Sponsor:	**ObsEva**		
Protocol:	**19-OBE2109-005**		
Document Version No.:	1.0	**Document Date:**	18-MAY-2021

Protocol 19-OBE2109-005

A Phase 3 extension study to assess the long-term efficacy and safety of of linzagolix in subjects with endometriosis-associated pain.

Protocol Number:	19-OBE2109-005
(Version Date)	Version 2.0, 24 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

Sponsor:	**ObsEva**		
Protocol:	**19-OBE2109-005**		
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SIGNATURE PAGE

Protocol Title:	A double-blind randomized extension study to assess the long-term efficacy and safety of linzagolix in subjects with endometriosis-associated pain.
Sponsor:	ObsEva S.A.
Protocol Number:	18-OBE2109-005
Document Date/Version:	18 May 2021 / Version 1.0

Cytel, Inc. Author:

Sponsor:	**ObsEva**		
Protocol:	**19-OBE2109-005**		
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]

Sponsor:	**ObsEva**		
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ABBREVIATIONS

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

Abbreviation	Definition
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
P4	Progesterone
PD	Pharmacodynamic

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Abbreviation	**Definition**
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

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1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

This is a prospective, randomized, double-blind study. Subjects who had completed the 6-month Treatment Period in the main study (18-OBE2109-002 - Edelweiss 2) were invited to enter the extension study. Month 6 visit of the main study was a decision point for Subjects to either end treatment and enter a post-treatment follow up period (part of the main study), or to opt for a 6-month treatment extension.

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

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

1.2. Objectives of Statistical Analysis

Following the early termination of the main study (18-OBE2109-002), this extension study was early terminated as well 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 extension study was to assess the maintenance of efficacy of linzagolix administered orally once daily for up to an additional 6 months (for up to 12 months of treatment in total) in women who had already completed 6 months of linzagolix treatment at a dose of 75 mg alone or of 200 mg in combination with add-back therapy (estradiol (E2) 1 mg / norethisterone acetate (NETA) 0.5 mg) in the management of moderate to severe endometriosis-associated pain (EAP) in women with surgically confirmed endometriosis. The two co-primary efficacy endpoints were clinically meaningful reduction over the last 28 days of randomized treatment up to the Month 12 visit, along with a stable or decreased use of analgesics for EAP, for 1) dysmenorrhea (DYS) and for 2) non menstrual pelvic pain (NMPP).

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

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

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

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

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

2. STUDY DESIGN

2.1. Synopsis of Study Design

This was a prospective, randomized, double-blind study. Subjects who completed the 6-month Treatment Period in the main study (18-OBE2109-002 - Edelweiss 2) were invited to enter the present extension study. Month 6 visit of the main study was a decision point for Subjects to either end treatment and enter a post-treatment follow up (part of the main study), or to opt for a 6-month treatment extension.

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

All subjects received once daily linzagolix 75 mg alone (with ABT placebo) or 200 mg combined with ABT for 6 months. Subjects who received placebo during the main study were randomized in a 1:1 ratio to either linzagolix 75 mg alone (with ABT placebo) or linzagolix 200 mg with ABT. Subjects who received active treatment during the main study continued with the same treatment.

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

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

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

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

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

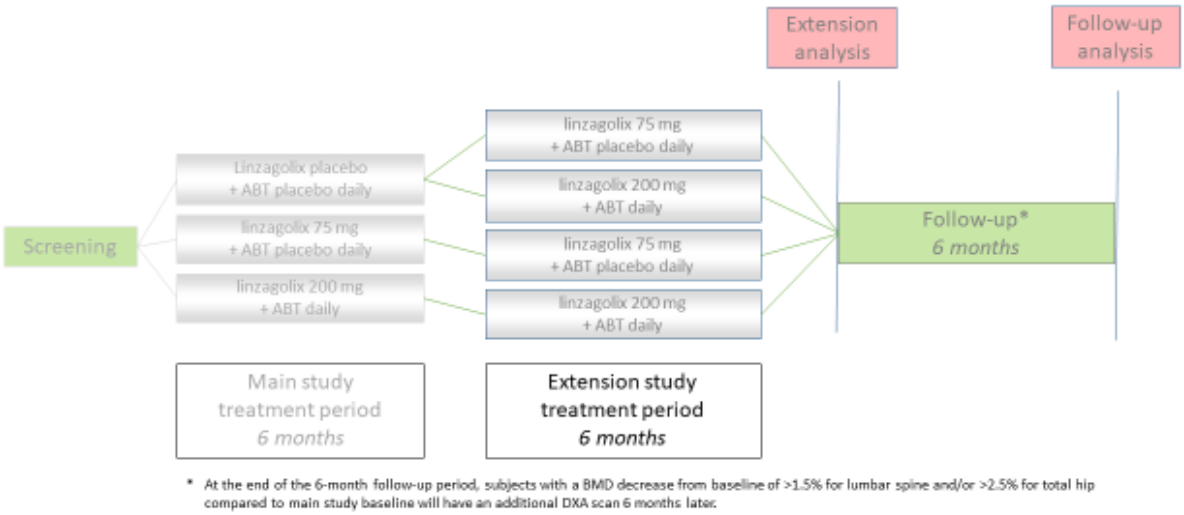

Figure 1: Study design

Two analyses were planned: one after all subjects completed the Treatment Period and one after all subjects completed the Post-Treatment Follow-up Period. 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

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

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

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

2.3. 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 was to be ended prematurely without asking for her consent.

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

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 during the Treatment Period:

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

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

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 – Extension Treatment Period

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

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

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

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

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

[5] Overnight fasting is required.

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

Schedule of study assessments – Extension Treatment Period (cont'd)							
Timing[1]	**Treatment Period**						
	M6[2]	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**
Contraceptive dispensing and counselling	x	x	x	x	x	x	x
Permitted analgesic prescribing/dispensing	x	x	x	x	x	x	x
Vitamin D and calcium dispensing	x	x	x	x	x	x	x
Subject eDiary completion check	x	x	x	x	x	x	x
IMP accountability	x	x	x	x	x	x	x
Dispense linzagolix/placebo kit	x	x	x	x	x	x	
Dispense ABT/placebo kit	x			x			
EHP-30, EQ-5D-5L and PROMIS[3]	x	x		x			x
mPGIS, PGIC, HRUQ and HRPQ[3]	x	x	x	x	x	x	x
SSIQ and PSIQ[3]	x						x
Blood sample for PK[4]	x	x	x	x	x	x	x
E2, LH, P4	x	x	x	x	x	x	x
SHBG	x			x			x
Bone biomarkers	x			x			x

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

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

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

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

Table 2 Schedule of study assessments - Extension Follow-up Period

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

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

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

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

[4] Overnight fasting is required.

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

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

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

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)
- 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 the statistical analysis:

Extension Safety Analysis Set: All subjects randomized who entered the extension study and received at least one dose of study drug in the extension study irrespective of the treatment received. Subjects will be analyzed according to treatment received

Follow-up Extension Safety Analysis Set: All subjects randomized who entered the extension study and who entered the drug free extension follow-up period. Subjects will be analyzed according to treatment received.

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

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

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

For combined planned treatment groups, the planned treatment during the main study and the planned treatment during the extension study comprise the following four combined planned treatment groups:

- Placebo / LGX 75 mg: for subjects randomized to placebo in the main study and randomized to LGX 75 mg in the extension study
- Placebo / LGX 200 mg + ABT: for subjects randomized to placebo in the main study and randomized to LGX 200 mg + ABT in the extension study
- LGX 75 mg: for subjects randomized to LGX 75 mg in the main study and continued with the same treatment in the extension study
- LGX 200 mg + ABT: for subjects randomized to LGX 200 mg + ABT in the main study and continued with the same treatment in the extension study

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

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

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

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 minor or major based on their effect on the right, safety or well-being of the subjects and/or the quality and integrity of the data. The following deviations will be considered as major:

- Non-compliance with inclusion criteria 2
- Non-compliance with exclusion criteria 2; 3; 4; 5; 6
- 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 and by treatment group on the Extension Safety Analysis Set.

All protocol deviations will be presented in the data listings.

4. STATISTICAL METHODS

4.1. Sample Size Justification

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

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, and safety parameters.

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

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

For continuous data and for ordered categorical data, if appropriate, the number of non-missing observations, mean, standard deviation, median, first and third quartiles, minimum and maximum will be calculated, including for change from baseline when applicable. The baseline mean will be calculated for all subjects based on the 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 formal hypothesis tests are planned for this extension study. Data will be summarized by timepoint for each treatment group.

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.

Withdrawal during treatment period:

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

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

Withdrawal during follow-up period:

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

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 allowed 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

4.2.9. **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 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 9 will be derived as the first non-missing DXA assessment with acceptable quality (accepted="Yes") and dated between Month 9 theoretical date (=Day 253) -28 days and Month 9 theoretical date + 28 days.
- The DXA assessment at Month 12 will be derived as the first non-missing DXA assessment with acceptable quality (accepted="Yes") and dated between Month 12 theoretical date (=Day 337 in the main study) -28 days and Month 12 theoretical date + 28 days.
- The DXA assessment at Month 6 Extension Follow-Up will be derived in the same way as the DXA assessment at Month 6. Theoretical date of Month 6 Extension Follow-up is 168 days after Month 12 theoretical date or after treatment discontinuation.

Other safety data:

For other safety data, data from early discontinuation should be compared to theoretical visits dates. Only assessments within the window of theoretical date +/-14 days will be used for analyses, if it is planned to have a such assessment at this visit and no other assessment is in the window. If a subject discontinued in the extension treatment period, date will be compared to the theoretical visit dates in extension treatment period as described in Table 3. If a subject discontinued in the extension follow-up period, date will be compared to the theoretical visit dates in extension Follow-up period from Table 4.

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

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

Table 3 Theoretical Visit Dates in Extension Treatment Period

Visit	Theoretical Date
Month 6	Day 169
Month 7	Day 197
Month 8	Day 225
Month 9	Day 253
Month 10	Day 281
Month 11	Day 309
Month 12	Day 337

Table 4 Theoretical Visit Dates in Extension Follow-up Period

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

4.2.11. Baseline Definitions

The baseline will be described in two ways:

- Main Baseline, defined in the Statistical Analysis Plan of the main study and calculated according to first dose of IMP taken during the main Study.
- Second Baseline (named Baseline 2), defined as the last assessment before the first active dose of IMP during the extension study. The baseline 2 will be calculated only for the subjects who are in the placebo arm (actual arm) in the main study.

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

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

For subjects who entered the extension, the end of the extension study date will be the last assessment date in the extension study defined as last assessment recorded in the eCRF (excluding end date of adverse events and concomitant medications) or ediary date.

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 the Month 6 date will be part of the extension for subjects entering the extension study, and will be part of the main Follow-up period for subjects entering the main study follow-up period.
- For Adverse Events, Concomitant Medications and Daily diaries, data collected on the Month 12 date will be part of the Extension Follow-up period for subjects entering the Extension follow-up period.

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

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

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 in the main study, including :

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

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

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

The following listings will be presented:

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

4.5. Demographic and Baseline Characteristics

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

No formal statistical comparisons will be performed.

4.5.1. Demographics

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

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

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

Demographic and Baseline data will be provided in data listings.

4.5.2. Baseline Disease Characteristics

For the 4 treatment groups (as detailed in section 4.2.1), the following parameters, recorded at baseline in the main study, will be calculated as described in section 4.5.2 of the SAP of the main study.

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

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

- The number and percentage of subjects with Normal, Abnormal, Abnormal clinically significant (or Not Assessable) results for Physical Examination, Gynecological Examination, Breast Examination, Mammography (if required), Endometrial Biopsy (if required), for baseline 2.

- Baseline 2 Transvaginal ultrasound data (i.e., presence of ovarian endometrioma with a diameter of 7 cm or greater, uterus length, width, and depth in mm and corresponding calculated uterine volume in cm3 (using the prolate ellipsoid formula [L x H x W x 0.523]), endometrium thickness in mm, and presence of any uterus, left ovary or right ovary abnormality).

Baseline Disease Characteristics will be reported in listings.

4.5.3. Medical History

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

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

Medical history will be reported in a listing.

4.5.4. Endometriosis History

For the 4 treatment groups (as detailed in section 4.2.1), the following parameters, recorded at baseline in the main study, will be calculated as described in section 4.5.2 of the SAP of the main study.

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

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

Endometriosis History will be reported in a listing.

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.

4.8. **Safety Analyses**

Safety analyses will be conducted using the Extension Safety Analysis Set.

4.8.1. **Extent of treatment exposure and compliance on the extension study**

4.8.1.1. Extent of treatment exposure in the extension study

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

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

Exposure data will be reported in listings.

4.8.1.2. Compliance in the extension study

Lingazolix/Placebo Grey blister (200 mg or matching placebo), Lingazolix/Placebo Pink blister (75 mg or matching placebo) and Add-back therapy compliances from the study treatment accountability page will be summarized on the extension treatment period 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/red capsule taken *100 divided by the number of days in the period (Month 12 visit date/discontinuation date - Month 6 visit date). Data from “Today” will be used primarily. If data from today is missing, date from “Yesterday” will be considered. If the e-diary is not completed for a day (neither “Today” nor “Yesterday), it will be assumed that no drug was taken on that day.

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

Compliance will be reported in a listing.

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 extension study drug through 30 days after discontinuation of study drug or Month 12 visit date, or any event that was present at Month 6 but worsened in intensity or was subsequently considered drug-related by the investigator through the end of the extension study.

Adverse Event tables will be presented for the following periods: Month 6 to Month 12 (Extension treatment period) and Month 12 to Month 6 ExFU (Extension follow-up period) as defined in section 4.2.12.

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

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

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

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

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

The number and percentage of subjects with any treatment-emergent adverse event will be summarized by treatment group and by SOC and PT.

If serious TEAEs are observed in the study, the number and percentage of subjects with any non-serious treatment-emergent adverse event will be summarized by treatment group.

Serious TEAE, TEAE assessed by the Investigator as related to treatment (definite, probable, or possible relationship), TEAE leading to permanent discontinuation of IMP, TEAE leading to permanent discontinuation of IMP leading to death and post-treatment AE will be only listed due to the low number of subjects included in the extension study.

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

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

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

The ongoing status collected in eCRF will be ignored.

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

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

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

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 9 (if required) Month 12 and Month 6 of the extension follow-up (if required). Unacceptable DXA assessments (accepted="No") will not be summarized (hip, spine and femur considered separately).

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

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

BMD, expressed as both absolute values and Z-scores will be summarized at each visit in terms of actual values, changes from baseline, changes from baseline 2 (only for the subjects who are in the placebo arm in the main study) for each anatomic location. For absolute values only, percent change from baseline, percent changes from baseline 2 (only for the subjects who are in the placebo arm in the main study) and 95% confidence interval for the mean percent change from baseline and for the mean percent change from baseline 2 within each group will be produced at each time point.

The definition of both baselines are described in section 4.2.11.

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

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

All data 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 extension treatment period (from M7 to M12), as well as at the M1 ExtFU and M3 ExtFU visits.

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

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

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

For Hematology, coagulation parameters, chemistry and lipids, the actual value, change from baseline and change from baseline 2 (only for the subjects who are in the placebo arm in the main study) will be summarized for each visit for each treatment group. In the event of repeated values, the last non-missing value per study day/time will be used.

Evaluation of shifts for changes from baseline and for changes from baseline 2 (only for the subjects who are in the placebo arm in the main study) to all visits according to the normal ranges with categories “Low”, “Normal”, “High” and according to normal/abnormal/abnormal clinically significant information collected otherwise, will be provided.

For Liver Function Test (LFT) parameters (ALT, AST, ALP, total bilirubin, direct bilirubin, indirect bilirubin, GGT, LDH, albumin 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 and the percent change from baseline 2 (only for the subjects who are in the placebo arm in the main study) to each on-study visit will also be summarized.

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.

Note that no serum levels of E2 is measured for subjects in extension study due to the early termination study.

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

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

- LDL ≥ 160 mg/dL

- LDL ≥ 190 mg/dL
- HDL < 40 mg/dL

will be reported at each visit.

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

LDL:

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

Triglycerides:

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

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

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

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

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

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

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

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

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

4.8.6. Electrocardiogram

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

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

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

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

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

4.8.7. Concomitant Medications

Concomitant medications will be coded using the WHO Drug dictionary. Frequencies and percentages will be presented for each treatment group and overall by the first level anatomical main (ATC 1) group and preferred name.

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

Concomitant medications tables will be presented for the following periods: Month 6 to Month 12 (Extension treatment period) and Month 12 to Month 6 ExFU (Extension follow-up period) as defined in section 4.2.12.

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

4.8.8. Transvaginal Ultrasound (TVUS)

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

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

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

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

4.8.9. Other Examinations

4.8.9.1. Endometrial biopsy

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

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

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

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

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

Results will also be reported in listings.

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 completed:

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

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

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

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

The 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 in the extension study, will be summarized from Month 6 up to Month 12.

- 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.

Same analysis will be repeated on the extension follow-up period.

4.9. Exploratory Analyses

Bone turnover markers will be listed on the Extension 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 (if data available) for these assessments will be displayed. The statistical analysis plan (SAP) will be focused on the safety analysis.

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:	**19-OBE2109-005**		
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 included in the extension study by Country and Site - Included in the extension study
- Table 14.1.2 Patient Disposition by treatment group – Randomized Subjects
- Table 14.1.3 Analysis Sets – Extension Safety Analysis Set
- Table 14.1.4 Number of Subjects by Visit - Extension Safety Analysis Set
- Table 14.1.4 Major Protocol Deviations – Extension Safety Analysis Set
- Table 14.1.5 Demographic and Baseline Characteristics – Extension Safety Analysis Set
- Table 14.1.6.1 Baseline Disease Characteristics: Menstrual Cycles and Pain – Extension Safety Analysis Set
- Table 14.1.6.2 Disease Characteristics before the first active dose of IMP: Menstrual Cycles and Pain – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.1.7.1 Baseline Disease Characteristics: Transvaginal Ultrasound – Extension Safety Analysis Set
- Table 14.1.7.2 Disease Characteristics before the first active dose of IMP: Transvaginal Ultrasound – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.1.8.1 Other Baseline examinations – Extension Safety Analysis Set
- Table 14.1.8.2 Other Baseline examinations before the first active dose of IMP – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.1.9 Medical History – Extension Safety Analysis Set
- Table 14.1.10 Endometriosis History – Extension Safety Analysis Set
- Table 14.1.11.1 Exposure and Compliance to Study Treatment – Extension Safety Analysis Set

Section 14.3.1 Adverse Events

- Table 14.3.1.1.1 Summary of Treatment-Emergent Adverse Events from Month 6 to Month 12 – Extension Safety Analysis Set
- Table 14.3.1.1.2 Summary of Treatment-Emergent Adverse Events from Month 12 to Month 6 ExFU - Follow-up Extension Safety Analysis Set
- Table 14.3.1.2.1 Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Month 6 to Month 12 – Extension Safety Analysis Set
- Table 14.3.1.2.2 Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Month 12 to Month 6 ExFU – Follow-up Extension Safety Analysis Set
- Table 14.3.1.3.1 Non-Serious Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Month 6 to Month 12 – Extension Safety Analysis Set (if applicable)
- Table 14.3.1.3.2 Non-Serious Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term from Month 12 to Month 6 ExFU – Follow-up Extension Safety Analysis Set (if applicable)

Section 14.4 Other Safety Data

- Table 14.4.1.1.1 Bone Mineral Density (BMD) by Dual-Energy X-ray Absorptiometry (DXA) from Month 7 up to Month 6 Extension Follow-up – Extension 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 Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.1.3.1 Bone Mineral Density (BMD) by Dual-Energy X-ray Absorptiometry (DXA) Z-scores from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.2.1 Hematology Parameters by Visit from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.2.2 Hematology Parameters - Shifts from Baseline Based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.2.3 Hematology Parameters - Shifts from Baseline 2* based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.2.4 Hematology Parameters - Shifts from Baseline Based on Normal Ranges from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set

- Table 14.4.2.5 Hematology Parameters - Shifts from Baseline 2* based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.3.1 Coagulation Parameters by Visit from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set See shell for Table 14.4.2.1.
- Table 14.4.3.2 Coagulation Parameters - Shifts from Baseline Based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.3.3 Coagulation Parameters - Shifts from Baseline 2* based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.3.4 Coagulation Parameters - Shifts from Baseline Based on Normal Ranges from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set See shell for Table 14.4.2.4.
- Table 14.4.3.5 Coagulation Parameters - Shifts from Baseline 2* based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.4.1 Chemistry Parameters by Visit from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set See shell for Table 14.4.2.1.
- Table 14.4.4.2 Chemistry Parameters - Shifts from Baseline Based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.4.3 Chemistry Parameters - Shifts from Baseline 2* based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.4.4 Chemistry Parameters - Shifts from Baseline Based on Normal Ranges from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.4.5 Chemistry Parameters - Shifts from Baseline 2* based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.5.1 Lipids by Visit from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set See shell for Table 14.4.2.1.

- Table 14.4.5.2 Lipids - LDL and HDL Categories by Visit from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.5.3 Lipids - Shifts from Baseline Based on LDL Categories from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.5.5 Lipids - Shifts from Baseline 2* Based on LDL Categories from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.5.6 Lipids - Shifts from Baseline Based on Triglycerides Categories from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.5.7 Lipids - Shifts from Baseline 2* Based on Triglycerides Categories from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.5.8 Lipids Parameters - Shifts from Baseline Based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.5.9 Lipids Parameters - Shifts from Baseline 2* based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.5.10 Lipids Parameters - Shifts from Baseline Based on Normal Ranges from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.5.11 Lipids Parameters - Shifts from Baseline 2* based on Clinical Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.6.1 Serum levels of P4, SHGB and LH from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.6.3 Proportions of Subjects with P4 at Least once >10.0 nMol/L from Month 6 to Month 12 – Extension Safety Analysis Set
- Table 14.4.7.1 Vital Signs by Visit from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.8.1 Physical Examination Findings from Month 9 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.8.2 Physical Examination Findings - Shifts from Baseline from Month 9 up to Month 6 Extension Follow-up – Extension Safety Analysis Set

- Table 14.4.8.3 Physical Examination Findings - Shifts from Baseline 2* from Month 9 up to Month 6 Extension Follow-up – Extension Safety Analysis Set – subset of subjects who are in the placebo arm (actual arm) in the main study
- Table 14.4.9.1 ECG - QTcF by Visit from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.9.2 ECG Findings from Month 7 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.10.1 Gynecological Examination Findings by Visit from Month 9 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.11.2 Breast Examination Findings by Visit from Month 9 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.12.1 Endometrial Biopsy Findings by visit from Month 12 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.12.2 Endometrial Biopsy Diagnosis by Classification and Primary Diagnosis from Month 12 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.13.1 Concomitant Medications From Month 6 to Month 12 – Extension Safety Analysis Set
- Table 14.4.13.2 Concomitant Medications From Month 12 to Month 6 Extension Follow-up– Follow-up Extension Safety Analysis Set
- Table 14.4.14.1 Transvaginal Ultrasound: Uterus Length, Width, Depth, uterine Volume and
- Thickness by Visit from Month 9 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.14.2 Transvaginal Ultrasound: Ovaries assessment by Visit from Month 9 up to Month 6 Extension Follow-up – Extension Safety Analysis Set
- Table 14.4.15.1 Suicide-related Treatment Emergent Events (C-SSRS) from Month 7 up to Month 12 – Extension Safety Analysis Set
- Table 14.4.15.2 Suicide-related Events (C-SSRS) from Month 1 ExFU to Month 6 ExFU – Follow-up Extension Safety Analysis Set

Post-text Listings

- Listing 16.1.7 Randomization scheme and codes (patient identification and treatment) – Extension Safety Analysis Set

- Listing 16.2.1.1 Subject Disposition and Study Termination Information – Part A - Extension Safety Analysis Set
- Listing 16.2.1.2 Subject Disposition and Study Termination Information – Part B – Extension Safety Analysis Set
- Listing 16.2.2.1 Inclusion Criteria – Extension Safety Analysis Set
- Listing 16.2.2.2 Exclusion Criteria – Extension Safety Analysis Set
- Listing 16.2.2.3 Protocol Deviations – Extension Safety Analysis Set
- Listing 16.2.3.1 Analysis Sets – Extension Safety Analysis Set
- Listing 16.2.3.2 Subjects with actual treatment not corresponding to any of the planned treatment groups – Extension Safety Analysis Set
- Listing 16.2.4.1 Demographic and Baseline Information – Extension Safety Analysis Set
- Listing 16.2.4.2 Menstrual Cycle – Extension Safety Analysis Set
- Listing 16.2.4.3 Biberoglu & Behrman at Screening – Extension Safety Analysis Set
- Listing 16.2.4.4 Pelvic Pain Scores and Analgesic Use at Baseline – Extension Safety Analysis Set
- Listing 16.2.4.5 Endometriosis History – Extension Safety Analysis Set
- Listing 16.2.4.6 Medical History – Extension Safety Analysis Set
- Listing 16.2.5.1 Dispensing and Study Treatment Administration – Extension Safety Analysis Set
- Listing 16.2.5.2 Study Treatment Overdose and Misuse – Extension Safety Analysis Set
- Listing 16.2.5.3 Treatment Compliance – Extension Safety Analysis Set
- Listing 16.2.6.1 Daily Diary – Endometriosis pelvic pain and analgesic use – Extension Safety Analysis Set
- Listing 16.2.6.2 Daily Diary – Daily function, daily difficulties, and other pains – Extension Safety Analysis Set
- Listing 16.2.6.3 Monthly severity questions – Extension Safety Analysis Set
- Listing 16.2.6.4 EHP-30 Questionnaire over Time – Extension Safety Analysis Set
- Listing 16.2.6.5 HRPQ Questionnaire over Time – Extension Safety Analysis Set

- Listing 16.2.6.6 HRUQ Questionnaire over Time – Non-study endometriosis related health visits – Extension Safety Analysis Set
- Listing 16.2.6.7 HRUQ Questionnaire over Time – Diagnostic or therapeutic procedures - Extension Safety Analysis Set
- Listing 16.2.6.8 HRUQ Questionnaire over Time – Nights in Hospital - Extension Safety Analysis Set
- Listing 16.2.6.9 Physician and Subject Surgery Intention Question over Time - Extension Safety Analysis Set
- Listing 16.2.6.10 PROMIS Fatigue Questionnaire over Time - Extension Safety Analysis Set
- Listing 16.2.6.11 EQ-5D-5L Questionnaire over Time - Extension Safety Analysis Set
- Listing 16.2.6.12 Patient Global Impression of Change over Time - Extension Safety Analysis Set
- Listing 16.2.6.13 Patient Global Impression of Severity over Time - Extension Safety Analysis Set
- Listing 16.2.7.1 All Adverse Events by Subject and MedDRA SOC/ PT and Verbatim Term - Extension Safety Analysis Set
- Listing 16.2.7.2 Treatment Emergent Adverse Events by Subject and MedDRA SOC/ PT and Verbatim Term - Extension Safety Analysis Set
- Listing 16.2.7.3 Related Treatment Emergent Adverse Events by Subject and MedDRA SOC/ PT and Verbatim Term - Extension Safety Analysis Set
- Listing 16.2.7.4 Serious Treatment Emergent Adverse Events by Subject and MedDRA SOC/ PT and Verbatim Term - Extension Safety Analysis Set
- Listing 16.2.7.5 Treatment-Emergent Adverse Events Leading to Discontinuation by Subject and MedDRA SOC/ PT and Verbatim Term - Extension Safety Analysis Set
- Listing 16.2.7.6 Treatment-Emergent Adverse Events Leading to Death by Subject and MedDRA SOC/ PT and Verbatim Term - Extension Safety Analysis Set
- Listing 16.2.7.7 Post-Treatment Adverse Events and MedDRA SOC/ PT and Verbatim Term - Extension Safety Analysis Set
- Listing 16.2.8.1.1 Central Laboratory Hematology - Extension Safety Analysis Set

- Listing 16.2.8.1.1 Central Laboratory Hematology: Abnormal Clinically Significant Values - Extension Safety Analysis Set
- Listing 16.2.8.2.1 Central Laboratory: Coagulation - Extension Safety Analysis Set
- Listing 16.2.8.2.2 Central Laboratory Coagulation: Abnormal Clinically Significant Values - Extension Safety Analysis Set
- Listing 16.2.8.3.1 Central Laboratory: Chemistry - Extension Safety Analysis Set
- Listing 16.2.8.3.2 Central Laboratory Chemistry: Abnormal Clinically Significant Values - Extension Safety Analysis Set
- Listing 16.2.8.4.1 Central Laboratory: Lipids - Extension Safety Analysis Set
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- Listing 16.2.8.6 Urinary Protein Dipstick / Urinary Pregnancy Test - Extension Safety Analysis Set
- Listing 16.2.9.1 Vital Signs - Extension Safety Analysis Set
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- Listing 16.2.9.6 PAP Smear - Extension Safety Analysis Set
- Listing 16.2.9.7 Prior Medications - Extension Safety Analysis Set
- Listing 16.2.9.8 Prior Interventional Surgeries/Procedures for Endometriosis/ Endometriosis Symptoms – Extension Safety Analysis Set
- Listing 16.2.9.9 Concomitant Medications - Extension Safety Analysis Set
- Listing 16.2.9.10 Bone Mineral Density (BMD) by Dual-Energy X-ray Absorptiometry (DXA) - Extension Safety Analysis Set
- Listing 16.2.9.11 Endometrial Biopsy - Extension Safety Analysis Set

- Listing 16.2.9.12 lead ECG - Extension Safety Analysis Set
- Listing 16.2.9.13 CSSR-S – Extension Safety Analysis Set
- Listing 16.2.9.14 Bone Turnover Markers – Extension Safety Analysis Set

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