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Protocol:	**18-OBE2109-002**		
Document Version No.:	1.0	**Document Date:**	18-MAY-2021

Protocol 18-OBE2109-002

A Phase 3 multicenter, randomized, double-blind, placebo-controlled, clinical study to assess the efficacy and safety of linzagolix in subjects with moderate to severe endometriosis-associated pain.

Protocol Number: 18-OBE2109-002
(Version Date) Version 4.0, 31 August 2020

Name of Test Drug: Linzagolix (OBE2109)

Phase: 3

Methodology: Randomized, double-blind, placebo-controlled

Sponsor: ObsEva S.A.

[redacted]

Sponsor Representative: [redacted]

Document Date: 18 May 2021

Document Version: Version 1.0

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SIGNATURE PAGE

Protocol Title: A Phase 3 multicenter, randomized, double-blind, placebo-controlled, clinical study to assess the efficacy and safety of linzagolix in subjects with moderate to severe endometriosis-associated pain.

Sponsor: ObsEva S.A.

[redacted]

Protocol Number: 18-OBE2109-002

Document Date/Version: 18 May 2021 / Version 1.0

Cytel, Inc. Author:

[redacted]

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Protocol:	**18-OBE2109-002**		
Document Version No.:	1.0	**Document Date:**	18-MAY-2021

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 statistical 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).

Sponsor Signatory:

[redacted]

Sponsor Signatory:

[redacted]

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ABBREVIATIONS

Abbreviation	Definition
ABT	Add-back therapy
AE	Adverse events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMH	Anti-Mullerian hormone
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
BCP	Best Cut Point
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

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Abbreviation	**Definition**
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQOL 5-Dimension 5-Level
FU	Follow-up
GCP	Good Clinical Practice
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
mB&B	Biberoglu & Behrman
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

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Abbreviation	**Definition**
P4	Progesterone
PD	Pharmacodynamic
PDF	Probability Density Function
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
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, placebo-controlled study to demonstrate the efficacy and safety of linzagolix administered orally once daily at doses of 75 mg alone and 200 mg in combination with low dose ABT (E2 1 mg/NETA 0.5 mg) versus placebo in the management of moderate to severe endometriosis associated pain (EAP) in women with surgically confirmed endometriosis.

1.2. Objectives of Statistical Analysis

Following the early termination of the study and due to the number of subjects randomized being substantially lower than the target number if the study had been fully enrolled, this statistical analysis plan (SAP) is focused on the safety analysis and all safety and efficacy data will be presented in listings. Consequently, this SAP is designed to outline the methods to be used in the analysis of study data to answer the safety and tolerability objectives.

The primary objective of this study was to demonstrate the efficacy and safety of linzagolix administered orally once daily for up to 3 months at a dose of 75 mg alone or of 200 mg in combination with ABT (E2 1 mg / NETA 0.5 mg) versus placebo, while under randomized treatment, in the management of moderate to severe EAP in women with surgically confirmed endometriosis. The two co-primary efficacy endpoints were clinically meaningful reduction over the last 28 days of randomized treatment up to the Month 3 visit along with a stable or decreased use of analgesics for EAP for 1) DYS and for 2) NMPP.

Secondary objectives included evaluation of persistence of efficacy over the last 28 days of randomized treatment up to the Month 6 visit, 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 BMD, endometrial health, cardiac safety including QT interval prolongation, standard laboratory safety parameters, gynecological assessments and AE frequency including specific hypoestrogenic AEs.

Exploratory objectives included assessment of bone turnover markers and collection of PK and PD 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. Synopsis of Study Design

This was a prospective, randomized, double-blind, placebo-controlled study to demonstrate the efficacy and safety of linzagolix administered orally once daily at doses of 75 mg alone and 200 mg in combination with low dose ABT (E2 1 mg/NETA 0.5 mg) versus placebo in the management of moderate to severe EAP in women with surgically confirmed endometriosis.

The study started with an approximately 3-month screening period during which subjects received no study drug. Eligibility was confirmed based on data collected during the screening period. After randomization, patients entered a 6-month Treatment Period. Subjects were to be randomized to one of the three treatment groups:

1. Linzagolix 75 mg

2. Linzagolix 200 mg combined with ABT

3. Placebo

Randomization was conducted via an interactive web response system (IWRS) in a 1:1:1 ratio. There was no stratification.

At 6 months, BMD change was to be assessed via DXA measurement. Eligible subjects who had completed the 6-month treatment period were invited to enter a separate extension study for 6 additional months of active treatment (no placebo control). In this extension study, subjects who previously received placebo were to be randomly switched to one of the two active treatments (Linzagolix 75 mg alone (with ABT placebo) or Linzagolix 200 mg combined with ABT). Subjects who received active treatment were to continue with the same treatment.

Subjects who declined to participate to or did not qualify for the extension study and who were exposed to at least 3 months of treatment were to enter a 6-month drug-free follow-up. At the end of the 6-month follow-up period, subjects with a BMD decrease from baseline of >1.5% for lumbar spine and/or >2.5% for total hip were to had an additional DXA scan 6 months later. Subjects who discontinued treatment prior to Month 3 were not eligible to enter the follow-up period.

The study was to be on average 15 months; 3-month Screening Period, 6-month Treatment Period and 6-month Follow-up (with 1 month being defined as 28 days/4 weeks). The duration excluded any washout period.

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

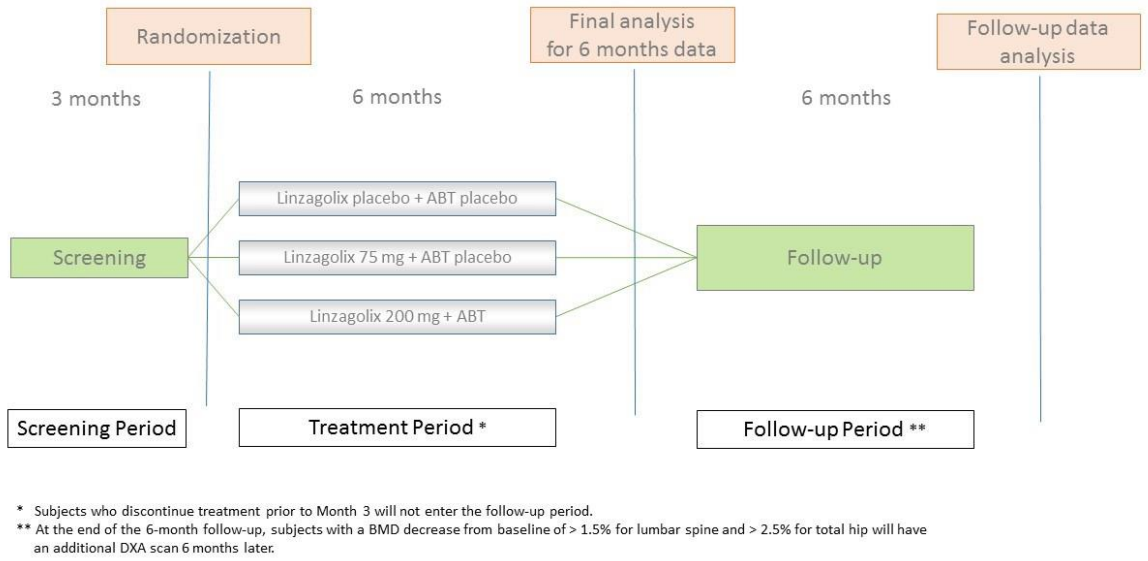

Figure 1: Study design

All subjects received once daily either linzagolix 75 mg alone (with ABT placebo) or linzagolix 200 mg combined with low dose ABT, or placebo (linzagolix placebo with ABT placebo) for 6 months. ABT was a combination of estradiol (E2) 1 mg and norethisterone acetate (NETA) 0.5 mg. Linzagolix or its corresponding placebo was supplied as tablets for oral administration. ABT or its corresponding placebo was supplied as capsules for oral administration.

Linzagolix/placebo treatments 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.

Blinded treatment kit numbers corresponding to each subject's randomized treatment were provided through an IWRS.

The main analysis was planned to be performed after 6 months of treatment on all of the subjects' data up to Month 6. However, due to the early termination of the study, one summary and report of the data will be performed and will be focused on the safety results from all subjects regardless of treatment duration.

2.2. Randomization Methodology

Randomization was performed via a centralized IWRS. Subjects were randomized on Day 1 to one of three treatment groups in a 1:1:1 ratio for linzagolix 75 mg, linzagolix 200 mg with ABT and placebo.

Subjects were randomized into permutated blocks of a pre-determined length.

There was no stratification.

2.3. Stopping Rules and Unblinding

2.3.1. 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 may 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.

A complete analysis with unblinded treatments was planned after all subjects had completed the Treatment Period (Month 6). Due to the early termination of the study, only one summary and report of data will be performed with unblinded treatments.

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

Discontinuation criteria

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 at Day 1: Subjects presenting with ALT, AST, GGT or total bilirubin ≥ 2 ULN were to be discussed with the Sponsor and may have had to discontinue study treatment if these results were indicative of liver involvement.

Subjects presenting with a clinically significant finding in the biopsy sample collected at screening and who had completed Day 1, had to discontinue study treatment.

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 the 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.

Bone mineral density 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.

2.3.2. Unblinding

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-OBE2109-002 - Edelweiss 2 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.

Following the early termination of the studies (main and extension), the lock was to be performed at the same time for the main and extension studies, and the unblinding done for all subjects for both studies.

2.4. Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1 and Table 2.

Table 1 Schedule of Assessments – Screening and Treatment Periods

Schedule of study assessments – Screening and Treatment Periods								
Timing[1]	Screening Period (up to 3 months[2])	Treatment Period						
		Day 1	M1	M2	M3	M4	M5	M6
Informed Consent	x							

[1] All post-baseline visits should take place at the end of the defined period (i.e. M1 visit should be scheduled at the end of Month 1, M2 visit should be scheduled at the end of Month 2, etc.). Post-baseline visits dates are calculated from Day 1 visit date. A month is defined as 28 days/4 weeks. Visits should be scheduled ± 3 days from the calculated date.

[2] If required for washout of oral contraceptives, other sex hormones, or GnRH antagonists/agonists (provided that the reason for discontinuing the previous GnRH-antagonist is not lack of efficacy), a period of up to 3 months is allowed between signing the informed consent and the screening visit.

Schedule of study assessments – Screening and Treatment Periods

Timing[1]	Screening Period (up to 3 months[2])	Treatment Period						
		Day 1	M1	M2	M3	M4	M5	M6
Inclusion-Exclusion criteria	x	x						
Demography, height, weight, medical history	x							x[3]
mB&B	x							
Columbia-Suicide Severity Rating Scale	x	x	x	x	x	x	x	x
ECG	x	x[4]	x	x	x	x	x	x
Physical examination	x				x			x

[3] Only weight will be recorded.

[4] ECG on Day 1 should be performed twice: once before treatment and once after treatment (just before PK sampling).

Schedule of study assessments – Screening and Treatment Periods

Timing[1]	Screening Period (up to 3 months[2])	Treatment Period						
		Day 1	M1	M2	M3	M4	M5	M6
Vital signs	x	x	x	x	x	x	x	x
Urine pregnancy test	x	x	x	x	x	x	x	x
TVUS of uterus	x				x			x
Gynecological examination	x				x			x
Endometrial biopsy	x							x[5]

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

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Schedule of study assessments – Screening and Treatment Periods

Timing[1]	Screening Period (up to 3 months[2])	Treatment Period						
		Day 1	M1	M2	M3	M4	M5	M6
Pap smear test	x							
Breast examination (mammogram if required)	x							x
Clinical laboratory & urinary protein dipstick	x	x[6]	x[6]	x	x[6]	x	x	x[6]
Blood sample for PK[7]		x	x	x	x	x	x	x
BMD by DXA	x							x
Adverse events	x	x	x	x	x	x	x	x

6 Overnight fasting is required.

7 PK samples should be taken after the ECG and before the daily dose of IMP, except on Day 1 when the PK sample should be taken at least 1.5 h after the IMP administration.

Schedule of study assessments – Screening and Treatment Periods

Timing[1]	Screening Period (up to 3 months[2])	Treatment Period						
		Day 1	M1	M2	M3	M4	M5	M6
Previous/concomitant medication	x	x	x	x	x	x	x	x
Contraceptive dispensing and counselling	x	x	x	x	x	x	x	x
Permitted analgesic prescribing/dispensing	x	x	x	x	x	x	x	x
Vitamin D and calcium dispensing		x	x	x	x	x	x	x
Subject eDiary completion training/check	x	x	x	x	x	x	x	x
IMP accountability			x	x	x	x	x	x
Dispense study drug		x	x	x	x	x	x	
Dispense ABT		x			x			

Schedule of study assessments – Screening and Treatment Periods

Timing[1]	Screening Period (up to 3 months[2])	Treatment Period						
		Day 1	M1	M2	M3	M4	M5	M6
EHP-30, EQ-5D-5L and PROMIS[8]		x	x		x			x
mPGIS, PGIC, HRUQ and HRPQ		x[9]	x	x	x	x	x	x
Specific monthly severity questions[8]		x			x			x
SSIQ and PSIQ[8]		x						x
AMH		x						
E2, LH, P4		x	x	x	x	x	x	x

8 ClinROs (Monthly dyspareunia question, 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, and specific monthly severity questions) will be filled in by the subject in the eDiary.

9 PGIC not done at Day 1.

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Schedule of study assessments – Screening and Treatment Periods

Timing[1]	Screening Period (up to 3 months[2])	Treatment Period						
		Day 1	M1	M2	M3	M4	M5	M6
SHBG		x			x			x
Bone biomarkers		x			x			x
Question regarding treatment received								x

Table 2 Schedule of study assessments - Follow-up Period

Schedule of study assessments – Follow-up Period						
Timing[1]	M1 FU	M2 FU	M3 FU	M4 FU	M5 FU	M6 FU
Previous/concomitant medication	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x
Columbia-Suicide Severity Rating Scale	x	x	x	x	x	x
ECG	x		x			x
Physical examination			x			x
Weight						x

[1] All follow-up study visits should take place at the end of the defined period (i.e. M1 FU visit should be scheduled at the end of the first month of follow-up, M2 FU visit should be scheduled at the end of the second follow-up visit, etc.). A month is defined as 28 days/4 weeks. Visits should be scheduled ± 7 days from the calculated date.

Schedule of study assessments – Follow-up Period						
Timing[1]	M1 FU	M2 FU	M3 FU	M4 FU	M5 FU	M6 FU
Vital signs	x		x			
Gynecological examination			x			
Breast manual examination			x			
Endometrium TVUS			x			x
Endometrial biopsy	x[2]	x[2]	x[2]	x[2]	x[2]	x[3]

[2] Endometrial biopsy will be taken only if diagnosis at preceding month was different than "benign endometrium" or if no endometrial biopsy was done at Month 6 nor at any visit since Month 6.

[3] An end-of-study biopsy is mandatory if no endometrial biopsy was obtained at M6 nor at any of the subsequent monthly visits.

Schedule of study assessments – Follow-up Period						
Timing[1]	M1 FU	M2 FU	M3 FU	M4 FU	M5 FU	M6 FU
Clinical laboratory & urinary protein dipstick	x		x[4]			
Subject eDiary completion check	x	x	x	x	x	x
Subject eDiary collection and deactivation						x
EHP-30, HRUQ, HRPQ, EQ-5D-5L and PROMIS			x			x
mPGIS and PPGIC	x	x	x	x	x	x
BMD by DXA						x[5]
E2, LH, P4	x		x			

[4] Overnight fasting is required.

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

Schedule of study assessments – Follow-up Period						
Timing[1]	M1 FU	M2 FU	M3 FU	M4 FU	M5 FU	M6 FU
FSH at local laboratory for subjects that do not resume menses at M3 FU visit			x			
Bone biomarkers			x			
Permitted analgesic prescribing/dispensing	x	x	x	x	x	
Vitamin D and calcium dispensing	x	x	x	x	x	
Urine pregnancy test and contraceptive dispensing and counselling	x	x	x			x

2.5. Efficacy, Pharmacokinetic, and Safety Variables

2.5.1. Efficacy Variables

The efficacy variables planned in the protocol will not be analyzed due to the early study termination and the low number of subjects randomized.

2.5.2. Pharmacokinetic Variables

The pharmacokinetic variables planned in the protocol will not be analyzed due to the early study termination and the low number of subjects randomized.

2.5.3. 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 4.8.

Note that the endpoint “Time to the first post-treatment menses” was initially planned in the protocol, but will not be described in this SAP, because the study was stopped prematurely, and all subjects couldn’t be followed to evaluate this endpoint.

2.5.4. Exploratory Variables

The exploratory variables planned in the protocol will not be analyzed due to the early study termination and the low number of subjects randomized.

3. SUBJECT POPULATIONS

3.1. Analyses Sets Definitions

The following data sets will be used for reporting of safety data from the trial:

Safety Analysis Set (SAF): All randomized subjects who received at least one dose of double-blind study drug irrespective of the treatment received. Subjects will be analyzed according to treatment received.

Follow-up Safety Set (FU SAF): All randomized subjects who entered the drug free follow-up period. Subjects will be analyzed according to treatment received.
Subjects who entered the drug free follow-up period are :

- subjects eligible to the 6 months treatment free follow-up (subject who completed the six months of treatment or discontinued the study treatment between Month 3 and Month 6),

  and

- with any data post month 6 or post treatment discontinuation assigned to a follow-up visit.

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

Subjects received a different kit of active linzagolix or placebo for each month, and a different kit for add-back or placebo for each 3-month period.

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 drug was taken on that day.

Further rules are as follows:

- Treatment administration errors:
  - If a subject received placebo with placebo ABT in more than 50% of days, then the actual treatment group will be placebo with placebo ABT.
  - Otherwise, the active treatment group (combined with add-back or placebo add-back) with the most days taken will be assigned.
  - If the number of days is equal for two treatments groups containing active treatment then LGX 200 mg with ABT will be assigned.
- If a subject discontinued, only data received up to discontinuation will be used.
- It is possible that the derived actual treatment group does not correspond to any of the planned treatment groups. In that case actual treatment group will be assigned to the planned treatment group with same dose of active treatment. Example: LGX 75mg with ABT

will be assigned to LGX 75mg with placebo ABT ; LGX 200mg with placebo ABT will be assigned to LGX 200mg with ABT. A listing with such cases will be provided.

3.2. Protocol Violations

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/REB per their policies. The site investigator was responsible for knowing and adhering to the reviewing IRB/REB requirements.

All Protocol Deviations were to be reported to the Sponsor and documented in the monitoring report. These will be classified as important or non-important based on their effect on the right, safety or well-being of the subjects and/or the quality and integrity of the data.

In addition, Protocol Deviations will be classified as minor or major, which major deviations mean potentially affecting the efficacy assessments up to Month 6. However, due to the early termination of the study and absence of efficacy analysis, major deviations will be identified as and limited to the following deviations:

- Non-compliance with inclusion criteria 3; 6; 8
- Non-compliance with exclusion criteria 2 to 10 inclusive; 12; 13; 17; 19; 20; 21; 22; 23; 24; 25; 28;
- IP Dispensing error;
- Randomisation code broken

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

Major protocol deviations will be summarized by category (if available) and by treatment group and overall on the Safety population.

All protocol deviations will be presented in the data listings.

4. STATISTICAL METHODS

4.1. Sample Size Justification

The planned sample size for this study was 150 subjects per treatment group (450 subjects in total).

An overall two-sided type I error of 0.05 was to be used. As there are two linzagolix versus placebo comparisons, Bonferoni corrected p-values will be produced (raw p-values will be multiplied by two prior to comparing to 0.05). The planned sample size considered the hierarchical, fixed sequence testing of the ranked secondary endpoints as well as the co-primary endpoints. The assumptions used for the sample size calculations were based on analyses of clinically meaningful reduction in pain with a stable or decreased use of analgesics from the Phase 2b Edelweiss study. Calculations were performed using East® 6.5 software.

One hundred and fifty (150) subjects per treatment group were estimated to provide a power greater than 95% to reject the null hypothesis for both co-primary endpoints for either treatment group, assuming a placebo response rate of 14.6% and an active treatment response rate of 48.6% (75 mg, Edelweiss Phase II study results) or 64.7% (200 mg, Edelweiss Phase II study result) for DYS, and a placebo response rate of 18.8% and an active treatment response rate of 42.1% (75 mg, Edelweiss Phase II study result; the response rate for 200 mg in Edelweiss was lower but was inconsistent with the other doses and also the other timepoints for the same dose and so has not been used) for NMPP. In addition, 150 subjects per treatment group were estimated to provide 85% power to reject all the ranked secondary endpoints based on the observed results from the placebo and 200 mg treatment group in the Edelweiss study.

The values used for the sample size calculations assumed that this was what would have been seen on average when under treatment including taking into account any subjects who might have withdrawn from treatment early and therefore the calculations did not need to be further adjusted for dropouts.

4.2. General Statistical Methods and Data Handling

4.2.1. 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.

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 (see section 4.2.11) will be calculated for all subjects based on the Safety Set. For Bone Mineral Density, 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.

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.4), unless otherwise noted. Medical History and adverse events will be coded MedDRA version 23.0. Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary B3 – Mar 2019.

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates

Not Applicable

4.2.5. Multiple Comparisons/Multiplicity

No more applicable, because the analysis will be only focused on the safety analysis, due to the early termination of the study and the number of subjects randomized being substantially lower than the target number if the study had been fully enrolled.

4.2.6. Subpopulations

Not Applicable.

4.2.7. 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.

Subjects who did not receive the study drug will be withdrawn from the study and no further study procedures will be performed.

Withdrawal during treatment period:

Subjects who discontinue between Day 1 and Month 3 should undergo the procedures required at Month 6 (except the DXA scan and the endometrium biopsy if a biopsy was obtained at screening) and will not enter the 6-month follow-up period.

Subjects discontinuing the study treatment between Month 3 and Month 6 should undergo the procedures required at Month 6. These subjects will enter a 6-month follow-up period and will continue daily eDiary recording for 6 months and up to Month 6 FU visit in order to continue to collect efficacy 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 should undergo the procedures required at Month 6 FU visit, which includes completion of all ClinRO and ePRO questionnaires, except the DXA in case of discontinuation before Month 3 FU visit.

Subject Replacement:

Discontinued subjects who did not receive the study drug may be replaced.

Additional subjects may be recruited due to subjects who were discontinued due to ALT, AST, GGT or total bilirubin ≥ 2 times the upper limit of normal at Day 1, or due to a clinically significant biopsy finding at Day 1 (treatment start), or due to high calcium level at Day 1.

4.2.8. Missing, Unused, and Spurious Data

4.2.8.1. 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."

- 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.

4.2.8.2. eDiary Devices Data Cleaning

Due to eDiary system errors, mapping rules are defined for data cleaning, as described in Appendix E in Section 7.1.

In addition, the following rules are defined for 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, the first record (with earliest date/time) should be used for analysis.

Additional rules to specific e-diary domains will be applied:

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 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) to be presented to the subject will depend on the answer chosen by the subject to the current question.

Due to device functioning, when an answer to a triggering question has been changed by 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 allow her to provide additional data or to modify data for the sub-questions (in contrast to the [redacted] device, with the 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” (ie 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

4.2.8.3. 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.

4.2.9. **TVUS data**

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

4.2.10. **Visit Windows**

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

All visit dates are calculated from the date the patient started treatment in the main study (Day 1 visit of 18-OBE2109-002 Edelweiss 2).

DXA data

Visit windows rules for DXA assessments will be the following:

- The baseline DXA assessment will be derived as the latest non-missing DXA assessment with acceptable quality (accepted="Yes") prior to the Baseline visit or the first non-missing assessment with acceptable quality (accepted="Yes") done up to 10 days after the baseline visit if there is no assessment prior to baseline.
- The DXA assessment at Month 6 will be derived as the first non-missing DXA assessment with acceptable quality (accepted="Yes") and dated between Month 6 theoretical date (=Day 169) -28 days and Month 6 theoretical date + 28 days.
- The DXA assessment at Month 6 Follow-Up will be derived in the same way as the DXA assessment at Month 6. Theoretical date of Month 6 Follow-up is 168 days after Month 6 theoretical date or after treatment discontinuation.

Other safety data:

The endometrial biopsy screening window will include any assessment done prior to the first IMP dose.

For other safety results, 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 main treatment period, date will be compared to the theoretical visit dates in main treatment period as described in Table 3. If a subject discontinued in the follow-up period, date will be compared to the theoretical visit dates in Follow-up period from

Table 4.

For unscheduled safety assessments, if the assessment occurs in a window of +/- 14 days of 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 entered extension study, the visit of assessment should be reassigned with the same rules described above for unscheduled safety assessment.

Table 3 Theoretical Visit Dates in Main Treatment Period

Visit	**Theoretical Date**
Month 1	Day 29
Month 2	Day 57
Month 3	Day 85
Month 4	Day 113
Month 5	Day 141
Month 6	Day 169

Table 4 Theoretical Visit Dates in Follow-up

Visit	Theoretical Date
Month 1 FU	Month 6 date or treatment discontinuation date + 28
Month 2 FU	Month 6 date or treatment discontinuation date + 56
Month 3 FU	Month 6 date or treatment discontinuation date + 84
Month 4 FU	Month 6 date or treatment discontinuation date + 112
Month 5 FU	Month 6 date or treatment discontinuation date + 140
Month 6 FU	Month 6 date or treatment discontinuation date + 168

4.2.11. Baseline Definition

Baseline dysmenorrhea, non-menstrual pelvic pain, analgesic use and uterine bleeding will be based on the calculation from daily e-diary data from menstrual cycles during the screening period. The screening period must cover at least two full menstrual cycles. The following rules apply to select the two baseline menstrual cycles for assessment of eligibility and baseline:

- If only two full screening cycles are covered prior to Day 1: those two screening cycles should be used for both eligibility assessment and baseline calculation.
- If 3 full screening cycles are covered during the screening period, for logistical reasons, as allowed per protocol: "If for logistical reasons beyond her control, the subject is unable to come to the clinic for Day 1 within the acceptable time window (1st to 7th day inclusive of the cycle) then the subject will be allowed to start Day 1 in the following cycle (again on the 1st to 7th day of the cycle). In this case, the eligibility assessments should be assessed based on the first two cycles only"; the two first screening cycles should be used for both eligibility assessment and baseline calculation.
- If more than 3 full screening cycles are covered during the screening period: the two last menstrual cycles prior to the baseline visit will be considered for both eligibility assessment and baseline calculation.
- Due to possible technical issues with the e-diary device, some data during the screening menstrual cycle may not be collected properly. Consequently the menstrual cycles may not be considered as valid for assessment of eligibility and baseline and other cycles than first and second ones might be used on a case-by-case basis. The sponsor will provide an excel file listing all the menstrual cycles that were used for measurement of eligibility and baseline.

The baseline DXA assessment will be derived as the latest non-missing DXA assessment with acceptable quality (accepted=”Yes”) prior to the Baseline visit or the first non-missing assessment

with acceptable quality (accepted="Yes") done up to 10 days after the baseline visit if there is no assessment prior to baseline.

For other data not specified before, baseline will be defined as the data most recently collected prior to the first dose of IMP.

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

The last treatment administration date will be defined as the date of treatment termination recorded in the main period eCRF page. If this date is missing, the last date with a drug intake in eDiary prior to the Month 6 date or, for subjects who discontinued, the last date with available drug intake information in the subject eDiary will be used.

The end of study date will be the last assessment date in the main study defined as last eCRF or ediary date prior to and not including Month 6 for subjects who entered the Extension, and the last eCRF or ediary date in the main study or main follow-up if not. This will not necessarily be the same date as last assessment date as recorded in the eCRF.

Note: For summaries by visit (efficacy or safety), the Month 6 assessments will be included in the main study analyses. For Adverse Events, Concomitant Medications and Daily diaries, data collected on Month 6 date will be part of the extension for subjects entering the extension study and be part of the Follow-up period for subjects entering the main study follow-up period.

The main treatment period will be defined as Day 1 up to (Month 6 date -1) or the treatment discontinuation date.

The main follow-up period will be defined as the Month 6 date or (treatment discontinuation date+1) up to the end of study date (for subjects who entered into the main follow-up period).

4.3. Interim Analyses

Not applicable

4.4. Subject Disposition

A tabulation of subject disposition will be presented by treatment group and overall, for randomized subjects and for safety population, including :

- Number of subjects screened, and reasons for screen failures,
- Number of subjects randomized,
- Number of subjects discontinued study between randomization and Day 1,
- Number of subjects who received at least one dose of study drug,
- Number of subjects who completed treatment period until Month 6
- Number of subjects who discontinued treatment period between Day 1 and Month 3 visit (included), and reasons for treatment discontinuation
- Number of subjects who discontinued treatment period between Month 3 visit and Month 6 (included), and reasons for treatment discontinuation
- Number of subjects who entered follow-up period
- Number of subjects who discontinued follow-up period, and reasons for follow-up discontinuation
- Number of subjects who completed the study

  Note that subjects who completed the treatment period and entered in the extension study will be considered as completed the study. For the other subjects, a subject will considered as completed the study if the subject complete the treatment period and the follow-up period.
- Number of subjects who entered in the extension study

The number in each subject population for analysis will be presented by treatment group and overall, for randomized subjects. The number of subjects who completed each visit will be summarized by treatment group and overall, for the Safety population.

The number of subjects screened and randomized by country and by site will be also provided.

The following listings will be presented:

- Study completion information, including the reason for premature study withdrawal, if applicable;
- Inclusion/exclusion criteria for Screened Subjects;
- Subject inclusion in each of the analysis sets (Safety Analysis Set and Follow-up Safety Set) and reasons of exclusion

4.5. Demographic and Baseline Characteristics

Baseline, demographic and medical history information will be analyzed for the safety set.

No formal statistical comparisons will be performed.

4.5.1. Demographics

Demographics and baseline characteristics 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.

4.5.2. Baseline Disease Characteristics

The definition of the two baseline menstrual cycles is described in section 4.2.11.

Baseline Dysmenorrhea (DYS) and Non-Menstrual Pelvic Pain (NMPP) will be calculated by averaging over the two baseline menstrual cycles, the e-diary daily answers of Endometriosis Related Pelvic Pain (PP VRS Questionnaire). Responses of "None," "Mild," "Moderate," and "Severe" will be assigned a score of 0, 1, 2, and 3, respectively. Dysmenorrhea will be computed using days with uterine bleeding, defined as those days on which the subject records any uterine bleeding or spotting in the subject eDiary; Non-Menstrual Pelvic Pain will use days with no uterine bleeding. Note that days with missing information on bleeding will not be used for analysis.

The baseline analgesic use will be calculated as the mean of daily pill count of analgesics over the two baseline menstrual cycles for each class of rescue analgesics (endometriosis-associated: Ibuprofen, Narcotic Analgesic) collected in the eDiary, separately for bleeding days, non-bleeding days and overall.

Dysmenorrhea, Non-Menstrual Pelvic Pain and Analgesic use will be summarized as continuous variables

The average duration of the two baseline menstrual cycles (days) will be summarized. The duration (days) of the two individual baseline menstrual cycle will be calculated using the menstrual period diaries (menstrual start date confirmed by subject). The duration is computed as (start date of $Cycle_{x+1}$ – start date of cycle).

The average number of days with uterine bleeding over the two baseline menstrual cycles will be summarized as continuous variables.

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 will be presented by treatment group and overall. Abnormality details will be provided in data listings.

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 abnormality (Fibroids, Adenomyosis, other), left ovary or right ovary abnormality) will be summarized.

Dysmenorrhea, Deep Dyspareunia, Non Menstrual Pelvic Pain, Total Pelvic Pain (None: 0, Mild: 1-3, Moderate: 4-6, Severe: 7-9), Pelvic Tenderness, Induration, Total Physical Sign Score (None: 0, Mild: 1-2, Moderate: 3-4, Severe: 5-6) and Composite Pelvic pain and Physical Sign Score (None: 0, Mild: 1-2, Moderate: 3-5, Severe: 6-10, Very Severe 11-15) from the Modified Biberoglu & Behrman symptom severity scale assessment as collected in eCRF will be summarized at baseline as categorical variables with the following categories: None, Mild, Moderate, Severe (Very Severe).

Baseline Disease Characteristics will be reported in listings.

4.5.3. Medical History

Medical history 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 is 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.

4.5.4. Endometriosis History

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 of 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.

4.6. Efficacy Evaluation

Following the early termination of the study and due to the number of subjects randomized being substantially lower than the target number if the study had been fully enrolled, no efficacy analyses are planned.

Efficacy data from eDiaries, eCRF, quality of life questionnaires and other ePROs questionnaires will be reported in listings.

4.7. Pharmacokinetic Evaluations

Following the early termination of the study and due to the number of subjects randomized being substantially lower than the target number if the study had been fully enrolled, no pharmacokinetic analysis is planned.

Pharmacokinetic data will be reported in a listing.

4.8. Safety Analyses

Safety analyses will be conducted using the Safety Population.

4.8.1. Extent of treatment exposure and compliance

4.8.1.1. Extent of treatment exposure

Duration of treatment (weeks) will be summarized for each treatment group. Duration is defined as: [(date of last treatment administration as described in section 4.2.12) - (date of first administration as collected in eCRF) +1] / 7.

Time on study (weeks) will be summarized for each treatment group, defined as: [(end of study date as described in section 4.2.12) – (first dose date) +1]/7

Exposure data will be reported in listings.

4.8.1.2. Compliance

Lingazolix/Placebo Grey blister (200 mg or matching placebo), Lingazolix/Placebo Pink blister (75 mg or matching placebo) and Add-back therapy compliance from the study treatment accountability page among the Day 1- End of main study treatment period will be summarized by treatment group.

If Lingazolix/Placebo and Add-back therapy 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/Add-back capsule taken *100 divided by the number of days in the period (Month 6 visit date/withdrawal date - Day 1). 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 intake of drug was taken on that day.

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

Compliances will be reported in a listing.

4.8.2. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using System/Organ/Class (SOC) and Preferred Term.

Analyses of adverse events will be performed for those events that are considered treatment emergent (TEAEs), where treatment emergent is defined as AEs with a start date on or after the first dose of study drug through 30 days after discontinuation of study drug or Month 6 visit date, or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the investigator through the end of the study.

Adverse Event tables will be presented for the following periods: Day 1 to Month 6 (treatment period) and Month 6 to Month 6 FU (follow-up period) as defined in section 4.2.12.

Adverse events starting more than 30 days after end of treatment will be considered as post-treatment AE.

Note: if an adverse event started after or at Month 6 visit date and if the subject entered the extension period, this adverse event will not be displayed for the main study, but only for the extension study.

For each of these 2 study periods, an overall summary table will be prepared presenting, by treatment group and overall, the number and percentage of subjects with

- any AE,
- any TEAE,
- any post-treatment AE (displayed only for the follow-up period)
- Severe TEAE,
- any TEAE assessed by the Investigator as related to Linzagolix,
- any TEAE assessed by the Investigator as related to add-back therapy,
- any TEAE leading to permanent discontinuation of IMP,
- any serious adverse event,
- any serious Treatment Emergent Adverse Event,
- any serious Treatment Emergent adverse event related to Linzagolix,
- any serious Treatment Emergent adverse event related to add-back therapy,
- Any TEAE leading to permanent discontinuation of IMP
- 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).

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), with any serious treatment-emergent adverse event, with any non-serious treatment-emergent adverse event, with treatment-emergent adverse event leading to permanent discontinuation of IMP and with fatal treatment-emergent adverse event will be summarized by treatment group and overall. 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 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.

The number and percentage of subjects with any post-treatment adverse event will be summarized on the follow-up period by treatment group and overall.

The number of events will be also displayed for summary of AEs, for analysis of TEAE, serious TEAE non-serious TEAE and for post-treatment AE, by SOC and PT.

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; post-treatment adverse event.

4.8.3. Bone Mineral Density (BMD) by DXA

BMD of femoral neck, total hip and lumbar spine will be assessed by DXA at Baseline, Month 6 and Month 6 follow-up. 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 for each anatomic location. For absolute values only, percent change from baseline and 95% confidence interval for the mean percent change from baseline within each group will be produced at each time point.

Percent change from baseline to Month 6 and Month 6 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 will be listed.

4.8.4. 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 treatment period, as well as at the M1 FU and M3 FU visits. E2, progesterone (P4) and LH are assessed at each visit during the treatment period (not at screening visit), as well as at the M1 FU and M3 FU visits. Serum levels of the anti-Müllerian hormone (AMH) and fasting glucose were assessed on Day 1 only. Serum levels of the sex hormone-binding globulin (SHBG) were assessed on Day 1 and Month 3 and Month 6 visits.

Blood samples were to be analyzed by the central laboratory.

For hematology, coagulation parameters, chemistry and lipids, the actual value and change from baseline 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.

Evaluation of shifts for changes from baseline to all visits, and to last on-treatment value (including unscheduled assessments) according to the normal ranges with categories "Low", "Normal", "High"

and according to normal/abnormal/abnormal clinically significant information collected otherwise, will be provided. Note that a value will be considered as "on-treatment" if the collection is performed between the first and last intake administration (included).

For Liver Function Test (LFT) parameters (ALT, AST, ALP, total bilirubin, direct bilirubin, indirect bilirubin, GGT, albumin, LDH and Creatine Kinase), 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 to each on-study visit will also be summarized.

For serum levels of 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.

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 Study Day 1 to Month 6 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 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

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

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

4.8.5. 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; Weight is assessed at Screening, Month 6 and Month 6 of the follow-up period. Other Vital Signs are assessed at Screening, Day 1, every month during the treatment period and at Months 1 and 3 from the follow-up period.

Physical Examination is assessed at Screening, Months 3 and 6 of treatment and follow-up periods.

The actual value and change from Baseline to each on study evaluation will be summarized by treatment group and overall 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 and overall; shifts from Baseline in physical examination findings to each on study visit will also be presented. All physical examination findings will be presented in a data listing.

4.8.6. Electrocardiogram

Local 12-lead ECG readings of QTcF are performed at Screening, Day 1 (pre and post-dose) and every month from the treatment period, as well as Months 1,3,6 from the follow-up period.

Baseline will be defined as the highest value prior to first dose.

Actual values and changes from baseline 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 Baseline and each study visit by treatment group and overall.

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

4.8.7. Prior and Concomitant Medications

Prior and 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.

Prior medications are those the subject used prior to the first day of treatment.

All medications administered between the date of the first dose of study drug and the date of the last dose of study drug, inclusive, (i.e., all medications starting or ongoing during the time interval) are concomitant. A medication taken prior to Study Day 1 and continuing post Study Day 1 will be considered both prior and concomitant.

Concomitant medications tables will be presented for the following periods: Day 1 to Month 6 (treatment period) and Month 6 to Month 6 FU (follow-up period) as defined in section 4.2.12.

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

Prior interventional surgeries/procedures for endometriosis/endometriosis symptoms will also be summarized.

The use of Prior interventional surgeries/procedures for endometriosis/endometriosis symptoms will be included in a by-subject data listing.

4.8.8. Transvaginal Ultrasound (TVUS)

TVUS is performed at Screening, Month 3, Month 6, Month 3 and Month 6 of the follow-up period.

Actual values and changes from baseline will be summarized by treatment group and overall for uterine 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 presence of any uterine, left or right ovarian abnormality overtime will be presented by treatment group and overall.

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

4.8.9. Other Examinations

4.8.9.1. Endometrial biopsy

At least two endometrial biopsies for histological assessment must be obtained for each subject:

- One at screening (unless an endometrial biopsy was performed within the past 6 months prior to screening visit, which shows no endometrial atypical hyperplasia or adenocarcinoma and for which slides are available for current study assessment through retrospective central laboratory reading.

If more than one biopsy is done for screening, the last one before the first IMP administration will be analyzed.

- One at Month 6 if endometrial thickness in TVUS is > 5 mm
- One at Month 1 FU, 2 FU, 3 FU, 4 FU, 5 FU or 6 FU if not obtained at Month 6 or if the preceding biopsy diagnosis is different than "benign endometrium"

On biopsies with a primary diagnostic 1 either "hyperplasia" or "Malignant Endometrial Neoplasm", a second read should be done at other visit than screening. For hyperplasia diagnostic, in case of multiple readings of the same sample, the most severe diagnostics will be selected for the statistical analysis, considering the following order, from less severe to more severe: simple without atypia hyperplasia < simple with atypia hyperplasia < complex without atypia hyperplasia < complex with atypia hyperplasia. For Malignant Endometrial Neoplasm, we assume that there will be no difference on diagnostic between the readings.

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.

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

4.8.9.2. Gynecological and Breast examination

Gynecological Examination is assessed at Screening, Month 3, Month 6 and Month 3 of Follow-Up period.

Breast examination (by palpation) will be performed at Screening, Month 6 and Month 3 FU visits.

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.

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

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

Subjects will complete:

- either the "Baseline" C-SSRS version, capturing lifetime history of suicidal ideation and behavior, for subjects under screening at the time of/after protocol amendment 3 implementation,

- or the "already enrolled subjects" C-SSRS version, for subjects already randomized at the time of protocol amendment 3 implementation, and who are 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 is completed during Screening, or at Day 1 if not done during Screening.

The following C-SSRS data will be summarized by time point (baseline "Lifetime" or Prior to Study Entry, "Since Study Start" and each post-baseline time point):

The number of subjects experiencing the following, at any time post-baseline, will be summarized up to Month 6

- Any suicidal ideation or behavior
- 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. 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 protocol amendment 3 implementation.

4.9. Exploratory Analyses

Bone turnover markers will be listed on the Safety Analysis Set.

5. CHANGES TO PLANNED ANALYSES

Following the early termination of the study and due to the number of subjects randomized being really less than the target number if the study had been fully enrolled, the analyses planned in the protocol on efficacy and pharmacokinetic assessments have been removed and only listings for these assessments will be displayed. The statistical analysis plan (SAP) will be focused on the safety analysis and all safety.

For safety endpoints, the endpoint “Time to the first post-treatment menses” was initially planned in the protocol, but will not be described in this SAP, because the study was stopped prematurely and all subjects couldn’t be followed to evaluate this endpoint.

6. REFERENCES

Not applicable

Sponsor:	**ObsEva**		
Protocol:	**18-OBE2109-002**		
Document Version No.:	1.0	**Document Date:**	18-MAY-2021

7. CLINICAL STUDY REPORT APPENDICES

7.1. Appendix A: Mapping rules for ediary data

Table 5 Mapping Rules for [redacted] Device

Case #	impacted visit	Patient status	Schedule of [redacted] 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	n/a - missing in final DB	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 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

4	Month 6	patient entered MAIN FU	remained in MAIN TREATMENT (due to Covid remote visit or to site error in diary completion)	Data regarding IMP intake will be present for this period	"Is the subject eligible to the 6 months treatment free follow-up?" is YES --> delete answers to YIMPI and IMPI	n/a	n/a - remain in MAIN DB	MONTH 6 visit date
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 - [redacted] 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 periods will be present	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

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	n/a - missing in final DB	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 in	data present in the Extension datasets should be	delete answers to Yesterday IMP intake and to Today IMP intake if any	n/a	from EXT TREAT to MAIN FU	MONTH 6 visit date

			diary completion)	considered for the analysis of the Main study				
4	Month 6	patient entered MAIN FU	remained in MAIN TREATMENT (due to Covid remote visit or to site error in diary completion)	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 - remain in MAIN DB	MONTH 6 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	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
6	Any Monthly visit of the Main	patient in MAIN TREATMENT	Set-up in screening period (due to site error in	Data regarding IMP intake will not be present for this period	n/a - missing in final DB	delete the answers to “is it your Menstrual period?” and	n/a - remain in MAIN DB	First IMP intake in MAIN

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

7.2. Appendix B: Statistical Tables/Figures/Listings to be Generated

Section 14.1 Demographic Data and Subject Characteristics

- Table 14.1.1 Patients Screened and Randomized by Country and Site - Screened Set
- Table 14.1.2.1 Patient Disposition by treatment group – Randomized Subjects
- Table 14.1.2.2 Patient Disposition by treatment group – Safety Analysis Set
- Table 14.1.3 Analysis Sets – Randomized Set
- Table 14.1.4 Number of Subjects by Visit – Safety Set
- Table 14.1.4 Major Protocol Deviations - Safety Set
- Table 14.1.5 Demographic and Baseline Characteristics – Safety Analysis Set
- Table 14.1.6 Baseline Disease Characteristics: Menstrual Cycles and Pain – Safety Analysis Set
- Table 14.1.7 Baseline Disease Characteristics: Transvaginal Ultrasound – Safety Analysis Set
- Table 14.1.8 Other Baseline examinations - Safety Analysis Set
- Table 14.1.9 Medical History - Safety Analysis Set
- Table 14.1.10 Endometriosis History – Safety Analysis Set
- Table 14.1.11.1 Exposure and Compliance to Study Treatment from Day 1 to Month 6 - Safety Analysis Set

Section 14.3.1 Adverse Events

- Table 14.3.1.1.1 Summary of Treatment-Emergent Adverse Events from Day 1 to Month 6 - Safety Analysis Set
- Table 14.3.1.1.2 Summary of Treatment-Emergent Adverse Events from Month 6 to Month 6 FU - Follow-up Safety Analysis Set
- Table 14.3.1.2.1 Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Day 1 to Month 6 - Safety Analysis Set
- Table 14.3.1.2.2 Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Month 6 to Month 6 FU – Follow-up Safety Analysis Set
- Table 14.3.1.3.1 Treatment-Emergent Adverse Events by Maximum Severity by MedDRA SOC and Preferred Term from Day 1 to Month 6 - Safety Analysis Set

- Table 14.3.1.3.2 Treatment-Emergent Adverse Events by Maximum Severity by MedDRA SOC and Preferred Term from Month 6 to Month 6 FU - Follow-up Safety Analysis Set
- Table 14.3.1.4.1 Treatment-Emergent Adverse Events Related to Linzagolix by MedDRA SOC and Preferred Term from Day 1 to Month 6 - Safety Analysis Set
- Table 14.3.1.4.2 Treatment-Emergent Adverse Events Related to Linzagolix by MedDRA SOC and Preferred Term from Month 6 to Month 6 FU - Follow-up Safety Analysis Set
- Table 14.3.1.5.1 Treatment-Emergent Adverse Events Related to Add-Back Therapy by MedDRA SOC and Preferred Term from Day 1 to Month 6 - Safety Analysis Set
- Table 14.3.1.5.2 Treatment-Emergent Adverse Events Related to Add-Back Therapy by MedDRA SOC and Preferred Term from Month 6 to Month 6 FU - Follow-up Safety Analysis Set
- Table 14.3.1.6.1 Non-Serious Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Day 1 to Month 6 - Safety Analysis Set
- Table 14.3.1.6.2 Non-Serious Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Month 6 to Month 6 FU - Follow-up Safety Analysis Set
- Table 14.3.2.1.1 Serious Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Day 1 to Month 6 - Safety Analysis Set
- Table 14.3.2.1.2 Serious Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Month 6 to Month 6 FU - Follow-up Safety Analysis Set
- Table 14.3.2.3.1 Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of IMP by MedDRA SOC and Preferred Term from Day 1 to Month 6 - Safety Analysis Set
- Table 14.3.2.3.2 Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of IMP by MedDRA SOC and Preferred Term from Month 6 to Month 6 FU - Follow-up Safety Analysis Set
- Table 14.3.2.4.1 Fatal Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Day 1 to Month 6 - Safety Analysis Set
- Table 14.3.2.4.2 Fatal Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Month 6 to Month 6 FU - Follow-up Safety Analysis Set
- Table 14.3.2.5.1 Post-treatment Adverse Events by MedDRA SOC and Preferred Term from Month 6 to Month 6 FU - Follow-up Safety Analysis Set

Section 14.4 Other Safety Data

- Table 14.4.1.1.1 Bone Mineral Density (BMD) by Dual-Energy X-ray Absorptiometry (DXA) up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.1.2.1 Bone Mineral Density (BMD) by Dual-Energy X-ray Absorptiometry (DXA) - Category of Percent Change from Baseline up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.1.3.1 Bone Mineral Density (BMD) by Dual-Energy X-ray Absorptiometry (DXA) Z-scores up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.2.1 Hematology Parameters by Visit up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.2.2 Hematology Parameters - Shifts from Baseline Based on Clinical Findings up to Month 6 Follow-up– Safety Analysis Set
- Table 14.4.2.3 Hematology Parameters - Shifts from Baseline Based on Normal Ranges up to Month 6 Follow-up– Safety Analysis Set
- Table 14.4.3.1 Coagulation Parameters by Visit up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.3.2 Coagulation Parameters - Shifts from Baseline Based on Clinical Findings up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.3.3 Coagulation Parameters - Shifts from Baseline Based on Normal Ranges up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.4.1 Chemistry Parameters by Visit up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.4.2 Chemistry Parameters - Shifts from Baseline on Clinical Findings up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.4.3 Chemistry Parameters - Shifts from Baseline on Reference Ranges up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.5.1 Lipids by Visit up to Month 6 Follow-up– Safety Analysis Set
- Table 14.4.5.2 Lipids - LDL and HDL Categories by Visit up to Month 6 Follow-up– Safety Analysis Set
- Table 14.4.5.3 Lipids - Shifts from Baseline Based on LDL Categories up to Month 6 Follow-up– Safety Analysis Set
- Table 14.4.5.4 Lipids - Shifts from Baseline Based on Triglycerides Categories up to 6 Month Follow-up – Safety Analysis Set
- Table 14.4.5.5 Lipids Parameters - Shifts from Baseline Based on Clinical Findings up to 6 Month Follow-up –Safety Analysis Set

- Table 14.4.5.6 Lipids Parameters - Shifts from Baseline Based on Normal Ranges from up to 6 Month Follow-up –Safety Analysis Set
- Table 14.4.6.1 Serum levels of E2, P4, SHGB and LH up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.6.2 Estradiol [E2] Categories by Visit up to 6 Month Follow-up – Safety Analysis Set
- Table 14.4.6.3 Proportions of Subjects with P4 at Least once >10.0 nMol/L from Study Day 1 to Month 6 – Safety Analysis Set
- Table 14.4.7.1 Vital Signs by Visit up to Month 6 Follow-up– Safety Analysis Set
- Table 14.4.8.1 Physical Examination Findings up to Month 6 Follow-up– Safety Analysis Set
- Table 14.4.8.2 Physical Examination Findings - Shifts from Baseline up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.9.1 ECG - QTcF by Visit up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.9.2 ECG Findings up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.10.1 Gynecological Examination Findings by Visit from Day 1 to Month 6 Follow-up– Safety Analysis Set
- Table 14.4.11.2 Breast Examination Findings by Visit up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.12.1 Endometrial Biopsy Findings by up to Month 6 Follow-up– Safety Analysis Set
- Table 14.4.12.2 Endometrial Biopsy Diagnosis by Classification and Primary Diagnosis up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.13.1 Prior Medications – Safety Analysis Set
- Table 14.4.13.2 Prior Interventional Surgeries/Procedures for Endometriosis/ Endometriosis Symptoms – Safety Analysis Set
- Table 14.4.14.1 Concomitant Medications up to Month 6– Safety Analysis Set
- Table 14.4.14.2 Concomitant Medications from Month 6 to Month 6 FU – Follow-up Safety Analysis Set
- Table 14.4.15.1 Transvaginal Ultrasound: Uterus Length, Width, Depth, uterine Volume and Thickness up to Month 6 Follow-up – Safety Analysis Set
- Table 14.4.15.2 Transvaginal Ultrasound: Ovaries assessment up to Month 6 Follow-up – Safety Analysis Set

- Table 14.4.16.1 Suicide-related Treatment Emergent Events (C-SSRS) up to Month 6 – Safety Analysis Set
- Table 14.4.16.2 Suicide-related Events (C-SSRS) from Month 1 FU to Month 6 FU – Follow-up Safety Analysis Set

Post-text Listings

- Listing 16.1.7 Randomization scheme and codes (patient identification and treatment) - Randomized Set
- Listing 16.2.1.1 Subject Disposition and Study Termination Information – Part A - Randomized Set
- Listing 16.2.1.2 Subject Disposition and Study Termination Information – Part B - Randomized Set
- Listing 16.2.2.1 Inclusion Criteria – Screened Set
- Listing 16.2.2.2 Exclusion Criteria – Screened Set
- Listing 16.2.2.3 Protocol Deviations - Randomized Set
- Listing 16.2.3.1 Analysis Sets - Randomized Set
- Listing 16.2.3.2 Subjects with actual treatment not corresponding to any of the planned treatment groups - Safety Analysis Set
- Listing 16.2.4.1 Demographic and Baseline Information – Randomized Set
- Listing 16.2.4.2 Menstrual Cycle – Randomized Set
- Listing 16.2.4.3 Biberoglu & Behrman at Screening – Randomized Set
- Listing 16.2.4.4 Pelvic Pain Scores and Analgesic Use at Baseline – Randomized Set
- Listing 16.2.4.5 Endometriosis History – Randomized Set
- Listing 16.2.4.6 Medical History – Randomized Set
- Listing 16.2.5.1 Dispensing and Study Treatment Administration - Randomized Set
- Listing 16.2.5.2 Study Treatment Overdose and Misuse - Safety Analysis Set
- Listing 16.2.5.3 Extent of exposure and Treatment Compliance on the main study treatment period - Safety Analysis Set
- Listing 16.2.6.1 Daily Diary – Endometriosis pelvic pain and analgesic use - Randomized Set
- Listing 16.2.6.2 Daily Diary – Daily function, daily difficulties, and other pains - Randomized Set

- Listing 16.2.6.3 Monthly severity questions - Randomized Set
- Listing 16.2.6.4 EHP-30 Questionnaire over Time - Randomized Set
- Listing 16.2.6.5 HRPQ Questionnaire over Time - Randomized Set
- Listing 16.2.6.6 HRUQ Questionnaire over Time – Non-study endometriosis related health visits - Randomized Set
- Listing 16.2.6.7 HRUQ Questionnaire over Time – Diagnostic or therapeutic procedures - Randomized Set
- Listing 16.2.6.8 HRUQ Questionnaire over Time – Nights in Hospital - Randomized Set
- Listing 16.2.6.9 Physician and Subject Surgery Intention Question over Time - Randomized Set
- Listing 16.2.6.10 PROMIS Fatigue Questionnaire over Time - Randomized Set
- Listing 16.2.6.11 EQ-5D-5L Questionnaire over Time – Randomized Set
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