effective sample size of 800 (assuming 20% dropout), the CI width at 12 months of follow-up is 2.2% and the expected precision of the proportion is 2.5%±1.1% (see Table 2). Assuming a further 20% yearly dropout rate, at 24 months of follow-up, the effective sample size is estimated to be 640 patients with a CI width of 2.4% and an expected precision of the proportion of 2.5%±1.2%. At 36 months of follow-up, the effective sample size is estimated to be 512 patients with a CI width of 2.8% and an expected precision of the proportion of 2.5%±1.4%. At 48 months of follow-up, the effective sample size is estimated to be 409 patients with a CI width of 3.0% and an expected precision of the proportion of 2.5%±1.5%.

Table 2 Precision and width of the confidence intervals for the estimated sample sizes at 1, 2, 3, and 4 years of follow-up

Follow-up	Effective sample size (20% annual dropout)	Expected precision (half width of CI)	95% CI
At enrolment	1,000		
At 12 months	800	±1.10%	0.014 – 0.036
At 24 months	640	±1.20%	0.013 – 0.037
At 36 months	512	±1.35%	0.011 – 0.039
At 48 months	409	±1.50%	0.010 – 0.040

9.6 Data Management

Before starting the PASS, the sites will be trained on the background and objectives of this PASS and on ethical as well as regulatory obligations.

A global contract research organisation (CRO) will develop an EDC system and will provide quality assurance, verification of the data collection, data analysis and data transfer to the MAH. All outcome variables and covariates will be recorded in a standardised eCRF. After data entry, missing or implausible data will be queried and the data will be validated. A check for patients being documented multiple times will be done.

The latest Medical Dictionary of Regulatory Activities (MedDRA) version will be used for coding of medical history, concomitant diseases, and AEs. Prior and concomitant medication/treatment will be coded with the most current version of the World Health Organization (WHO) Drug Dictionary (coding system version numbers will be stated in the SAP). The SAP is kept as a stand-alone document and listed in section 15.1.

A Data Management Plan (DMP) will be prepared and contains detailed information on checks for completeness, accuracy, plausibility, and validity. This plan will also specify measures for handling of missing data and permissible clarifications. The DMP is kept as a stand-alone document and listed in section 15.1.

National and international data protection laws as well as regulations on PASS will be followed.

9.7 Data Analysis

9.7.1 Statistical Considerations

Statistical analyses will be of an exploratory and descriptive nature. All variables will be analysed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by descriptive statistics (i.e., number of patients, mean, standard deviation, minimum, median, quartiles, and maximum). Continuous variables will be summarised by absolute value and changes from baseline per analysis time point, if applicable.

The sample size and disposition information by analysis time point will be displayed in a frequency table.

Procedures and routines for capturing associated data strongly depend on country specific standards of care, type of healthcare provider, and insurance status of patients. Therefore, missing data in non-interventional research are informative categories indicating coverage of services.

No imputation of missing information will be applied. The number and frequency of patients with missing data will be presented as separate category.

All issues concerning patient data validity, data consistency checks, and permissible data modifications will be described in detail in the DMP. All statistical issues including calculated variables and the proposed format and content of tables will be detailed in the SAP. The SAP will be finalised before study database lock.

Information on the interim analysis is presented in section 9.7.5. The final data analysis will be performed after the study has been completed and the database has been declared to be clean.

9.7.2 Study Population

All analyses will be performed for the total study population (overall analysis). Separate analyses for each participating country will be provided if patient numbers are sufficient and if required for local reasons. In addition, data will be stratified whenever reasonable and dependent on the number of patients by the following parameters: country, age, race, dosing regimen, long- vs. short-term use of Yselty®, and other relevant clinical characteristics and will be specified in the SAP.

9.7.3 Analysis of Variables

9.7.3.1 Analysis of Demography, Disease History, Comorbidities, Prior and Concomitant Medication and Other Baseline Data

Baseline data such as patient demographics, comorbidities, prior and concomitant medication will be described by presenting frequency distributions and/or basic summary statistics.

Stratified analyses to estimate possible protective or damaging effects through prior medication or concomitant medication will be conducted if the sample size is sufficient and will be detailed further in the SAP.

9.7.3.2 Analysis of Treatment Data

Analysis of treatment data is part of the analysis of exploratory objectives, presented in section 9.7.3.4.

9.7.3.3 Analysis of Primary Endpoint

The primary objective will only be assessed in users with the long-term treatment (>12 months) and where z-scores of lumbar spine, total hip, or femoral neck are available. For rates of events of BMD z-scores below the age-related threshold of -2 standard deviations, the number and percentage of patients with these events will be provided including 95% CIs.

The aggregated number, frequency of DXA scans, anatomic site of DXA scan, machine type, and imaging parameters of DXA scans during the observational period will be analysed by descriptive statistics. If results of DXA scans can be interpreted in a categorised way, shift tables for the change from baseline, will be provided, where available. If images of the DXA scans can be provided by the doctors, they will be reviewed by 1 independent expert for their suitability and included in an additional sensitivity analysis.

Sensitivity analyses using different criteria (e.g., machine type) to select DXA scans that ensure their comparability will be performed to evaluate the primary endpoint if the sample size allows (e.g., if more than 30 patients remain after selection of suitable cases) and will be further detailed in the SAP.

9.7.3.4 Analysis of Exploratory Endpoints

For incidence rates of osteoporosis or suspected osteoporosis-related bone fractures, the number and percentage of patients with fractures will be provided including 95% CIs.

The frequency of laboratory assessments of liver enzyme levels will be analysed by descriptive statistics. Laboratory values of liver enzyme levels will be assessed by means of descriptive statistics at each assessment time and by absolute and relative changes to

baseline. For rates of AEs[11]indicative for liver injury and of liver enzyme elevation, the number and percentage of patients with these events and the total number of events as well as the EAIR (exposure adjusted incidence rate) will be provided including 95% CIs. A preliminary list of included liver enzyme elevation events is provided as a stand-alone document (see section 15.1), with complete specification to be done in the SAP based on the MedDRA coding system version available at the time of statistical analysis. The incidence rates, as well as the number and percentage of patients, are also presented for the subgroup of patients in whom the AEs were categorised as ADRs.

For rates of AEs[11] indicative for mood disorders, the number and percentage of patients and the total number of events as well as the EAIR will be provided including 95% CIs. Events including the PTs mood swings, affect lability, emotional disorder, irritability, mood altered, anxiety, bipolar disorder, mania, depression, depressed mood will be specified in the SAP based on the MedDRA coding system version available at the time of statistical analysis. The incidence rates, as well as the number and percentage of patients, are also presented for the subgroup of patients in whom the AEs were categorised as ADRs.

For rates of uterine endometrial adenocarcinoma events and mammary gland adenocarcinoma events, the number and percentage of patients with each of these event categories and the total number of events in each category as well as the EAIR will be provided including 95% CIs for each category. Events contained in each category will be specified in the SAP based on the MedDRA coding system version available at the time of statistical analysis.

Summary statistics for the treatment duration will be provided. The dosing regimen patterns and reasons for dosing regimen switch will be evaluated by descriptive statistics. Summary statistics will be provided for incidences and reasons for dosing regimen interruption or premature discontinuation of Yselty® and/or ABT. A transition table will be provided to compare prescribed baseline regimens with prescribed end of study regimens.

For reported adherence to the prescribed treatment, documented deviations from the prescribed dosing regimen will be evaluated by descriptive statistics.

For rates of AEs regarding cardiac disorders (ventricular arrhythmias [e.g., ventricular tachycardia and ventricular fibrillation], cardiac arrest, and sudden cardiac death) indicative of potential QT prolongation, the number and percentage of patients with these events and total number of events as well as the EAIR will be provided including 95% CIs. Events indicative of potential QT interval prolongation will be specified in the SAP based on the MedDRA coding system version available at the time of statistical analysis. Number and percentage of patients with QT interval prolongation as reported by physicians following ECG measurement will be evaluated by descriptive statistics. The incidence rates, as well

[11]Additional analyses on ADRs will be performed.[12] Considered as special situations in this study. See definition at end of this section.

as the number and percentage of patients, are also presented for the subgroup of patients in whom the AEs were categorised as ADRs.

Frequency of DXA scans in defined time periods (see section 9.1.2) and frequency of DXA scans prior to treatment initiation in patients with risk factors for osteoporosis and bone loss will be evaluated by descriptive statistics. The results will also be displayed stratified by dose (100mg/100mg + ABT/200mg + ABT)

Number and percentage of patients with an initial treatment dose of 200 mg without ABT that are not treated with ABT after ≥ 6 months, ≥ 9 months, ≥ 12 months, ≥ 15 months (continuing at 3-month intervals) while continuing a 200 mg dose of Yselty® will be evaluated by descriptive statistics.

For ADRs and SADRs, the incidence as well as EAIR, will be provided including 95% CIs on MedDRA system organ class (SOC) and preferred term (PT) level.

BMD will be displayed as absolute and relative change in density (g/cm^2) and absolute value and relative change of z-scores and t-scores over time by means of summary statistics; e.g., DXA scans performed at baseline (if available) vs. timepoint 1 – 1st year (+/-6 months) after treatment initiation, timepoint 1 – 1st year (+/-6 months) after treatment initiation vs. DXA scans performed at timepoint 2 – 2nd year (+/-6 months), where the measurements are at least 6 months apart. This is continued in the same way for further years if the sample size is at least 5 patients. Changes are only analysed if e.g., the machine types, the location of the scan and other criteria that allow comparability are consistent. A subgroup analysis of t-scores for the subgroup of postmenopausal patients and of z-scores in the subgroup of premenopausal patients will be conducted, if sample size allows. Additionally, patients who experienced BMD decrease during the study but continued to be observed in the study, regardless of the reason for which Yselty® treatment was discontinued, will be investigated as a separate subgroup. This subgroup analysis will include the presentation of both absolute value and relative change of z-scores and t-scores after discontinuation. If the sample size permits, this subgroup will be stratified based on whether alternative treatments administered after discontinuation may also lead to a decrease in BMD (refer to "previous systemic treatments" in section 9.3.3).

9.7.3.5 Analysis of Other Information

Descriptive statistics will be provided for alcohol/nicotine/drug/stimulant consumption.

Frequency tables with incidences and EAIR of AEs, SAEs, ADRs, and SADRs will be provided on MedDRA SOC and PT level. The incidence and EAIR will be provided including 95% CIs. Listings of special situations (drug interactions, medication abuse, medication misuse, medication overdose, medication errors, unexpected therapeutic, or clinical benefit from product use, pregnancy or lactation exposure with the product, lack of efficacy, off-label use, and occupational exposure) will also be provided.

Further details will be specified in the SAP, which will be finalised before study database lock.

9.7.4 Bias, Confounding and Effect-Modifying Factors

The results in any observational study could be affected by potential bias and confounding. Potential selection bias with regards to the selection of patients being enrolled, the patients who consent to participate in the study or those who complete the study cannot be ruled out. To reduce selection bias, a consecutive enrolment of eligible patients is planned whenever possible.

In this study, careful attention should be paid to describe the patient population, and caution should be applied to the interpretation of results as there may be confounding factors, measured or unmeasured. Other potential biases may include differential or non-differential misclassification of exposure and outcome, as well as information bias due to missing information.

Possible confounding factors include site and baseline disease severity. These possible confounding factors will be addressed by means of stratification, if applicable. For more details see the SAP.

9.7.5 Interim Analysis

The first interim report is expected in Q3/Q4 2028. Further interim analyses will be provided every 2 years unless the final report is delivered until Q4 2030.

9.8 Quality Control

9.8.1 Data Quality

A Steering Committee will review the study enrolment and make recommendations on the study's progress based on recruitment speed and characteristics of the patient population included to ensure that the study fulfils the pre-defined study objectives. These recommendations could relate to defining time points for interim analysis, assessing the need for any additional interim analyses, and providing insight into potential study amendments and adjustments of study related procedures, if necessary, in order to achieve the study goals. These recommendations would be presented in the progress or interim reports, as appropriate. The Steering Committee is also responsible for overseeing possible publications from the study.

Before starting the PASS, the sites will be trained on the background and objectives of this study and on ethical as well as regulatory obligations. Training and discussion on the usage of the EDC system and completion of the eCRF will be provided.

A CRO will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to the MAH.

All outcome variables and covariates will be recorded in a standardised eCRF. After data entry, missing or implausible data will be queried and the data will be validated. A check for multiple documented patients will be done. Information from the RMP targeted follow-up questionnaires will be examined and utilised, as appropriate (further information to be provided in the DMP).

Detailed information on checks for completeness, accuracy, plausibility, and validity are given in the DMP. The same plan will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request (see section 15.1).

National and international data protection laws as well as regulations on observational studies will be followed.

9.8.2 Monitoring

Quality review will be done in two steps: in the first step the site's training status will be assessed via standardised telephone interviews. In the second step, source data verification (SDV) will be conducted in approximately 20% of sites by on-site visits. The monitoring process will be defined in the monitoring plan. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. The documents must be available for review in the event the site is selected for monitoring, audits, or inspections. The monitoring plan is kept as a stand-alone document and listed in section 15.1.

9.8.3 Storage of Records and Archiving

The marketing authorisation holder (MAH) will make sure that all relevant documents of this PASS including eCRFs and other patient records will be stored after end or discontinuation of the study at least for 25 years. Other instructions for storage of medical records will remain unaffected.

The physicians participating in the study have to archive documents at their sites according to local requirements, considering possible audits and inspections from the MAH and/or local authorities. It is recommended to also store documents for a retention period of at least 10 years. The documents must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived.

9.9 Limitations of the Research Methods

Possible limitations of the study are based on the observational design and the fact of voluntary participation of physicians and patients. Physicians and patients who voluntarily agree to participate in this study might differ from those who do not agree. Consecutive enrolment should avoid any selection bias and increase the likelihood of representativeness.

Although the study aims to include participants from a variety of geographic regions, there may be local limitations that reduce the representativeness of patients recruited, such as

patient access to recruiting physicians (including differences in patient profile in specialized, recruiting sites vs local general practice), Yselty® availability and reimbursement, and decisions relating to local standard of care.

The main objective depends on two factors that are crucial but beyond the control of the study: First, the overall uptake of Yselty® and the proportion of patients treated beyond 12 months. Second, the extent to which doctors perform DXA scans after 1 year (as recommended in the SmPC) as part of their routine care. Depending on the country, this could be either facilitated or hindered by the reimbursement status of DXA scans.

BMD measurements, the primary objective, have a good reproducibility under highly controlled conditions, but such conditions do not generally apply in clinical practice. Many factors could affect the accuracy of BMD testing, including inter-machine variance as well as the experience of the operator. In addition, a high rate of missing BMD measurements at week 24 and week 52 due to study discontinuations was observed in the two pivotal studies [11]. This indicates that BMD assessment may become difficult due to the low number of observations recorded, especially for long-term users which are of special interest in this study. When interpreting the proportion of patients with z-scores below -2 standard deviations indicating loss of bone density, it should be kept in consideration that normalisation of z-scores is usually based on BMD measurements for a single bone. If multiple measurements have been taken in a patient, the likelihood of results being below threshold increases with the number of bone sites examined for each patient.

9.10 Other Aspects

Not applicable.

10 Protection of Human Subjects

10.1 Ethical Conduct of the Study

This study is a non-interventional PASS. Yselty® is prescribed in the usual manner in accordance with the SmPC under the sole decision of the treating physician. The treatment decision falls within current established practice. No additional diagnostic, therapeutic or monitoring processes are required for participation or during the study and the prescription of the medicine is clearly separated from the decision to include the patient in the study. Epidemiological methods will be used for the analysis of the collected data.

10.2 Regulatory Authorities Approvals/Authorisations

The study will be carried out within an approved indication in accordance with guidelines and regulations of EMA, and applicable local law(s) and regulation(s) (e.g., Regulation (EU) No 520/2012 [12]). Recommendations given by other organisations will be followed as well (e.g., EFPIA [13], ENCePP [14]). ICH-GCP guidelines will be followed whenever possible.

In addition, the guidelines on Good Pharmacovigilance Practices (GVP [15, 16]) will be followed; the relevant competent authorities of the EU member states will be notified according to Volume 9A [16].

10.3 Independent Ethics Committee/Institutional Review Board

In all countries where reference to an Independent Ethics Committee (IEC) is required, documented approval from appropriate IECs will be obtained for all participating centres prior to study start. When necessary, an extension, amendment or renewal of the IEC approval must be obtained and forwarded to the MAH. The IEC must supply to the MAH, upon request, a list of the IEC members involved in the vote and a statement to confirm that the IEC is organised and operates according to applicable laws and regulations.

10.4 Patient Information and Consent

Informed consent is obtained from the patient in writing before documentation of any data. In countries where required by law or regulation, the physician must have the IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to patients prior to the start of the observation.

10.5 Patient Insurance

In this study, data on routine treatment of patients in daily practice will be documented. Data will be analysed using epidemiological methods. Treatment including diagnosis and monitoring of therapy will exclusively follow routine daily practice. Current medical daily practice will be observed, and for the patient no risks beyond regular therapy exist, so that there is no additional hazard arising from study participation. As no study related risks

exist, there is no need to protect the patient additionally by a patient insurance. The general regulations of medical law and the professional indemnity insurance of the physicians and, respectively, the institutions involved provide sufficient protection for both patient and physician.

Furthermore, no study medication will be provided to participants. Thus, product insurance is covered by the existing product liability.

10.6 Confidentiality

The MAH as well as all physicians participating in this study ensure adherence to applicable data privacy protection regulation. Data will only be transferred in an encoded form (pseudonymised form). The entire documentation made available to the MAH does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The physicians participating in this study are obligated to ensure that no documents contain such data.

All records identifying the patient will be kept confidential and will not be made publicly available. Patient names will not be supplied to the MAH. If a patient name appears on any document, it must be obliterated before a copy of the document is supplied to the MAH. Study findings stored on a computer will be stored in accordance with local data protection laws.

The physician will maintain a list to enable patient records to be identified in case of queries. In case of a report of an event (i.e., AEs, SAEs, ADRs, SADRs, special situations), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the physician.

11 Management and Reporting of Adverse Events/ Adverse Drug Reactions

11.1 Definitions

AE

An AE is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product [15].

The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An unwanted effect of the study medication
- An unwanted effect of concomitant therapy
- Treatment exposure via mother (exposure during conception, pregnancy, childbirth, and breastfeeding)[12]
- An effect related to lack of drug effect[12]
- An effect related to drug interactions[12]
- An effect related to medication errors[12]
- An effect related to off-label use[12]
- An effect related to overdose, drug abuse (use for nonclinical reasons) or drug misuse, drug dependency[12]
- An effect related to pre-existing condition improved (unexpected therapeutic or clinical benefits are observed)[12]
- Any combination of one or more of these factors

As mentioned above no causal relationship with a study medication is implied by the use of the term "AE".

ADR

An ADR is any AE suspected as being "at least possibly related" to Yselty®. It is defined as a response to a medicinal product which is noxious and unintended. The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF. The

[12] Considered as special situations in this study. See definition at end of this section.

assessment is based on the question whether it is "at least possibly related" to Yselty® in accordance with WHO-Uppsala Monitoring Centre (UMC) Causality Categories (see Table 3). It is the reporting physician's responsibility to evaluate whether an AE is related to Yselty® prior to reporting the AE to MAH.

Table 3 WHO-UMC Causality Categories

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

SAE/SADR

An AE or ADR is serious if it:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above.

Special Situations

For this study, special situations are reports of the use of Yselty® with or without AE during pregnancy and/or breast feeding (see section 11.2), drug interactions, medication abuse, medication misuse, medication overdose, medication errors, unexpected therapeutic or clinical benefit from product use, lack of efficacy, off-label use, and occupational exposure.

Special situations may occur independently or in conjunction with an associated AE. Instances of special situations without an associated AE or special situation associated with a non-serious AE/ADR are required to be reported within 7 calendar days. Instances of special situations associated with a SAE or SADR, are required to be reported as per timelines for the SAE or SADR reporting i.e., within 24 hours of awareness.

11.2 Drug Exposure Before or During Pregnancy or Lactation

If a pregnancy occurs during the study, although it is not an SAE itself, it must be documented and forwarded to the MAH within the same time limits as an SAE (see section 11.3) and the process below will be followed; all other data collection will cease.

Drug exposure before or during pregnancy, where the embryo or foetus may have been exposed to Yselty® (through maternal exposure), will be followed up in order to collect information on the outcome of the pregnancy and development of the child after birth.

For pregnancies, the following information will be collected: prior pregnancies (including outcome of pregnancy), expected date of delivery, prenatal tests, pregnancy outcome, information on the child (e.g., sex, height, weight), complications, and causal relationship to study drug Yselty® (if abnormal outcome).

Individual cases with an abnormal outcome associated with Yselty® following exposure before or during pregnancy will be collected as an SAE. This especially refers to:

- Reports of congenital anomalies or developmental delay, in the foetus or the child
- Reports of foetal death and spontaneous abortion
- Reports of AEs considered related to Yselty® (suspected ADRs) in the neonate that are classified as serious

Drug exposure during lactation is not considered an AE. However, events will be followed up in order to collect information on the drug effects during lactation and development of the child.

Additionally, data will be collected and utilised, as appropriate, from the RMP targeted follow-up questionnaire on exposure in pregnancy/pregnancy outcome.

11.3 Documentation

All AEs under exposure to Yselty® that have been reported by the patient to the physician (i.e., AEs, SAEs, ADRs, SADRs, special situations) will be documented on the AE Report form in the eCRF/EDC system. Assessment on seriousness and relationship to product, treatment duration, action taken, and outcome of the event will be provided by the treating physician, who will also be responsible for following up on the outcome of SAEs, if this information is not available when first reported. Where required, physicians might be contacted directly, per the MAH's internal follow-up procedure, to obtain further information.

In addition, for selected events (see section 9.4), the MAH will utilise the targeted follow-up questionnaires, where applicable, as per the latest version of the RMP (see section 15.1). The purpose is the ongoing monitoring and safety evaluation of these events.

The documentation of any event within the eCRF ends with the completion of the follow-up of the patient or until it is no longer possible (e.g., lost to follow-up, death, withdrawal). In case of discontinuation of Yselty® for any reason, all events will be collected that occurred up to 30 days after the last administration. Since the t½ elimination time of linzagolix is 15 hours, exposure has well ended after 30 days. However, patients who discontinued treatment with Yselty® but experienced BMD decrease or osteoporosis during the study will continue to be followed up unless they have completely withdrawn from the study, and all AEs associated with BMD loss (e.g., osteoporosis, osteopenia, fractures) and all ADRs will be collected irrespective of treatment discontinuation.

All AEs will be summarised in tabulated forms in the interim safety analysis and final study report.

11.4 Management and Reporting

The management of events will be performed as per standard practice according to protocol section 11.4. Overall, the handling of events will follow GVP Module VI and VIII [17, 18].

Non-serious AEs
Non-serious AEs must be documented and reported to the MAH within 7 calendar days.

Non-serious ADRs
Non-serious ADRs must be documented and reported to the MAH within 7 calendar days.

All non-serious ADRs related to Yselty® treatment will be submitted to the relevant authorities according to EU PV legislation and according to national regulations by the MAH; however, all physicians must obey local legal requirements.

For non-serious ADRs related to non-MAH products (e.g., ABT), the physician has to account for and comply with the reporting system of the product's MAH within the frame of local laws and regulations as well as other locally applicable laws and regulations.

SAEs/SADRs
SAEs and SADRs must be documented and reported to the MAH immediately (within 24 hours of awareness) for SAE processing.

All SADRs related to Yselty® treatment will be submitted to the relevant authorities according to EU PV legislation and according to national regulations by the MAH; however, all physicians must obey local legal requirements.

For SADRs related to non-MAH products (e.g., ABT), the physician has to account for and comply with the reporting system of the product's MAH within the frame of local laws and regulations as well as other locally applicable laws and regulations.

Special situations
Special situations of drug interactions, medication abuse, medication misuse, medication overdose, medication errors, unexpected therapeutic or clinical benefit from product use, lack of efficacy, off-label use, and occupational exposure must be documented and forwarded to the MAH within 7 calendar days. Drug exposure during pregnancy or lactation must be documented and forwarded to the MAH by the physician immediately (within 24 hours of awareness) (see section 11.2).

Further assessment
Any AE or patient safety relevant information attributed to any MAH product that has been detected during the conduct of the study shall be reported to the MAH via established channels for reporting in the country.

The MAH or appointed representative will capture and review all reported events throughout the study. In addition to the treating physician's assessment, the MAH or appointed representative will assess the seriousness and likelihood of a causal relationship (see Table 3) to Yselty® and/or to ABT for each event. When the reporting HCP suspected a causal relationship to a non-MAH product, the case will be shared with the respective MAH where possible and where required locally. For any events occurring after study end, the country regulations that are in place for spontaneous reporting have to be followed.

11.5 Evaluation

Whenever new important safety information is received, e.g., case reports from a physician, the reports are processed and entered into the global pharmacovigilance safety database of the MAH. These reports will be reviewed on a regular basis. If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to MAH's internal standard operating procedures, for further evaluation within the context of benefit risk.

12 Plans for Disseminating and Communicating Study Results

This study will be registered in the EU PAS register at “https://catalogues.ema.europa.eu/”. The final report will be submitted to the EMA 12 months after end of data collection. A summary of the final results will be published in the EU PAS Register.

13 Administrative and Legal Obligations

The study will only be stopped after consultation with the regulatory authorities.

14 References

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15 Annexes

15.1 List of Stand-Alone Documents

Number	Document reference number	Date	Title
1	V1.1	08 Feb 2024	EU Risk Management Plan
2	V1.0	13 Jul 2023	MedDRA terms for hepatic events
3	V1.0	13 Jul 2023	Criteria to identify high-risk patients
4	In progress	In progress	List of investigators
5	In progress	In progress	Statistical Analysis Plan
6	In progress	In progress	Data Management Plan
7	In progress	In progress	Monitoring Plan

15.2 ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[13]	☒	☐	☐	6.
1.1.2 End of data collection[14]	☒	☐	☐	6.
1.1.3 Progress report(s)	☒	☐	☐	6.
1.1.4 Interim report(s)	☒	☐	☐	6.
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6.
1.1.6 Final report of study results.	☒	☐	☐	6.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8.
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7., 8.
2.1.2 The objective(s) of the study?	☒	☐	☐	8.
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1

[13] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[14] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1, 9.2.6
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☒	☐	☐	9.1
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.1, 9.2.6
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2, 9.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.4
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.4
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1.2, 9.3.5, 9.3.6
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.4
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.7.4
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.7.4

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.5
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.1
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2, 9.7.3
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1, 9.8.1
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.3.3

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8.3
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10.6

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5.

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.

Comments:

Name of the main author of the protocol: Marina Todorova

Date: 01-Apr-2025

Signature: _____