Protocol 19-OBE2109-006

A double-blind randomized extension study to assess the long-term efficacy and safety of linzagolix in subjects with endometriosis-associated pain

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Sponsor:	Kissei Pharmaceutical Co., Ltd. [redacted]
Sponsor Representative:	[redacted]
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SIGNATURE PAGE

Protocol Title:	A double-blind randomized extension study to assess the long-term efficacy and safety of linzagolix in subjects with endometriosis-associated pain
Sponsor:	Kissei Pharmaceutical Co., Ltd. [redacted]
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Cytel, Inc. Author:	[redacted]

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned pharmacokinetic analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

[redacted]

Sponsor Signatory:

[redacted]

MODIFICATION HISTORY

Current Version	Date	Amended by	Summary of Changes from previous version	Reason
1.0			Original document	
2.0	13-JUN-2022	Marie Boff	See section 7.	See section 7.
3.0	28-AUG-2023	Holly Ge	See section 7.	See section 7.

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ABBREVIATIONS

Abbreviation	Definition
ABT	Add-back therapy
AE	Adverse events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic class
AUC	Area under the concentration versus time curve
AUC_{0-24}	Area under the concentration versus time curve from time 0 to the end of the dosing interval 24 hours later, calculated using linear trapezoid rule
BMD	Bone Mineral Density
BMI	Body Mass Index
CDF	Cumulative Distribution Function
CI	Confidence Interval
ClinRO	Clinician Reported Outcome
CM	Concomitant Medication
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of Variation
DXA	Dual-energy X-ray absorptiometry
DYS	Dysmenorrhea
E2	Estradiol
EAP	Endometriosis Associated Pain
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EHP-30	30-Item Endometriosis Health Profile
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQOL 5-Dimension 5-Level
FU	Follow-up
GCP	Good Clinical Practice

Abbreviation	Definition
GGT	Gamma Glutamyl Transferase
Gnrh	Gonadotropin releasing hormone
HDL	High-density lipoprotein
HRPQ	Health Related Productivity Questionnaire
HRUQ	HealthCare Resource Utilization Questionnaire
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Investigational Review Board
ITT	Intent-to-treat
IWRS	Interactive Web Response System
LDL	Low density lipoprotein
LH	Luteinizing hormone
LOQ	Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MME	Morphine Milligram Equivalent
mmHg	Millimeters of mercury
mPGIS	Monthly Patient Global Impression of Severity
Ms	Millisecond
NETA	Norethisterone acetate
NMPP	Non-Menstrual Pelvic Pain
NRS	Numeric Rating Scale
NSAIDS	Non-steroidal anti-inflammatory drugs
OR	Odds-ratio
P4	Progesterone
PD	Pharmacodynamic
PGIS	Patient Global Impression of Severity
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PP	Per Protocol Set
PPGIC	Post-treatment Global Impression of Change
PPV	Pelvic Pain Verbal Rating Scale
PROMIS	Patient Reported Outcomes Measurement Information System

Abbreviation	Definition
PSIQ	Physician Surgery Intention Question
QOL	Quality of Life
Qt	Qt interval
Qtc	Corrected Qt interval
Qtcf	Corrected Qt interval Fridericia
REB	Research Ethics Board
ROC	Receiver operating characteristic
SAP	Statistical analysis plan
SHBG	Sex hormone-binding globulin
SOC	System Organ Class
SSIQ	Subject Surgery Intention Question
TBL	Total Bilirubin
TVUS	TransVaginal UltraSound
ULN	Upper Limit of Normal
VRS	Verbal Rating Scale

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

This is a prospective, randomized, double-blind study.

Subjects who had completed the 6-month Treatment Period in 18-OBE2109-003 - Edelweiss 3 study (herein referred to as main study) were invited to enter the present extension study. Month 6 visit of the main study was a decision point for Subjects to either end treatment and enter a post-treatment follow up (part of the main study), or to opt for a 6-month treatment extension.

The purpose of this SAP is to describe the statistical analyses for the Edelweiss 3 Extension Treatment and Extension Follow-up Periods.

1.2. Objectives

The primary objective of this extension study was to assess the maintenance of efficacy of linzagolix administered orally once daily for up to an additional 6 months (for up to 12 months of treatment in total) in women who had already completed 6 months of linzagolix treatment at a dose of 75 mg alone or of 200 mg in combination with add-back therapy (estradiol (E2) 1 mg / norethisterone acetate (NETA) 0.5 mg) in the management of moderate to severe endometriosis-associated pain (EAP) in women with surgically confirmed endometriosis. The two co-primary efficacy endpoints were clinically meaningful reduction over the last 28 days of randomized treatment up to the Month 12 visit, along with a stable or decreased use of analgesics for EAP, for 1) dysmenorrhea (DYS) and for 2) non menstrual pelvic pain (NMPP).

Secondary objectives included evaluation of efficacy over the last 28 days of randomized treatment up to the Month 12 visit based on the following parameters: evaluation of pain associated with sexual intercourse (dyspareunia) and defecation (dyschezia), difficulty of doing daily activities, analgesic use, assessment of subject perception of severity, change in uterine bleeding, Quality of Life (QoL) questionnaires, pharmacoeconomic burden of endometriosis by assessing changes in patient productivity, assessment of endometriosis-related number of non-study health visits, number of days in hospital and type of medical procedures performed during the Treatment Period.

Safety and tolerability objectives included assessment of bone mineral density (BMD), endometrial health, cardiac safety including QT interval prolongation, standard laboratory safety parameters, gynecological assessments and adverse event (AE) frequency including specific hypoestrogenic AEs.

Exploratory objectives included assessment of bone turnover markers and collection of pharmacokinetic (PK) and pharmacodynamic (PD) related data of linzagolix for a separate modelling exercise.

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

2. STUDY DESIGN

2.1. Introduction

This was a prospective, randomized, double-blind study. Subjects who completed the 6-month Treatment Period in the main study (18-OBE2109-003 - Edelweiss 3) were invited to enter the present extension study. Month 6 visit of the main study was a decision point for Subjects to either end treatment and enter a post-treatment follow up (part of the main study), or to opt for a 6-month treatment extension.

The extension study started at the Month 6 visit of the main study. Subjects were required to sign a specific informed consent form (ICF) for this extension study. Only subjects who completed the full 6-month Treatment Period in the main study and met the inclusion criteria were eligible for entry in the extension study.

All subjects received once daily linzagolix 75 mg alone (with ABT placebo) or 200 mg combined with ABT for 6 months. Subjects who received placebo during the main study were randomized to either linzagolix 75 mg alone (with ABT placebo) or linzagolix 200 mg with ABT. Subjects who received active treatment during the main study continued with the same treatment.

Linzagolix/placebo tablets were provided in monthly treatment kits, packaged, labelled and administered in the same manner to protect the blinded nature of the trial.

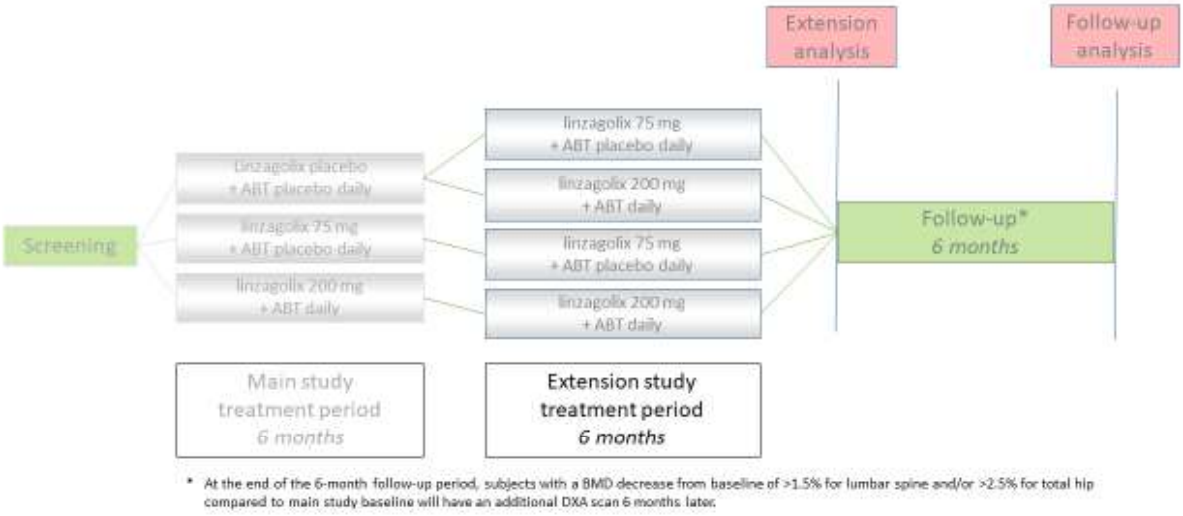
ABT/placebo treatments were supplied as 3-monthly kits, packaged, labelled and administered in the same manner to protect the blinded nature of the trial.

After end of treatment in the extension study (6-month Treatment Period: from Month 6 to Month 12), subjects entered a post-treatment Follow-Up Period of 6 months with no investigational medicinal product (IMP).

The total duration of the present extension study was to be 12 months.

A schematic of the study design is shown in Figure 1.

Figure 1: Study design



The schedule of assessments is in Appendix 9.6, further details available in the study protocol.

2.2. Sample Size and Power

With 150 subjects per each of the three treatment groups in the main study (450 subjects in total), the power was greater than 95% to reject the null hypothesis for both co-primary endpoints and 85% to reject all the null hypothesis for the ranked secondary endpoints. All subjects who had completed the full 6-month Treatment Period in the main study and who met the inclusion criteria were to be offered to enter the extension study. It was estimated that up to 288 subjects would enter the extension study, assuming that 80% of the patients randomized in the main study would complete the study (namely 360 subjects) and that up to 80 % thereof would enter the extension study.

2.3. Randomization Methodology

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

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

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

2.4. Stopping Rules

Subjects were informed that they had the right to withdraw from the study at any time, without prejudice to their medical care, and that they were not obliged to state the reason(s). Any withdrawal must be fully documented in the eCRF exit form.

The Investigator may have withdrawn a subject at any time if this was considered to be in the subject's best interest.

In addition, the sponsor could make a decision to temporarily or permanently discontinue the study for safety, ethical, compliance or other reasons. In this case, the subject's participation was to be ended prematurely without asking for her consent.

In addition, an Independent Data Monitoring Committee (IDMC) regularly reviewed safety data and made recommendations concerning the continuation, modification or termination of the study.

Withdrawal during Treatment Period:

Subjects discontinuing participation in the study during the Treatment Period were to undergo the procedures required at Month 12, except the DXA in case of discontinuation before Month 9 visit. These subjects would enter the 6-month Follow-Up Period and would continue daily eDiary recording for 6 months and up to Month 6 ExFU visit in order to continue to collect efficacy and safety data.

PK sampling is not required if the subject had no IMP administration the day prior to the withdrawal visit.

Withdrawal during Follow-Up Period:

Subjects discontinuing participation in the study during the Follow-Up Period were to undergo the procedures required at Month 6 ExFU visit, which included completion of all ClinRO and ePRO questionnaires, except the DXA in case of discontinuation before Month 3 ExFU visit.

Discontinuation criteria

During the course of the study, the subject may have been discontinued for the following reasons:

During the course of the study, the subject may have been discontinued for the following reasons:

- Adverse Event
- Subject's request
- Protocol Violation

- Lost to Follow-up
- Pregnancy
- Other

Details are provided in the Protocol.

Discontinuation Rules during the Treatment Period:

Endometrial biopsies: in case of an endometrial biopsy diagnosis of endometrial hyperplasia of any type or worse, the subject was to discontinue study treatment (and was not eligible to enter the extension study) and was to be advised to undergo gynecological evaluation and treatment.

Serum calcium: Subjects with a serum calcium level on treatment above 2.9 mmol/L was to have calcium supplements interrupted. If serum calcium level on treatment was above 3.1 mmol/L, calcium supplements and study treatment were to be interrupted. A repeat test of this parameter within 2 weeks under fasting conditions was to be performed. If the results of the repeat remained above 2.9 mmol/L, study treatment was to be discontinued and the subject was to be advised to consult an endocrinologist for further evaluation.

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

Liver function tests: following the Food and Drug Administration (FDA) guidance on drug-induced liver injury, subjects who had an elevation of hepatic enzymes were to be withdrawn immediately from treatment if:

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Withdrawn subjects were to be followed up until hepatic parameters returned to normal.

ECG : subjects with a QTcF > 500 ms or increase > 60 ms from the highest value prior to first dose were to be withdrawn from study treatment and followed up until return to QTcF < 480 ms or – if not reached after 3 months of treatment cessation- be referred to a cardiologist. They were to enter the 6-month Follow-Up Period and undergo follow-up ECGs according to the schedule of events.

2.5. Blinding

The study design was double-blind for the subject, the clinical site and the operational team. The Sponsor was planned to be unblinded to active treatment groups, following the analysis of Month 6 visit data from the main study (18-OBE2109-003 - Edelweiss 3 study), but was to be blinded to the treatment allocated to patients who had previously received placebo.

A database lock was to be performed prior to unblinding of treatment.

2.6. Interim Analyses

Not applicable.

3. STUDY ENDPOINTS

3.1. Efficacy Variables

Primary efficacy endpoints:

The two co-primary, composite, efficacy endpoints are clinically meaningful reduction from baseline to the last 28 days preceding the Month 12 visit (the 4-week period preceding Month 12 visit), along with a stable or decreased use of analgesics for EAP, in the mean daily assessment of 1) DYS and of 2) NMPP, both measured on a Verbal Rating Scale (VRS) using an electronic diary (eDiary).

Secondary efficacy endpoints:

- Change from baseline to Month 12 in DYS (VRS)
- Change from baseline to Month 12 in NMPP (VRS)
- Change from baseline to Month 12 in dyschezia (Numeric Rating Scale - NRS)
- Change from baseline to Month 12 in overall pelvic pain (NRS)
- Change from baseline to Month 12 in the interference of pain with the ability to perform daily activities, measured using the pain dimension of the Endometriosis Health Profile-30 (EHP-30)
- Change from baseline to Month 12 in dyspareunia (VRS)
- No analgesics use for EAP during the preceding 4-week period at each scheduled assessment
- No opiate use for EAP during the preceding 4-week period at each scheduled assessment
- Responder rate at scheduled visit other than Month 12 visit, for DYS and NMPP (VRS)
- Change from baseline to each scheduled assessment in the mean pelvic pain scores for DYS, NMPP and overall pelvic pain, during the previous 4-week period assessed on the NRS and VRS
- Change from baseline to each scheduled assessment in the number of days with moderate to severe pelvic pain during the previous 4-week period assessed on the VRS
- Change from baseline to each scheduled assessment in the mean worst pelvic pain score defined as the mean of the 5 highest daily pain scores reported during the previous 4-week period assessed on the NRS
- Change from baseline to each scheduled assessment in the mean of daily dyspareunia scores reported during the previous 4-week period on the dyspareunia VRS
- Change from baseline to each scheduled assessment in the mean of daily dyschezia scores reported during the previous 4-week period assessed on the dyschezia NRS

- Change from baseline to each scheduled assessment in non-opioid, opioid and combined analgesic use for EAP during the previous 4-week period based on pill count in the eDiary
- Change from baseline to each scheduled assessment in opioid analgesic use for EAP as reported in the eDiary during the previous 4-week period based on morphine milligram equivalent (MME)
- Change from baseline to each scheduled assessment in the number of days of analgesic use (including any class) for EAP during the previous 4-week period as assessed in the eDiary
- Change from baseline to each scheduled assessment in the number of days of opioid analgesic use for EAP during the previous 4-week period as assessed in the eDiary
- Change from baseline to each scheduled assessment in the number of pelvic pain-free days (assessed on the VRS) during the previous 4-week period
- Change from baseline to each scheduled assessment in ability to perform daily activities during the previous 4-week period, as assessed in the eDiary (daily function NRS)
- Change from baseline to each scheduled assessment in the number of days with no difficulty in doing daily activities due to EAP during the previous 4-week period as assessed in the eDiary (daily function NRS)
- Change from baseline to each scheduled assessment in the number of days when dyspareunia was a problem during the previous 4-week period (including days when sexual intercourse was avoided because of anticipation of pain) as assessed on the dyspareunia VRS
- Change from baseline to each scheduled assessment in the number of days when sexual intercourse was avoided because of anticipation of pain during the previous 4-week period as assessed on the dyspareunia VRS
- Change from baseline to each scheduled assessment in the number of days with uterine bleeding (including spotting) during the previous 4-week period measured by eDiary
- Change from baseline to each scheduled assessment in the number of days when school or work was missed due to EAP in the previous 4-week period as reported in the eDiary
- Change from baseline to each scheduled assessment in the number of days when the subject had to go to bed or lie down due to EAP in the previous 4-week period as reported in the eDiary
- Change from baseline to each scheduled assessment in the Pain, Control and powerlessness, Emotional well-being, Social support, Self-image dimensions and the Modular sexual relationship questionnaire of EHP-30 scores

- Change from baseline to each scheduled assessment in the Health-Related Productivity Questionnaire (HRPQ) scores
- Number of non-study endometriosis related health visits, number of days in hospital and type of procedures performed based on Health Resource Utilization Questionnaire (HRUQ) at each scheduled assessment
- Change from baseline to each scheduled assessment in the Physician/Subject Surgery Intention Question (PSIQ/SSIQ)
- Change from baseline to each scheduled assessment in the PROMIS Fatigue – Short Form 6a
- Change from baseline to each scheduled assessment in the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire
- Response at each scheduled assessment according to Patient Global Impression of Change (PGIC) (and Post-treatment Patient Global Impression of Change, PPGIC)
- Change from baseline to each scheduled assessment in the monthly PGIS (mPGIS) score

3.2. Pharmacokinetic Variables

PK blood samples will be collected from each subject at each study visit during the Treatment Period for determining linzagolix and KP017 plasma levels.
At the visits where IMP intake is at site, i.e. at Months 6, 7, 8, 9, 10 and 11 visits, PK sampling will be performed before IMP intake. The approximate time of dose administration on the four previous days and time of PK sampling will be recorded in the eCRF.

In case of early discontinuation visit, PK sampling is not required at the withdrawal visit if the subject had no IMP administration the day prior to the withdrawal visit.

Pharmacokinetic analyses will be considered exploratory. Analyses are described in Section 6.4.3.33.

3.3. Safety Variables

Safety endpoints include:

- Change from baseline to each scheduled assessment in BMD measured by DXA of lumbar spine (L1-L4), femoral neck, and total hip
- Incidence and severity of treatment emergent adverse events (TEAEs)
- Incidence and severity of hypoestrogenic TEAEs (hot flush)

- Time to the first post-treatment menses
- Changes in clinical laboratory assessments (hematology, biochemistry, coagulation parameters, hormones, lipids and urinalysis) from baseline to each scheduled assessment
- Any pathological changes from baseline in the endometrium as assessed by histology from endometrial biopsies
- Changes from baseline to each scheduled assessment in any other safety parameter including weight, vital signs, ECG, gynecological assessments and endometrial thickness

Safety analyses are described in Section 6.6.

3.4. **Exploratory Variables**

Exploratory endpoints include:

- Change from baseline in bone turnover markers at each scheduled assessment
- PK and PD of linzagolix

Exploratory analyses are detailed in Section 6.8 (and Section 6.4.3.33.for PK).

4. ANALYSIS SETS

4.1. Analysis Set Definitions

The following data sets will be used for the statistical analysis:

1. **Treatment Extension Analysis Set (TEAS)**: All subjects from the main study who entered the extension study and received at least one dose of study drug with the exception of subjects whose Month 6 assessments subsequently met any of the discontinuation criteria. These subjects will be withdrawn from study treatment and will enter the Follow-Up Period. Subjects will be analyzed according to randomized treatment.

Discontinuation criteria at Month 6 are the following and will programmatically identified for the analyses sets derivations purpose, based on the Month 6 locked database from the main study, and applying Month 6 analysis visit windows from the main study SAP:

- Endometrial Biopsy: in case of endometrial biopsy diagnosis being an endometrial hyperplasia of any type or worse (malignant endometrial neoplasm) at the Month 6 assessment.
- Serum calcium: Subjects who have a serum calcium level on treatment at the Month 6 assessment above 3.1 mmol/L study treatment are to be interrupted. A repeat test of this parameter within 2 weeks under fasting conditions is to be performed. If the results of the repeat remain above 2.9 mmol/L, study treatment should definitively be discontinued
- BMD loss: subjects who experience more than 8% BMD loss or a Z-score ≤ -2.5 at any site (femoral neck, hip or spine) at the Month 6 assessment.

  Per protocol, assessments with BMD loss >5% should be confirmed with a second scan. For assessments with BMD loss “Confirmed (no repeat)” the initial scan will be used to check the discontinuation criteria. The repeated confirmatory scan will be used otherwise. Only confirmatory scans within the +/-28 days window of theoretical Month 6 date will be included.
- Liver function tests: subjects who have an elevation of hepatic enzymes at the Month 6 assessment are to be withdrawn immediately from treatment if:
  - ALT or AST >8xULN
  - ALT or AST >5xULN for more than 2 weeks. Repeats assessments within 2 weeks after the initial assessment will be checked for this criteria.
  - ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
  - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ECG: subjects who have a QTcF > 500 ms at the Month 6 assessment or increase > 60 ms from the highest value prior to the first dose in the main study

2. **Per Protocol Extension Analysis Set (PP EAS)**: All subjects from Treatment Extension Analysis Set, excluding those identified as having major protocol deviations that could potentially affect the efficacy assessments up to Month 12. Subjects will be analyzed according to randomized treatment.

3. **Follow-up Extension Analysis Set (FU EAS)**: All subjects from the main study who entered the extension study and received at least one dose of study drug with the exception of subjects whose Month 6 assessment subsequently met any of the discontinuation criteria, and who entered the Post-Treatment Follow-Up Period. Subjects will be analyzed according to randomized treatment.

4. **Extension Safety Analysis Set (ESAF)**: All subjects randomized into the extension study who received at least one dose of study drug irrespective of the treatment received. Subjects will be analyzed according to treatment received.

5. **Follow Up Safety Analysis Set (FU SAF)**: All subjects randomized into the extension study who received at least one dose of study drug irrespective of the treatment received, and who entered the Post-Treatment Follow-Up Period. Subjects will be analyzed according to treatment received.

6. **Extension Pharmacokinetic (PK) Set**: all subjects who were randomized and received active study medication in the main study, had no major protocol deviations impacting PK throughout the main study or extension and with available PK data. Subjects will be analyzed according to treatment received.

7. **Extension Pharmacodynamic (PD) Set**: all subjects who were randomized and received active study medication in the main study, had no major protocol deviations impacting PD throughout the main study or extension and with available PD data. Subjects will be analyzed according to treatment received.

In general, analyses of efficacy will be conducted using the TEAS, PP EAS (when specified) and FU EAS sets, analyses of safety will be conducted using the ESAF and FU SAF, and analyses of PK and PD will be conducted using the PK and PD Sets accordingly.

The actual treatment will be derived as follows, based on daily e-diary IMP intake data:

Treatment kits will be dispensed to the subjects as follows:

- on Month 6 and Month 9 visits, subject will receive two kits, one for linzagolix/placebo (monthly kit) and one for the ABT/ABT placebo (3-monthly kit).

- On Month 7, Month 8, Month 10 and Month 11 visits, subject will receive one kit only, for linzagolix/placebo. The number of days with one pink tablet, one grey tablet and one red capsule taken based on e-diary IMP intake data for each treatment will be computed. Data from “Today” will be used primarily. If data from today is missing, data from “Yesterday” of the

following day will be considered. If the e-diary is not completed for a day (neither “Today” nor “Yesterday” of following day), it will be assumed that no intake of drug was taken on that day.

Further rules are as follows:

- Treatment administration errors:
    - If a subject received placebo with placebo ABT on more than 50% of days (even if it is not planned), then the actual treatment group will be placebo with placebo ABT for the extension period.
    - Otherwise, the active treatment (combined with add-back or placebo add-back) with the most days taken will be assigned for the extension period.
    - If the number of days is equal for two treatments groups containing active treatment, then LGX 200 mg with ABT will be assigned for the extension period.
- If a subject discontinued, only data received up to discontinuation will be used.

All analyses for the extension study will be described according to the combined treatment group based on the treatment on the main study and the extension study.

For the combined actual treatment groups, the actual treatment during the main study and the actual treatment during the extension study comprise the following four combined actual treatment groups. It is possible that the derived actual treatment group will not correspond to any of the combined planned treatment groups; thus the combined actual treatment group will be derived as follows:

Actual treatment Main study	**Actual treatment Extension study**	**Combined actual treatment group**
Combination planned in the protocol		
Placebo	LGX 75 mg	Placebo / LGX 75 mg
Placebo	LGX 200 mg + ABT	Placebo / LGX 200 mg + ABT
LGX 75 mg	LGX 75 mg	LGX 75 mg
LGX 200 mg + ABT	LGX 200 mg + ABT	LGX 200 mg + ABT
Combination not planned in the protocol (but possible with treatment administration errors)		
Placebo	Placebo	Placebo / LGX 75 mg
LGX 75 mg	Placebo	LGX 75 mg

LGX 200 mg + ABT	Placebo	LGX 200 mg + ABT
LGX 75 mg	LGX 200 mg + ABT	LGX 75 mg
LGX 200 mg + ABT	LGX 75 mg	LGX 200 mg + ABT

4.2. **Protocol Deviations**

A protocol deviation is any noncompliance with the clinical trial protocol or International Conference on Harmonization Good Clinical Practice (ICH GCP) requirements. It was the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations were to be addressed in study source documents and reported to the reviewing IRB/IEC per their policies. The site investigator was responsible for knowing and adhering to the reviewing IRB/IEC requirements.

All Protocol Deviations were to be reported to the Sponsor and documented in the monitoring report. These will be classified as minor or major based on their effect on the right, safety or well-being of the subjects and/or the quality and integrity of the data. Major deviations that could potentially affect the efficacy assessments up to Month 12 and thus may exclude subjects from the PP Extension Analysis Set may include:

- Non-compliance with inclusion criteria 2
- Non-compliance with exclusion criteria 2; 3; 4; 6
- IP Dispensing error;
- Randomisation code broken
- Subjects with a gap of at least 28 days between end of treatment in main study and treatment start in Extension
- Non-compliance with study treatment: threshold to be defined during blinded data review meeting (e.g. IMP compliance in tablets <60% for Month 6-Month 12)
- Unauthorised prior or concomitant therapy;
- M12 Visit performed outside the +/-14 days of the theoretical visit date;

The final rating of all deviations will be confirmed prior database lock. The final protocol deviation file (formatted as a Microsoft Excel file) will be provided to Cytel.

Major protocol deviations will be summarized by category and by treatment group on the Treatment Extension Analysis Set.

All protocol deviations will be presented in the data listing. Protocol deviation records with missing subject ID and thus not related to any particular subject will be excluded in the listings.

5. DATA HANDLING

5.1. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4 OR HIGHER), unless otherwise noted. Medical History and adverse events will be coded using MedDRA available version. Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary available version.

5.2. Data Conventions

5.2.1. Last extension treatment administration date, End of extension Study date and Period definitions

The last extension treatment administration date will be defined as the date from the treatment termination reported in the extension period eCRF page. If this date is missing, the last date with a drug intake in the eDiary that is inferior or equal to Month 12 visit or the last available date with a drug intake in the eDiary if the subject discontinued the extension treatment will be used.

For subjects who entered the extension, the end of the extension study date will be the last assessment date in the extension study defined as last assessment recorded in the eCRF (excluding end date of adverse events and concomitant medications) or ediary date (excluding drug intakes recorded after last extension treatment administration date). This will not necessarily be the same date as last assessment date as recorded in the eCRF.

For each 28-day period prior to Month X (except Month 12), the end of the period will be defined as the Month X visit date. If subject discontinued prior to Month X, the end of the period will be the date from the treatment termination of extension period eCRF page or the last date with a drug intake in the eDiary if missing. If the subject missed the Month X visit (but did not discontinue), the subject might still have filled the diary during that time: the theoretical Month X date will be used to define the end of the 28-day period. The theoretical Month X is defined with respect to Day 1 as Month X= Day 1+ 28*X.

For the 28-day period prior to Month 12, the end of the period will be defined as the last extension treatment administration date.

Note:

For Adverse Events, Concomitant Medications and Daily diaries data collected on the Month 6 date will be part of the extension for subjects entering the extension study.

For Adverse Events, Concomitant Medications and Daily diaries, data collected on the Month 12 date will be part of the Extension Follow-up period for subjects entering the Extension follow-up period.

The extension treatment period will be defined as Month 6 up to (Month 12 date -1) or treatment discontinuation date.

The extension follow-up period will be defined as the Month 12 date or (treatment discontinuation date+1) up to the extension follow-up end date (for subjects who entered the extension follow-up).

5.3. Methods of Pooling Data

Not Applicable

5.4. Withdrawals, Dropouts, Loss to Follow-up

In general, there will be no substitutions made to accommodate missing data points due to withdrawals, dropouts and loss to follow-up. All data recorded in the CRF will be included in data listings that will accompany the clinical study report.

In case of early discontinuation, the subject was to be instructed to complete the relevant eDiary questionnaires as soon as possible upon treatment discontinuation.

Withdrawal during treatment period:

Subjects discontinuing participation in the study during the Extension Treatment Period were to undergo the procedures required at Month 12, except the DXA in case of discontinuation before Month 9 visit. These subjects were to enter the 6-month Extension Follow-Up Period and were to continue daily eDiary recording for 6 months and up to the Month 6 ExFU visit in order to continue to collect efficacy and safety data.

PK sampling was not required if the subject had no IMP administration the day prior to the withdrawal visit.

Withdrawal during follow-up period:

Subjects discontinuing participation in the study during the Extension Follow-Up Period were to undergo the procedures required at the Month 6 ExFU visit, which included completion of all ClinRO and ePRO questionnaires, except for DXA scans in subjects who discontinued before the Month 3 ExFU visit.

5.5. Visit Windows

For all analyses except for the DXA assessments and the diary questionnaires, the visits as collected in the eCRF will be used.

The rules for visit day calculations are listed in Table 1 below.

E-diary questionnaires:

For diary questionnaires (EHP-30, EQ-5D-5L, HRPQ, HRUQ, PGIC, PPGIC, PGIS, PROMIS, SSIQ) except for the PSIQ, the e-diary dates of assessment of each visit will be checked versus the dates of same visit in eCRF to handle for e-diary visit errors. Only assessments within the window of the date of eCRF+/-14 days will be used in analyses. In case of multiple assessments falling within the same window of an eCRF date, the non-empty record with completion date closest to the eCRF date will be used.
Due to the war situation in Ukraine, some subjects from Ukraine sites may have completed visits and e-diary questionnaires but not collected the data in the eCRF. For all ediary questionnaires data of subjects from Ukraine sites with a later questionnaire date of 24FEB2022, the e-diary dates will be compared to theoretical visits dates instead of eCRF visits dates if eCRF dates are missing.

For data from discontinued visits, the discontinuation visit date should be compared to theoretical visit dates. Only assessments within the window of theoretical date +/-14 days will be used for analyses, if it is planned to have a such assessment at this visit and no other assessment is in the window. If a subject discontinued in the extension treatment period, date will be compared to the theoretical visit dates in the extension treatment period as described in Table 1. If a subject discontinued in the extension follow-up period, date will be compared to the theoretical visit dates in extension Follow-up period from Table 2.

Note that assessments from discontinued visits in [redacted] eDiary device are entered under Month 12 (Month 6 Extension FU in follow-up). They will be recoded as discontinued visits before applying the windowing rules.

Pharmacokinetics data

Visit windows rules for PK data will be the following:

- PK assessments will be included in analysis if:
  - Assessment is Pre-dose (or PK time = dose time), or IMP intake is not done on the day of PK sampling (i.e. considered as pre-dose), and,
  - PK assessment date is within +/-10 days of the theoretical visit and up to 2 days after last IMP intake for Month 12 visit.

If the PK sampling time is missing, or the IMP intake on the same day is done and the IMP intake time is missing then assessments will not be included.

IMP intake status (done/not done) and IMP intake time from the Pharmacokinetics eCRF page will be used.

PK samples analysed after the period of long term stability will be excluded.

DXA data

Visit windows rules for DXA assessments will be the following:

- The DXA assessment at Month 9 will be derived as the first non-missing DXA assessment with acceptable quality (accepted="Yes") and dated between Month 9 theoretical date (=Day 253) -28 days and Month 9 theoretical date + 28 days.
- The DXA assessment at Month 12 will be derived as the first non-missing DXA assessment with acceptable quality (accepted="Yes") and dated between Month 12 theoretical date (=Day 337 in the main study) -28 days and Month 12 theoretical date + 28 days.
- The DXA assessment at Month 6 Extension Follow-Up will be derived in the same way as the DXA assessment at Month 12. Theoretical date of Month 6 Extension Follow-up is 168 days after Month 12 theoretical date or after treatment discontinuation.

Other safety data:

For other safety data, data from early discontinuation should be compared to theoretical visits dates. Only assessments within the window of theoretical date +/-14 days will be used for analyses, if it is planned to have a such assessment at this visit and no other assessment is in the window. If a subject discontinued in the extension treatment period, date will be compared to the theoretical visit dates in extension treatment period as described in Table 1. If a subject discontinued in the extension follow-up period, date will be compared to the theoretical visit dates in extension Follow-up period from Table 2.

For unscheduled safety assessments, if the assessment occurs within a window of theoretical date +/- 14 days for a planned eCRF visit for which it was planned per protocol to have such assessment, and no assessment was done for that visit, the assessment will be assigned to that visit. If the assessment is equally distant from two eCRF visits with no corresponding safety assessment, the assessment will be assigned to the next visit.

For biopsy, DXA assessment or laboratory assessment, if an assessment has been assigned in external data to a follow-up visit of the main study for subjects who entered in the extension study, the visit of assessment should be reassigned with the same rules described above for unscheduled safety assessment.

Table 1 Theoretical Visit Dates in Extension Treatment Period

Visit	Theoretical Date
Month 6	Day 169
Month 7	Day 197

Month 8	Day 225
Month 9	Day 253
Month 10	Day 281
Month 11	Day 309
Month 12	Day 337

Table 2 Theoretical Visit Dates in Extension Follow-up Period

Visit	Theoretical Date
Month 1 ExFU	Month 12 or treatment discontinuation date + 28
Month 3 ExFU	Month 12 date or treatment discontinuation date + 84
Month 6 ExFU	Month 12 date or treatment discontinuation date + 168

6. STATISTICAL METHODS

6.1. Sample Size Justification

With a planned sample size of 150 subjects per each of the three treatment groups in the main study (450 subjects in total), the power was to be greater than 95% to reject the null hypothesis for both co-primary endpoints and 85% to reject all the null hypothesis for the ranked secondary endpoints. All subjects who completed the full 6-month Treatment Period in the main study and who met the inclusion criteria were to be offered to enter the extension study. It was estimated that up to 288 subjects would enter the extension study, assuming that 80% of the patients randomized in the main study would complete the study (namely 360 subjects) and that up to 80 % thereof would enter the extension study.

6.2. General Statistical Methods

6.2.1. General Methods

All output will be incorporated into Microsoft Excel or Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, pharmacokinetic and safety parameters.

The analyses will be performed on 4 treatment groups (taking into account the treatment taken in the main study):

- linzagolix 75 mg / linzagolix 75 mg
- linzagolix 200 mg with ABT / linzagolix 200 mg with ABT
- Placebo / linzagolix 75 mg (subject receiving placebo in main study and treated with linzagolix 75 mg in extension study)
- Placebo / linzagolix 200 mg with ABT (subject receiving placebo in main study and treated with linzagolix 200 mg with ABT in extension study)

For continuous data and for ordered categorical data, if appropriate, the number of non-missing observations, mean, standard deviation, median, first and third quartiles, minimum and maximum will be calculated, including for change from baseline when applicable.

The baseline mean will be calculated for all subjects based on the Extension Safety Analysis Set

For efficacy endpoints and BMD, a baseline mean will also be calculated for each visit using the baseline data for the subset of subjects who attended that visit, such that the same subjects contribute to the mean for the visit and the mean for the corresponding baseline values. Summary

statistics will be based primarily on non-missing values. For ordered categorical data and nominal data, absolute counts and relative frequencies (in %) will be calculated.

Raw and derived data will be listed.

6.2.2. Definition of Baseline

The baseline will be described in two ways:

- Main Baseline (named Baseline), defined in the Statistical Analysis Plan of the main study and calculated according to first dose of IMP taken during the main Study.
- Second Baseline (named Baseline 2), defined as the last assessment before the first active dose of IMP during the extension study. For efficacy endpoints based on daily diary data, the Baseline 2 will be based on the last 28 days prior to and including last treatment administration in main study.

The baseline 2 will be calculated only for the subjects who are in the placebo arm (actual arm) in the main study.

6.2.3. Adjustments for Covariates

Not Applicable

6.2.4. Multiple Comparisons/Multiplicity

No formal hypothesis tests are planned for this extension study. Data will be summarized by timepoint for each treatment group.

6.2.5. Subgroups

Not Applicable

6.2.6. Missing, Unused, and Spurious Data

6.2.6.1. Efficacy Endpoints Missing Data

Summary statistics will be based primarily on non-missing values. The planned statistical analyses aim to estimate the efficacy of linzagolix versus placebo while under randomized treatment and therefore lack of data after treatment discontinuation will not be considered as missing for these analyses.

There may be missing data during the screening period (from the main study) and whilst under treatment, for example, missed days of completing the eDiary. The primary analyses will use observed data only in such cases provided that a minimum number of completed daily eDiary

entries are available. This effectively assumes that the individual values such as daily eDiary assessments (observed or not) are independent of being missing.

6.2.6.2. Adverse events and Concomitant Medication Missing Dates

Imputation of missing/partial AE and CM dates will be done only to identify treatment-emergent AEs.

AE onset dates:

- Partially missing AE onset dates will be imputed as follows:
  - When only Day is missing:
    - If Month & Year of the onset date are the same as Month & Year of the first administration date, the imputed onset date will be imputed as the minimum of the first administration date and the AE resolution date (imputed if needed).
    - Else if the subject entered the Extension Study and Month & Year is the same as Month & Year of the first administration date in Extension, the imputed onset date will be imputed as the minimum of the first administration date in Extension and the AE resolution date (imputed if needed).
    - Otherwise, the missing day will be replaced by "1"
  - When Day & Month are missing:
    - If the subject entered the Extension Study and if Year of the onset date is the same as Year of the first administration date in Extension, the imputed onset date will be imputed as the minimum of the first administration date in Extension and the AE end date (imputed if needed).
    - Else if Year of the onset date is the same as Year of the first administration date, the imputed onset date will be imputed as the minimum of the first administration date and the AE end date (imputed if needed).
    - Otherwise, the missing Day & Month will be replaced by "01 JAN.", unless other information provides evidence that the event should not be defined as treatment-emergent AE.
- Completely missing AE onset dates will be imputed as follows:
  - If the subject entered the Extension, the AE onset date will be imputed by the first administration date in Extension and the AE will be considered as treatment-emergent, unless the end date of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the first administration date in Extension.

- If the subject did not enter the Extension, or if the end of the AE is before the first administration date in Extension, the AE onset date will be imputed by the first administration date and the AE will be considered as treatment-emergent, unless the end date of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the first administration date. If the end date is before the first administration date, the AE will not be considered as treatment-emergent.

AE end dates

- If Day only is missing, incomplete end dates will be replaced by the last day of the month, if not resulting in a date later than the date of the subject's death or date of study discontinuation. In the latter case, the date of death/date of study discontinuation will be used to impute the incomplete end date.
- If Day & Month are missing, Day & Month will be replaced by 31DEC, if not resulting in a date later than the date of the subject's death or date of study discontinuation. In the latter case, the date of death/ date of study discontinuation will be used to impute the incomplete end date.
- In all other cases the incomplete end date will not be imputed.

Concomitant Medications dates

Partially missing dates for prior and concomitant medications and procedures will be imputed. Of note, imputation of missing/partial dates will be done only to identify the treatment period assignment.

- End date: Missing day will be imputed as the last day of the month, and missing month will be imputed by December, if not resulting in a date later than the date of the subject's death or date of study discontinuation. In the latter case, the date of death/date of study discontinuation will be used to impute the incomplete end date.
- Start date: Missing day will be imputed as the first day of the month, and missing month will be imputed by January.
- If the start date is completely missing, then:
  - If the end date is prior to the date of first administration of the study drug, then the medication is considered as prior
  - If the end date is prior to the date of last administration of the study drug, then the medication is considered as prior and concomitant
  - If the end date is completely missing or after the date of last administration of the study drug, then the medication is considered as prior, concomitant and post.

Following imputation of the dates, the concomitant medications will be assigned to the main study and/or the extension study according to imputed start and end dates. Note that a concomitant medication starts before the first IMP administration in the main study and stops during the extension study will be assigned to both studies.

6.2.6.3. eDiary Devices Data Cleaning

To handle eDiary system issues, mapping rules are defined for data analysis, as described in Appendix E in Section 9.1

In addition, the following rules are defined.

Diary completed in English language for Subjects from non-US sites

Due to a system error in Signant Health device, some subjects from non-US sites wrongly completed diaries in the Extension study in English language instead of a specific language. Data with English language (when evaluation is done by subject, i.e. QSEVAL=SUBJECT) for such subjects should not be considered in analysis.

Handling of duplicate records

- A change of eDiary device vendor ([redacted] vendor to Signant Health vendor) occurred during the study.
- Some subjects may have entered data in the two different devices during the transition period. In case of duplicates results on the same day for daily diaries or on the same visit for monthly questionnaires, data from the new vendor (Signant Health) will be used for analysis.
- In case of duplicates within the same device (same date, same name), the first non-empty record (with earliest date/time) should be used for analysis.

Daily Records entered after 00:00

For daily diaries, records entered with a time between 00:00 (midnight) and 02:00 AM should be considered for the previous day.

Additional rules to specific eDiary domains:

Analgesic use data:

- Analgesic use data from “Today” will be used primarily. If data from” Today” is missing, data from “Yesterday” of the following day will be considered

IMP Intake Data:

- IMP Intake data from “Today” will be used primarily. If data from” Today” is missing, data from “Yesterday” of the following day will be considered

[redacted] device specific rules

NOTE: by design, when a subject is completing a questionnaire (daily or monthly) on a [redacted] device, the device automatically saves all answers provided by the subject as soon as

recorded, unless the subject uses the “previous” button to come back to already answered question(s) within the questionnaire and changes her answer(s) prior to finishing the questionnaire.
There are several triggering questions in the study questionnaires: the next question(s) presented to the subject will depend on the answer chosen by the subject to the current question.

Due to device design issue, when an answer to a triggering question has been changed by the subject (using previous button), the device keeps subsequent answer(s) to the previously triggered question(s), even if this/these question(s) is/are no longer relevant considering the new answer to the triggering question.

The agreed rules consider the last entry made by the subject i.e. the entry that would have not allowed her to provide additional data if it had been her initial answer (in Signant Health device, the intermediate answers are not saved and will not be present in the database; the agreed rules are aligned with this functioning).

Analgesic use data:

- If answer to question “Did you take any provided/prescribed analgesic for your endometriosis related pain?” is “Yes” or empty but the number of ibuprofen intakes and narcotic analgesics intakes are both 0, it will be considered that no analgesic was used on that day.
- If answer to question “Did you take any provided/prescribed analgesic for your endometriosis related pain?” is “Yes” or empty, but question to Ibuprofen intake is “No” and the number of ibuprofen intakes is not zero, it will be considered that no ibuprofen was used on that day. The same rule will be applied for narcotic analgesics.
- If answer to question “Did you take any provided/prescribed analgesic for your endometriosis related pain?” is “No” and the number of ibuprofen intakes and narcotic analgesics intakes are not 0, it will be considered that no analgesic was used on that day and following answers will be ignored.
- If answer to “Did you take any provided/prescribed analgesic for your endometriosis related pain?” is “No” and answer to question Ibuprofen intake is “Yes”, but the number of Ibuprofen intakes is 0, it will be considered that no ibuprofen was used on that day. The same rule will be applied for narcotic analgesics.

Dyspareunia VRS Data:

- when question “Did you have any sexual intercourse?” is answered “No, I was not sexually active for reasons other than my endometriosis” or “No, I avoided sexual intercourse because of anticipation of pain” and there is an answer to question “How did your endometriosis related pain interfere with sexual intercourse?”, only the “No” answer will be considered.

- when question “Did you have any sexual intercourse?” is blank and there is an answer to question “How did your endometriosis related pain interfere with sexual intercourse?”, consider that “Yes” was answered to “Did you have any sexual intercourse”.

HRUQ Data:

- when answer to triggering question 1 is “No” and at least one answer to question 2 to 6 (any answer different from 0) is present, ignore answer 2-6 in the analysis
- when answer to triggering question 7 is “No” and at least one answer to questions 8 to 9 (any answer different from 0) is present, ignore answers 8-9 in the analysis
- For questions 8-9, consider the number of times whatever the answer provided for “procedures” (i.e., if it is NO include number of times if different than 0)

HRPQ Data:

- when answer to question 9 is different than “endometriosis symptoms or its treatment(s) forced me to work part-time when I wanted to work full-time” and question 9bis is different than 0, ignore answer 9bis in the analysis.
- when answer to question 9 is different than “endometriosis symptoms or its treatment(s) kept me from having a job when I wanted to work full-time” and question 9ter is different than 0, ignore answer 9ter in the analysis.
- when answer to question 9 is different than “endometriosis symptoms or its treatment(s) kept me from having a job when I wanted to work part-time” and question 9quater is different than 0, ignore answer 9quater in the analysis

6.2.6.4. Transvaginal Ultrasound

If the depth recorded for a TVUS of uterus is 0 mm, the depth and the volume should be considered as missing (i.e., this means that the assessment was done in 2 dimensions instead of 3 dimensions).

6.2.6.5. Partial and Missing Dates of diagnosis

For partial date of first medical diagnosis/treatment, first surgical diagnosis and most recent surgical diagnosis the following rules of imputation will be applied:

- If only Day is missing, Day will be imputed to 01.
- If Day and Month are missing:
    - if Year is the same as the screening date, Date will be imputed to Screening Date.
    - Otherwise, Day will be imputed to 01 and Month will be imputed to 07.
- If Date is completely missing, no imputation will be done.

6.3. Study Population

6.3.1. Subject Disposition

A tabulation of subject disposition will be presented by treatment group and overall, for randomized subjects in the main study, including:

- Number of subjects randomized in the main study,
- Number of subjects who completed the main treatment period until Month 6
- Number of subjects who signed consent form for the extension study,
- Number of subjects who discontinued the study between informed consent for extension study and the first day of study drug in extension study,
- Number of subjects who received at least one dose of study drug in the extension study,
- Number of subjects who met discontinuation criteria at Month 6
- Number of subjects who completed the extension treatment period until Month 12
- Number of subjects who discontinued the extension treatment period prior to Month 12 (excluding those who met discontinuation criteria at Month 6), and reasons for extension treatment discontinuation
- Number of subjects who entered the extension follow-up period
- Number of subjects who discontinued the extension follow-up period, and reasons for the extension follow-up period discontinuation
- Number of subjects who completed the extension study (complete the extension treatment period and the extension follow-up period)

The number of subjects included in the extension study by country and by site will be also provided.

The number of subjects who completed each visit of the extension study will be summarized by treatment group and overall, for the Treatment Extension Analysis Set.

The following listings will be presented:

- Study completion information, including the reason for premature study withdrawal, if applicable;
- Inclusion/exclusion criteria;
- Subject inclusion in each of the analysis sets (Treatment Extension Analysis Set, Follow-up Extension Analysis Set, Extension Safety Analysis Set, Follow-up Extension Safety Set, Extension PD and Extension PK Analysis Sets) and reasons for exclusion for Treatment Extension Analysis Set and Per Protocol Extension Analysis Set.

6.3.2. Demographic and Baseline Characteristics

Baseline, demographic and medical history information will be analyzed by treatment group and overall, for the Treatment Extension Analysis Set and Extension Safety Analysis Set.

No formal statistical comparisons will be performed.

6.3.3. Demographics

Demographics and baseline characteristics recorded at baseline in the main study will be summarized by treatment group and overall using descriptive statistics.

Demographics and baseline data include Age (years), Gender, Ethnicity, Race, Height (cm), Weight (kg), Body Mass Index (kg/m2), Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Heart Rate (beats/minute), QTc interval (Fridericia) (ms).

BMI is auto-calculated, defined as: Weight (kg)/(Height(m)*Height(m)).

Demographic and Baseline data will be provided in data listings.

6.3.4. Baseline Disease Characteristics

For the 4 treatment groups (as detailed in section 6.2.1), the following parameters, recorded at baseline in the main study, will be calculated as described in section 4.5.2 of the SAP of the main study.

- Baseline Dysmenorrhea (DYS)
- Baseline Non-Menstrual Pelvic Pain (NMPP)
- Baseline analgesic use.
- The average duration of the two baseline menstrual cycles (days)
- The number and percentage of subjects with Normal, Abnormal, Abnormal clinically significant (or Not Assessable) results for Physical Examination, Gynecological Examination, Breast Examination, Mammography, Endometrial Biopsy and PAP Smear assessments at baseline.
- Transvaginal ultrasound data (i.e., presence of ovarian endometrioma with a diameter of 7 cm or greater, uterus length, width, and depth in mm and corresponding calculated uterine volume in cm3 (using the prolate ellipsoid formula [L x H x W x 0.523]), endometrium thickness in mm, and presence of any uterus, left ovary or right ovary abnormality).

Only for subjects receiving Placebo in the main study, these baseline characteristics will be described as the definition of the second baseline (section 4.2.11 of this SAP):

- Dysmenorrhea (DYS)
- Non-Menstrual Pelvic Pain (NMPP)

- Analgesic use.
- The number and percentage of subjects with Normal, Abnormal, Abnormal clinically significant (or Not Assessable) results for Physical Examination, Gynecological Examination, Breast Examination, Mammography (if required), Endometrial Biopsy (if required), for baseline 2.
- Baseline 2 Transvaginal ultrasound data (i.e., presence of ovarian endometrioma with a diameter of 7 cm or greater, uterus length, width, and depth in mm and corresponding calculated uterine volume in cm3 (using the prolate ellipsoid formula [L x H x W x 0.523]), endometrium thickness in mm, and presence of any uterus, left ovary or right ovary abnormality).

Baseline Disease Characteristics will be reported in listings.

6.3.5. Medical History

Medical history, recorded at baseline in the main study, will be summarized by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA), by treatment group and overall.

Medical history will be summarized by subject incidence rates; therefore, a subject contributes only once to the count for a given medical history (SOC or preferred term).

Medical history will be reported in a listing.

6.3.6. Endometriosis History

For the 4 treatment groups (as detailed in Section 6.2.1), the following parameters, recorded at baseline in the main study, will be calculated as described in section 4.5.4 of the SAP of the main study.

Time since first medical diagnosis/treatment, first surgical diagnosis and most recent surgical diagnosis in years defined as (randomization date – date of diagnosis)/365.25 will be summarized.

Presence within 2 months before screening and ongoing symptoms at baseline of the main study for the following symptoms will be summarized, by treatment group and overall: Dyspareunia, Dyschezia, Dysuria, Adenomyosis, Rectovaginal endometriosis nodes.

Endometriosis History will be reported in a listing.

6.3.7. Prior Medication

Not Applicable

6.3.8. Exposure and Compliance

6.3.8.1. Extent of treatment exposure in the extension study

Duration of treatment (in weeks and in days) will be summarized for each treatment group. Duration of treatment in Extension is defined as: [(date of last extension treatment administration as described in section 5.2.1) - (date of first administration in extension as collected in eCRF) +1] / 7 (weeks), [(date of last extension treatment administration as described in section 5.2.1) - (date of first administration in extension as collected in eCRF) +1] (days) .

Duration of treatment overall is defined as: [(date of last extension treatment administration as described in section 5.2.1) - (date of first administration in mains study as collected in eCRF) +1] / 7 (weeks), [(date of last extension treatment administration as described in section 5.2.1) - (date of first administration in main study as collected in eCRF) +1] (days) .

Time on extension study (in weeks and in days) will be summarized for each treatment group, defined as: [(end of extension study date as described in section 5.2.1) – (date of first administration in extension as collected in eCRF) +1.]/7 (weeks), [(end of extension study date as described in section 5.2.1) – (date of first administration in extension as collected in eCRF) +1.] (days).

Time on study overall (in weeks and in days) will be summarized for each treatment group, defined as: [(end of extension study date as described in section 5.2.1) – (date of first administration in main study as collected in eCRF) +1.]/7 (weeks), [(end of extension study date as described in section 5.2.1) – (date of first administration in main study as collected in eCRF) +1.] (days).

Exposure data will be reported in listings.

6.3.8.2. Compliance in the extension study

Linzagolix/Placebo Grey blister (200 mg or matching placebo), Linzagolix/Placebo Pink blister (75 mg or matching placebo) and ABT/Placebo compliances from the study treatment accountability page will be summarized on the extension treatment period and overall (main and extension treatment period) by treatment group.

Compliance in extension is defined as the total used count of Grey blister/Pink blister/ABT from the Month 12 or Withdrawal Extension accountability pages divided by end of treatment date in Extension – first dose date in Extension+1.

Compliance overall is defined as the sum of total used count of Grey blister/Pink blister/ABT from the Month 6 and Month 12 or Withdrawal Extension accountability pages divided by end of treatment date in Extension – Day 1 date+1.

If Linzagolix/Placebo and ABT/Placebo compliances from accountability data are missing, compliance will be computed from daily diary data:

Compliance will be computed as the number of days with pink tablet/grey tablet/red capsule taken *100 divided by the number of days in the period (end of treatment - first dose date in Extension+1 or end of treatment date – Day 1 +1 date for overall compliance). Data from “Today” will be used primarily. If data from today is missing, date from “Yesterday” will be considered. If the e-diary is not completed for a day (neither “Today” nor “Yesterday), it will be assumed that no drug was taken on that day.

Study treatment overdose and misuse will be reported in a listing.

Compliance will be reported in a listing.

6.4. Efficacy Evaluation

Efficacy analysis will be conducted using the Treatment Extension Analysis Set, the Follow-up Extension Analysis Set and the Per Protocol Extension Analysis Set when specified. Data from the main study, the extension study and the Month 6 Extension follow-up will be summarized and listed as relevant.

Efficacy endpoints will be derived in the same way as in the main study. The same criterion for defining a subject as being a responder by having a clinically meaningful reduction in DYS and in NMPP, along with a stable or decreased use of analgesics for EAP, will be used as per the criteria used in the main study.

6.4.1. **Meaningful Change Threshold Estimation**

6.4.2. **Primary efficacy analysis**

6.4.2.1. Primary Endpoint Specifications

The primary efficacy analysis aims to estimate the effect of linzagolix versus placebo on DYS and NMPP over the last 28 days up to and including the Month 12 visit or, for subjects who discontinued randomized treatment prior to the Month 12 visit, over the last 28 days of randomized treatment (i.e. 28-day period before last treatment administration date in Extension). Use of analgesic medication for EAP will be included in the responder definitions. A responder for each of the co-primary endpoints needs to demonstrate both a reduction in pain (DYS or NMPP, depending on the endpoint) and a stable or decreased use of analgesics for EAP. Any subject who does not meet both of these criteria will be defined as a non-responder.

For each of the co-primary endpoints, the criterion for defining a subject as a responder over the last 28 days of randomized treatment up to the Month 12 visit will include a reduction of 1.10 or greater from baseline in Dysmenorrhea and reduction of 0.80 or greater from baseline in Non-Menstrual Pelvic Pain, as well as stable or decreased use of analgesics for EAP, i.e. thresholds obtained at the Month 3 meaningful change threshold analysis. The thresholds obtained at the Month 6 meaningful change threshold analysis will also be used: reduction of 1.25 or greater for Dysmenorrhea and reduction of 0.85 for Non-Menstrual Pelvic Pain.

Mean pelvic pain scores for DYS and for NMPP will be calculated by averaging over the corresponding 28 calendar days immediately prior to and including the last treatment administration day. DYS will use days with uterine bleeding, defined as those days on which the subject records any uterine bleeding or spotting in the subject eDiary; NMPP will use days with no uterine bleeding. If a subject's mean score for DYS is undefined numerically because her daily eDiary reports indicate that she did not experience uterine bleeding on any days during the 28 calendar day period, then the mean score for DYS will be set equal to zero (which reflects the absence of any DYS during that reporting time period). Similarly, if a subject's diary reports indicate that she only experienced days with uterine bleeding during the period, then the mean score for NMPP will be set equal to zero. For subjects who discontinue treatment prior to Month 12 the last available observations prior to discontinuation will be used, in order to estimate the treatment effect while under treatment, that is the 28 calendar days immediately prior to and including the last dose date. The baseline mean overall pelvic pain scores for DYS and NMPP will be calculated by averaging over the two baseline menstrual cycles (as defined in section 6.2.2), which may not be exactly 28 days each. For both DYS and NMPP, responses of "None," "Mild," "Moderate," and "Severe" will be assigned a score of 0, 1, 2, and 3, respectively.

For the assessment of stable or decreased use of analgesics for EAP (assessed separately for DYS and NMPP), the analgesic use for any defined period will be based on the mean of the total pill count for each class of rescue analgesics (endometriosis-associated). The total pill count for each class of rescue analgesic is the sum of the pill count of the corresponding class of rescue analgesic, as reported in the eDiary during the time period of interest. Baseline analgesic use will be calculated as the mean of the daily pill count of analgesics over the two baseline menstrual cycles (as defined in section 4.5.2 of main study SAP). For the purposes of determining a stable or decreased use of analgesics, the averaging will be done over the same calendar days as used for the pelvic pain scores (i.e. for DYS days with uterine bleeding, defined as those days on which the subject records any uterine bleeding or spotting in the subject eDiary; for NMPP days with no uterine bleeding). The evaluation of stable or decreased use of analgesics will be done per the specification in 9.1 9.1 Appendix A.

6.4.2.1.1. **Primary Efficacy Analysis**

The primary efficacy analysis will be conducted using the Treatment Extension Analysis Set.

The number and percentage of subjects with:

- Reduction of X for DYS,
- Reduction of X for NMPP,
- Stable or decreased use of analgesics for EAP during bleeding days, during non-bleeding days, and overall,
- Reduction of X for DYS and stable or decreased use of analgesics for EAP,
- Reduction of X for NMPP and stable or decreased use of analgesics for EAP,

will be presented.

There may be missing data during the screening period and whilst under treatment, for example, missed days of completing the eDiary. The primary analyses will use observed data only in such cases, provided that a minimum number of completed daily eDiary entries are available. This effectively assumes that the individual values such as daily eDiary assessments (observed or not) are independent of being missing. Subjects who have less than the minimum number of days available will be excluded from the analysis. This is valid under the assumption that such data is MAR, conditional on the baseline value.

The required minimum number of completed daily eDiary entries will be set to 12 days of each 28-day period (two Baseline menstrual cycles and the 28-day period prior to Month 12), i.e., 43% of non-missing assessments for the primary analysis, consistent with the use of 3 days per week as the minimum number of completed diary entries as suggested in recent research ((Griffiths & al, 2018), (Cappelleri & Bushmakin, Biopharmaceutical Report, 2020), (Cappelleri & Bushmakin, Biopharmaceutical Report, 2021)). The analysis will be repeated using subjects with at least 75% (21 days) and 35% (10 days) of completed daily eDiaries for DYS, NMPP and analgesic use.

The primary efficacy analysis will be repeated on the Per Protocol Extension Analysis Set.

6.4.2.2. Sensitivity analysis

Due to the war situation in Ukraine, data from subjects in Ukraine sites may be incomplete, missing or uncleaned. A sensitivity analysis of the primary endpoint analysis will be performed, excluding data collected after 24FEB2022 for subjects from Ukraine sites. An additional listing including subjects from Ukraine only will be provided.

6.4.3. Secondary/other/exploratory analysis

All secondary efficacy endpoints will be summarized by descriptive statistics for each treatment group, for each time point, including summaries of change from baseline when applicable.

Values for all endpoints that are collected daily using the eDiary (from Section 6.4.3.1 to Section 6.4.3.24) will be based on the 28 calendar days immediately prior to and including the day of the corresponding visit or prior to and including the last treatment administration date for Month 12, or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to the visit in question (or fewer if treatment is stopped less than 4 weeks after first dose date), in order to estimate the treatment effect while under treatment. The last 28 days on treatment will be used at all subsequent scheduled visits for those discontinued subjects. Descriptive summaries for each 28-day period will be performed in two ways however:

- Once including only values of 28 days prior to Month X, i.e. using the last 28 days prior to Month X eCRF visit date for subjects who have not discontinued up to that month. If subjects discontinued prior to Month X the corresponding value will be missing from the summary at Month X;
- Once applying the while on treatment strategy, i.e. using the last 28 days prior to Month X eCRF visit date for subjects who have not discontinued up to that month, and for subjects who discontinued prior to Month X, the last 28 days prior to treatment discontinuation will be used. For all subsequent timepoints (Month X+1, etc.) the same last 28 days prior to treatment discontinuation will be used.

Corresponding baseline values will be calculated based on the two baseline menstrual cycles, which may not be exactly 28 days each.

The values for other endpoints (monthly and 3-monthly questionnaires from Section 6.4.3.25 to Section 6.4.3.32) are defined as the value at the corresponding visit or value falling into the corresponding visit window as described in section 5.5. For these other endpoints, descriptive summaries by visit will be performed in two ways, once including values at the corresponding visit or value falling into the corresponding visit window as described in section 5.5, and once applying the while on treatment strategy, i.e., including values from the discontinued visits at each next scheduled visit.

For endpoints based on daily ediary data, analyses will use observed data only in such cases, provided that a minimum number of 43% (at least 12 days of each 28-day period) completed daily eDiary entries are available. Subjects who have less than the minimum number of days available will be excluded from the analysis. This is valid under the assumption that such data is MAR, conditional on the baseline value.

6.4.3.1. Change from baseline to Month 12 in DYS (VRS) and in NMPP (VRS)

Mean pelvic pain scores for DYS and for NMPP for each subject will be calculated in the same way as for the primary endpoints. The change from baseline to Month 12 (the last 28 days of randomized treatment up to the Month 12 visit, will be defined as the last 28 days prior to and including the last treatment administration date as defined in Section 5.2.1, or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to Month 12) in DYS using the VRS, and the change from baseline to Month 12 (the last 28

days of randomized treatment up to the Month 12 visit, will be defined as the last 28 days prior to and including last treatment administration date as defined in Section 5.2.1 or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to Month 12) in NMPP using the VRS.The mean pelvic pain scores for DYS and NMPP and change from baseline will be descriptively summarized. Summary will be repeated on the Per Protocol Extension Analysis Set.

Cumulative distribution functions (CDF) for change from baseline at Month 12 for DYS and NMPP will be provided, with separate lines for each treatment group. The x-axis will present the different values for the DYS or NMPP change from baseline, and the y-axis will present the proportion of subjects reaching each value of change. Vertical lines of the relevant responder thresholds will be displayed on the plots.

6.4.3.2. Change from baseline to Month 12 in dyschezia (Numeric Rating Scale - NRS)

Mean dyschezia scores for each subject will be calculated by averaging over the corresponding 28 calendar days immediately prior to and including the day of the last treatment administration as defined in Section 5.2.1 (or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to Month 12). The baseline mean dyschezia score will be calculated by averaging scores over the two baseline menstrual cycles. The mean dyschezia score and change from baseline will be descriptively summarized. Summary will be repeated on the Per Protocol Extension Analysis Set.

The number and percentage of subjects with a reduction of 1.5 from baseline to Month 12 for dyschezia will be presented. The reduction will be defined in a similar way as for the primary endpoint but using dyschezia scores at the Month 12 timepoint.

6.4.3.3. Change from baseline to Month 12 in overall pelvic pain (NRS)

The change from baseline to Month 12 (the last 28 days of randomized treatment up to the Month 12 visit, defined as the last 28 days prior to and including last treatment administration date as defined in Section 5.2.1 or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to Month 12) in overall pelvic pain using the NRS will be descriptively summarized. The baseline will be computed as the mean of the overall pelvic pain score over the two baseline menstrual cycles. Summary will be repeated on the Per Protocol Extension Analysis Set.

The number and percentage of subjects with a reduction of 2.7 from baseline to Month 12 for Overall Pelvic Pain will be presented. The reduction will be defined in a similar way as for the primary endpoint, but for Overall Pelvic Pain score at the Month 12 timepoint.

6.4.3.4. Change from baseline to Month 12 in the interference of pain with the ability to perform daily activities, measured using the pain dimension of the Endometriosis Health Profile-30 (EHP-30)

The EHP-30 pain dimension consists of 11 items each addressing the effect of pain on various activities and each assessed on a 5-point scale (0=Never through to 4=Always). The EHP-30 Pain Impact Domain comprises the following items:

During the last 4 weeks, because of your endometriosis, how often have you...

1. Been unable to go to social events because of the pain?
2. Been unable to do jobs around the house because of the pain?
3. Found it difficult to stand because of the pain?
4. Found it difficult to sit because of the pain?
5. Found it difficult to walk because of the pain?
6. Found it difficult to exercise or do the leisure activities you would like to do because of the pain?
7. Lost your appetite and/or been unable to eat because of the pain?
8. Been unable to sleep properly because of the pain?
9. Had to go to bed/lie down because of the pain?
10. Been unable to do the things you want because of the pain?
11. Felt unable to cope with the pain?

This endpoint shall be scored as per the Appendix B in Section 9, resulting in a score on a scale from 0 (best possible health status) to 100 (worst possible health status). The score will be computed as the sum of raw scores of each item (ranging from 0 to 4) divided by the maximum possible raw score (11*4), multiplied by 100. EHP-30 score at baseline and Month 12 and change from baseline will also be descriptively summarized. Summary will be repeated on the Per Protocol Extension Analysis Set.

The number and percentage of subjects with a reduction of 28 from baseline to Month 12 for the EHP-30 Pain Dimension score will be presented.

6.4.3.5. Change from baseline to Month 12 in dyspareunia (VRS)

Responses to the daily dyspareunia questions will be scored as follows. Responses on days where the subject was not sexually active for reasons other than their endometriosis will not be included in the analysis.

Response	Score
No pain during sexual intercourse.	0

I was able to tolerate the pain during sexual intercourse.	1
Intercourse was interrupted due to pain.	2
I avoided sexual intercourse because of anticipation of pain.	3

Mean dyspareunia scores for each subject will be calculated by averaging over the corresponding days during the 28 calendar days immediately prior to and including the last treatment administration date as defined in Section 5.2.1 (or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to Month 12). The baseline mean dyspareunia score will be calculated by averaging scores over the two baseline menstrual cycles.

Dyspareunia scores will be summarized using the TEAS, PP EAS and for the subgroup of subjects who have a mean dyspareunia score > 1 at baseline.

The number and percentage of subjects with a reduction of 0.9 from baseline to Month 12 for Dyspareunia will be presented. The reduction will be defined in a similar way as for the primary endpoint, but for Dyspareunia score and for the Month 12.

6.4.3.6. No analgesic use / no opiate use for EAP during the preceding 4-week period at each scheduled assessment

The analysis of the proportion of subjects reporting no analgesic use for EAP, and the proportion of subjects reporting no opiate use for EAP during the preceding 4-week period at each scheduled assessment will be conducted using descriptive statistics.

In addition to analgesic use for EAP as collected in the eDiary, concomitant medications in the study will be reviewed and medications to be considered as analgesic use for endometriosis associated pain will be confirmed by the Sponsor and be provided in an excel file prior to Database Lock. They may include any medication with the ATC codes from WHO drug dictionary version March 2016 as listed in Table 3

Table 3 List of ATC codes for analgesics and opioids

ATC code	Description
A03D	Antispasmodics in combination with analgesics

A03EA	Antispasmodics, psycholeptics and analgesics in combination
C03AH	Thiazides, combinations with psycholeptics and/or analgesics
M01	Anti-inflammatory and anti-rheumatic products
M02	Topical products for joint and muscular pain
M03	Muscle relaxants
N02	Analgesics
N07BC	Drugs used in opioid dependence
S02DA	Analgesics and anesthetics

Among those analgesic medications, all medications with Pharmacological Subgroup (3rd level of the ATC classification) equal to 'OPIOIDS' (ATC code = N02A) will be considered as opiate medications. Other analgesic medications will be considered as non-opiate medications.

In addition to analyzing the absence of analgesic use for EAP, the amount of analgesics used for each 4-week period up to Month 12 will be summarized as a continuous variable, including the change from baseline. This analysis will be based on e-diary data only, as subjects did not record analgesic intake in the concomitant medication page on a tablet-by-tablet basis.

Due to a low number of subjects using any opioids, opioids use will not be analyzed as a continuous variable, only a listing with by subject opioid use mean daily pill count will be provided.

The baseline amount of analgesic used will be computed by averaging the amount used during the two baseline menstrual cycles.

Summary will be repeated on the Per Protocol Extension Analysis Set.

6.4.3.7. Responder rate at scheduled visit other than Month 12 visit, for DYS and NMPP (VRS)

The responder rate at each scheduled visits other than Month 12 visit, for DYS and NMPP will be analyzed the same way as described for the primary analysis endpoint in Section 6.4.2.

6.4.3.8. Change from baseline to each scheduled assessment in mean pelvic pain scores for DYS, NMPP and overall pelvic pain, during the previous 4-week period assessed on the NRS and VRS

The change from baseline to each scheduled assessment in mean pelvic pain scores for DYS, NMPP and overall pelvic pain will be descriptively summarized.

6.4.3.9. Change from baseline to each scheduled assessment in the number of days with moderate to severe pelvic pain during the previous 4-week period assessed on the VRS

The actual value and change from baseline of number of days with moderate or severe pelvic pain collected in the e-diary on the VRS will be summarized for each 28-day period. The baseline value will be computed by averaging the number of days with moderate or severe pelvic pain of the two baseline menstrual cycles.

6.4.3.10. Change from baseline to each scheduled assessment in the mean worst pelvic pain score defined as the mean of the 5 highest daily pain scores reported during the previous 4-week period assessed on the NRS

The actual value and change from baseline of the mean worst pelvic pain score, defined as the mean of the 5 highest daily pain scores reported during each 28-day period will be summarized for each 28-day period. The baseline mean worst pelvic pain score will be the average of the mean pelvic pain score of each of the two baseline menstrual cycles.

If less than 5 days of pain score data is available, the mean worst pelvic pain will be defined as the mean of the available daily pain scores.

6.4.3.11. Change from baseline to each scheduled assessment in mean daily dyspareunia scores reported during the previous 4-week period on the dyspareunia VRS

The actual value and change from baseline in mean daily dyspareunia scores will be summarized as a continuous variable for each 28-day period.

Subjects not sexually active for reasons other than endometriosis will have missing values for the corresponding 4-week periods. Subjects not sexually active for reasons other than endometriosis at baseline will be excluded from the analysis.

6.4.3.12. Change from baseline to each scheduled assessment in mean daily dyschezia scores reported during the previous 4-week period assessed on the dyschezia NRS

The actual value and change from baseline in mean daily dyschezia scores will be summarized as a continuous variable for each 28-day period.

6.4.3.13. Change from baseline to each scheduled assessment in non-opioid, opioid and combined analgesic use for EAP during the previous 4-week period based on pill count in the eDiary

Non-opioid, opioid and combined analgesic use for EAP will be measured using the mean of daily pill count collected in the eDiary over each 28-day period. For non-opioid and combined analgesic use, descriptive summary (actual values and changes from baseline) for each period will be performed. Due to a low number of subjects using any opioids, opioids use will not be analyzed as a continuous variable, only a listing with by subject opioid use mean daily pill count will be provided.

6.4.3.14. Change from baseline to each scheduled assessment in opioid analgesic use for EAP as reported in the eDiary during the previous 4-week period based on morphine milligram equivalent (MME)

Opioid analgesic use for EAP will also be assessed based on morphine milligram equivalent (MME). The mean daily amount for each 28-day period reported in eDiary as pill count will be converted in MME.

Conversion to MME by country is described in Table 4.

Table 4 Morphine Milligram Equivalents for Narcotic Analgesics

Country	Permitted rescue analgesic: Narcotic analgesic local equivalent	Conversion in morphine milligram equivalents
Austria	tramadol 37.5mg + paracetamol 325mg	3.75 MME
Bulgaria	tramadol 37.5mg + paracetamol 325mg	3.75 MME
Czech Republic	codeine 30mg	4.125 MME

	paracetamol 500 mg+ codeine 30 mg tramadol 37.5mg + paracetamol 325mg	
France	paracetamol 500 mg+ codeine 30 mg tramadol 37.5mg + paracetamol 325mg	4.125 MME
Hungary	paracetamol 500 mg+ codeine 30 mg codeine 30mg tramadol 37.5mg + paracetamol 325mg	4.125 MME
Poland	tramadol 37.5mg + paracetamol 325mg	3.75 MME
Romania	codeine 30mg paracetamol 500 mg+ codeine 30 mg	4.5 MME
Spain	paracetamol 500 mg+ codeine 30 mg tramadol 37.5mg + paracetamol 325mg	4.125 MME
Ukraine	No Narcotic Analgesic allowed	
US	5 mg hydrocodone + 300 mg acetaminophen	5 MME

No opioids are allowed in Ukraine. Subjects from Ukraine will therefore be excluded from the analysis in MME. If some opioids are nevertheless recorded for subjects from Ukraine, they will not be considered, as the conversion in MME would be unknown. Those opioids records will however be considered for other analgesic use analyses not requiring conversion in MME.

Due to a low number of subjects using any opioids, opioids use will not be analyzed, only a listing with by subject mean daily opioid use in MME will be provided.

6.4.3.15. Change from baseline to each scheduled assessment in the number of days of analgesic use (including any class) for EAP during the previous 4-week period as assessed in the eDiary

The actual value and change from baseline in the number of days with analgesic use for EAP collected in the e-diary will be summarized for each 28-day period. The baseline value will be computed by averaging the number of days with analgesic use of the two baseline menstrual cycles.

6.4.3.16. Change from baseline to each scheduled assessment in the number of days of opioid analgesic use for EAP during the previous 4-week period as assessed in the eDiary

The actual value and change from baseline in the number of days with opioid analgesic use for EAP collected in the e-diary will be calculated for each 28-day period. The baseline value will be computed by averaging the number of days with opioid analgesic use of the two baseline menstrual cycles.

Due to a low number of subjects using any opioids, number of days with opioid analgesic use will not be analyzed, only a by subject listing will be provided.

6.4.3.17. Change from baseline to each scheduled assessment in the number of pelvic pain-free days (assessed on the VRS) during the previous 4-week period

The actual value and change from baseline of number of pelvic pain-free days collected in the e-diary will be summarized for each 28-day period. The baseline value will be computed by averaging the number of pelvic pain-free days of the two baseline menstrual cycles.

6.4.3.18. Change from baseline to each scheduled assessment in ability to perform daily activities during the previous 4-week period, as assessed in the eDiary (daily function NRS)

Daily activities score for each subject will be calculated by averaging over the corresponding 28 calendar days immediately prior to and including the day each visit (or the 28 calendar days

immediately prior to and including the last dose date for subjects who discontinue treatment prior to Month 12). The baseline mean of daily activities score will be calculated by averaging over the two baseline menstrual cycles. The actual value and change from baseline of daily activities score will be summarized as a continuous variable.

6.4.3.19. Change from baseline to each scheduled assessment in the number of days with no difficulty in doing daily activities due to EAP during the previous 4-week period as assessed in the eDiary (daily function NRS)

The actual value and change from baseline of number of days with no difficulty in doing daily activities due to EAP collected in the e-diary will be summarized for each 28-day period. The baseline value will be computed by averaging the number of days of the two baseline menstrual cycles.

6.4.3.20. Change from baseline to each scheduled assessment in the number of days when dyspareunia was a problem during the previous 4-week period (including days when sexual intercourse was avoided because of anticipation of pain) as assessed on the dyspareunia VRS

The actual value and change from baseline of number of days with answer to Sexual Intercourse in the last 24H questionnaire is "Intercourse was interrupted due to pain" or "No, I avoided sexual intercourse because of anticipation of pain" collected in the e-diary will be summarized for each 28-day period. The baseline value will be computed by averaging the number of days of the two baseline menstrual cycles.

6.4.3.21. Change from baseline to each scheduled assessment in the number of days when sexual intercourse was avoided because of anticipation of pain during the previous 4-week period as assessed on the dyspareunia VRS

The actual value and change from baseline in the number of days with answer to Sexual Intercourse in the last 24H questionnaire is "No, I avoided sexual intercourse because of anticipation of pain" collected in the e-diary will be summarized for each 28-day period. The baseline value will be computed by averaging the number of days of the two baseline menstrual cycles.

In addition, the proportion of days when sexual intercourse was avoided because of anticipation of pain will be also summarized for actual values and changes from baseline.

The proportion is defined as:

Number of days when sexual intercourse was avoided because of anticipation of pain/ (Number of days in period – Number of days with missing data – Number of days with no sexual intercourse for other reasons)

The number of days in each period will be equal to 28, except at baseline, for which it will be the number of days in each baseline menstrual cycle.

6.4.3.22. Change from baseline to each scheduled assessment in the number of days with uterine bleeding (including spotting) during the previous 4-week period measured by eDiary

The actual value and change from baseline in the number of days with uterine bleeding ("Bleeding", "Spotting", "Heavy Bleeding") collected in the e-diary will be summarized for each 28-day period. The baseline value will be computed by averaging the number of days with uterine bleeding during the two baseline menstrual cycles.

6.4.3.23. Change from baseline to each scheduled assessment in the number of days when school or work was missed due to EAP in the previous 4-week period as reported in the eDiary

The actual value and change from baseline in the number of days when school or work was missed due to EAP as collected in the e-diary will be summarized for each 28-day period. The baseline value will be computed by averaging the number of days during the two baseline menstrual cycles when school or work was missed due to EAP.

6.4.3.24. Change from baseline to each scheduled assessment in the number of days when the subject had to go to bed or lie down due to EAP in the previous 4-week period as reported in the eDiary

The actual value and change from baseline in the number of days when the subject had to go to bed or lie down due to EAP as collected in the e-diary will be summarized for each 28-day period. The baseline value will be computed by averaging the number of days during the two baseline menstrual cycles when the subject had to go to bed or lie down due to EAP.

6.4.3.25. Change from baseline to each scheduled assessment in the Pain, Control and powerlessness, Emotional well-being, Social support, Self-image dimensions and the Modular sexual relationship questionnaire of EHP-30 scores

The EHP-30 is a disease-specific self-administered questionnaire used to measure health-related quality of life in women with endometriosis. The EHP-30 is composed of two parts: a core questionnaire containing five scales that are applicable to all women with endometriosis and a

modular part containing six scales which do not necessarily apply to all women with endometriosis. This study will employ the Core EHP-30 and modular section C (Part 2) as outlined in Appendix D of protocol.

The questionnaire is composed of five scales and of the sexual relationship scale in the modular part:

- Pain (Questions 1-11): See Section 6.4.3.4 for items included in Pain dimension
- Control and powerlessness (Questions 12-17):
    - Generally felt unwell?
    - Felt frustrated because your symptoms are not getting better?
    - Felt frustrated because you are not able to control your symptoms?
    - Felt unable to forget your symptoms?
    - Felt as though your symptoms are ruling your life?
    - Felt your symptoms are taking away your life?
- Social support (Questions 24-27):
    - Felt unable to tell others how you feel?
    - Felt others do not understand what you are going through?
    - Felt as though others think you are whining?
    - Felt alone?
- Emotional well-being (Questions 18-23):
    - Felt depressed?
    - Felt weepy/tearful?
    - Felt miserable?
    - Had mood swings?
    - Felt bad-tempered or short-tempered?
    - Felt violent or aggressive?
- Self-image (Questions 28-30):
    - Felt frustrated that you cannot always wear the clothes you would choose?
    - Felt your appearance has been affected?
    - Lacked confidence?
- Modular sexual relationship questionnaire

Refer to Appendix B in Section 9.2 9.2 for scoring. Each scale is standardized on a scale of 0 – 100, where 0 indicates the best health status and 100 the worst health status. Scale scores for each scale are calculated from the total of the raw scores of each item in the scale divided by the maximum possible raw score of all the items in the scale, multiplied by 100.

Each item of each scale will be summarized by category at each visit. The actual value and change from baseline of each scale score will be summarized as a continuous variable.

6.4.3.26. Change from baseline to each scheduled assessment in the Health-Related Productivity Questionnaire (HRPQ) scores

The Health-Related Productivity Questionnaire (HRPQ) is a validated, 9-item, self-reported questionnaire that has been used to evaluate health-related productivity.

The HRPQ includes items on employment status; effect of health issues or treatment on working scheduled hours (absenteeism); effect of health issues or their treatment on work output (presenteeism); effect of health issues or their treatment on planned hours of household chores; effect of health issues or their treatment impact work output for household chores actually performed; how long since health issues developed; and effect of health issues on life.

The questionnaire follows a skip pattern so that subjects can answer only the items applicable to them according to whether they work outside the home (eg, full- or part-time employment). Two subject groups are defined: employed and household (employed and not employed, combined).

See Appendix C in Section 9.3 9.3 for HRPQ Scoring.

At Day 1, the following will be summarized:
- Employment status,
- Time since symptoms developed,
- Number of subjects and time for which Endometriosis symptoms or its treatment(s) forced to work part-time when wanted to work full-time,
- Number of subjects and time for which Endometriosis symptoms or its treatment(s) kept from having a job when wanted to work full-time,
- Number of subjects and time for which Endometriosis symptoms or its treatment(s) kept from having a job when wanted to work part-time.

The following scores (actual values and changes from baseline) will be summarized at each visit (from baseline to Month 6 Extension follow-up):
- For “Employed” group:
    - Number of hours of work lost due to absenteeism (“How many hours of work did you miss because of illnesses/treatments the last week?”)
    - Number of hours of work lost due to presenteeism (“For the hours that you did work during the past week, how did illnesses/treatments impact your work output?”)
    - Total number of hours of work lost
    - Percent of scheduled work lost due to absenteeism (Number of hours lost/Number of scheduled hours*100)
    - Percent of scheduled work lost due to presenteeism (Number of hours lost/Number of scheduled hours*100)
    - Percent of scheduled work lost in total (Number of hours lost/Number of scheduled hours*100)
- For “Household” group:

- Number of hours household work lost due to absenteeism ("How many hours of work did you miss because of illnesses/treatments the last week?")
- Number of hours household work lost due to presenteeism ("For the hours of household chores that you did during the past week, how did illnesses/treatments impact your work output?")
- Total number of hours of household work lost
- Percent of scheduled household work lost due to absenteeism (Number of hours lost/Number of scheduled hours*100)
- Percent of scheduled household work lost due to presenteeism (Number of hours lost/Number of scheduled hours*100)
- Percent of scheduled household work lost in total (Number of hours lost/Number of scheduled hours*100)

The HRPQ items at each visit will be presented in a by-subject listings, for both Treatment Extension Analysis Set and Follow-up Extension Analysis Set.

6.4.3.27. Number of non-study endometriosis related health visits, number of days in hospital and type of procedures performed based on Health Resource Utilization Questionnaire (HRUQ) at each scheduled assessment

The number of non-study endometriosis related health visits, number of subjects by type of clinician/clinic visit, number of subjects by type of therapeutic procedures, and number of nights spent in hospital will be summarized at each visit (from baseline to Month 6 Extension follow-up). In case of many clinician/clinic types and therapeutic procedures, types may be regrouped for the descriptive summaries.

6.4.3.28. Change from baseline to each scheduled assessment in the Physician/Subject Surgery Intention Question (PSIQ/SSIQ)

The PSIQ/SSIQ answers will be summarized as continuous at Month 6 and Month 12.

6.4.3.29. Change from baseline to each scheduled assessment in the PROMIS Fatigue – Short Form 6a

The PROMIS Fatigue Short Form 6a is composed of 6 items on 5-point scales (1-5). The total score is measured as the sum of answers of each item and will range from 6 to 30. The higher the total score, the more severe the symptom. Missing data will not be imputed.

Each item will be summarized by category at each visit (from Month 6 to Month 12). The total score will be summarized as a continuous variable.

The PROMIS Fatigue items at each visit will be presented in a by-subject listings, for both Treatment Extension Analysis Set and Follow-up Extension Analysis Set.

6.4.3.30. Change from baseline to each scheduled assessment in the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire

The EuroQoL 5-dimension questionnaire (EQ-5D) is a self-administered, generic utility instrument developed by the EuroQoL Group in 1990. The EQ-5D consists of 2 parts, a descriptive system of 5 dimensions and a 20-cm vertical visual analogue scale (VAS) with endpoints 0 and 100. It is collected by the subject in the eDiary from Month 6 to Month 12.

The descriptive system includes five single-item dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Subjects must choose between five levels of difficulty (from 1 to 5) in accomplishing tasks in each dimension. The health states will be described in terms of five-digit numbers based on the answers to each of the five questions. The states will then be converted to a single index score using the TTO (Time Trade-Off) method. The TTO method has been chosen since this is the only one available for the United States (US) and also because for economic studies where cost utility analysis is anticipated, most health economists are recommending a value set that has been derived using a choice-based method. An index score based on the individual dimensions will be calculated using a scoring algorithm (see Reference document EQ-5D-5L_UserGuide_2015.pdf) and the US Index from Crosswalk value set downloaded from the EuroQol website.

In the present study, the available US-specific scoring will be used (see Appendix D in Section 9. how to compute EQ-5D-5L crosswalk index values with SAS using the United States value set as an example).

Answers to each dimension will be summarized by category at each visit. The index value and VAS Score will be summarized as continuous variables (actual values and changes from baseline). The EQ-5D-5L items, VSA score and index value at each visit will be presented in a by-subject listings, for both Treatment Extension Analysis Set and Follow-up Extension Analysis Set.

6.4.3.31. Response at each scheduled assessment according to Patient Global Impression of Change (PGIC) (and Post-treatment Patient Global Impression of Change, PPGIC)

Responses to the Patient Global Impression of Change questionnaire range from 0- Very much worse to 6-Very much improved. Responses will be summarized by category at each visit (up to Month 6 Extension follow-up).

6.4.3.32. Change from baseline to each scheduled assessment in the monthly PGIS (mPGIS) score

Responses to the Patient Global Impression of Severity range from 0- No symptoms to 4-Severe. Responses will be summarized by category at each visit (up to Month 6 Extension follow-up).

6.4.3.33. Daily Patient Global Impression of Severity (dPGIS), Daily Event Cancelled, Daily Difficulty Sleeping

The dPGIS, Event Cancelled and Difficulty Sleeping daily diaries were collected for subjects enrolled prior to amended Protocol V4.0 only.

The dPGIS mean scores and changes from baseline, the number of days with difficulty sleeping, the number of days for which events were cancelled and the number of days with no event planned will be computed for each 4-week period and reported in listings only.

The dPGIS scores will be calculated by averaging over the corresponding 28 calendar days immediately prior to and including the day of each scheduled assessment (or prior to and including the last dose date for subjects who discontinue treatment).

6.5. Pharmacokinetic Evaluations

Pharmacokinetic analyses will be conducted using the Extensions Pharmacokinetic Set.

PK samples are collected at each monthly visit during the treatment extension period.

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

All plasma concentration data will be displayed in listings. PK assessment day and time, IMP intake status and IMP intake time on the day of PK assessment and on the previous days will be included in the listings.

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

6.6. Safety Evaluations

Summaries will be performed using the Extension Safety Analysis Set and the Follow-up Extension Safety Analysis Set.

Data from the main study (i.e. before Month 6), the extension study and the Month 6 Extension follow-up will be summarized and listed as relevant

6.6.1. Adverse Events

All AEs recorded during the course of the study will be coded according to the MedDRA dictionary (26.0) and assigned to a system organ class (SOC) and Preferred Term (PT). The NCI-CTCAE (version 4.3) will be used to grade the severity of AEs.

The following definitions will be used for the analysis of adverse events (AEs). All analysis described below will be based on the Treatment Emergent Adverse Events (TEAEs), unless otherwise specified.

	Definition
Treatment emergent adverse event (TEAE)	AEs with a start date on or after the first dose of extension study drug through 30 days after discontinuation of study drug or Month 12 visit date, or any event that was present at Month 6 but worsened in intensity or was subsequently considered drug-related by the investigator through the end of the extension study
Treatment Related TEAE/AEs	LGX-related AEs, defined as having "definite, probable or possible" relationship to study drug ABT-related AEs, defined as having "definite, probable or possible" relationship to add-back therapy
Serious Adverse Events (SAEs)	Any AE with "Serious?" = Yes in the CRF "Adverse event" page.
Adverse Events Leading to Permanent Treatment Discontinuation	Any AE action taken = Drug Withdrawn in the CRF "Adverse event" page.
Adverse Events Leading to Death	Any AE with fatal outcome

Post-Treatment Adverse Events	Adverse events starting more than 30 days after end of treatment

TEAEs tables will be presented for the below periods/populations:

- Extension treatment period on Extension Safety Analysis Set
- Extension follow-up period on Follow-up Safety Analysis Set,
- Combined Extension treatment and follow-up period on Follow-up Safety Analysis Set
- Combined Main treatment period and Extension treatment period on Extension Safety Analysis Set:
- Combined Main treatment period and Extension treatment period on Safety Analysis Set
- Day 1 (from main study) to end of Extension follow-up period, or end of Main follow-up period for subjects not entering extension, on Safety Analysis Set

Post-treatment AEs tables will be presented for below periods/populations:

- Combined Extension treatment and follow-up period on Follow-up Safety Analysis Set
- Extension follow-up period on Follow-up Safety Analysis Set
- Day 1 (from main study) to end of Extension follow-up period, or end of Main follow-up period for subjects not entering extension, on Safety Analysis Set

All AEs tables will be presented for the below periods/populations:

- Day 1 (from main study) to end of Extension follow-up period, or end of Main follow-up period for subjects not entering extension, on Safety Analysis Set

Periods are defined in section 5.2

Tables based on Safety Analysis Set will use the following treatment groups, with the note that subjects can have a different time of treatment exposure (up to 6 months for subjects not in extension, up to 12 months for subjects entering extension):

- linzagolix 75 mg / linzagolix 75 mg
- linzagolix 200 mg with ABT / linzagolix 200 mg with ABT
- Placebo / linzagolix 75 mg (subject receiving placebo in main study and treated with linzagolix 75 mg in extension study)
- Placebo / linzagolix 200 mg with ABT (subject receiving placebo in main study and treated with linzagolix 200 mg with ABT in extension study)
- Placebo

If, for a subject not entering the Extension follow-up period, an AE occurs after Month 12-1 or treatment discontinuation, then the AE will be counted in the Extension treatment period.

For all study periods, an overall summary table will be prepared presenting, by treatment group, the number and percentage of subjects with

- any AE,
- any TEAE,
- any post-treatment AE (displayed only for the Extension follow-up period),
- Severe TEAE,
- any TEAE assessed by the Investigator as related to linzagolix ((definite, probable, or possible relationship),
- any TEAE assessed by the Investigator as related to add-back therapy ((definite, probable, or possible relationship),
- any TEAE leading to permanent discontinuation of IMP,
- any serious adverse event (SAE),
- any serious treatment emergent adverse event (Serious TEAE),
- any non-serious TEAE
- any serious treatment emergent adverse event (SAE) related to linzagolix,
- any serious treatment emergent adverse event (SAE) related to add-back therapy,
- any fatal TEAE (where outcome is “Fatal”)

In these tabulations, each subject will contribute only once (i.e., via the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes experienced.

Adverse events are summarized by subject incidence rates, therefore, in any tabulation, a subject contributes only once to the count for a given adverse event (SOC or preferred term).

For the Extension treatment period, Extension follow-up period and combined Extension treatment and follow-up period, the number and percentage of subjects with any treatment-emergent adverse event, with any treatment-emergent adverse events assessed by the Investigator as related to treatment (definite, probable, or possible relationship), and with any treatment-emergent serious adverse event and with any treatment-emergent non-serious adverse event will be summarized by treatment group and overall, by SOC and PT. Tabulation by severity will also be made. In these tabulations, each subject will contribute only once (i.e., the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes.

The number of events will be also displayed for summaries on TEAE and for analysis of TEAE and non-serious TEAE by SOC and PT.

The ongoing status of each Adverse Event will be derived based on Adverse Event Outcome as the following:

AE Outcome	**AE Ongoing Status**
Fatal	No
Not recovered/not resolved	Yes
Recovering/resolving	Yes
Recovered/resolved	No
Recovered/resolved with sequelae	No
Unknown	Unknown
Missing	Missing

The ongoing status collected in eCRF will be ignored.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

All adverse events occurring on study will be listed in subject data listings.

By-subject listings also will be provided for the following: Treatment Emergent Adverse event, serious Treatment Emergent adverse events; Treatment Emergent adverse events leading to permanent discontinuation of IMP and leading to permanent discontinuation of IMP leading to death.

6.6.2. Bone Mineral Density (BMD) by DXA

BMD of femoral neck, total hip and lumbar spine will be assessed by DXA at Baseline, Month 9 (if required) Month 12 and Month 6 of the extension follow-up (if required). Unacceptable DXA assessments (accepted=”No”) will not be summarized (hip, spine and femur considered separately).

In case of repeated values due to BMD loss ≥5%, the initial scan will be used in summaries. Initial and repeated scan values will be reported in the listings.

Calibrated values will be used if available, otherwise initial values will be considered.

BMD, expressed as both absolute values and Z-scores will be summarized at each visit in terms of actual values, changes from baseline, changes from baseline 2 (only for the subjects who are

in the placebo arm in the main study) for each anatomic location. For absolute values only, percent change from baseline, percent changes from baseline 2 (only for the subjects who are in the placebo arm in the main study) and 95% confidence interval for the mean percent change from baseline and for the mean percent change from baseline 2 within each group will be produced at each time point.

The definition of both baselines are described in section 6.2.2.

Percent change from baseline and percent change from baseline 2 to Month 9, Month 12 and Month 6 extension follow-up will be described and will also be summarized in categories of percentage with the following classes:

- No change or increase,
- Decrease ≤ 3%,
- Decrease > 3% and ≤ 5%,
- Decrease > 5% and ≤ 7%,
- Decrease > 7% and ≤ 8%,
- Decrease > 8%.

All data except unacceptable DXA measurements (accepted=”No”) will be listed.

Due to the war situation in Ukraine, data from subjects in Ukraine sites may be incomplete, missing or uncleaned. A sensitivity analysis of the BMD will be performed, excluding data collected after 24FEB2022 for subjects from Ukraine sites. An additional listing including subjects from Ukraine only will be provided.

6.6.3. **Laboratory Data**

Clinical laboratory values will be expressed using conventional SI units.

Hematology, coagulation parameters, chemistry and lipids were assessed at screening and at each visit during the extension treatment period (from M7 to M12), as well as at the M1 ExtFU and M3 ExtFU visits.

E2, progesterone (P4) and LH were assessed at each visit during the extension treatment period (from M6 to M12), as well as at M1 ExtFU and M3 ExtFU visits.

Serum levels of sex hormone-binding globulin (SHBG) were assessed on Month 6, Month 9 and Month 12 visits.

Blood samples were to be analyzed by the central laboratory. Due to the covid-19 situation, some samples may be collected by local laboratories.

For Hematology, coagulation parameters, chemistry and lipids, the actual value, change from baseline and change from baseline 2 (only for the subjects who are in the placebo arm in the

main study) will be summarized for each visit for each treatment group. In the event of repeated values, the last non-missing value per study day/time will be used.

Semi-quantitative laboratory results will be imputed as follows: "<X.X" will be imputed as "X.X/2" and ">X.X" will be imputed as "X.X".

Evaluation of shifts for changes from baseline and for changes from baseline 2 (only for the subjects who are in the placebo arm in the main study) to all visits according to the normal ranges with categories "Low", "Normal", "High" where available (for ALT, AST, ALP, Bilirubin, Albumin, Calcium, Creatine Kinase) and according to normal/abnormal/abnormal clinically significant information collected otherwise, will be provided.

For Liver Function Test (LFT) parameters (ALT, AST, ALP, total bilirubin, albumin), evaluation of shifts for changes from baseline will be extended by the worst (highest) on-treatment value (including unscheduled assessments) according to the normal ranges with categories "Low", "Normal", "High" will be provided.

For the lipid panel (Triglycerides, HDL, LDL, Total Cholesterol, LDL/HDL ratio), the percent change from baseline and the percent change from baseline 2 (only for the subjects who are in the placebo arm in the main study) to each on-study visit will also be summarized.

Assessments from local laboratories will not be included in summaries and shift tables, as normal ranges may not be comparable.

For serum levels of E2, P4, SHBG and LH, only the actual values at each time point will be summarized. Note: in the event of repeated values, the last non-missing value per study day/time will be used.

In addition, for E2, the proportion of subjects with the following categories:

- E2 <20 pg/mL,
- E2 between ≥20 and <60 pg/mL,
- E2 ≥60 pg/mL

at each visit and for each treatment group will be provided in tables and graphically (bar charts).

For E2, samples analysed after the period of long-term stability should be excluded from analysis.

The relationship between E2 serum levels and bone mineral density loss will be explored graphically in different ways:

- First, the E2 serum level measured at Month 12 will be plotted on the x-axis against the percent BMD change from baseline measured at Month 12 on the left side y-axis and the percentage of subjects with clinically meaningful reduction of DYS (resp. NMPP) with stable or decreased use of analgesics for EAP on the right side y-axis. Thresholds from the Month 3 Meaningful Change Threshold analysis will be used for DYS and NMPP. A second plot showing the BMD percent change from baseline 2 (for subjects who are in placebo arm in the main study) and reduction of DYS and NMPP from baseline 2 will be produced.

- Second, bar charts will be produced at each visit from Month 6 to Month 12 and presented with the percent BMD change from baseline to Month 12 on the y-axis and the proportion of subjects with the E2 categories described above on the x-axis. Similar graphs will be produced for each of the BMD sites (femoral neck, hip, and spine), and for the BMD percent change from baseline 2 (for subjects who are in placebo arm in the main study).
- Lastly, bar charts of the proportion of subjects with the E2 categories described above on the x-axis will be plotted against the percentage of responders according to the primary endpoint, using DYS and NMPP thresholds from the Month 3 Meaningful Change Threshold analysis. Bar charts with percentage of responders from baseline 2 will be shown as well.

For P4, since P4 above 10 nMol/L may suggest luteal activity and hence ovulation, the proportion of subjects with P4 >10.0 nMol/L at least once from Month 6 to Month 12 will also be provided in tables.

The number and percentage of subjects with cholesterol values in the following categories

- LDL ≥ 160 mg/dL
- LDL ≥ 190 mg/dL
- HDL < 40 mg/dL

will be reported at each visit.

Shift tables from baseline and shift tables from baseline 2 (only for the subjects who are in the placebo arm in the main study) to each visit will be provided for the following LDL and Triglycerides categories (after rounding to integer values if necessary).

LDL:

- 0: ≤ 130 mg/dL
- 1: 131 to 159 mg/dL
- 2: 160 to 189 mg/dL
- 3: ≥ 190 mg/dL

Triglycerides:

- 0: ≤ 150 mg/dL
- 1: 151 to 300 mg/dL
- 2: 301 to 500 mg/dL
- 3: 501 to 1000 mg/dL
- 4: >1000 mg/dL

Follicle-Stimulating Hormone (FSH) at local laboratory for subjects that do not resume menses at M3 ExFU visit will be summarized and listed.

All laboratory data will be provided in data listings. Day 1 Serum levels of the anti-müllerian hormone (AMH) and fasting glucose will be included in the listings.

A subset listing will be presented for all abnormal clinically significant laboratory values.

6.6.4. Vital Signs and Physical Examinations

Vital signs include: Height (cm), Weight (kg), Body Mass Index, Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg) and Heart Rate (beats/min).

Height is assessed at Screening (main study); Weight is assessed at Month 6, Month 9, Month 12, as well as at M3 ExtFU and M6 ExtFU visits. Other Vital Signs are assessed at every monthly visit during the extension treatment period and at Month 1, 3 and 6 from the extension follow-up period.

Physical Examination was to be assessed Month 6, Month 9, Month 12, as well as at M3 ExtFU and M6 ExtFU visits.

The actual value, change from baseline and change from baseline 2 (only for the subjects who are in the placebo arm in the main study) for each on-study evaluation will be summarized by treatment group for vital signs.

By-subject listings of vital sign measurements will be presented in data listings.

Physical examination results at each time point will be summarized by treatment group; Shifts from Baseline and shift from baseline 2 (only for the subjects who are in the placebo arm in the main study) in physical examination findings to each on study visit will also be presented.

All physical examination findings will be presented in a data listing.

6.6.5. Electrocardiogram

Local 12-lead ECG readings of QTcF are performed at every monthly visit during the extension treatment period, as well as Months 1,3 and 6 from the extension follow-up period.

Baseline will be defined as the highest QTcF value prior to first dose of the main study.

Baseline 2 will be defined as the highest QTcF value prior to first active dose of the extension study from screening to Month 6 (only for subjects in the placebo arm of the main study).

The actual value, change from baseline and change from baseline 2 (only for the subjects who are in the placebo arm in the main study) of ECG results will be summarized descriptively, as well as the number and percent of subjects with normal, abnormal and clinically significant abnormal results at each study visit by treatment group.

All ECG data for each subject will be provided in data listings.

6.6.6. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary. Frequencies and percentages will be presented for each treatment group and overall by the first level anatomical main (ATC 1) group and preferred name. Vitamin D and Calcium supplementation as collected in the eCRF at each visit will be summarized as well.

All medications administered between the date of the Month 6 visit and the date of the last dose of extension study drug, inclusive, (i.e., all medications starting or ongoing during the time interval) are concomitant to the extension treatment period.

Concomitant medications tables will be presented for the following periods: Month 6 to Month 12 (Extension treatment period) and Month 12 to Month 6 ExFU (Extension follow-up period) as defined in section 5.2.1.

The use of prior and concomitant medications will be included in a by-subject data listing.

6.6.7. Transvaginal Ultrasound (TVUS)

TVUS was to be performed at Month 6, Month 9, Month 12, as well as Month 3 and Month 6 of Extension Follow-up period.

The actual value, change from baseline and change from baseline 2 (only for subjects in the placebo arm in the main study) will be summarized by treatment group for uterus length, width, and depth in mm and corresponding uterine volume in cm3, endometrium thickness in mm.

The number and percentage of subjects with ovarian endometrioma with a diameter of 7 cm or greater, and development of any uterus, left ovary or right ovary abnormality over time will be presented by treatment group.

All TVUS data for each subject will be provided in data listings.

6.6.8. Other Examinations

6.6.8.1. Endometrial biopsy

Biopsies for histological assessment were obtained for each subject at the following timepoints:

- Month 6 or one at Month 12 if endometrium thickness via TVUS is > 5 mm
- Month 1 ExtFU, 3 ExtFU, or 6 ExtFU if not obtained at Month 12 or if the preceding biopsy diagnosis is different than “benign endometrium”

For biopsies with reported primary diagnosis “Hyperplasia” or “Malignant Endometrial Neoplasm” at other visits than screening, a second read of the biopsy was to be performed. If the diagnosis of the two reads was different, then the sample was to be re-read a 3rd time. In case of multiple readings, the following rules will be applied for the statistical analysis:

- If 2 readings out of 3 lead to the same diagnosis, one of these 2 records will be selected.

- Otherwise, the record corresponding to the most severe diagnosis should be selected considering the following order, from less severe to more severe: simple without Atypia hyperplasia < complex without Atypia hyperplasia < simple with atypia hyperplasia < complex with Atypia hyperplasia < endometrial malignant neoplasm < other malignant neoplasm.

In addition, in order to perform a quality check of the readings, 15% of biopsies were sent blinded for a second read when the primary diagnosis was “Benign Endometrium”. In case of multiple readings when the primary diagnosis from the first read is “Benign Endometrium”, this first read will be used for the analysis. Biopsies with a primary diagnostic 1 “Benign Endometrium” will be analyzed in the classification “Benign Endometrium without Hyperplasia or Atypia”.

A summary at each time point will be performed (number and percentage of subjects with normal, abnormal, not assessable).

Biopsy assessment will be summarized by classification (primary diagnosis 1) and primary diagnoses (diagnoses 2, 3 and 4) at each visit. Subjects will be counted only once for classification (primary diagnosis 1) and a subject could be in several diagnoses (e.g. if for example diagnoses 2 and 3 are fulfilled).

Possible results by classification (primary diagnosis 1) and primary diagnoses (diagnoses 2, 3 and 4) are:

- Benign Endometrium without Hyperplasia or Atypia: Proliferative, Atrophic, Metaplastic Changes, Secretory, Indeterminate, Inactive, Polyp, Endometritis, Menstrual phase, Other
- Hyperplasia: Simple with Atypia, Simple without Atypia, Complex with Atypia, Complex without Atypia
- Malignant Endometrial Neoplasm: Carcinoma, Sarcoma, Other Malignant.

If any diagnosis does not correspond to any on the list, the diagnosis will be coded as: Other Malignant if classification is Malignant Endometrial Neoplasm, and Other for any other classification.

Endometrial biopsy results, including multiple readings, will be reported in listings.

Due to the war situation in Ukraine, some biopsy samples may have been collected and analyzed by local laboratories. Those assessments will be flagged in the listings. Information about local biopsy assessment is reported in Data Management Close queries file. This file will be provided by data management department and reviewed by Sponsor. Biopsy assessments performed locally can be identified in the queries list from Endometrial Biopsy page, by subject and visit and by word search, with answer to query containing the word “local”.

6.6.8.2. Gynecological and Breast examination

Gynecological Examination was to be assessed at Month 6, Month 9 and Month 12, as well as Month 3 of the extension Follow-Up period.

Breast examination (by palpation) was to be performed at Month 6 and Month 12, as well as Month 3 of the extension Follow-Up period.

A summary at each time point will be performed (number and percentage of subjects with normal, abnormal, abnormal significant) for Gynecological and Breast Examinations.

Results will also be reported in listings.

6.6.8.3. PAP Smear

PAP Smear is collected at Screening. A listing of abnormality information and a listing of diagnosis results will be provided, including possible unscheduled assessments.

6.6.8.4. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS questionnaire prospectively assess the occurrence of treatment-emergent suicidal ideation and behavior.

Subjects completed:

- either the "Baseline" C-SSRS version, capturing lifetime history of suicidal ideation and behavior, for subjects who were still in screening period in the main study,

- or the "already enrolled subjects" C-SSRS version, for subjects already enrolled in the main or in the Extension study, and who were providing answers to the C-SSRS for the first time during the study

- the "since last study visit" C-SSRS version, dedicated to subjects for whom the C-SSRS was completed at the previous study visit, for use at all remaining study visits.

The "Baseline" C-SSRS version was to be completed during Screening, or at Day 1 if not done during Screening.

The number of subjects experiencing the following, at baseline and at any time post-baseline in the extension study, will be summarized for each month from Day 1 to Month 12 and from Month 6 up to Month 12. For Month 6 to Month 12 period, the "since study start" questions from already enrolled questionnaire will not be included, as it cannot be identify whether the event occurred between Day 1 and Month 6 or Month 6 and Month 12.

- Any suicidal ideation or behavior
    - Wish to be dead.
    - Non-specific active suicidal thoughts.
    - Active suicidal ideation with any methods (not plan) without intent to act.
    - Active suicidal ideation with some intent to act, without specific plan.
    - Active suicidal ideation with specific plan and intent.
- Any Suicidal Behavior
    - Actual attempt.

  - Interrupted attempt.
  - Aborted attempt.
  - Preparatory acts or behavior.
  - Completed suicide (Actual attempt leading to death) (not at baseline)
- Emergence of suicidal ideation.
- Worsening of suicidal ideation.
- Emergence of suicidal behavior.

Any suicidal ideation or behavior is defined as an answer "Yes" for at least one of five questions for suicidal ideation or for at least one of five questions for suicidal behavior.

Emergence of suicidal ideation/behavior is defined as having no suicidal ideation/behavior at baseline and having reported any type of suicidal ideation/behavior at any time post-baseline (including "Since Study Start" answers).

Worsening of suicidal ideation is defined to occur when the most severe suicidal ideation rating since study start at any time post-baseline is more severe than its rating at baseline. The Suicidal ideation rating is defined as the following, as recommended in the C-SSRS scoring and analysis guide in https://cssrs.columbia.edu/wp-content/uploads/ScoringandDataAnalysisGuide-for-Clinical-Trials-1.pdf:

Maximal suicidal ideation category during the period (baseline, post-baseline up to Month 12 FU period) where categories range from 0 to 5:

0. No ideation
1. Wish to be dead
2. Non-specific active suicidal thoughts.
3. Active suicidal ideation with any methods (not plan) without intent to act.
4. Active suicidal ideation with some intent to act, without specific plan.
5. Active suicidal ideation with specific plan and intent.

If data of suicidal ideation or behavior is missing at baseline then the subject will not be included in summaries of emergence or worsening of suicidal ideation or behavior. The "already enrolled subjects" C-SSRS version ("Prior to Entry Study") will be used as baseline for subjects already randomized at the time of C-SSRS questionnaire implementation.

Same analysis will be repeated on the extension follow-up period (from Month 1 to Month 6 of the Extension FU Period).

6.6.8.5. Time to the first post-treatment menses

The first post-treatment menses will be defined from the Vaginal Bleeding daily ediary, as the first day for which the subject recorded bleeding after the last treatment administration date of the extension study, i.e., the first day with "BLEEDING" or "HEAVY BLEEDING" after the last treatment administration date of the extension study.

Time to first post-treatment menses is defined as:

Time to first post-treatment menses (days) = (day of first post-treatment menses – last treatment administration date in extension) + 1

Only data from the follow-up extension period will be included, and the analysis will be provided on the Follow-up Extension Safety Analysis Set, by treatment group.

Subjects who have not recorded any bleeding up to the end of the follow-up extension period will be considered as right-censored data at the last ediary vaginal bleeding record date before the end of the extension follow-up period (as defined in section 5.2) with time of censoring = last non-missing ediary vaginal bleeding record date – last treatment administration date in extension +1.

The probability of subjects having bleeding will be displayed by treatment group in the form of cumulative probability curves estimated using the non-parametric Kaplan-Meier method. Point estimates and corresponding 2-sided 95% CIs using the Greenwood's variance estimate will be provided at 28 days, 56 days, 84 days, 112 days, 140 days, 168 days, 196 days after the last treatment administration date in extension. Percentiles (25th, 50th, and 75th) and corresponding 2-sided 95% CIs will also be provided; "N/A" will be presented for any of the percentiles not reached.

Subjects with or without first post-treatment menses, time to first post-treatment menses, end of study status and end of study date will be presented in a by-subject listing.

6.7. Unblinding of subjects

Subjects that were unblinded during the course of the study will be summarized and listed. The cumulative unblinding history report from IWRS will be provided by the Sponsor in an excel format. This file will only contain unblinding status but no treatment information.

6.8. Exploratory Analyses

Bone turnover markers will be analyzed on the Extension Safety Analysis Set.

Blood samples for exploratory bone biomarkers include, but may not be limited to, collagen type 1 β-carboxy-telopeptide (CTx), procollagen 1 Intact N-Terminal (P1NP), bone-specific alkaline phosphatase (B-ALP) and osteocalcin as part of clinical chemistry, and are collected at Month 6, Month 9 and Month 12 and Month 3 Extension Follow-up. These exploratory data will be kept blinded up to the unblinding of the database.

Actual values and changes from baseline will be summarized overtime by treatment group. Bone marker data will be reported in listings as well.

7. CHANGES TO PLANNED ANALYSES

The Follow-up Extension Analysis Set, defined in protocol as:

All subjects from the main study who completed the 6 months of treatment in the extension study and who entered the Post-Treatment Follow-Up Period. Subjects will be analyzed according to randomized treatment.

Is changed to:

All subjects from the main study who entered the extension study and received at least one dose of study drug with the exception of subjects whose Month 6 assessment subsequently met any of the discontinuation criteria, and who entered the Post-Treatment Follow-Up Period. Subjects will be analyzed according to randomized treatment.

The rationale for this modification is that subjects that entered the Follow-up period, even if they did not complete the 6 months of extension treatment should be followed up for efficacy.

Updates from SAP Amendments since SAP V1.0 are summarized in the table below:

SAP Version	Update description	SAP Section	Reason
V2.0	Assessments from Local Laboratories (due to Covid-19 situation) will be excluded from summary tables of laboratory data	Section 6.6.3	Local laboratories may not have comparable normal ranges, thus it does not make sense to pool them with central laboratory data in numeric summaries.
V2.0	Biopsy assessments from Local Laboratories (due to war situation in Ukraine) should be flagged in listings. Information is available in Data Management Closed Queries File.	Section 6.6.8.1	Due to war situation in Ukraine, there were some Biopsies assessed locally. This information should be incorporated in listings.
V2.0	Addition of listings for PAP Smear for both abnormality and diagnosis information.	Section 6.6.8.3	PAP Smear listings were missing from original SAP Version.
V3.0	All protocol deviations related to a particular subject will be presented in the data listings.	Section 4.2	There were PD records which had missing subject ID and thus were not

			related to any particular subject. These records were excluded in the listings.
V3.0	Added additional condition when imputing missing date for AE onset: The missing Day & Month will be replaced by "01 JAN.", unless other information provides evidence that the event should not be defined as treatment-emergent AE.	Section 6.2.6.2	When imputing the missing Day & Month for AE onset date, other information (time course and onset timing for events) may help provide evidence to define treatment-emergent AE.
V3.0	Assessments from the main study (i.e before Month 6) will be also displayed in the safety and efficacy tables and listings.	Section 6.4. Section 6.6	To provide more efficacy/safety information.
V3.0	The summary tables for HRPQ, HRUQ, PGIC, mPGIS will be summarized up to Month 6 Extension FU and not up to Month 12.	Section 6.4.3.26, Section 6.4.3.27, Section 6.4.3.31, Section 6.4.3.32	To provide more efficacy information.
V3.0	Added by-subject listings for HRPQ, PROMIS, EQ-5D-5L for follow-up extension analysis set.	Section 6.4.3.26, Section 6.4.3.29, Section 6.4.3.30	To provide more efficacy information.
V3.0	For AEs and post-treatment AEs, summary tables and tables by SOC and PT are presented for selected periods/population, not all periods/populations.	Section 6.6.1	Only TAEAs summary tables and tables by SOC and PT will be presented for all periods/populations.
V3.0	Not all measurements of Bone Mineral Density (BMD) by Dual-Energy X-ray Absorptiometry (DXA) will be presented. Only those	Section 6.6.2	Only acceptable measurement will be presented.

	measurements with an acceptable DXA measurement will be listed.		
V3.0	Added the summary table and listing for Follicle-Stimulating Hormone (FSH) at local laboratory for subjects that do not resume menses at M3 ExFU visit.	Section 6.6.3	Added as part of safety analyses.

8. REFERENCES

Not applicable

9. APPENDICES

9.1. Appendix A: Analgesic change during treatment period

Use of No Analgesics at Baseline		
Analgesic used during Screening	**Analgesic dose status at end of study**	**Assessment of Change**
None	None**	Stable/Decrease
	Narcotic analgesic and/or ibuprofen is started	Increase
Use of Only Ibuprofen at Baseline		
Analgesic uses at Baseline	**Analgesic dose status at end of study**	**Assessment of Change**
ibuprofen	Dose stopped, decreases, or is stable**	Stable/Decrease
	Dose increases by 15% or more	Increase
	Narcotic analgesic is substituted or added	Increase
Use of Only Narcotic Analgesic at Baseline		
Analgesic uses at Baseline	**Analgesic dose status at end of study**	**Assessment of Change**
Narcotic analgesic	Dose stopped, decreases, or is stable**	Stable/Decrease
	Dose stopped and ibuprofen substituted (any dose)	Stable/Decrease
	Dose decreases and ibuprofen added (any dose)	Stable/Decrease

	Dose stable and ibuprofen added (any dose)**	Increase
	Dose increases by 15% or more	Increase
Use of Ibuprofen and Narcotic Analgesic at Baseline		
Analgesic uses at Baseline	**Analgesic dose status at end of study**	**Assessment of Change**
ibuprofen + narcotic analgesic	Ibuprofen dose stops + narcotic analgesic use stops, decreases, or is stable**	Stable/Decrease
	Ibuprofen use stops + narcotic analgesic dose increases by more than 15%	Increase
	Ibuprofen dose decreases + narcotic analgesic use stops, decreases, or is stable**	Stable/Decrease
	Ibuprofen dose decreases + narcotic analgesic dose increases by more than 15%	Increase
	Ibuprofen dose stable + narcotic analgesic use stops, decreases, or is stable**	Stable/Decrease
	Ibuprofen dose stable + narcotic analgesic dose increases by more than 15%	Increase

	Ibuprofen dose increases by more than 15% + narcotic analgesic use stops	Stable/Decrease
	Ibuprofen dose increases by more than 15% + narcotic analgesic dose decreases	Stable/Decrease
	Ibuprofen dose increases by more than 15% + narcotic analgesic dose is stable**	Increase
	Ibuprofen dose increases by more than 15% + narcotic analgesic dose increases by 15% or more	Increase

**Stable =Dose is the same as the screening dose or increases by less than or equal to 15% of the screening dose. In addition, a subject can increase the monthly total dose of analgesics by one pill of analgesic (either ibuprofen or narcotic) and still be considered stable.

9.2. Appendix B: EHP-30 Scoring

The mapping of the response categories for the EHP-30 core questionnaire and the modular questionnaire is as follows:
0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often, 4 = Always
For the modular questionnaire, records indicating "Not Applicable" will be excluded from summary/analysis.

Missing data will not be imputed.

The EHP-30 core questionnaire is structured into the following five dimensions.
1. Pain (Questions 1 – 11)
2. Control and Powerlessness (Questions 12 – 17)
3. Emotional Well-Being (Questions 18 – 23)
4. Social Support (Questions 24 – 27)
5. Self-Image (Questions 28 – 30)

Each dimension for the core and modular questionnaire is calculated on a scale from 0 to 100.
0 = best possible health status as measured by the questionnaire; 100 = worst possible

health status as measured by the questionnaire. Within each dimension, assessment will be based on the following equation:

Sum of scores for each dimension / 4 (maximum score per item) * number of items in the dimension

Sum of the scores for each item in the dimension
Core questionnaire: Pain
((Ql + Q2 + Q3 + Q4 + Q5 + Q6 + Q7 + Q8 + Q9 + Q10 + Q11)/44) × 100
2. Core questionnaire: Control and Powerlessness
((Q12 + Q13 + Q14 + Q15 + Q16 + Q17)/24) × 100
3. Core questionnaire: Emotional well-being
((Q18 + Q19 + Q20 + Q21 + Q22 + Q23)/24) × 100
4. Core questionnaire: Social Support
((Q24 + Q25 + Q26 + Q27)/16) × 100
5. Core questionnaire: Self-Image
((Q28 + Q29 + Q30)/12) × 100
Modular questionnaire: Sexual intercourse
((C1 + C2 + C3 + C4 + C5)/(total or 20)) × 100
For Modular questionnaire: Sexual intercourse, if a "not applicable" box is checked for one or more of the five items (Questions C1 – C5), the score is calculated by omitting those "not applicable" items from the numerator and the denominator.
If any of the components of a dimension on the core or modular questionnaire is missing, no score will be calculated for that dimension. For example, if answer for Q1 is missing, no score for Core questionnaire: Pain is calculated. If answer for C1 is missing, no score for Modular questionnaire: Sexual intercourse will be calculated.

9.3. Appendix C: HRPQ Scoring

Data Cleaning
1. No imputation of data should be conducted. Missing data fields should be treated as missing.
2. For respondents indicating they are not currently employed (checking box 1c), Responses 2 – 4 should be coded as missing.
3. Code Response 3b to zero if Response 3c is checked. Code Response 6b to zero if Response 6c is checked.
4. The hours of work missed at work or in the home cannot be greater than the hours of work for which they were scheduled.

a. If Response 3b is > Response 2, Response 3b = Response 2
b. If Response 6b is > Response 5, Response 6b = Response 5
Note: Respondents with no reported scheduled hours (zero hours or missing values) of paid work (Response 2) or planned hours of work in the household (Response 5), should be excluded from the analyses regarding productivity in those respective venues.
-

Calculation of hours of lost work due to absenteeism by class of work
5. Calculate the number of hours absent by class of work:
a. Workplace: Response 3b
b. Household: Response 6b

Calculation of hours of lost work due to presenteeism by class of work
6. Calculate the number of hours worked by class of work:
a. Workplace: Response 2 – Response 3b
b. Household: Response 5 – Response 6b
7. Calculate the hours of work lost due to presenteeism by class of work:
a. Workplace: Calc 6a × (Response 4/100)
b. Household: Calc 6b × (Response 7/100)

Calculation of total [absenteeism + presenteeism] hours of lost work by class of work
8. Calculate the sum by class of work:
a. Workplace: Calc 5a + Calc 7a
b. Household: Calc 5b + Calc 7b

Calculation of the % of scheduled work lost due to absenteeism, presenteeism, and total productivity loss by class of work
9. Calculate the % of work lost due to absenteeism
a. Workplace: (Calc 5a/Response 2) × 100
b. Household: (Calc 5b/Response 5) × 100
10. Calculate the % of work lost due to presenteeism
a. Workplace: (Calc 7a/Response 2) × 100
b. Household: (Calc 7b/Response 5) × 100
11. Calculate the total % of work lost
a. Workplace: Calc 9a + Calc 10a
b. Household: Calc 9b + Calc 10b

Calculation of the workplace productivity impacts by current employment status
12. Subset subjects by their current employment status to report productivity impacts among those employed full-time and those employed part-time

Calculation of hours of lifetime productivity lost until the time of measurement due to illness impacts on workforce participation

Note: Calculations 13 and 14 should be made for only those respondents who have non-zero non-missing responses to Question 2

13. Mean weekly hours of scheduled work in previous week for subjects full-time employed

a. Mean of Response 2 among subjects selecting Response 1a at baseline

14. Mean weekly hours of scheduled work in previous week for subjects part-time employed at baseline

a. Mean of Response 2 among subjects selecting Response 1b at baseline

Note: Calculations 15 through 17 should be made for only those respondents indicating they have experienced that workforce participation impact

15. Hours of lifetime productivity lost due to illness induced part-time employment when subject would have continued full-time employment

a. ((Response 9a × 4.33 wks/mo) + (Response 9b × 52 wks/yr)) × (Calc 13 – Calc 14)

16. Hours of lifetime productivity lost due to illness induced premature retirement when subject would have continued full-time employment

a. ((Response 9c × 4.33 wks/mo) + (Response 9d × 52 wks/yr)) × Calc 13

17. Hours of lifetime productivity lost due to illness induced premature retirement when subject would have continued part-time employment

a. ((Response 9e × 4.33 wks/mo) + (Response 9f × 52 wks/yr)) × Calc 14

18. Total hours of lifetime productivity lost due to illness impact on workforce participation

a. Calc 15 + Calc 16 + Calc 17

9.4. Appendix D: EQ-5D TTO Scoring

Computing EQ-5D-5L crosswalk index values with SAS using the United States (US) value set:

The variables for the 5 dimensions of the EQ-5D-5L descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'. If they are given different names the syntax code below will not work properly. The 5 variables should contain the values for the different dimensions in the EQ-5D health profile (i.e. 1, 2, 3, 4, or 5). The variable 'EQindex' contains the values of the EQ-5D-5L crosswalk index values on the basis of the US set of weights.

You can copy and paste the syntax below directly into a SAS syntax window.

```
************************************************************
*SAS syntax code for the computation of index*
*values with the US TTO value set*
************************************************************;

data Euroqol.US_tto;
        set Euroqol.EQ5D_states;
        EQindex = .;

if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=1) then EQindex = 1.000;
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=2) then EQindex = 0.876;
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=3) then EQindex = 0.844;
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=4) then EQindex = 0.700;
if (mobility=1 and selfcare=1 and activity=1 and pain=1 and anxiety=5) then EQindex = 0.550;
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=1) then EQindex = 0.861;
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=2) then EQindex = 0.820;
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=3) then EQindex = 0.809;
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=4) then EQindex = 0.669;
if (mobility=1 and selfcare=1 and activity=1 and pain=2 and anxiety=5) then EQindex = 0.524;
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=1) then EQindex = 0.827;
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=2) then EQindex = 0.806;
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=3) then EQindex = 0.800;
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=4) then EQindex = 0.661;
if (mobility=1 and selfcare=1 and activity=1 and pain=3 and anxiety=5) then EQindex = 0.517;
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=1) then EQindex = 0.682;
```

```
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=2) then EQindex = 0.663;
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=3) then EQindex = 0.659;
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=4) then EQindex = 0.544;
if (mobility=1 and selfcare=1 and activity=1 and pain=4 and anxiety=5) then EQindex = 0.426;
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=1) then EQindex = 0.463;
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=2) then EQindex = 0.450;
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=3) then EQindex = 0.446;
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=4) then EQindex = 0.369;
if (mobility=1 and selfcare=1 and activity=1 and pain=5 and anxiety=5) then EQindex = 0.289;
if (mobility=5 and selfcare=5 and activity=5 and pain=1 and anxiety=1) then EQindex = 0.178;
if (mobility=5 and selfcare=5 and activity=5 and pain=1 and anxiety=2) then EQindex = 0.165;
if (mobility=5 and selfcare=5 and activity=5 and pain=1 and anxiety=3) then EQindex = 0.162;
if (mobility=5 and selfcare=5 and activity=5 and pain=1 and anxiety=4) then EQindex = 0.113;
if (mobility=5 and selfcare=5 and activity=5 and pain=1 and anxiety=5) then EQindex = 0.063;
if (mobility=5 and selfcare=5 and activity=5 and pain=2 and anxiety=1) then EQindex = 0.152;
if (mobility=5 and selfcare=5 and activity=5 and pain=2 and anxiety=2) then EQindex = 0.132;
if (mobility=5 and selfcare=5 and activity=5 and pain=2 and anxiety=3) then EQindex = 0.127;
if (mobility=5 and selfcare=5 and activity=5 and pain=2 and anxiety=4) then EQindex = 0.083;
if (mobility=5 and selfcare=5 and activity=5 and pain=2 and anxiety=5) then EQindex = 0.037;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=1) then EQindex = 0.145;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=2) then EQindex = 0.124;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=3) then EQindex = 0.118;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=4) then EQindex = 0.075;
if (mobility=5 and selfcare=5 and activity=5 and pain=3 and anxiety=5) then EQindex = 0.030;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=1) then EQindex = 0.078;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=2) then EQindex = 0.060;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=3) then EQindex = 0.055;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=4) then EQindex = 0.015;
if (mobility=5 and selfcare=5 and activity=5 and pain=4 and anxiety=5) then EQindex = -0.026;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=1) then EQindex = -0.024;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=2) then EQindex = -0.037;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=3) then EQindex = -0.040;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=4) then EQindex = -0.074;
if (mobility=5 and selfcare=5 and activity=5 and pain=5 and anxiety=5) then EQindex = -0.109;

if (mobility = .) or (selfcare = .) or (activity = .) or (pain = .) or (anxiety = .) then EQindex = . ;

output;
run;
```

9.5. Appendix E: Mapping rules for ediary data

Table 5 Mapping Rules for Kayentis Device

Case #	impacted visit	Patient status	Schedule of Kayentis daily diary	impact on data	Cytel action on IMP intake data	Cytel action on Menstrual data	Cytel mapping	cut off date (from eCRF)
1	Month 6	patient was included in EXT	remained in MAIN TREATMENT (due to Covid remote visit or to site error in diary completion)	data present in the Main datasets should be considered for the analysis of the extension study	mapping	n/a	from MAIN TREAT to EXT TREAT	First IMP intake in EXT
2	Month 6	patient was included in EXT	rescheduled to MAIN FU (due to site	data present in the Main datasets should be	n/a - missing in final DB	n/a	from MAIN FU to EXT TREAT	First IMP intake in EXT

			error in diary completion)	considered for the analysis of the extension study				
3	Month 6	patient entered MAIN FU	rescheduled to EXT TREATMENT (site error in diary completion)	data present in the Extension datasets should be considered for the analysis of the Main study	"Is the subject eligible to the 6 months treatment free follow-up?" is YES --> delete answers to YIMPI and IMPI	n/a	from EXT TREAT to MAIN FU	MONTH 6 visit date
	Month 12	patient entered Extension FU	remained in Extension TREATMENT (due to Covid remote visit or	Data regarding IMP intake will be present for this period	delete answers to YIMPI and IMPI	n/a	n/a - remain in MAIN Extension DB	MONTH 12 visit date

			to site error in diary completion)					
5	Month 6	whatever status: DUPLICATE ENTRIES	patient entered diary data in both Main and Extension studies each day	duplicates data will be present across the datasets	CASE by CASE review - Kayentis cleaning needed			
6	Day 1	patient entered MAIN TREATMENT	remained in SCREENING (due to site error in diary completion)	Data regarding IMP intake will not be present for this period and data regarding menstrual	n/a - missing in final DB	delete the answers to “is it your Menstrual period?” and start date questions, if any	n/a - remain in MAIN DB	First IMP intake in MAIN

				periods will be present				

Table 6 Mapping Rules for Signant Health Device

Case #	impacted visit	Patient status	Schedule of Signant Health daily diary	impact on data	Cytel action on IMP intake data	Cytel action on Menstrual data	Cytel mapping	cut off date (from eCRF)
1	Month 6	patient was included in EXT	remained in MAIN TREATMENT (due to Covid remote visit or to site error in diary completion)	data present in the Main datasets should be considered for the analysis of the extension study	mapping	n/a	from MAIN TREAT to EXT TREAT	First IMP intake in EXT
2	Month 6	patient was included in EXT	rescheduled to MAIN FU (due to site error in diary completion)	data present in the Main datasets should be considered for the analysis of the extension study	mapping	n/a	from MAIN FU to EXT TREAT	First IMP intake in EXT
3	Month 6	patient entered MAIN FU	rescheduled to EXT TREATMENT (site error	data present in the Extension datasets	delete answers to Yesterday IMP intake and to	n/a	from EXT TREAT to MAIN FU	MONTH 6 visit date

			in diary completion)	should be considered for the analysis of the Main study	Today IMP intake if any			
4	Month 12	Patient entered Extension FU	Remained in Extension Treatment	Data regarding IMP intake will be present for this period	delete answers to Yesterday IMP intake and to Today IMP intake if any	n/a	n/a	Month 12 visit date
5	Day 1	patient entered MAIN TREATMENT	remained in SCREENING (due to site error in diary completion)	Data regarding IMP intake will not be present for this period and data regarding menstrual periods will be present	mapping	delete the answers to “is it your Menstrual period?” and start date questions, if any	n/a - remain in MAIN DB	First IMP intake in MAIN
6	Any Monthly visit of the Main	patient in MAIN TREATMENT	Set-up in screening period (due to site error	Data regarding IMP intake will not be present for	mapping	delete the answers to “is it your Menstrual period?” and	n/a - remain in MAIN DB	First IMP intake in MAIN

	Treatment period		in diary completion)	this period and data regarding menstrual periods will be present		start date questions, if any		

9.6. Appendix F: Schedule of Assessments

Table 7 Schedule of Assessments – Extension Treatment Period

Schedule of study assessments – Extension Treatment Period							
Timing[1]	**Treatment Period**						
	M6[2]	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**
Informed Consent	x						
Inclusion-Exclusion criteria	x						
Physical examination (including weight)	x			x			x
Columbia-Suicide Severity Rating Scale	x	x	x	x	x	x	x
ECG[3]	x	x	x	x	x	x	x
Vital signs	x	x	x	x	x	x	x
Urine pregnancy test	x	x	x	x	x	x	x
Endometrium TVUS	x			x			x
Gynecological examination	x			x			x
Endometrial biopsy	x[4]						x[4]
Manual breast examination	x						x
Clinical laboratory & urinary protein dipstick	x[5]	x	x	x[5]	x	x	x[5]
BMD by DXA	x			x[6]			x
Adverse events	x	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x

[1] All visits should take place at the end of the defined period (i.e. M7 visit should be scheduled at the end of Month 7, M8 visit should be scheduled at the end of Month 8, etc.). All visit dates should be calculated from the date of Day 1 visit (in the main study). A month is defined as 28 days/4 weeks. Visits should be scheduled ± 3 days (-3/+ 2 days for Month 7 visit) from the calculated date.

[2] All Month 6 assessments except informed consent and inclusion/exclusion criteria would have been performed as part of the main study (18-OBE2109-002 - Edelweiss 2).

[3] ECG should be performed at about the same time but before the PK sample

[4] If endometrium thickness in TVUS is ≤ 5 mm, no endometrial biopsy will be necessary.

[5] Overnight fasting is required.

[6] Only for subjects who met the following criterion at any site on the M6 DXA scan: -2.5 < Z-score ≤ -1.5

Schedule of study assessments – Extension Treatment Period (cont'd)							
Timing[1]	Treatment Period						
	M6[2]	M7	M8	M9	M10	M11	M12
Contraceptive dispensing and counselling	x	x	x	x	x	x	x
Permitted analgesic prescribing/dispensing	x	x	x	x	x	x	x
Vitamin D and calcium dispensing	x	x	x	x	x	x	x
Subject eDiary completion check	x	x	x	x	x	x	x
IMP accountability	x	x	x	x	x	x	x
Dispense linzagolix/placebo kit	x	x	x	x	x	x	
Dispense ABT/placebo kit	x			x			
EHP-30, EQ-5D-5L and PROMIS[3]	x	x		x			x
mPGIS, PGIC, HRUQ and HRPQ[3]	x	x	x	x	x	x	x
SSIQ and PSIQ[3]	x						x
Blood sample for PK[4]	x	x	x	x	x	x	x

Schedule of study assessments – Extension Treatment Period (cont'd)							
Timing[1]	Treatment Period						
	M6[2]	M7	M8	M9	M10	M11	M12
E2, LH, P4	X	X	X	X	X	X	X
SHBG	X			X			X
Bone biomarkers	X			X			X

[1] All visits should take place at the end of the defined period (i.e. M7 visit should be scheduled at the end of Month 7, M8 visit should be scheduled at the end of Month 8, etc.). All visit dates should be calculated from the date of Day 1 visit (in the main study). A month is defined as 28 days/4 weeks. Visits should be scheduled ± 3 days from the calculated date.

[2] All Month 6 assessments except informed consent and inclusion/exclusion criteria would have been performed as part of the main study.

[3] ClinROs (PSIQ and HRUQ) will be administered to the subject by the site staff and the responses will be filled in the eDiary. ePROs (EHP-30, EQ-5D-5L, PROMIS, PGIS, PGIC, HRPQ and SSIQ) will be filled in by the subject in the eDiary.

[4] PK samples should be taken after the ECG and before the daily dose of IMP.

Table 8 Schedule of study assessments - Extension Follow-up Period

Schedule of study assessments – Extension Follow-up Period			
Timing[1]	M1 ExFU	M3 ExFU	M6 ExFU
Concomitant medication	x	x	x
Adverse events	x	x	x
Columbia-Suicide Severity Rating Scale	x	x	x
ECG	x	x	x
Physical examination (including weight)		x	x
Vital signs	x	x	x
Gynecological examination		x	
Manual breast examination		x	
Endometrium TVUS		x	x
Endometrial biopsy	x[2]	x[2]	x[2]
Clinical laboratory & urinary protein dipstick	x	x[4]	
Subject eDiary completion check	x	x	x
Subject eDiary collection and deactivation			x
EHP-30, EQ-5D-5L, PROMIS, HRUQ, HRPQ		x	x
mPGIS and PPGIC	x	x	x
BMD by DXA			x[5]

[1] All follow-up study visits should take place at the end of the defined period (i.e. M1 ExFU visit should be scheduled at the end of the first month of follow-up, M3 ExFU visit should be scheduled at the end of the third month of follow-up, etc.). A month is defined as 28 days/4 weeks. Visits should be scheduled ± 7 days from the calculated date.

[2] Endometrium biopsy will be taken only if diagnosis at preceding visit was different than "benign endometrium" or if no endometrial biopsy was done at M12 nor at any visit since M12.

[3] An end-of-study biopsy is mandatory if no endometrium biopsy was obtained at M12 nor at any of the subsequent visits.

[4] Overnight fasting is required.

[5] Subjects with a BMD decrease from main study baseline of > 1.5% for lumbar spine and/or > 2.5% for total hip at M6 ExFU visit will have an additional DXA scan 6 months later.

Schedule of study assessments – Extension Follow-up Period			
Timing[1]	**M1 ExFU**	**M3 ExFU**	**M6 ExFU**
E2, LH, P4	x	x	
FSH at local laboratory for subjects that do not resume menses at M3 ExFU visit		x	
Bone biomarkers		x	
Permitted analgesic prescribing/dispensing	x	x	
Vitamin D and calcium dispensing	x	x	
Urine pregnancy test and contraceptive dispensing and counselling	x	x	x

[1] All follow-up study visits should take place at the end of the defined period (i.e. M1 ExFU visit should be scheduled at the end of the first month of follow-up, M3 ExFU visit should be scheduled at the end of the third month of follow-up, etc.). A month is defined as 28 days/4 weeks. Visits should be scheduled ± 7 days from the calculated date.

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