CLINICAL STUDY PROTOCOL

Protocol Number:	**19-OBE2109-005**
Investigational Medicinal Product:	**Linzagolix (OBE2109)**
Study Title:	**A double-blind randomized extension study to assess the long-term efficacy and safety of linzagolix in subjects with endometriosis-associated pain.**
Short Study Title:	**A phase 3 extension study to assess the efficacy and safety of linzagolix to treat endometriosis-associated pain**
Study Name:	**Edelweiss 2 extension**
Version number:	Version 2.0
Date:	24 August 2020
Replacing:	Version 1.0 – 14 October 2019
Study Sponsor:	**ObsEva S.A.** [redacted]
Clinical Trial Director:	[redacted]
Medical Responsible:	[redacted]
CRO	[redacted]
CRO Project Director:	[redacted]

VERSION HISTORY			
Amendment Number	**Amendment Date**	**General / Country-Specific/ Site-Specific**	**Amended Protocol version and date**
01	24 Aug 2020	General	V2.0 – August 24, 2020

CONFIDENTIAL AND PROPRIETARY

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*Note: Other ObsEva **or delegate personnel** who may be contacted by study site personnel for this study are listed in a separate document, which will be updated on a regular basis when necessary.*

SPONSOR AND CONTRACT RESEARCH ORGANIZATION(S) SIGNATORY APPROVAL PAGE

The below signatories have read this trial protocol and agree with its principles. They agree to carry out the clinical trial in compliance with this protocol, with ICH Good Clinical Practice (ICH GCP) and the applicable regulatory requirements.

Sponsor:

ObsEva S.A., [redacted]

[redacted]

Signature Date of signature

[redacted]

(Clinical Trial Director)

[redacted]

Signature signature

[redacted]

(Medical Responsible)

Contract Research Organization(s):

[redacted]

[redacted]

Signature Date of signature

[redacted]

(Project Director)

INVESTIGATOR ENDORSEMENT PAGE

I, the undersigned, am responsible for the conduct of the study at this site and agree to the following:

- I understand and will conduct the study according to the protocol, any approved protocol amendments, ICH GCP and all applicable regulatory authority requirements and national laws.
- I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent any immediate danger to the subject.
- I have read and understand fully the Investigator Brochure (IB) for linzagolix, and I am familiar with the Investigational Medicinal Product (IMP) and its use according to this protocol.
- I have sufficient time to properly conduct and complete the trial within the agreed trial period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- I will ensure that any staff at my site(s) who are involved in the study conduct are adequately trained regarding the IMP, the protocol and their responsibilities. In the case of delegating any of my study responsibilities I will provide the Sponsor with a Delegation of Activities certificate.
- I understand that some regulatory authorities require sponsors of clinical studies to obtain and supply, when required, details about the Investigators' ownership interests in the Sponsor or the Investigational Medicinal Product and information regarding any financial ties with the Sponsor. The Sponsor will use any such information that is collected solely for the purpose of complying with regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children), and to provide updates as necessary.

Signature	Date of signature

PI Name:

Institution:

1 TABLE OF CONTENTS

2 LIST OF FIGURES

3 LIST OF ABBREVIATIONS

ABT	Add-Back Therapy
AE	Adverse Event
ALT	ALanine amino Transferase
APTT	Activated Partial Thromboplastin Time
AST	ASpartate amino Transferase
AUC	Area Under the Curve
B-ALP	Bone-specific Alkaline Phosphatase
BMD	Bone Mineral Density
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats Per minute
°C	Degree Celsius
CK	Creatine Kinase
ClinRO	Clinician Reported Outcome
COC	Combined Oral Contraceptive
CRA	Clinical Research Associate
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTx	C-terminal telopeptide
CV	Coefficient of Variation
CYP	Cytochrome P
DMC	Data Monitoring Committee
dPGIS	Patient Global Impression of Severity – daily recall
DXA	Dual-energy X-ray Absorptiometry
DYS	Dysmenorrhea
E2	Estradiol

EAP	Endometriosis-Associated Pain
ECG	ElectroCardioGram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EHP-30	Endometriosis Health Profile – 30
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQol 5 Dimension 5 Level questionnaire
EU	European Union
ExFU	Extension Follow-Up
FD	Fixed Dose
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
γGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRPQ	Health-Related Productivity Questionnaire
HRUQ	Health Resource Utilization Questionnaire
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intra-Uterine Device

IWRS	Interactive Web Response System
LDH	Lactate DeHydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LH	Luteinizing Hormone
LOQ	Limit Of Quantification
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	Milligram
min	Minute
MME	Morphine Milligram Equivalent
mPGIS	Patient Global Impression of Severity – monthly recall
mmHg	millimeter of mercury
msec	Millisecond
NETA	NorEThisterone Acetate
NMPP	Non-Menstrual Pelvic Pain
NRS	Numeric Rating Scale
NSAID	Non Steroidal Anti-Inflammatory Drug
OAT3	Organic Anion Transporter 3
OBE2109	(2-Hydroxyethyl)trimethylammonium-3-[2-fluoro-5-(2,3-difluoro-6-methoxybenzyloxy)-4-methoxyphenyl]-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,4-d]pyrimidine-5-carboxylate
P1NP	Procollagen type 1 N-terminal Propeptide
P4	Progesterone
PAP	PAPanikolaou test
PD	PharmacoDynamic
PGIC	Patient Global Impression of Change

PPGIC	Post-treatment Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	PharmacoKinetic
PSF	Pregnancy Surveillance Form
PSIQ	Pysician Surgery Intention Question
PVC/Al	PolyVinyl Chloride/Aluminum
QC	Quality Control
QD	Once daily (from the Latin Quaque Die)
QoL	Quality of Life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate (QTc) using Fridericia's correction formula
RBC	Red Blood Cell
REB	Research Ethics Board
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SERM	Selective Estrogen Receptor Modulator
SHBG	Sex Hormone-Binding Globulin
SIN	Subject Identification Number
SPRM	Selective Progesterone Receptor Modulator
SSIQ	Subject Surgery Intention Question
SUSAR	Suspected Unexpected Serious Adverse Reaction
TD	Titrated Dose
TEAE(s)	Treatment Emergent Adverse Event(s)
TVUS	TransVaginal UltraSound
ULN	Upper Limit of Normal
US/USA	United States/United States of America

VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
WBC	White Blood Cell

4 SYNOPSIS

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

Code/Name ObsEva Investigational Drug: linzagolix (OBE2109)	**Phase of Development:** 3

Objectives:

The primary objective of this extension study is 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 have 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 will be 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 include 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 include 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 include assessment of bone turnover markers and collection of pharmacokinetic (PK) and pharmacodynamic (PD) related data of linzagolix for a separate modelling exercise.

Endpoints:

Efficacy endpoints

- **Primary efficacy endpoints:**

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

- **Secondary efficacy endpoints:**
- Change from baseline to Month 12 in DYS (VRS)
- Change from baseline to Month 12 in NMPP (VRS)
- Change from baseline to Month 12 in dyschezia (Numeric Rating Scale - NRS)
- Change from baseline to Month 12 in overall pelvic pain (NRS)
- Change from baseline to Month 12 in the interference of pain with the ability to perform daily activities, measured using the pain dimension of the Endometriosis Health Profile-30 (EHP-30)
- Change from baseline to Month 12 in dyspareunia (VRS)
- No analgesics use for EAP during the preceding 4-week period at each scheduled assessment
- No opiate use for EAP during the preceding 4-week period at each scheduled assessment
- Responder rate at scheduled visit other than Month 12 visit, for DYS and NMPP (VRS)
- Change from baseline to each scheduled assessment in the mean pelvic pain scores for DYS, NMPP and overall pelvic pain, during the previous 4-week period assessed on the NRS and VRS
- Change from baseline to each scheduled assessment in the number of days with moderate to severe pelvic pain during the previous 4-week period assessed on the VRS
- Change from baseline to each scheduled assessment in the mean worst pelvic pain score defined as the mean of the 5 highest daily pain scores reported during the previous 4-week period assessed on the NRS
- Change from baseline to each scheduled assessment in the mean of daily dyspareunia scores reported during the previous 4-week period on the dyspareunia VRS
- Change from baseline to each scheduled assessment in the mean of daily dyschezia scores reported during the previous 4-week period assessed on the dyschezia NRS
- Change from baseline to each scheduled assessment in non-opioid, opioid and combined analgesic use for EAP during the previous 4-week period based on pill count in the eDiary
- Change from baseline to each scheduled assessment in opioid analgesic use for EAP as reported in the eDiary during the previous 4-week period based on morphine milligram equivalent (MME)
- Change from baseline to each scheduled assessment in the number of days of analgesic use (including any class) for EAP during the previous 4-week period as assessed in the eDiary

- Change from baseline to each scheduled assessment in the number of days of opioid analgesic use for EAP during the previous 4-week period as assessed in the eDiary
- Change from baseline to each scheduled assessment in the number of pelvic pain-free days (assessed on the VRS) during the previous 4-week period
- Change from baseline to each scheduled assessment in ability to perform daily activities during the previous 4-week period, as assessed in the eDiary (daily function NRS)
- Change from baseline to each scheduled assessment in the number of days with no difficulty in doing daily activities due to EAP during the previous 4-week period as assessed in the eDiary (daily function NRS)
- Change from baseline to each scheduled assessment in the number of days when dyspareunia was a problem during the previous 4-week period (including days when sexual intercourse was avoided because of anticipation of pain) as assessed on the dyspareunia VRS
- Change from baseline to each scheduled assessment in the number of days when sexual intercourse was avoided because of anticipation of pain during the previous 4-week period as assessed on the dyspareunia VRS
- Change from baseline to each scheduled assessment in the number of days with uterine bleeding (including spotting) during the previous 4-week period measured by eDiary
- Change from baseline to each scheduled assessment in the number of days when school or work was missed due to EAP in the previous 4-week period as reported in the eDiary
- Change from baseline to each scheduled assessment in the number of days when the subject had to go to bed or lie down due to EAP in the previous 4-week period as reported in the eDiary
- Change from baseline to each scheduled assessment in the Pain, Control and powerlessness, Emotional well-being, Social support, Self-image dimensions and the Modular sexual relationship questionnaire of EHP-30 scores
- Change from baseline to each scheduled assessment in the Health-Related Productivity Questionnaire (HRPQ) scores
- Number of non-study endometriosis related health visits, number of days in hospital and type of procedures performed based on Health Resource Utilization Questionnaire (HRUQ) at each scheduled assessment
- Change from baseline to each scheduled assessment in the Physician/Subject Surgery Intention Question (PSIQ/SSIQ)
- Change from baseline to each scheduled assessment in the PROMIS Fatigue – Short Form 6a
- Change from baseline to each scheduled assessment in the EuroQoL 5-Dimension 5-Level (EQ-5D-5L) questionnaire

- Response at each scheduled assessment according to Patient Global Impression of Change (PGIC) (and Post-treatment Patient Global Impression of Change, PPGIC)
- Change from baseline to each scheduled assessment in the monthly PGIS (mPGIS) score

Safety endpoints

- Change from baseline to each scheduled assessment in BMD measured by Dual-energy X-ray Absorptiometry (DXA) of lumbar spine (L1-L4), femoral neck, and total hip
- Incidence and severity of treatment emergent adverse events (TEAEs)
- Incidence and severity of hypoestrogenic TEAEs (hot flush)
- Time to the first post-treatment menses
- Changes in clinical laboratory assessments (hematology, biochemistry, coagulation parameters, hormones, lipids and urinalysis) from baseline to each scheduled assessment
- Any pathological changes from baseline in the endometrium as assessed by histology from endometrial biopsies
- Changes from baseline to each scheduled assessment in any other safety parameter including weight, vital signs, electrocardiogram (ECG), gynecological assessments and endometrial thickness

Exploratory endpoints

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

Study Design: This is a prospective, randomized, double-blind study. Subjects who have completed the 6-month Treatment Period in the main study (18-OBE2109-002 - Edelweiss 2) will be invited to enter the present extension study. Month 6 visit of the main study is 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 starts at the Month 6 visit of the main study. Subjects will be 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 meet the inclusion criteria will be eligible for entry in the extension study.

All subjects will 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 will be 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 will continue with the same treatment.

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

ABT/placebo treatments will be 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 will enter a post-treatment Follow-Up Period of 6 months with no investigational medicinal product (IMP).

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

Study Population: All subjects who have completed the full 6-month Treatment Period in the main study and who meet the inclusion criteria will be invited to enter the extension study.

It is estimated that up to 288 subjects will enter the extension study, assuming that 80% of the patients randomized in the main study will complete the study (namely 360 subjects) and that up to 80 % thereof will enter the extension study.

The study will be conducted at the same investigational sites as in the main study.

Eligibility Criteria:

Inclusion Criteria

To be eligible for inclusion into this extension study, the subjects must **fulfil all** of the following criteria:

1. The subject must provide written informed consent specific to this study prior to starting the extension study treatment.
2. The subject has completed the 6-month treatment in the main study.
3. The subject is willing and able to continue to comply with the requirements of the study protocol for the duration of the extension study.
4. The subject agrees to continue to use only the analgesic rescue medication permitted by the protocol during the Treatment and Follow-up Periods.
5. If of childbearing potential, the subject agrees to continue to use one of the following birth control methods during the entire Treatment Period of the study and until 3 months after the end of treatment:
    a. Sexual abstinence, if this is the subject's habitual practice and/or the subject is routinely abstinent from heterosexual intercourse,
    b. Partner with a vasectomy with confirmed azoospermia,
    c. Double non-hormonal barrier contraception such as condom or diaphragm each combined with spermicide.

Exclusion Criteria

To be eligible for inclusion in this extension study the subject must **not** meet any of the following criteria:

1. The subject is pregnant or is planning a pregnancy within the duration of the study (including the Follow-up Period).
2. The subject is likely to require treatment during the study with any of the medications listed below:
   a. GnRH antagonists
   b. GnRH agonist injections/3-month depot injections
   c. Danazol
   d. Oral contraceptives and other sex hormones
   e. Depot contraceptives
   f. Selective Progesterone Receptor Modulators (SPRMs), Selective Estrogen Receptor Modulators (SERMs) and aromatase inhibitors
   g. Long acting narcotics (i.e. requiring less than once daily dosing)
   h. Systemic glucocorticoid treatments for acute diseases (not depot)
   i. In situ copper intra-uterine device (IUD)
   j. In situ IUD with progestogen
3. The subject is likely to use cannabinoids during the study.
4. The subject has any other clinically significant gynecologic condition identified during the main study on transvaginal ultrasound (TVUS), on endometrial biopsy or at the manual breast examination, which might interfere with the study efficacy and safety objectives.
5. The subject has met any of the main study discontinuation criteria including:
   a. Serum calcium level confirmed on a repeated fasting test above 2.9 mmol/L
   b. BMD decrease from baseline > 8% or a Z-score ≤ -2.5 at either femoral neck, hip or spine on the Month 6 DXA scan during the main study.
   c. QTcF > 500 ms or increase > 60 ms from the highest value prior to first dose during the main study.
   d. Any of the following elevation of hepatic enzymes:
      - 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%)

6. The subject has any condition that, in the opinion of the Investigator, constitutes a risk or a contraindication to the participation of the subject in this extension study, or that could interfere with the study objectives, conduct or assessments.

Investigational Medicinal Product(s) (IMP): the term "Investigational Medicinal Product" (IMP) will refer to the ObsEva investigational drug linzagolix 75 mg tablets and 200 mg tablets, the ABT (E2 1 mg/NETA 0.5 mg) capsules or their matching placebos.

Data Analysis and Statistics

The primary objective of this extension study is 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 the subset of subjects who are treated with linzagolix up to the time point of interest. As such, the focus will be on subjects who received active treatment in the main study. The assessment of subjects who switched from placebo in the main study to active treatment in the extension study will be conducted as a secondary objective.

No formal hypothesis tests are planned for this extension study. Data will be summarized by timepoint for each treatment group. Subjects will be analyzed according to actual treatment received. The following four treatment groups will be analyzed: linzagolix 75 mg and linzagolix 200 mg with ABT fixed dose groups, linzagolix 75 mg and linzagolix 200 mg with ABT after 6 months of placebo treatment. Only subjects with assessments at both baseline and the given time points will be included in the summaries. Baseline values are the same as in the main study (18-OBE2109-002 - Edelweiss 2), i.e. data collected prior to the treatment administration in the main study.

Efficacy analysis methodology

Summaries will be performed using the Treatment Extension Analysis Set and the Follow-up Extension Analysis Set. Data from both the main study and the extension study will be summarized.

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

Safety analysis methodology

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

Data from both the main study and the extension study will be summarized.

Pharmacokinetic analysis methodology

Descriptive statistics of plasma concentrations will include mean (arithmetic and geometric) and standard deviation, median, 1st and 3rd quartiles, minimum, maximum, coefficient of variation (CV%) and number of observations. Concentrations below the limit of quantification (LOQ) will be assigned a value of zero. Explorative analyses of correlations between plasma concentrations and intrinsic PK factors such as e.g. body weight/body mass index (BMI), race, age may be performed, as appropriate, and will be reported separately.

PK analyses will be based on the Extension PK Set.

Pharmacodynamic (and other) analysis methodology

Pharmacodynamic parameters, such as for example estradiol and other hormones, will be summarized by time point for each treatment group, and listed for each subject by visit day and dose regimen. Where appropriate, changes from baseline will be presented. Potential PK-PD relationships may be investigated graphically and through statistical modeling, whilst also exploring possible covariates, and will be reported separately.

Study Specific Data Analyses

End-of-Treatment Period Analysis

After all subjects have completed the Treatment Period, a complete analysis will be performed. This analysis will include all data up to the end of treatment visit. A database lock will be performed, with any discrepant data clarified before the lock.

Post-Treatment Follow-up Period Analysis

After all subjects have completed the Post-Treatment Follow-up Period, a final database lock will be performed followed by a second analysis. This analysis will include all data collected during the Post-Treatment Follow-up Period.

5 BACKGROUND INFORMATION

5.1 INTRODUCTION TO LINZAGOLIX

Linzagolix is a new, orally active, non-peptide gonadotropin releasing hormone (GnRH) antagonist. It has been shown to significantly reduce endometriosis-associated pain (EAP) in women with surgically confirmed endometriosis at once daily doses between 50 and 200 mg with a good safety and tolerability profile. It is being developed for the long-term treatment of moderate to severe EAP.

5.2 ENDOMETRIOSIS

Endometriosis is a chronic disease with debilitating pelvic pain symptoms (such as dysmenorrhea, dyspareunia, non-menstrual pelvic pain, dyschezia) affecting quality of life and requiring long-term management.

5.3 CONVENTIONAL TREATMENT OF ENDOMETRIOSIS

First-line medical therapies for EAP such as combined oral contraceptives (COCs) and progestins, have limited long-term efficacy, and second-line therapies (eg, high-dose progestins, injectable depot formulations of GnRH receptor agonists) are effective but associated with troublesome side effects including progressive bone loss and severe vasomotor symptoms (1, 2).

GnRH receptor antagonists are a new potential treatment option allowing dose-dependent reduction of estradiol (E2) levels alleviating EAP (3) whilst reducing the negative impact on bone mineral density (BMD).

For long term use of GnRH-analogues, concurrent treatment with add-back (progestin and/or estrogen) hormone replacement therapy (ABT) has been shown to be effective in reducing associated BMD loss (4,5) and is generally recommended as part of long-term treatment with GnRH receptor agonists to minimize side effects.

Linzagolix is a new, orally active, GnRH receptor antagonist. In Phase 1 and 2 studies, it was shown to dose-dependently suppress luteinizing hormone (LH) and E2 and to significantly reduce EAP in women with moderate to severe EAP, with a good safety and tolerability profile (see section 5.5.2 and 5.5.3).

The purpose of the present study is to collect long-term (up to 12 months) data on the safety and efficacy of linzagolix in subjects with EAP. This is a 6-month active treatment extension study offered to all subjects who have completed 6-months of active or non-active treatment in study 18-OBE2109-002 (Edelweiss 2).

5.4 SUMMARY OF NON-CLINICAL STUDIES

The data in the nonclinical package have shown linzagolix to be an orally available, potent, selective GnRH receptor antagonist. Anti-GnRH effects have been demonstrated in a range of pharmacology studies, both *in vitro* and *in vivo*, and these also dominate the findings in the toxicology studies. Toxicology evaluation in mice, rats, dogs and monkeys confirmed exaggerated pharmacological activity

but no overt toxicity. No genotoxicity or unexpected reproduction toxicology findings in rats and rabbits were seen.

In conclusion, the nonclinical package supports clinical long-term dosing regimens up to 200 mg per day.

5.5 SUMMARY OF CLINICAL STUDIES

The efficacy, safety and pharmacokinetics (PK) of linzagolix were investigated by the originator company (Kissei Pharmaceutical Co., LTD. from Japan) in two Phase 1 studies (Study KLH1101 and KLH1103) in Japanese and/or Caucasian volunteers in single and multiple doses up to 400 mg, and in three Phase 2a studies (Studies KLH1201, KLH1202 and KLH1203) in Japanese endometriosis patients at doses up to 200 mg daily for up to 12 weeks. An additional Phase 2b study (KLH1204) has been performed in Japan. Its objective was to assess the efficacy and safety of daily doses of linzagolix 25 mg, 50 mg, 75 mg and 100 mg for up to 24 weeks in Japanese subjects with EAP. Overall, 455 subjects were randomized.

The PK and pharmacodynamics (PD) of linzagolix have been further investigated in eight Phase 1 studies investigating the use of estrogen/progestin ABT, potential drug-drug interactions, bioequivalence of forumulations and the effect of linzagolix on the QT interval.

The efficacy and safety of linzagolix have been investigated in US and European patients with moderate to severe EAP in a dose-ranging Phase 2b study at doses from 50 to 200 mg daily for up to 12 months (study 15-OBE2109-001, also known as Edelweiss).

The efficacy and safety of linzagolix in moderate to severe EAP are also being investigated in two ongoing Phase 3 placebo-controlled studies: 18-OBE2109-002 (Edelweiss 2) and 18-OBE2109-003 (Edelweiss 3). A total of 450 subjects per study are planned to be enrolled in the USA, Canada and Europe. Daily doses of 75 mg alone and 200 mg in combination with low dose ABT (E2 1 mg/ norethisterone acetate (NETA) 0.5 mg) are administered for up to 6 months. The study described herein is the extension of 18-OBE2109-002 (Edelweiss 2) study. The extension of 18-OBE2109-003 (Edelweiss 3) study is described in a separate protocol.

In addition to the endometriosis indication, two placebo-controlled Phase 3 studies (16-OBE2109-008 and 16-OBE2109-009) assessing the efficacy and safety of linzagolix in subjects with heavy menstrual bleeding associated with uterine fibroids are on going. Approximately 500 subjects per study are planned to be enrolled in the USA and Europe. Daily doses of 100 and 200 mg of linzagolix are administered with or without ABT (E2 1mg/NETA 0.5mg) for up to 52 weeks.

5.5.1 Pharmacokinetics/Pharmacodynamics

Linzagolix was evaluated in a Phase 1 single/repeated-dose study (Study KLH1101) in which Japanese and Caucasian pre- and post-menopausal women received single doses of linzagolix from 12.5 to 700 mg and repeated once daily doses of 100 to 400 mg once daily for 7 days under fed and fasted conditions. Linzagolix was safe and well-tolerated, showed linear PK, a half-life of about 15–20 hours, and little difference between pre- and post-menopausal women or between Japanese and Caucasian women. There was a dose-dependent suppression of E2, LH and follicle-stimulating hormone (FSH).

Study 17-OBE2109-001 evaluated the tolerability and PK of a single supra-therapeutic dose of 700 mg linzagolix, and effects of therapeutic and supratherapeutic doses of linzagolix on the QTc interval (QT interval corrected for heart rate). Subjects received a 200 mg dose of linzagolix (therapeutic target exposure), a 700 mg dose of linzagolix (supratherapeutic target exposure), a 400 mg dose of moxifloxacin (positive control), and placebo with an appropriate washout. Linzagolix at 700 mg was well tolerated. A borderline effect of linzagolix on the QTc interval was identified with prolongations exceeding the threshold of concern by less than 2 msec. The categorical data for QTc showed no values greater than 480 msec and no changes greater than 30 msec following administration of the supratherapeutic and therapeutic doses. Thus, based on the magnitude of the QTc prolongation, the observed effects are not considered to be clinically significant.

The open-label study, KLH1103, assessed the absorption, metabolism, and excretion of linzagolix in 6 women of non-childbearing potential. Linzagolix was the predominant component in plasma and all plasma metabolites were present at less than 10% of the total drug related exposure. Similarly, unchanged linzagolix was also a major component in urine and feces. Linzagolix was eliminated in urine (52%) and, to a lesser extent, in feces (38%).

Study 16-OBE2109-011 assessed the PD and safety of linzagolix alone and combined with E2/ NETA ABT on E2 levels and vaginal bleeding. In this single-center, open-label, randomized, parallel-group study, 76 healthy premenopausal women were randomized to linzagolix (100 mg), linzagolix/ E2/ NETA (100 mg/0.5 mg/0.1 mg), linzagolix/ E2/ NETA (100 mg/1 mg/0.5 mg), linzagolix (200 mg) or linzagolix/E2/NETA (200 mg/1 mg/0.5 mg) once daily for 6 weeks. The study showed that ABT may be needed to prevent adverse bone impact in subjects treated at 200 mg.

A single-center, open-label, randomized, parallel-group study (study 17-OBE2109-008) in 32 healthy pre-menopausal women was performed to assess whether co-administration of ABT following 4 weeks of high-dose linzagolix administration alone would result in improved bleeding patterns compared to combined linzagolix/ABT administration. Subjects were randomized to once daily linzagolix (200 mg)/ABT for 10 weeks or linzagolix (200 mg) for 4 weeks followed by once daily linzagolix (200 mg)/ABT for 6 weeks. Starting the administration of linzagolix and hormonal ABT together provided better bleeding control than delaying the ABT treatment start for 4 weeks.

In a drug-drug interaction study with women of child bearing potential (Study 16-OBE2109-005), linzagolix did not induce CYP3A4 and there was no clinically significant food effect. In another drug-drug interaction study (Study 17-OBE2109-006) the OATP1B1/1B3 inhibitor rifampicin (600 mg single dose) had no clinically relevant effects on the PK of linzagolix. Studies 18-OBE2109-006 and 18-OBE2109-007 assessed the effect of linzagolix on the PK of CYP2C8 and OAT3 substrates. Linzagolix had no clinically relevant effects on the PK of OAT3 substrates and was shown to be a weak inhibitor of the CYP2C8 enzyme.

A single-center, open-label, randomized, two-period cross-over study in 20 healthy pre-menopausal women (Study 17-OBE2109-004) aimed to demonstrate the bioequivalence of linzagolix formulation A (reference formulation), used in Phase 2b Edelweiss study 15-OBE2109-001, and formulation B (test formulation) planned to be used in the current Phase 3 extension study. After single oral administration of linzagolix, the test formulation was found to be bioequivalent to the reference formulation for Cmax and area under the curves (AUCs) of linzagolix and KP017 (metabolite). A single administration of linzagolix formulations A and B to healthy female participants was safe and well tolerated.

5.5.2 Efficacy

The clinical efficacy of linzagolix has been investigated in five Phase 2 studies.

In a Phase 2 clinical study (Study KLH1201) conducted in Japan in patients with endometriosis, 50 or 200 mg linzagolix was orally administered once daily for 8 weeks. Linzagolix improved endometriosis symptoms and continuously suppressed E2 in a dose-dependent manner.

In a Phase 2 clinical study (Study KLH1202) conducted in Japan in patients with endometriosis, 50, 100, or 200 mg linzagolix or placebo was orally administered once daily for 12 weeks. Linzagolix significantly reduced endometriosis pain symptoms compared with placebo.

In a Phase 2 clinical study (Study KLH1203) conducted in Japan in patients with endometriosis, 75 or 150 mg linzagolix was orally administered once daily for 8 weeks. Linzagolix improved endometriosis symptoms and continuously suppressed E2 in a dose-dependent manner.

A Phase 2b study (KLH1204) conducted in Japan assessed the efficacy and safety of once daily doses of linzagolix 25 mg, 50 mg, 75 mg and 100 mg for up to 24 weeks in subjects with EAP. There was a dose-dependent improvement of EAP, with significant improvement compared to placebo at the 75 and 100 mg doses.

In a Phase 2b study (Study 15-OBE2109-001, also known as Edelweiss) conducted in US and Europe in patients with endometriosis, doses of 50, 75, 100, 200 mg linzagolix or placebo were administered orally, once daily for up to 52 weeks. Linzagolix significantly decreased EAP after 12 weeks at doses of 75, 100 and 200 mg and the effects were maintained or increased at Week 24. For those subjects continuing treatment up to Week 52, the obtained treatment effects were generally maintained until Week 52. Overall, the greatest improvements on all efficacy endpoints were reported at dose levels of 75 mg and above during the main study (75 mg, 100 mg, 200 mg), as well as treatment extension (75 mg, 100 mg).

The 75 mg group demonstrated the ability for long-term treatment (52 weeks of continuous dosing with linzagolix) of a dose combining significant treatment benefit with a good safety profile and without the need for hormonal ABT; the 200/100 mg group is considered as a benchmark group to characterize efficacy and safety of a high-dose linzagolix regimen following 52 weeks of continuous dosing.

5.5.3 Safety

More than 1,500 subjects were exposed to a range of doses (25, 50, 75, 100, 200, 400 mg) of linzagolix from 13 completed and two ongoing clinical studies. Ongoing studies include two Phase 3 studies for the indication of heavy menstrual bleeding associated with uterine fibroids.

Repeated once daily dosing at up to 700 mg linzagolix was safe and well-tolerated by premenopausal healthy volunteers. In endometriosis patients, doses up to 200 mg once daily for up to 24 weeks of treatment were well tolerated.

Hepatic impairment had no relevant effect on total plasma linzagolix exposure. In women with severe hepatic impairment (Child-Pugh C), 2- to 3-fold unbound mean exposures were recorded. In hepatic impaired subjects, a single dose of 200 mg was well tolerated.

Renal impairment had no relevant effect on total plasma linzagolix exposure. In women with severe renal impairment (eGFR <30 mL/min/1.73 m2) or end-stage renal disease, approximately 2-fold

unbound mean exposures were recorded. In renal impaired subjects, a single dose of 200 mg was well tolerated.

The expected side effects of linzagolix are disturbances of the menstrual cycle and hypoestrogenic adverse events (AEs) (e.g., metrorrhagia and hot flush).

In multiple-dose studies, a dose-dependent occurrence of hot flush was observed (14.63%, 27.27%, 27.8%, 30% and 40.7% at 50 mg, 75 mg, 100 mg, 150 mg and 200 mg linzagolix, respectively). In the Phase 2b Edelweiss trial (15-OBE2109-001), a moderate proportion of patients reported a dose-dependent increase in hot flushes (at week 12, placebo: 10.9% reporting at least one hot flush; 75mg: 18.4%; 200 mg: 42.1% - at week 24, 75 mg: 19.0%; 200 mg: 45.6%).

Anticipated AEs are events that were not necessarily observed with linzagolix but can be anticipated based on the drug's pharmacological action and/or class effects, such as: increase in liver function test (LFT) parameters, headache, dizziness, nausea, hyperhidrosis, blood cholesterol increased, low density lipoprotein increased and BMD loss.

In few subjects, an increase in transaminase values exceeding 3>ULN (Upper Limit of Normal) was observed under treatment. Most often the increase in transaminase values was reversible and decreased spontaneously back to normal levels under treatment. Increases in transaminase values were not associated with increased bilirubin values.

A borderline effect of linzagolix on the QTc interval was identified with prolongations exceeding the threshold of concern by less then 2 msec. The categorical data for QTc showed no values greater than 480 msec and no changes greater than 30 msec following the supratherapeutic and therapeutic doses. Thus, based on the magnitude of the QTc prolongation, the observed effects are not considered to be clinically significant.

The vast majority of related AEs were reported as being of "mild" or "moderate" intensity; very few related events were reported as being of "severe" intensity.

In the Phase 2b Edelweiss trial (15-OBE2109-001), changes from baseline to week 24 in BMD were measured by dual-energy X-ray absorptiometry (DXA) scan, using central reading. Partial E2 suppression achieved with linzagolix 75 mg was associated with a mean percent change from baseline in spine BMD (the site of greatest bone loss) of -0.8% (95% CI -1.57, -0.03) after 6 months of treatment, while achieving improvement in symptoms in the majority of patients. As expected, full E2 suppression with linzagolix 200 mg lowers BMD by more than 2.5% after 6 months of treatment, which indicates the need for hormonal ABT for use beyond 6 months.

In the Phase 2b Edelweiss trial (15-OBE2109-001), following the main study, subjects willing to continue treatment were entered into an extension study for an additional 28 weeks of treatment, followed by 24 weeks of post-treatment follow-up. Subjects received either 50 mg, 75 mg, or 100 mg of linzagolix, once daily in accordance with the treatment received in Part B, except for those subjects who had been randomized to 200 mg dose, which was reduced during the extension phase to 100 mg daily. AEs were collected throughout the study. BMD of femoral neck, total hip, and lumbar spine were assessed by DXA at week 52.

Of the 253 subjects who completed the 24 weeks of treatment in the main study, 176 subjects received treatment in the extension. A summary of the safety findings is below:

At Week 52, BMD loss was seen in the lumbar spine in all treatment groups, except for the 50 mg group. Mean BMD loss in the lumbar spine was below 1.5% in the 75 mg fixed dose (FD) and 100 mg groups, with mean percent decreases (and lower 95% CI) from baseline of -1.139% (-2.21%), and -1.399% (-3.35%), respectively. The greatest reductions were observed in the 75 mg titrated dose (TD), placebo/100 mg, and 200/100 mg groups with mean percent decreases (and lower 95% CI) from baseline of -2.646% (-4.46%), -2.503% (-4.04%), and -2.188% (-3.59%), respectively.

At Week 52, BMD loss was detected in the femoral neck in all treatment groups, except for the 75 mg FD group. Mean BMD loss was similar in the 50 mg,75 mg TD, and 100 mg groups, with mean percent decreases (and lower 95% CI) from baseline of -0.992% (- 1.84%), -0.843% (-2.58%), and -1.102% (-3.10%), respectively. The greatest reduction was observed in the 200/100 mg group with a mean percent decrease (and lower 95% CI) from baseline of -2.592% (-4.49%).

At Week 52, BMD loss was detected in the total hip in all treatment groups. Mean BMD loss in the total hip was below 1% in the placebo/100 mg, 50 mg,75 mg FD, and 100 mg groups, with mean percent decreases (and lower 95% CI) from baseline of -0.807% (- 1.82%), -0.411% (-1.22%), -0.297% (-1.36%), and -0.597% (-1.61%), respectively. The greatest reductions were observed in the 200/100 mg and 75 mg TD groups with mean percent decreases (and lower 95% CI) from baseline of -2.025% (-3.58%) and - 1.363% (-3.23%), respectively.

For the lumbar spine, the site most sensitive to BMD loss, an increase in the proportion of subjects >3% BMD loss was reported in a dose-dependent manner across linzagolix groups at Week 52: 4.8%, 18.2%, 23.1% and 50% for the 50 mg, 75 mg FD, 100 mg, and 200/100 mg groups.

At Week 24, the greatest mean BMD loss was in the 200/100 mg group for the lumbar spine: -2.887% (-4.07%). At Week 52, after receiving 28 weeks of 100 mg linzagolix, there appeared to be no additional BMD loss: mean percent change from baseline of - 2.188% (-3.59%). This observation may be due to increased E2 levels observed after the dose was lowered from 200 mg to 100 mg at Week 24. Of note, a similar proportion of subjects had a decrease >3% in the 200/100 mg group at Week 24 (51.9%) and Week 52 (50.0%).

Median Z scores, interquartile ranges and total ranges for femoral neck, total hip and lumbar spine at baseline, Week 24 and Week 52 did not change importantly over time: medians remained within the range of -0.20 to 0.30, 0 to 0.40, and -0.25 to 0.35 in all treatment groups for the femoral neck, total hip and lumbar spine, respectively. Median absolute change from baseline to Week 52 ranged from -0.10 to 0.00, -0.10 to 0.00 and -0.20 to -0.10, respectively.

Over the 52-week treatment period, 154/176 (87.5%) of subjects reported treatment emergent adverse events (TEAEs). The incidence of TEAEs was not dose-dependent across treatment groups, ranging from 81.8% in the 100 mg group to 93.3% in the 200/100 mg group. The majority of the TEAEs (616/846; 72.8%) were reported during the first 24 weeks of treatment.

The most commonly reported TEAEs were headache (32.4%) and hot flush (28.4%). The majority of these events occurred during the first 24 weeks of treatment. Headaches were reported with a similar frequency across treatment groups, ranging from 22.2% in the 75 mg FD group to 44.8% in the placebo/100 mg group, with no apparent dose relationship. Conversely, the incidence of hot flushes was dose-dependent and increased with increasing exposure to linzagolix: 16.7% (50 mg), 20.7% (75 mg FD), 22.2% (75 mg TD), 24.1% (placebo/100 mg), 27.3% (100 mg), and 60.0% (200/100 mg). Of note, there was no worsening in the incidence of hot flushes during the treatment extension; only 2/61 hot flush events were reported.

Ten serious AEs (SAEs) were reported in nine subjects. None of the SAEs were considered as related to study treatment. The SAEs of ruptured ectopic pregnancy (50 mg), pelvic pain (50 mg), pneumonia (75 mg TD), and anxiety disorder (200/100 mg) led to subject withdrawal from treatment during the extension phase of the study.

During treatment extension, 12 subjects (6.8%) reported 17 TEAEs leading to treatment withdrawal. In the 200/100 mg group, one subject discontinued treatment due to bone loss and one subject due to bone pain. In the 75 mg FD group, one subject discontinued treatment due to bone density decreased.

There were no subjects with AST and/or ALT values >2×ULN during the treatment extension.

Overall, there were no clinically meaningful changes from baseline in laboratory parameters, vital signs, physical examination, or lipid measurements including HDL cholesterol, LDL cholesterol, and triglycerides in any group.

Gynecological examinations showed a small number of abnormal clinically significant results, but with a higher frequency noted for uterus and ovaries. At Week 24, reductions from baseline in endometrial thickness and uterus volume were more notable at the higher doses of linzagolix (100 mg and 200 mg) compared to the lower doses. This pattern was not observed at Week 52. Endometrial biopsy did not raise any safety concern.

Overalll, the safety findings at the end of 52 weeks of treatment revealed no new safety issues. Patterns of BMD loss were similar to the main study.

5.6 RATIONALE FOR THE CURRENT STUDY

Endometriosis is a chronic disease requiring long-term continuous treatment. The results of the Phase 2b, Edelweiss study (study 15-OBE2109-001) supported the sustained efficacy and overall safety of 12-month treatment with linzagolix in symptomatic endometriosis (see sections 5.5.2 and 5.5.3).

In the present study, we will collect long-term (up to 12 months) data on the safety and efficacy of linzagolix in subjects with EAP who have completed 6 months of treatment in study 18-OBE2109-002 (Edelweiss 2).

5.7 SUMMARY OF OVERALL RISKS AND BENEFITS

Linzagolix efficacy compared to placebo was demonstrated at daily doses of 75–200 mg for 3 months and maintenance of effect has been shown up to 6 months.

Linzagolix was well-tolerated at these doses. The most commonly reported AEs in the Phase 2 studies were headache and hot flush which are related to the biological activity of linzagolix.

Eleven pregnancies were in the Phase 2 studies. No fetal or newborn abnormalities were reported in any of the pregnancies.

There were no clinically relevant findings in laboratory measurements, vital signs or electrocardiogram (ECG) recordings. The administration of linzagolix results in infrequent, transient, moderate and non-dose-related increases in transaminase levels which were not associated with changes in bilirubin levels. A borderline increase in QTc interval was observed in healthy volunteers which was not considered clinically significant. Nevertheless, all subjects in the current study will be monitored monthly with ECG.

A modest degree of BMD loss has been seen in linzagolix-treated subjects with doses below 100 mg QD. Clinically significant BMD loss was observed with a dose of 200 mg QD at 6 months of treatment and requires combined use of hormonal ABT to mitigate BMD loss. As linzagolix 200mg will be combined with ABT in this extension study, no major impact on BMD is expected. In addition, the BMD loss will be monitored during the study and subjects who experience more than 8% confirmed BMD loss or a Z-score ≤ -2.5 will be discontinued from treatment. Moreover, subjects will be provided with vitamin D and calcium supplements which they will be recommended to take.

In addition, an independent Data Monitoring Committee (DMC) will oversee the safety of study subjects, including a regular review of transaminase levels, BMD values and ECG parameters.

In conclusion, linzagolix has a favorable benefit/risk ratio and represents a potential therapy for treating EAP.

The overall benefit/risk of this study was re-evaluated by ObsEva in light of the COVID-19 pandemic and evolving regulatory guidance.

For subjects who could not attend their visits due to quarantine, travel restrictions, site closure or other unforeseen reasons, remote study visits and shipment of materials and study drugs from site to subject were setup, whenever feasible, based on local restrictions related to the pandemic. Sites scheduled telephone calls to subjects as replacement for on-site visits, to ensure continuity in patient's safety monitoring, treatment and study data collection.

6 OBJECTIVES

6.1 EFFICACY OBJECTIVES

6.1.1 Primary

The primary objective of this extension study is 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 have already completed 6 months of linzagolix treatment at a dose of 75 mg alone or 200 mg in combination with ABT (E2 1 mg / NETA 0.5 mg) in the management of moderate to severe EAP in women with surgically confirmed endometriosis. The two co-primary efficacy endpoints will be 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).

6.1.2 Secondary

Secondary objectives include 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.

6.2 SAFETY OBJECTIVES

Safety and tolerability objectives include assessment of BMD, endometrial health, cardiac safety including QT interval prolongation, standard laboratory safety parameters, gynecological assessments and AE frequency including specific hypoestrogenic AEs.

6.3 EXPLORATORY OBJECTIVES

Exploratory objectives include assessment of bone turnover markers and collection of PK and PD related data of linzagolix for a separate modelling exercise.

7 ENDPOINTS

7.1 EFFICACY ENDPOINTS

7.1.1 Primary

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

7.1.2 Secondary

The secondary endpoints include:

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

- Change from baseline to each scheduled assessment in the mean worst pelvic pain score defined as the mean of the 5 highest daily pain scores reported during the previous 4-week period assessed on the NRS
- Change from baseline to each scheduled assessment in the mean of daily dyspareunia scores reported during the previous 4-week period on the dyspareunia VRS
- Change from baseline to each scheduled assessment in the mean of daily dyschezia scores reported during the previous 4-week period assessed on the dyschezia NRS
- Change from baseline to each scheduled assessment in non-opioid, opioid and combined analgesic use for EAP during the previous 4-week period based on pill count in the eDiary
- Change from baseline to each scheduled assessment in opioid analgesic use for EAP as reported in the eDiary during the previous 4-week period based on morphine milligram equivalent (MME)
- Change from baseline to each scheduled assessment in the number of days of analgesic use (including any class) for EAP during the previous 4-week period as assessed in the eDiary
- Change from baseline to each scheduled assessment in the number of days of opioid analgesic use for EAP during the previous 4-week period as assessed in the eDiary
- Change from baseline to each scheduled assessment in the number of pelvic pain-free days (assessed on the VRS) during the previous 4-week period
- Change from baseline to each scheduled assessment in ability to perform daily activities during the previous 4-week period, as assessed in the eDiary (daily function NRS)
- Change from baseline to each scheduled assessment in the number of days with no difficulty in doing daily activities due to EAP during the previous 4-week period as assessed in the eDiary (daily function NRS)
- Change from baseline to each scheduled assessment in the number of days when dyspareunia was a problem during the previous 4-week period (including days when sexual intercourse was avoided because of anticipation of pain) as assessed on the dyspareunia VRS
- Change from baseline to each scheduled assessment in the number of days when sexual intercourse was avoided because of anticipation of pain during the previous 4-week period as assessed on the dyspareunia VRS
- Change from baseline to each scheduled assessment in the number of days with uterine bleeding (including spotting) during the previous 4-week period measured by eDiary
- Change from baseline to each scheduled assessment in the number of days when school or work was missed due to EAP in the previous 4-week period as reported in the eDiary
- Change from baseline to each scheduled assessment in the number of days when the subject had to go to bed or lie down due to EAP in the previous 4-week period as reported in the eDiary
- Change from baseline to each scheduled assessment in the Pain, Control and powerlessness, Emotional well-being, Social support, Self-image dimensions and the Modular sexual relationship questionnaire of EHP-30 scores

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

7.2 SAFETY ENDPOINTS

- Change from baseline to each scheduled assessment in BMD measured by DXA of lumbar spine (L1-L4), femoral neck, and total hip
- Incidence and severity of treatment emergent adverse events (TEAEs)
- Incidence and severity of hypoestrogenic TEAEs (hot flush)
- Time to the first post-treatment menses
- Changes in clinical laboratory assessments (hematology, biochemistry, coagulation parameters, hormones, lipids and urinalysis) from baseline to each scheduled assessment
- Any pathological changes from baseline in the endometrium as assessed by histology from endometrial biopsies
- Changes from baseline to each scheduled assessment in any other safety parameter including weight, vital signs, ECG, gynecological assessments and endometrial thickness

7.3 EXPLORATORY ENDPOINTS

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

8 STUDY DESIGN

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

Subjects who have completed the 6-month Treatment Period in 18-OBE2109-002 - Edelweiss 2 study (herein referred to as main study) will be invited to enter the present extension study. Month 6 visit of

the main study is 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 starts at the Month 6 visit of the main study. Subjects will be 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 meet the inclusion criteria will be eligible for entry in the extension study.

All subjects will 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 will be 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 will continue with the same treatment.

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

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

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

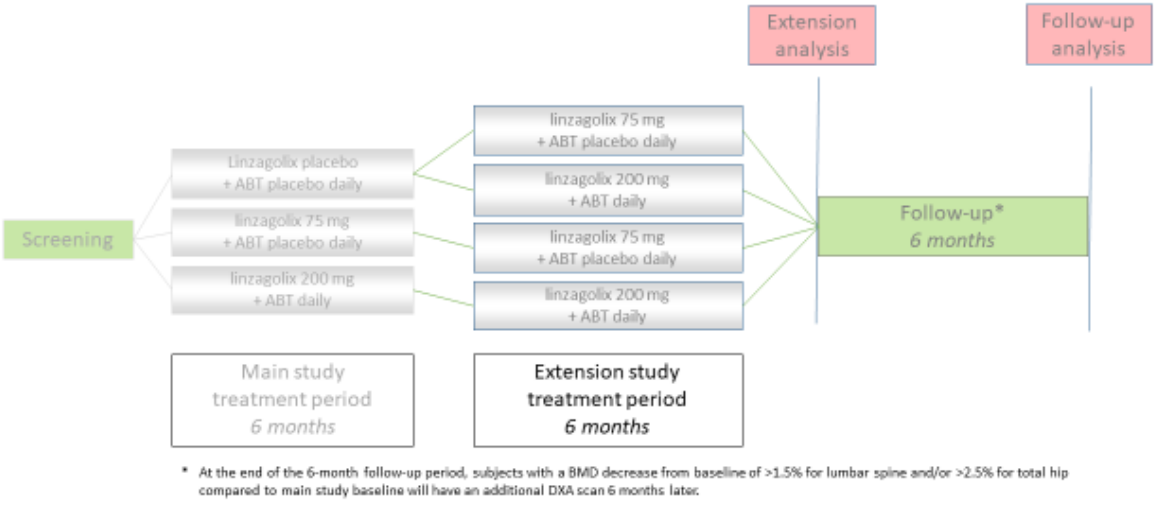


Figure 1 : Study design

All subjects will receive once daily either linzagolix 75 mg alone (with ABT placebo) or linzagolix 200 mg combined with low dose ABT for 6 months. ABT is a combination of estradiol (E2) 1 mg and norethisterone acetate (NETA) 0.5 mg.

Since linzagolix 75 mg and 200 mg tablets have a different appearance, a double-dummy design will be used in order to maintain the blinding of the study.

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

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

Each treatment kit will be labelled with a unique kit number. Treatment kit numbers will be provided through IWRS.

9 STUDY POPULATION

9.1 SUBJECTS

9.1.1 Description of the target population

All subjects who have completed the full 6-month Treatment Period in the main study and who meet the inclusion criteria will be offered to enter the extension study.

9.1.2 Number of subjects

It is estimated that up to 288 subjects will enter the extension study, assuming that 80% of the patients randomized in the main study will complete the study (namely 360 subjects) and that up to 80 % thereof will enter the extension study.

9.1.3 Study region/location

The study will be conducted at the same investigational sites as in the main study.

9.2 ENTRY CRITERIA

9.2.1 Inclusion Criteria

To be eligible for inclusion into this extension study, the subjects must **fulfil all** of the following criteria:

1. The subject must provide a written informed consent specific to this study prior to starting the extension study treatment.
2. The subject has completed the 6-month treatment in the main study.

3. The subject is willing and able to continue to comply with the requirements of the study protocol for the duration of the extension study.
4. The subject agrees to continue to use only the analgesic rescue medication permitted by the protocol during the Treatment and Follow-up Periods.
5. If of childbearing potential, the subject agrees to continue to use one of the following birth control methods during the entire Treatment Period of the study and until 3 months after the end of treatment:
    a. Sexual abstinence, if this is the subject's habitual practice and/or the subject is routinely abstinent from heterosexual intercourse,
    b. Partner with a vasectomy with confirmed azoospermia,
    c. Double non-hormonal barrier contraception such as condom or diaphragm each combined with spermicide.

9.2.2 Exclusion Criteria

To be eligible for inclusion in this extension study the subject must **not** meet any of the following criteria:

1. The subject is pregnant or is planning a pregnancy within the duration of the study (including the Follow-up Period).
2. The subject is likely to require treatment during the study with any of the medications listed below:
    a. GnRH antagonists
    b. GnRH agonist injections/3-month depot injections
    c. Danazol
    d. Oral contraceptives and other sex hormones
    e. Depot contraceptives
    f. Selective Progesterone Receptor Modulators (SPRMs), Selective Estrogen Receptor Modulators (SERMs) and aromatase inhibitors
    g. Long acting narcotics (i.e. requiring less than once daily dosing)
    h. Systemic glucocorticoid treatments for acute diseases (not depot)
    i. In situ copper intra-uterine device (IUD)
    j. In situ IUD with progestogen
3. The subject is likely to use cannabinoids during the study.
4. The subject has any other clinically significant gynecologic condition identified during the main study on transvaginal ultrasound (TVUS), on endometrial biopsy or at the manual breast examination, which might interfere with the study efficacy and safety objectives.
5. The subject has met any of the main study discontinuation criteria including:

a. Serum calcium level confirmed on a repeated test above 2.9 mmol/L

b. BMD decrease from baseline > 8% or a Z-score ≤ -2.5 at either femoral neck, hip or spine on the Month 6 DXA scan during the main study.

c. QTcF > 500 ms or increase > 60 ms from the highest value prior to first dose during the main study.

d. Any of the following elevation of hepatic enzymes:

- 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%)

6. The subject has any condition that, in the opinion of the Investigator, constitutes a risk or a contraindication to the participation of the subject in this extension study or that could interfere with the study objectives, conduct or assessments.

10 STUDY PROCEDURES AND ASSESSMENTS

10.1 GENERAL INSTRUCTIONS

The extension study starts at the Month 6 visit of 18-OBE2109-002 - Edelweiss2 study (herein referred to as the main study). At Month 5 visit of the main study, the subject will have been informed of the possibility to enter the extension study at Month 6 (if eligible) and will have been provided with a copy of the subject information sheet, specific to the extension study, to read prior to the Month 6 visit.

After all Month 6 assessments have been made, if the subject is eligible, one original copy of the extension-specific ICF will be signed and personally dated by both the subject and the Investigator or legally acceptable designee. The original signed copy will be kept in the confidential investigator file and a copy will be given to the subject. Once the ICF is signed, the subject will be dispensed new treatment kits. She will take her daily dose of study medication at the study site from these newly dispensed kits.

During the whole study, the subject will be identified using a Subject Identification Number (SIN) for all documentation and discussion. The subjects will be identified with the same SIN than in the main study. SINs will be made of 6 digits, as follows:

- 1st, 2nd and 3rd digits: site identifier (100 to 999)
- 4th, 5th and 6th digits: subject number (001 to 999)

An electronic Case Report Form (eCRF) will be completed for all subjects who signed the ICF.

Subjects who previously received placebo in the main study will be 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 in the main study will continue with the same treatment (linzagolix 75 mg alone with ABT placebo or linzagolix 200 mg with ABT).

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

Treatment kits will be dispensed to the subjects as follows:

- on Month 6 and Month 9 visits, subject will receive two kits, one for linzagolix/placebo (monthly kit) and one for the ABT/ABT placebo (3-monthly kit).
- On Month 7, Month 8, Month 10 and Month 11 visits, subject will receive one kit only, for linzagolix/placebo.

The treatment kit numbers for linzagolix/placebo and for ABT will refer to unique kits present at site and corresponding to the randomization allocation.

10.2 OUTLINE OF STUDY PROCEDURES AND ASSESSMENTS

The first visit for this extension study is combined with the Month 6 visit of the main study. Therefore, the Month 6 assessments from the main study will not have to be duplicated at the start of the extension study. The study visit schedule is depicted in Figure 2 and the schedule of assessments is detailed in Appendix A and Appendix B.

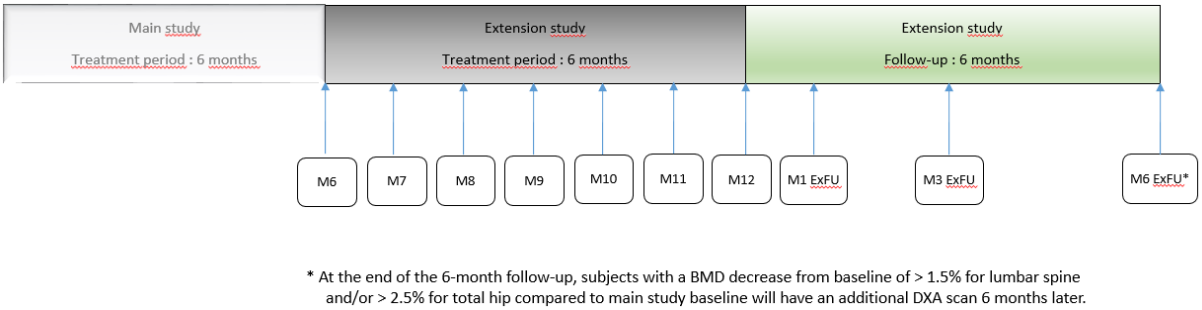


Figure 2 : Schedule of Visits

All visits should take place at the end of the defined period (i.e. Month 7 visit should be scheduled at the end of Month 7, Month 8 visit should be scheduled at the end of Month 8, etc.). One month is defined as 28 days/4 weeks. 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):

- Month 7 (Day 197), Month 8 (Day 225), Month 9 (Day 253), Month 10 (Day 281), Month 11 (Day 309) and Month 12 (Day 337) for the Treatment Period,
- Month 1 Extension FU (Day 365), Month 3 Extension FU (Day 421) and Month 6 Extension FU (Day 505) for the Follow-up Period.

A window of -3/+2 days is allowed for Month 7 visit, and of ± 3 days for each of the following visits during the Treatment Period. A window of ± 7 days/1 week is allowed for each visit scheduled during the Follow-Up Period.

The timing of events is shown in the Schedule of Assessments (Appendix A and Appendix B).

10.2.1 Treatment Period

During the entire Treatment Period:

- the subject will use the same eDiary as during the main study. The eDiary should be completed daily, in the evening at approximately the same time, for use of provided/prescribed analgesics, uterine bleeding, pelvic pain, dyspareunia, dyschezia and daily function.
- the subject will take her daily dose of study medication at home except on the day of study visits where she will take her daily dose at site. There will be no IMP intake at the Month 12 visit. The last dose of study medication in this extension study will be the dose taken the day before Month 12 visit.
- the subject will be asked to bring her eDiary and her IMP kits at each visit to the site.
- the subject will receive contraception counselling at each visit.
- the subject will be provided/prescribed a limited quantity (as per Investigator's judgement) of standard doses of permitted analgesics as rescue medication for EAP for the duration of the study.
- the subject will receive calcium 500 to 1000 mg and vitamin D 400 IU supplementation which she will be advised to take daily (at least 4 hours from the intake of the study drug) until the end of the study. Intake should be recorded at each study visit in eCRF.
- AEs and concomitant medications will be recorded in the eCRF (excluding any provided/prescribed analgesics used for EAP will be recorded daily in the eDiary only).

10.2.1.1 Study visit: Month 6 (Day 169 ± 3 days)

After all Month 6 assessments pertaining to the main study have been made and the subject has been confirmed to be eligible to proceed in the extension study (see section 9.2), the subject will be requested to sign the extension-specific ICF that she was given at the Month 5 visit.

Note: inclusion in the extension study will not be postponed if the results of any Month 6 assessment are not available on the day of Month 6 visit. Subjects will be required to stop the treatment if the results obtained after enrollment meet the discontinuation criteria defined in Section 10.7.2.1.

After signature of the extension-specific ICF, the subject will be dispensed new treatment kits. The subject will take her daily dose of study medication at the study site from these newly dispensed kits. The exact time of dosing (hour/minute) will be recorded in eCRF.

In addition, the subject will:

- receive contraception counselling and will be given double barrier contraception (condoms with spermicide), if requested, to be used until 3 months after treatment end. If the subject is at risk for

acquiring HIV, she must be reminded to use double non-hormonal barrier contraception without spermicides (eg: condoms and diaphragms).

· be provided/prescribed a limited quantity (as per Investigator's judgement) of standard doses of permitted analgesics as rescue medication for EAP for the duration of the study.

· receive calcium 500 to 1000 mg and vitamin D 400 IU supplementation

Upon completion of the visit, the subject will be provided with emergency contact phone numbers and will be scheduled for her next visits.

10.2.1.2 Study visits: Month 7 (Day 197 -3/+2 days) and Month 8 (Day 225 ± 3 days)

The following tests and evaluations will be performed :

- eDiary completion compliance check
- ePRO and ClinRO completion, ideally before any other procedures or assessments:
  - · at Month 7 visit: EHP-30, EQ-5D-5L, PROMIS, mPGIS, PGIC, HRUQ, HRPQ with mPGIS and PGIC completed last
  - · at Month 8 visit: mPGIS, PGIC, HRUQ and HRPQ with mPGIS and PGIC completed last.
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire (version for "already enrolled subjects" (see Appendix R) for patients responding to the C-SSRS for the first time during the study, or version "since last study visit" (see Appendix S) for patients for whom the C-SSRS was completed at the previous study visit)
- IMP accountability based on blisters
- ECG (at about the same time as but before the PK sample)
- Vital signs (blood pressure (BP) and heart rate)
- Urine pregnancy test
- Urinary protein dipstick
- Blood samples for haematology, coagulation parameters, chemistry, hormones (E2, LH and progesterone (P4))
- Pre-dose PK sample (the time of study medication administration on previous 4 days and time of PK sampling will be recorded)
- Contraception dispensing (if applicable) and counselling
- Prescribe/dispense permitted analgesics as rescue medication
- Dispense calcium and vitamin D supplementation

- Dispensing via IWRS of one new kit of linzagolix

The subject will take her daily dose of study medication at the study site from the newly dispensed linzagolix/placebo kit, and from the ABT/placebo kit dispensed at the Month 6 visit.

10.2.1.3 Study visit: Month 9 (Day 253 ± 3 days)

The following tests and evaluations will be performed:

- eDiary completion compliance check
- ePRO and ClinRO completion, ideally before any other procedures or assessments: EHP-30, EQ-5D-5L, PROMIS, mPGIS, PGIC, HRUQ, HRPQ (mPGIS and PGIC must be completed last)
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire (version for "already enrolled subjects" (see Appendix R) for patients responding to the C-SSRS for the first time during the study, or version "since last study visit" (see Appendix S) for patients for whom the C-SSRS was completed at the previous study visit)
- IMP accountability based on blisters
- ECG (at about the same time as but before the PK sample)
- Physical examination, including weight recording
- Vital signs (BP and heart rate)
- Urine pregnancy test
- Gynecological examination
- TVUS of the uterus
- Urinary protein dipstick
- Fasting (overnight) blood samples for haematology, coagulation parameters, chemistry, lipids, hormones (E2, LH, P4 and sex hormone-binding globulin (SHBG)) and bone biomarkers
- Pre-dose PK sample (the time of dose administration on previous 4 days and time of PK sampling will be recorded)
- BMD assessed by DXA for femoral neck, hip and spine for subjects who met the following criterion at any site on the Month 6 DXA scan: $-2.5 < \text{Z-score} \leq -1.5$
- Contraception dispensing (if applicable) and counselling
- Prescribe/dispense permitted analgesics as rescue medication
- Dispense calcium and vitamin D supplementation

- Dispensing via IWRS of one new kit of linzagolix/placebo and one new kit of ABT/placebo

The subject will take her daily dose of study medication at the study site from the newly dispensed kits.

10.2.1.4 Study visits: Month 10 (Day 281 ± 3 days) and Month 11 (Day 309 ± 3 days)

The following tests and evaluations will be performed :

- eDiary completion compliance check
- ePRO and ClinRO completion, ideally before any other procedures or assessments: mPGIS, PGIC, HRUQ, HRPQ with mPGIS and PGIC completed last
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire (version for "already enrolled subjects" (see Appendix R) for patients responding to the C-SSRS for the first time during the study, or version "since last study visit" (see Appendix S) for patients for whom the C-SSRS was completed at the previous study visit)
- IMP accountability based on blisters
- ECG (at about the same time as but before the PK sample)
- Vital signs (BP and heart rate)
- Urine pregnancy test
- Urinary protein dipstick
- Blood samples (fasting not required) for haematology, coagulation parameters, chemistry, hormones (E2, LH and P4)
- Pre-dose PK sample (the time of study medication administration on previous 4 days and time of PK sampling will be recorded)
- Contraception dispensing (if applicable) and counselling
- Prescribe/dispense permitted analgesics as rescue medication
- Dispense calcium and vitamin D supplementation
- Dispensing via IWRS of one new kit of linzagolix/placebo

The subject will take her daily dose of study medication at the study site from the newly dispensed linzagolix/placebo kit, and from the ABT/placebo kit dispensed at the Month 9 visit.

10.2.1.5 Study visit: Month 12 (Day 337 ± 3 days)

The following tests and evaluations will be performed :

- eDiary completion compliance check

- ePRO and ClinRO completion, ideally before any other procedures or assessments: EHP-30, EQ-5D-5L, PROMIS, mPGIS, PGIC, HRUQ, HRPQ, SSIQ andd PSIQ (mPGIS and PGIC must be completed last)
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire (version for "already enrolled subjects" (see Appendix R) for patients responding to the C-SSRS for the first time during the study, or version "since last study visit" (see Appendix S) for patients for whom the C-SSRS was completed at the previous study visit)
- Final IMP accountability based on blisters
- ECG (at about the same time as but before the PK sample)
- Physical examination, including weight recording
- Vital signs (BP and heart rate)
- Urine pregnancy test
- Gynecological examination
- Manual breast examination (by palpation)
- TVUS of uterus
- Urinary protein dipstick
- Fasting (overnight) blood samples for haematology, coagulation parameters, chemistry, lipids, hormones (E2, LH, P4 and SHBG) and bone biomarkers
- PK sample (the time of dose administration on previous 4 days and time of PK sampling will be recorded)
- Endometrial biopsy, unless the endometrium thickness in TVUS is ≤ 5 mm, in which case no endometrial biopsy will be necessary (see section 10.4.5). Appropriate photo documentation of the endometrium thickness is mandatory.
- BMD assessed by DXA for femoral neck, hip and spine. DXA can be performed up to 10 days prior to the study visit which allows to get the DXA results ideally at the time of the Month 12 study visit at the latest.
- The subject will be verbally asked which treatment she believed she received during the Treatment Period in the extension study. The answer will be recorded in the eCRF.
- Contraception dispensing (if applicable) and counselling
- Prescribe/dispense permitted analgesics as rescue medication
- Dispense calcium and vitamin D supplementation

An additional question will be asked to the subject about the burden of filling in the eDiary (0 = not at all a burden, 10 = very much a burden). The answer will be recorded in the eCRF.

The Month 12 study visit constitutes the end of the Treatment Period pertaining to this extension study.

The subject will continue in the post-treatment 6-month Follow-Up (FU) Period.

10.2.2 Post-treatment Follow-Up Period

Up to Month 6 Extension FU visit, the subject will continue to record on her eDiary, daily at approximately the same time each evening, her use of provided/prescribed analgesics, uterine bleeding, pelvic pain, dyspareunia, dyschezia and daily function.

The subject will be asked to bring her eDiary at each visit to the site during the entire Follow-Up Period.

10.2.2.1 Study visit: Month 1 Extension FU (Month 1 ExFU)

Month 1 ExFU visit should be scheduled on Day 365 ± 7 days after main study Day 1 (or 28 days ± 7 days after last IMP intake for early discontinued subjects).

The following tests and evaluations will be performed at Month 1 ExFU visit:

- eDiary completion compliance check
- ePRO completion, ideally before any other procedures or assessments: mPGIS and PPGIC (must be completed last)
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire (version for “already enrolled subjects” (see Appendix R) for patients responding to the C-SSRS for the first time during the study, or version “since last study visit” (see Appendix S) for patients for whom the C-SSRS was completed at the previous study visit)
- ECG
- Vital signs (BP and heart rate)
- Urine pregnancy test and contraception dispensing and counselling
- Urinary protein dipstick
- Blood samples for haematology, coagulation parameters, chemistry, hormones (E2, LH and P4)
- Endometrial biopsy only if diagnosis at Month 12 was different than “benign endometrium” or if no endometrial biopsy was done at Month 12 (see section 10.4.5).
- Prescribe/dispense permitted analgesics as rescue medication
- Dispense calcium and vitamin D supplementation

10.2.2.2 Study visit: Month 3 Extension FU (Month 3 ExFU)

Month 3 ExFU visit should be scheduled on Day 421 ± 7 days after Day 1 (or 84 days ± 7 days after last IMP intake for early discontinued subjects).

The following tests and evaluations will be performed at Month 3 ExFU Visit:

- eDiary completion compliance check
- ePRO and ClinRO completion, ideally before any other procedures or assessments: EHP-30, EQ-5D-5L, PROMIS, mPGIS, PPGIC, HRUQ, HRPQ (mPGIS and PPGIC must be completed last)
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire (version for "already enrolled subjects" (see Appendix R) for patients responding to the C-SSRS for the first time during the study, or version "since last study visit" (see Appendix S) for patients for whom the C-SSRS was completed at the previous study visit)
- ECG
- Physical examination, including weight recording
- Vital signs (BP and heart rate)
- Urine pregnancy test and contraception counselling
- Gynecological examination
- Manual breast examination (by palpation)
- TVUS of uterus
- Urinary protein dipstick
- Fasting (overnight) blood samples for haematology, coagulation parameters, chemistry, lipids, hormones (E2, LH and P4) and bone markers. For subjects who do not resume menses by the Month 3 ExFU visit, an FSH test should be performed at a local laboratory and the subject should be advised to consult for gynaecological evaluation.
- Endometrial biopsy only if diagnosis at preceding biopsy was different than "benign endometrium" or if no endometrial biopsy was done at Month 12 nor at any visit after Month 12 (see section 10.4.5).
- Prescribe/dispense permitted analgesics as rescue medication
- Dispense calcium and vitamin D supplementation

10.2.2.3 Study visit: Month 6 Extension FU (Month 6 ExFU) – End of Follow-up visit

Month 6 ExFU visit should be scheduled on Day 505 ± 7 days after Day 1 (or 168 days ± 7 days after last IMP intake for early discontinued subjects).

The following evaluations and tests will be performed at Month 6 ExFU Visit:

- eDiary completion compliance check
- ePRO and ClinRO completion, ideally before any other procedures or assessments: EHP-30, EQ-5D-5L, PROMIS, mPGIS, PPGIC, HRUQ, HRPQ (mPGIS and PPGIC must be completed last)
- Collection and deactivation of eDiary
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire version "since last study visit" (see Appendix S) for patients for whom the C-SSRS was completed at the previous study visit.
- ECG
- Physical examination, including weight recording
- Vital signs (BP and heart rate)
- Urine pregnancy test
- TVUS of uterus
- Endometrial biopsy if no endometrial biopsy was obtained at Month 12 nor at any visit since Month 12 (see section 10.4.5). If inadequate/no tissue is available for pathology evaluation, the biopsy should be repeated as soon as possible in the following days.
- BMD assessed by DXA for femoral neck, hip and spine. This DXA can be performed ± 10 days from the Month 6 ExFU study visit.

This visit constitutes the end of study participation except for subjects with a BMD decrease > 1.5% from the main study baseline for lumbar spine and/or > 2.5% for total hip. These subjects should have a repeat DXA scan 6 months later for BMD follow-up assessment.

10.2.2.4 Study visit: BMD Follow-up visit

BMD Follow-up visit should be scheduled on Day 674 ± 10 days after main study Day 1 (or 168 days ± 10 days after Month 6 ExFU visit).

This visit is applicable only to subjects with a BMD decrease of > 1.5% from the main study baseline for lumbar spine and/or > 2.5% for total hip at the Month 6 ExFU visit.

BMD of the femoral neck, hip and spine will be assessed by DXA.

Subjects who have ≥ 3% BMD decrease from their main study baseline at any site (femoral neck, hip or spine) at this visit should be referred to a bone specialist for evaluation.

10.3 EFFICACY OBSERVATIONS AND MEASUREMENTS

All the questionnaires described below will be completed in the eDiary by the subject and/or the site staff. If the subject forgets to bring her eDiary to one site visit, the completion of ePRO and ClinRO will be done on a site back-up device.

10.3.1 Daily eDiary

The subject will use the same eDiary as in the main study. If needed, she will be re-trained at Month 6 visit by the Investigator or delegate on how to use and complete it correctly.

The eDiary should be completed daily, in the evening at approximately the same time, during the entire extension study (including the Treatment and Follow-Up Periods). A daily alarm will be set up in the eDiary to remind the patient to complete her daily questions. In addition, appropriate email alerts will be sent to the site staff and to the operational team in case of missed diary entries. eDiary compliance will be checked remotely on an ongoing basis by a dedicated data management team and by the CRO and the Sponsor's clinical operations teams.

10.3.1.1 Pelvic pain

The subject's assessment of pelvic pain will be collected daily via the eDiary using an NRS and a VRS.

NRS: The subject will be asked to rate her worst endometriosis-associated pelvic pain in the last 24 hours on a 0–10 scale with 0 representing no pelvic pain and 10 representing the worst pelvic pain imaginable.

VRS: The subject will be asked to choose the category that best describes her endometriosis-associated pelvic pain in the last 24 hours*:*

0	*No pain.*
1	*Mild pain but I was easily able to do the things I usually do.*
2	*Moderate pain. I had some difficulty doing the things I usually do.*
3	*Severe pain. I had great difficulty doing the things I usually do.*

10.3.1.2 Daily function (difficulty of doing daily activities)

The subject will complete a daily questionnaire in the eDiary if she had any difficulty doing her daily activities in the last 24 hours on a 0–10 scale (NRS) with 0 representing no difficulty doing daily activities and 10 representing inability to do daily activities.

10.3.1.3 Uterine bleeding

The subject will complete a daily questionnaire in the eDiary assessing strength of uterine/vaginal bleeding in the last 24 hours. The strength of uterine bleeding will be assessed using the following scale:

Please choose the category that best describes your vaginal bleeding or spotting in the last 24 hours	
None	*No bleeding nor spotting*
Spotting	*Blood loss not requiring sanitary protection (except for panty liners)*
Bleeding	*Blood loss requiring sanitary protection (tampons or pads)*
Heavy Bleeding	*Heavy blood loss requiring sanitary protection (tampons or pads) for example:* • *Need for double protection to manage menstrual bleeding* • *Menstrual bleeding accompanied by sensation of "gushing" or "flooding"* • *Soaking one pad and/or tampon or more per hour for three or more consecutive hours* • *Needing to change the tampon or pad at night or soiling bedclothes*

10.3.1.4 Analgesic use

The subject will report daily in the eDiary whether she has taken any provided/prescribed analgesic (including the dose) for her EAP during the last 24-hour period.

Analgesic use for any other reason will be reported by the subject to the site staff and recorded in the eCRF.

10.3.1.5 Dyspareunia (pain associated with sexual intercourse)

The subject will be asked daily about dyspareunia via the eDiary using a VRS.

She will be asked to rate how her EAP interfered with sexual intercourse in the last 24 hours, with the following response options:

0	*No pain during sexual intercourse.*
1	*I was able to tolerate the pain during sexual intercourse.*
2	*Intercourse was interrupted due to pain.*
3	*I avoided sexual intercourse because of anticipation of pain.*

She will also be given the option to answer that she was not sexually active for reasons other than her endometriosis, in which case no score would be allocated.

10.3.1.6 Dyschezia (pain associated with defecation)

Dyschezia will be assessed daily via the eDiary and will be scored by the subject using a 0–10 NRS, where 0 represents no pain and 10 represents the worst pain imaginable.

10.3.1.7 School or work missed

The subject will be asked whether she missed school or work in the last 24 hours due to EAP.

10.3.1.8 Event cancelled

The subject will be asked if she had to cancel an event in the last 24 hours due to EAP.

Following a request from the FDA, this question was removed in protocol version 2.0 to reduce respondent burden and maximize the quality and completeness of clinical outcome assessment data. This question has been asked only to subjects who were enrolled prior to implementation of protocol version 2.0.

10.3.1.9 Sleeping or lying down during the day

The subject will be asked whether she slept or laid down during the day in the last 24 hours due to EAP.

10.3.1.10 Difficulty sleeping

The subject will be asked whether she had difficulty sleeping in the last 24 hours due to EAP.

Following a request from the FDA, this question was removed in protocol version 2.0 to reduce respondent burden and maximize the quality and completeness of clinical outcome assessment data. This question has been asked only to subjects who were enrolled prior to implementation of protocol version 2.0.

10.3.1.11 Patient Global Impression of Severity – daily recall (dPGIS)

The subject will record on a daily basis in the eDiary the severity of her endometriosis symptoms assessed on a 5-point scale with the following possible answers: no symptoms, very mild, mild, moderate, severe (see Appendix I).

Following a request from the FDA, this assessment was removed in protocol version 2.0 to reduce respondent burden and maximize the quality and completeness of clinical outcome assessment data. This assessment has been collected only for subjects who were enrolled prior to implementation of protocol version 2.0.

10.3.2 Outcome rating scales assessed at site visits

ePROs are self-administered questionnaires completed by the subject. ePROs completed by the subject during the site visits include: EHP-30, HRPQ, SSIQ, PROMIS, EQ-5D-5L, mPGIS and PGIC/PPGIC.

ClinROs are questionnaires administered by the site staff to the subject during the site visits and completed by the site staff in the eDiary. ClinROs include HRUQ and PSIQ.

During site visits, ePRO and ClinRO should be completed ideally prior to any other study procedures, with the mPGIS and PGIC/PPGIC being completed last (in this order). Assessments will be performed according to the schedule indicated in Appendix A and Appendix B.

If needed, site personnel will be re-trained on all rating scales (ePROs, ClinROs and scales of daily diary) used in this study.

10.3.2.1 Endometriosis Health Profile-30 (EHP-30)

The EHP-30 is a disease-specific self-administered questionnaire used to measure health related quality of life in women with endometriosis. The EHP-30 is composed of two parts: a core questionnaire containing five scales that are applicable to all women with endometriosis and a modular part containing six scales which do not necessarily apply to all women with endometriosis. This study will employ the Core EHP-30 and modular section C (Part 2) as outlined in Appendix C.

10.3.2.2 PROMIS Fatigue Short Form 6a14

This questionnaire is composed of six questions to evaluate the severity of fatigue (see Appendix D).

10.3.2.3 Health Related Productivity Questionnaire (HRPQ)

The HRPQ consists of nine questions measuring the impact of EAP and its treatment on work productivity and daily activities at home (see Appendix E).

10.3.2.4 Health Resource Utilization Questionnaire (HRUQ)

The HRUQ records use of health resources (emergency room, physician visit, hospitalization, etc.) during the study. This includes the number of non-study health visits – the total, the reason, primary reason, and type of clinician for the visit; Diagnostic/therapeutic procedures performed (Hysteroscopy, SIS, Colposcopy, Biopsy, Ultrasound or Other) and Emergency Room/Outpatient Procedures (see Appendix F).

10.3.2.5 Patient Global Impression of Change (PGIC)

The PGIC is used by the subject to evaluate the change in her endometriosis symptoms since initiation of study drug on a 7-point scale with following possible answers: very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse (see Appendix G).

10.3.2.6 Post-treatment Patient Global Impression of Change (PPGIC)

Subjects will evaluate the change in their endometriosis symptoms after discontinuation of study drug on a 7-point scale with the following possible answers: very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse (see Appendix H).

10.3.2.7 Patient Global Impression of Severity - monthly recall (mPGIS)

At each study visit and up to the end of the Follow-Up Period, the subject will be asked to evaluate the severity of her endometriosis symptoms over the past 28 days using a 5-point scale with the following possible answers: no symptoms, very mild, mild, moderate, severe (see Appendix I).

10.3.2.8 Subject Surgery Intention Question (SSIQ)

The SSIQ evaluates subject willingness to opt for endometriosis-related surgery if current symptoms continue (see Appendix J).

10.3.2.9 Physician Surgery Intention Question (PSIQ)

The PSIQ evaluates physician likelihood of recommending endometriosis-related surgery(s) to the subject if current symptoms continue (see Appendix K).

10.3.2.10 EQ-5D-5L

Subjects' health related quality of life will be measured using the EQ-5D-5L (see Appendix L). The EQ-5D-5L essentially consists of two pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems.

The EQ VAS records the subject's self-rated health on a vertical VAS, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'.

10.4 SAFETY OBSERVATIONS AND MEASUREMENTS

10.4.1 Adverse Events

AE data will be collected continuously during the study as described in Section 12.2.

AE data will be obtained at scheduled study visits based on physical examination, vital signs, ECG and biological laboratory assessments (see flowchart in Appendix A and Appendix B). In addition, subjects will report AEs spontaneously and/or through questioning.

Complete appropriate data on all AEs experienced for the duration of the reporting period will be reported on an ongoing basis in the AE pages of the eCRF.

10.4.2 Physical Examination

A complete physical examination, i.e. examination of organ systems, including thyroid gland, lungs, heart, abdomen, liver, kidneys and peripheral pulses (by palpation, auscultation or percussion), eyes, ears, nose, throat and skin (by inspection) and neurological reflexes will be performed every three months (i.e. at Month 9, Month 12, Month 3 ExFU and Month 6 ExFU visits).

In addition, a manual breast examination (by palpation) will be performed at Month 12 and at Month 3 ExFU visits. Results of the examinations will be recorded on source data files and in the eCRF. Baseline medical conditions (see section 12.1.3) that worsen in severity and/or frequency during the study and that are considered as clinically significant by the Investigator will be reported as AEs in the corresponding eCRF page.

The physical examination should be performed after the ECG.

10.4.3 Vital signs

BP and heart rate will be measured in sitting position. In case of abnormal vital signs (i.e. BP ≥ 150/100 mmHg or ≤ 90/50 mmHg and/or heart rate ≥ 100 bpm or ≤ 40 bpm) and if abnormality was not pre-existing, a repeat assessment after 5 min should be taken. In case of confirmed abnormality, which was not pre-existing or worsened in severity and/or frequency during the study and is considered as clinically significant by the Investigator, an AE must systematically be reported by the Investigator in the eCRF AE page. The Investigator is to provide a diagnosis rather than reporting individual vital signs parameters whenever possible.

BP and heart rate should be measured after performing the 12-lead ECG.

10.4.4 Transvaginal ultrasound

Endometrial thickness, uterus volume and abnormality (fibroids, adenomyosis, etc…) and left/right ovary abnormality status will be assessed by TVUS. If TVUS is not possible, abdominal ultrasound can be used. The printouts of the ultrasound will be interpreted and commented by the gynecologist and kept as source data. Results of the examination will be recorded on source data forms and in the eCRF.

TVUS should be recommended (for cause) for subjects with heavy/suspicious bleeding.

10.4.5 Endometrial biopsies

At the end of the Treatment Period (i.e. at Month 12 visit), endometrial biopsy for histological assessment will have to be obtained for each subject unless the endometrium thickness in TVUS is ≤ 5 mm, in which case no endometrium biopsy will be necessary (

Figure 3).

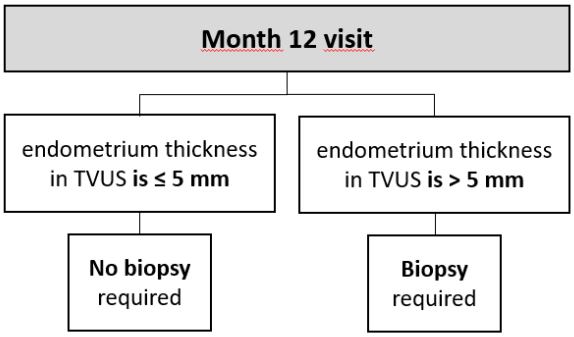
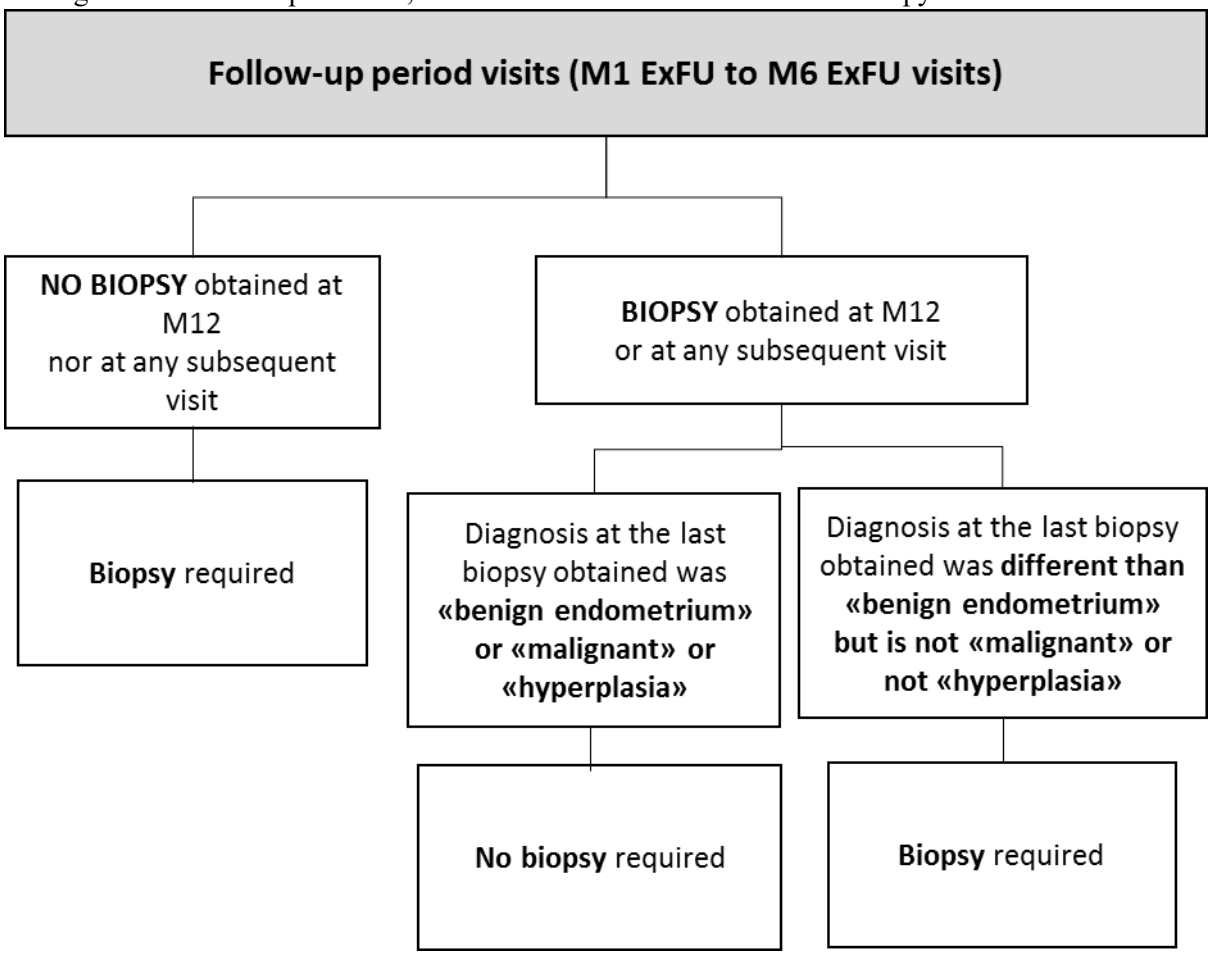


Figure 3 : Biopsy process for Month 12 visit

During the Follow-Up Period, the schedule for endometrial biospy is as described in Figure 4 below.



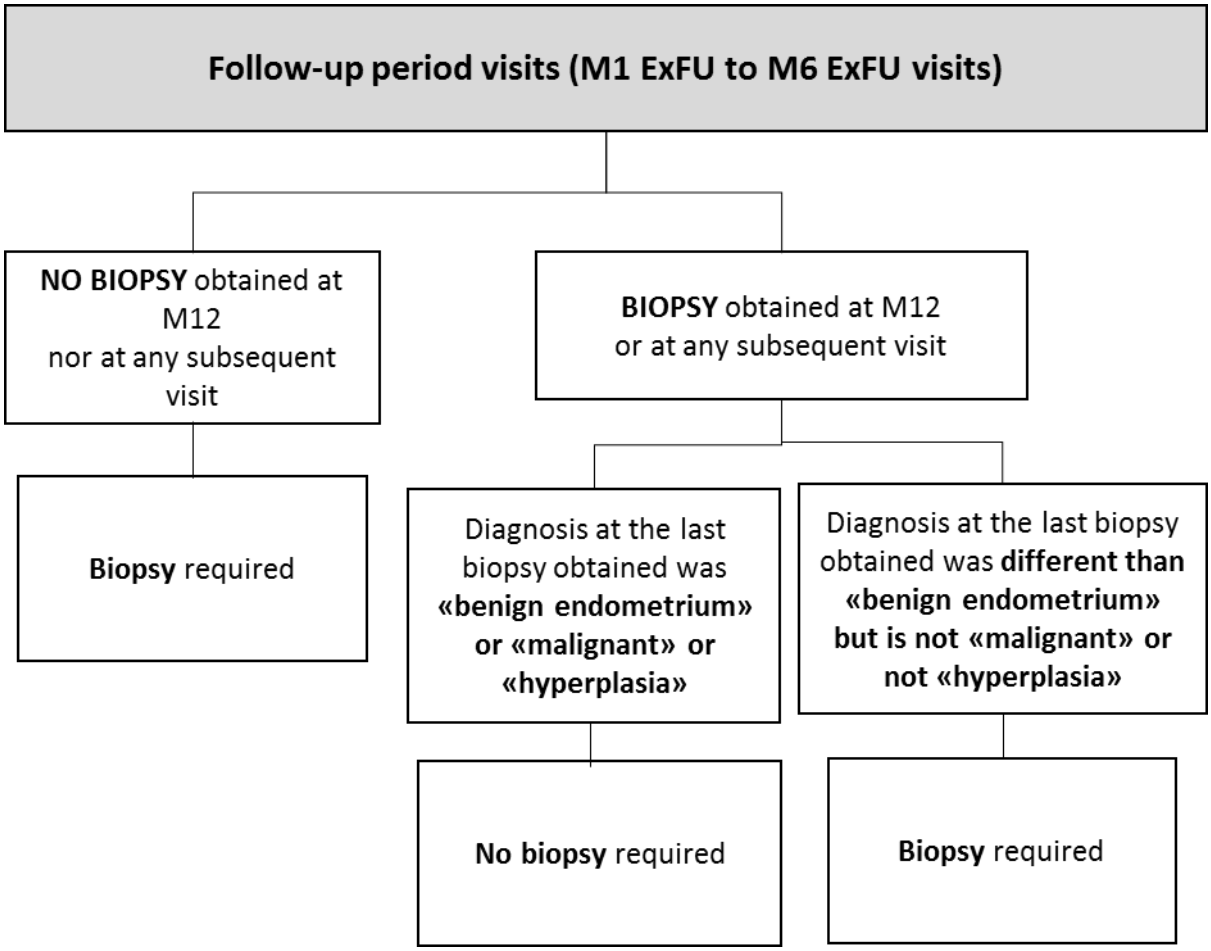


Figure 4 : Biopsy process for the Follow-Up Period visits

The endometrial biopsies will be analyzed by a central laboratory blinded to treatment group. Endometrial biopsies of hyperplasia of any type will be submitted for assessment by three independent expert pathologists who are blinded to the treatment and to one another's assessment.

At any time during the study, in case of endometrial biopsy diagnosis being hyperplasia of any type (with or without atypia) or worse (neoplasm) for patient on treatment, the laboratory will send an alert to the site and the Sponsor. The medical monitor will contact the sites to discuss the proceeding in line with local practice. The subject will be discontinued from the treatment, will enter the follow-up period and will be advised to consult for gynecological evaluation and treatment.

Biopsy should be recommended (for cause) for subjects with heavy/suspicious bleeding. Results from these procedures should be documented in the eCRF.

Endometrial biopsy samples will be performed with the Pipelle de Cornier® (or equivalent), as described in the manual provided by the central laboratory.

10.4.6 Bone mineral density and DXA

BMD of the femoral neck, total hip and lumbar spine will be assessed by DXA at the end of the Treatment Period (i.e. at Month 12 visit) and at the end of the Follow-Up Period (i.e. at Month 6 ExFU visit), under the supervision of a nominated primary technologist at the site. BMD for femoral neck, hip and spine will also be assessed at Month 9 for subjects who met the following criterion at any site on the Month 6 DXA scan: $-2.5 < \text{Z-score} \leq -1.5$.

A repeat DXA scan will be performed 6 months after the Follow-Up Period DXA for subjects with a BMD decrease from main study baseline > 1.5% for lumbar spine and/or **>** 2.5% for total hip.

For each subject, the same DXA machine must be used for all scan acquisitions.

All DXA scans will be read by a central imaging laboratory blinded to treatment group. There will also be centralized monitoring of DXA scan quality for each site including a pre-qualification phantom scan and a monthly review of daily quality control (QC) data.

In the event a scan does not meet quality standards, the site will be asked to repeat the scan. A repeated scan will be required for each scan showing 5% or more BMD loss from baseline.

Instructions to measure the BMD, detailed information on the centralized reading and QC and the stopping rules for subjects will be included in a specific imaging manual.

10.4.7 Bone markers

Blood samples for exploratory bone biomarkers such as, but not limited to, collagen type 1 β-carboxy-telopeptide (CTx), procollagen 1 Intact N-Terminal (P1NP), bone-specific alkaline phosphatase (B-ALP) and osteocalcin will be collected as part of clinical chemistry at Month 9 and Month 12 visits as well as at Month 3 ExFU visit. These exploratory data will not be communicated to keep the operational team and the sites blinded to treatment administration.

10.4.8 Laboratory parameters

Haematology, coagulation parameters and chemistry will be assessed at each visit during the Treatment Period, as well as at Month 1 ExFU and Month 3 ExFU visits. Fasting lipids will be assessed at Month 9, Month 12 and Month 3 ExFU visits.

E2, P4 and LH will be assessed at each visit during the treatment period, as well as at M1 ExFU and M3 ExFU visits. Serum levels of SHBG will be assessed at Month 9 and Month 12 visits.

Overnight fasting is required for Months 9, 12 and Month 3 ExFU visits.

Blood samples will be analyzed by the central laboratory. Details of blood sampling process, sample handling and shipment are described separately in a laboratory manual provided by the central laboratory. Central laboratory reference ranges will be filed in the investigator site file and in the trial master file. All laboratory results except E2, P4, LH and SHBG levels will be assessed by the Investigator/sub-Investigator. Clinically significant abnormalities compared to main study baseline status will be reported as AEs in the eCRF. E2, P4, LH and SHBG levels will not be communicated to keep the operational team and the sites blinded to treatment administration.

The laboratory parameters are listed in Appendix M.

There may be some additional laboratory parameters to be analysed as requested by the medical monitor in order to follow-up on existing abnormalities.

10.4.9 Electrocardiogram

Local 12-lead ECG readings of QTcF will be performed at each visit during the entire duration of the study.

ECGs should be performed prior to blood sampling, physical examination and vital signs.

10.4.10 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS questionnaire prospectively assesses the occurrence of treatment-emergent suicidal ideation and behavior. The questions will be administered by the site staff to the subject and completed by the site staff, using one of the following paper versions:

- either the "already enrolled subjects" C-SSRS version, dedicated to subjects who are providing answers to the C-SSRS for the first time during the study (see Appendix R).

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

10.5 LINZAGOLIX AND KP017 PLASMA LEVELS

PK blood samples will be collected from each subject at each study visit during the Treatment Period for determining linzagolix and KP017 plasma levels.

At the visits where IMP intake is at site, i.e. at Months 6, 7, 8, 9, 10 and 11 visits, PK sampling will be performed before IMP intake. The approximate time of dose administration on the four previous days and time of PK sampling will be recorded in the eCRF.

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

Details of the blood sampling process, sample handling and shipment are described separately in a laboratory manual provided by the central laboratory.

10.6 CONCOMITANT MEDICATIONS AND THERAPIES

The Investigator will record in the appropriate section of the eCRF all concomitant medications taken by the subject during the entire study duration.

However, the use of provided/prescribed analgesics for EAP will be recorded solely in the eDiary.

10.6.1 Permitted Medicines

Any medications other than those excluded by the protocol (see section 10.6.2), which are considered necessary for the subject's welfare and/or which will not interfere with the study medication, may be given at the discretion of the Investigator.

Analgesics:

Only the analgesics provided/prescribed by Sponsor will be allowed during the study (Treatment and Follow-up Periods). Other analgesics will be prohibited. Provided/prescribed analgesics should be taken only when required for treatment of pain. Prophylactic use of analgesics will be prohibited.

Permitted opioid analgesics will be prescribed and dispensed as required according to local practice.

Subjects will be required to restrict the use of analgesics to those permitted by the protocol as listed in Table 1.

Table 1: Permitted rescue analgesics

Analgesic class	Name and dose*
NSAID	ibuprofen 200 mg
Narcotic Analgesic	5 mg hydrocodone + 300 mg acetaminophen**

* Use of these analgesic medications should be according to the product prescribing information.

** Or local equivalent

Other:

In order to prevent or minimize possible impact on BMD, subjects will receive calcium 500 to 1000 mg and vitamin D 400 IU supplementation which they will be advised to take daily until the end of study. Intake should be recorded at each study visit in eCRF. As the interaction potential is unknown, the intake should be separated of at least 4 hours from the intake of the study drug.

If necessary, the dose of calcium or vitamin D supplementation may be reduced or discontinued at the discretion of the Investigator.

10.6.2 Prohibited Medicines

Medication listed in Appendix N will be prohibited up to Month 12.

Strong CYP3A4 inhibitors or inducers are prohibited up to end of treatment in view of the ABT (Appendix O).

Linzagolix is considered to be a weak inhibitor of CYP2C8. Substrates to CYP2C8 with a narrow therapeutic index should be administered with caution.

Hormonal contraception, including use of hormonal IUDs, must not be taken until 3 months after end of treatment.

When a prohibited medication or treatment is necessary for the subject's well-being, the Sponsor must be notified, and possible alternatives are to be discussed before administration of the prohibited medication or treatment whenever possible.

10.6.3 Non-Drug Therapies

Contraceptive use:

For subjects of childbearing potential and requiring contraception, non-hormonal contraception is required until 3 months after the end of treatment. Two forms of non-hormonal contraception will be required e.g. condom with spermicide (if in the opinion of the Investigator a woman is at risk of acquiring HIV, spermicide should be avoided; condom with diaphragm may be used). Suitable condoms with spermicide will be provided free of charge to subjects over the duration of the study.

Contraception is still required from 3 months after the end of the Treatment Period until the end of the post-treatment Follow-up Period; hormonal contraception is allowed.

10.7 SUBJECT COMPLETION AND WITHDRAWAL

10.7.1 Subject Completion

A subject will be considered as a "completer" when she has completed all study procedures/visits according to the protocol.

10.7.2 Subject Withdrawal

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

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

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

In case of early discontinuation, the subject will 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 should undergo the procedures required at Month 12, except the DXA in case of discontinuation before Month 9 visit. These subjects will enter the 6-month Follow-Up Period and will continue daily eDiary recording for 6 months and up to Month 6 ExFU visit in order to continue to collect efficacy and safety data.

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

Withdrawal during Follow-Up Period:

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

10.7.2.1 Discontinuation criteria

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

- **Adverse Event:** Includes clinically significant new or worsening existing condition as judged by the Investigator. Document in the AE form.

- **Subject's Request:** Consent withdrawal, subject moved, schedule conflicts, etc. Specify the reason in the comment section of the eCRF Exit Form.

- **Protocol Violation:** Major protocol violation which may affect the subject's safety. Specify the protocol violation in the comment section of the eCRF Exit Form.

- **Lost to Follow-up:** Document with at least two phone calls and a certified letter requesting return receipt without response. Document in the comment section of the eCRF Exit Form**.**

- **Pregnancy:** Subjects who have been exposed to study treatment and who become pregnant during the Treatment Period will be immediately withdrawn from treatment. Pregnancies that have been exposed to study treatment and occurred up to Month 3 ExFU visit, or started up to 4 weeks after treatment discontinuation in case of early withdrawal will be followed up for pregnancy and neonatal outcomes at birth. Any pregnancy must be reported with the Pregnancy Surveillance Form (see section 12.6).

- **Other:** Specify in the Comments section in the eCRF Exit Form. This reason should only be used if the reason for discontinuation is not better accounted for by another category.

Discontinuation Rules:

Endometrial biopsies: in case of endometrial biopsy diagnosis being an endometrial hyperplasia of any type or worse, the subject will have to discontinue treatment and will be advised to consult for gynecological evaluation and treatment.

Serum calcium: Subjects who have a serum calcium level on treatment above 2.9 mmol/L should have calcium supplements interrupted. If serum calcium level on treatment is above 3.1 mmol/L calcium supplements **and study treatment** are to be interrupted. A repeat test of this parameter within 2 weeks under fasting conditions is to be performed. If the results of the repeat remain above

2.9 mmol/L, study treatment should definitively be discontinued and the subject should be advised to consult an endocrinologist for further evaluation.

BMD loss: subjects who experience more than 8% BMD loss or a Z-score ≤ -2.5 at any site (femoral neck, hip or spine) will be discontinued from study treatment and will enter the Follow-Up Period.

Liver function tests: following the Food and Drug Administration (FDA) guidance on drug-induced liver injury (8), subjects who have an elevation of hepatic enzymes are 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 will be followed up until hepatic parameters return to normal.

ECG : subjects who have a QTcF > 500 ms or increase > 60 ms from the highest value prior to the first dose in the main study will have 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 will enter the 6-month Follow-Up Period and undergo the follow-up ECGs according to the schedule of events.

10.7.3 Subject Replacement

Not applicable.

11 INVESTIGATIONAL MEDICINAL PRODUCT

11.1 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCTS

The term “Investigational Medicinal Product” (IMP) will refer to the ObsEva investigational drug linzagolix, the ABT (E2 1 mg/NETA 0.5 mg) or their matching placebos.

	Investigational drug	Investigational drug placebo	ABT	ABT placebo
International nonproprietary name **(INN)**	Linzagolix	NA	E2 and NETA	NA
Name of active ingredient	Linzagolix	NA	E2 and NETA	NA
Form	Film-coated tablet	Film-coated tablet	Capsule	Capsule
Strength	75 mg and 200 mg	placebo for 75 mg and placebo for 200 mg	1.0 mg/0.5 mg	Placebo
Dose or concentration of active treatment	75 mg and 200 mg	0 mg	1.0 mg/0.5 mg	0 mg
Frequency and duration of administration	Once daily for up to 6 months			
Route of administration	Oral			
Manufacturer (Name and address)	Patheon, Canada		Sharp Clinical Services Inc. 2400 Baglyos Cir, Bethlehem, PA 18020, United States	
Primary packaging	PVC-PVdC/Al blister containing 15 tablets		PVC/Al blister containing 7 capsules	
Secondary packaging (1 kit)	4 blisters attached into a child-resistant wallet card*		14 blisters in a carton box	
Storage Requirements	As indicated on the study drug kit label			

*The blisters being linked together inside the wallet card, the kit is considered as a single unit and therefore labelling on the wallet is sufficient (individual blisters are not labelled).

11.2 DOSAGE AND ADMINISTRATION

Linzagolix treatments and matching placebo will be supplied as film-coated tablets for oral administration and given as monthly treatment kits (Figure 5).

ABT and corresponding placebo will be supplied as red capsules and given as 3-monthly treatment kits.

IMP treatment will be administered once daily up to Month 12 inclusive. The subjects will have to swallow one tablet of linzagolix, one tablet of linzagolix placebo and one capsule of ABT or ABT placebo, ideally at the same time each day.

On the day of a study visit, the subject must take the study medication at site. The site staff will record in the eCRF the time of study medication intake. The linzagolix/placebo tablets must be taken from the kits dispensed on that visit (and not from the previously dispensed kits). On Month 6 and Month 9 visits, ABT/placebo capsules must be taken from the kits dispensed during these visits. On Month 7, 8, 10 and 11 visits, ABT/placebo capsules must be taken from the previously dispensed kits.

The treatment groups are described below:

Treatment group	**Daily dose Month 6 to Month 12**			
	Linzagolix active tablets	Linzagolix placebo tablets	ABT active capsules	ABT placebo capsules
75 mg	1 × 75 mg	1 × placebo 200 mg	None	1 capsule
200 mg + ABT	1 × 200 mg	1 × placebo 75 mg	1 capsule	None

11.3 PACKAGING AND LABELLING

Linzagolix/placebo will be provided by the Sponsor (or delegate) as monthly kits.

On Month 6, 7, 8, 9, 10 and 11 visits, the subject will be given a wallet card containing four blisters in total:

- Two blisters of 15 tablets each of 200 mg linzagolix or matching placebo (corresponding to the grey card on Figure 5),
- Two blisters of 15 tablets each of 75 mg linzagolix or matching placebo (corresponding to the pink card on Figure 5).

This kit covers 30 days of treatment.

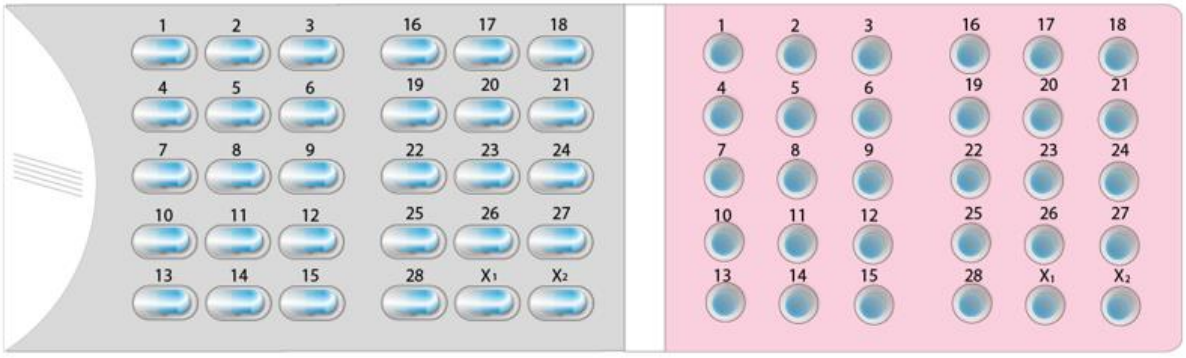


Figure 5 : Linzagolix kit design

Each linzagolix/placebo kit will be labeled with a unique kit number from K50001 to K60000 (6-characters). The blisters being attached into the wallet card, linzagolix/placebo kit is considered as a single unit and therefore labelling on the wallet is sufficient (individual blisters are not labelled).

ABT and matching placebo will be provided by the Sponsor (or delegate) as 3-monthly kits.

On Month 6 and 9 visits, the subject will be given a carton box containing 14 blisters of seven capsules each of ABT or matching placebo. This kit covers 98 days of treatment.

Each ABT kit will be labeled with a unique kit number (different from the linzagolix kit number), from A50001 to A70001.

Each kit of linzagolix/placebo or ABT/placebo will have a label including a tear-off part. The tear-off part containing the study number and the kit number will be placed into a drug accountability form at site.

Labels will be printed in the local language of the countries where the study will take place in accordance with applicable local regulations, the recommendations of GMP guideline (Annex 13) and FDA 21 CFR 312.6 part.

The kit label, i.e. on the secondary packaging, will indicate at least the following items:

- Protocol number
- Kit number
- Batch number
- Storage conditions
- Sponsor name and address

Label examples are filed in the study file at the Investigator's site and in the trial master file.

11.4 PREPARATION, HANDLING AND STORAGE

The investigational site will store the IMP according to the specifications of the Sponsor. The IMP storage conditions will be indicated on each kit label.

The storage facility at site should be locked and temperature-controlled.

Linzagolix and ABT must be stored at 68°F to 77°F (20°C to 25°C), excursions permitted between 59°F and 77°F (between 15°C and 25°C). The storage temperature at the clinical site must be recorded by using a minimum/maximum thermometer or electronically 24 hours a day with printouts available on request.

The IMP may be dispensed only by the pharmacist or by a member of staff specifically authorized by the Investigator.

Any deviations from the recommended storage conditions at the site should be immediately reported to the Sponsor (or delegate), and the IMP should not be used until authorization has been given by the Sponsor (or delegate).

11.5 IMP ACCOUNTABILITY

The Investigator is responsible for ensuring IMP accountability, including reconciliation and maintenance of drug records.

- Upon receipt of the IMP, the Investigator (or delegate) will check for accurate delivery and acknowledge receipt in IWRS. A copy of acknowledgement of receipt will be retained in the investigator file. In case the IMP received is damaged upon delivery (including temperature excursion), this should be immediately reported to the Sponsor (or delegate), and the IMP should not be used until authorization has been given by the Sponsor (or delegate).
- The dispensing of the IMP will be carefully recorded on the appropriate drug accountability form provided by the Sponsor (or delegate) and in eCRF, and an accurate accounting will be available for verification by the study monitor at each monitoring visit.
- IMP accountability records will include:
    - Confirmation of IMP delivery to the trial site
    - The inventory at the site of IMP delivered
    - The use of each dose by each subject (accountability to be done at each visit)
    - Dates, quantities, batch numbers and kit numbers assigned to the subject.
    - The return to the Sponsor (or delegate) or alternative disposition of used and unused IMP
- The Investigator should maintain records that adequately document:
    - The subjects were provided with the doses specified by the protocol/amendment(s).
    - All IMP provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present study. IMP that has been partially dispensed to a subject must not be re-dispensed to a different subject.

The Study monitor will check on an ongoing basis the IMP accountability form and verify all IMP dispensations and returns (both unused and used treatments) during the entire study period and prior to making arrangements for their return to the Sponsor (or delegate) or authorizing their destruction by the study site in agreement with the Sponsor.

11.6 ASSIGNMENT TO TREATMENT GROUPS

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

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

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

11.7 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT COMPLIANCE

The subject will record her IMP intake daily in the eDiary.

Each subject must be instructed to bring with her to each visit both opened and unopened IMP packages, in order to allow the assessment of compliance with study treatment.

The decision to withdraw a non-compliant subject from the study will be discussed between the Investigator and the Sponsor.

During the entire study period, the study monitor will perform drug accountability and the assessment of compliance with study treatment by checking both opened and unopened IMP packages, as well as empty blisters.

11.8 METHOD OF BLINDING

The study design is double-blind for the subject, the site and the operational team. The Sponsor will be unblinded to active treatment groups, following analysis of Month 6 visit data of the main study (18-OBE2109-002 - Edelweiss 2 study), but will be blinded to the treatment allocated to patients who previously received placebo.

Linzagolix 75 mg and 200 mg tablets having a different appearance, a double-dummy design will be used in order to maintain the blinding of the study.

The randomization list will be secured in a computer file with restricted access to only the designated personnel including those responsible for labelling and handling the study medication until the study database is locked and ready to be unblinded.

Every effort will be done to keep the Investigator, the site personnel and the subject fully blinded.

11.9 EMERGENCY UNBLINDING

The study blind may be broken for an individual subject **only in the case of an emergency** when knowledge of the IMP is essential for the clinical management of the subject. The Investigator can break the blind for a subject by using the IWRS that permits immediate unblinding. In case of doubt as to whether emergency unblinding is necessary, the Investigator should contact the Sponsor prior to breaking the study blind.

In the case of a code break, the Investigator must inform the Sponsor immediately without revealing the code to the Sponsor study personnel nor the complete Study Team.

11.10 TREATMENT OF OVERDOSE AND MISUSE

An overdose is defined as any dose (i.e. quantity of drug given per administration or per day) above the maximum dosage defined in the protocol (200 mg per day).

Misuse is the term used if more precise information is not available and additional information is needed to determine if there was a "medication error", "drug abuse" or "overdose".

Any details of overdose or misuse must be recorded in the eCRF.

Any case of overdose or misuse associated with an AE or a SAE must be reported as per the instructions detailed in Sections 12.2.3 for AEs or 12.3.2 for SAEs.

The effects of an overdose of linzagolix are unknown, but repeated once daily dosing at up to 700 mg linzagolix was safe and well-tolerated by premenopausal healthy volunteers, and doses up to 200 mg daily for 3 months were safe in endometriosis subjects (see Section 5.5.3).

11.11 OTHER SUPPLIES TO BE USED IN THE STUDY

A limited quantity (as per Investigator's judgement) of standard doses of permitted analgesics will be provided/prescribed to the subject as rescue medication for EAP (see Section 10.6.1). These will be provided by the Sponsor free of charge to the subject or reimbursed.

Electronic diaries will be provided for subjects to use. These remain the property of the Sponsor.

Calcium 500 to 1000 mg and vitamin D 400 IU supplements will also be provided by the Sponsor free of charge to the subject. Intake should be separated by at least 4 hours from the intake of the study drug.

Condoms with spermicide will also be supplied by the Sponsor free of charge to the subject. If required, spermicide-free condoms, latex-free condoms and diaphragms may be reimbursed to the subject.

12 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Comprehensive assessments of any apparent toxicity experienced by the subject will be performed throughout the course of the study from the time of subject's signature of informed consent. Study site personnel will report any AE, whether observed by the Investigator or reported by the subject (see section 12.2.1).

The safety profile of linzagolix will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, ECGs, vital signs, laboratory tests, BMD assessments.

The reporting period for AEs is described in section 12.5.

12.1 ADVERSE EVENTS

12.1.1 Definitions

Adverse Event:

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial subject administered an investigational medicinal product (IMP) and which does not necessarily have a causal relationship with this treatment. It can therefore be any unfavourable sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Any event occurring after signature of the informed consent form should be reported on an AE form or an SAE form, as appropriate.

Severity:

The severity of AEs must be assessed by the Investigator according to the following definitions. The term "severity" is used to describe the intensity of a specific event. This has to be distinguished from the term "serious".

Mild:	The subject is aware of the event or symptom, but the event or symptom is easily tolerated (e.g. no reduction in daily activities is required).
Moderate:	The subject experiences sufficient discomfort to interfere with or reduce her usual level of activity.
Severe:	Significant impairment of functioning: the subject is unable to carry out usual activities and/or the subject's life is at risk from the event.

Causality assessment:

The causality assessment of an AE to the linzagolix and/or ABT will be rated as follows by the Investigator:

Not related:	There is no reasonable possibility of causal relationship between an AE and IMP.
Related:	There is at least a reasonable possibility of a causal relationship between an AE and an IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Unexpected Adverse Event:

Any AE which is not consistent in specificity or severity with the current Investigator's Brochure (section 6.7.1), including all amendments, is considered unexpected.

Outcome:

Outcome describes the status of the AE. The Investigator will provide information regarding the subject outcome of each AE, and the options include:

Fatal	Termination of life as a result of an AE.
Not recovered/not resolved	Subject has not recuperated or the AE has not improved.
Recovering/resolving	Subject is recuperating or the AE is improving.
Recovered/resolved	Subject has recuperated or the AE has resolved.
Recovered with sequelae/resolved with sequelae	AE has resolved, but the subject has symptoms or pathology.
Unknown	Unknown, not observed, not recorded, or refused.

Action taken regarding study drug:

The Investigator will provide the action taken regarding study drug in response to each AE, and the options include:

Dose not changed	No change in the administration of study drug.
Drug (study drug) interrupted	Study drug is being temporarily interrupted due to AE.
Drug (study drug) withdrawn	Decision was made to withdraw the study drug due to AE.
Unknown	Unknown, not observed or not recorded.
Not applicable	AE started before dosing or after dosing finalized.

12.1.2 Abnormal laboratory findings and other objective measurements

Abnormal laboratory findings and other objective measurements (e.g. vital signs) must be reported as an AE only if assessed by the Investigator as "clinically significant" e.g. meeting at least one of the following conditions:

1. The abnormality suggests a disease and/or organ toxicity AND this abnormality was not present at the main study screening visit or is assessed as having evolved since this visit.
2. The abnormality is a Serious Adverse Event.
3. The abnormality results in discontinuation of the IMP.
4. The abnormality requires medical intervention or concomitant therapy.

The Investigator must initial and date each laboratory report/eCRF page and note directly on the report/eCRF page whether or not each out-of-range laboratory result is clinically significant. The outcome of this assessment will be reported using an AE or SAE form, as appropriate.

When reporting an abnormal finding for laboratory parameters or other objective measurements on the AE page of the eCRF, a clinical diagnosis should be recorded rather than the abnormal value itself, if available (for example, "anaemia" rather than "decreased red blood cell count").

For all of these AEs, whether or not related to the treatment, the laboratory test(s) will be followed-up as appropriate.

12.1.3 Baseline Medical Conditions

Medical conditions present at the Screening visit(s) in the main study, including results of the study screening assessments, are defined as Baseline Medical Conditions. These medical conditions should have been adequately documented on the "medical history page of the eCRF". Baseline Medical Conditions that worsen in severity or frequency during the study should be recorded and reported as AEs.

12.1.4 Exacerbation of endometriosis

In this protocol, symptoms and signs of exacerbation or worsening of endometriosis will usually be captured in the context of efficacy assessment. Therefore, symptoms, exacerbation or worsening of endometriosis will NOT be considered as AEs nor captured on the AE page of the eCRF unless clinically significant AND not consistent with the anticipated natural progression of the disease.

Lack of efficacy of the study drug is NOT considered as an AE.

12.1.5 Adverse Events of Special Interest

Not Applicable.

12.2 PROCEDURES FOR ELICITING, RECORDING AND REPORTING ADVERSE EVENTS

12.2.1 Eliciting Adverse Events

Data on AEs will be obtained at scheduled or unscheduled study visits, based on information spontaneously provided by the subject and/or through questioning of the subject.

To elicit AEs, questioning at each study visit should begin with simple non-leading questions. For example:

- How have you felt since your last visit?
- Have you had any health problems since you were here last?

If a subject is seen by a physician not involved with the study in relation to an AE, the Investigator should make every effort to contact the treating physician in a timely manner in order to obtain all information necessary for the appropriate reporting of the event.

12.2.2 Recording of Adverse Events in the eCRF

As the quality and precision of acquired AE data are critical, Investigators should use the AE definitions provided in the above sections and should follow this guideline when completing the AE pages of the eCRF:

- Whenever possible, recognized medical terms should be used to describe AEs rather than colloquialisms (for example, 'influenza' rather than 'flu'), and abbreviations should be avoided in provided AE term.
- AEs should be described using a specific clinical diagnosis, if this is available, rather than a list of component signs or symptoms (for example, 'congestive heart failure' rather than 'dyspnoea, rales and cyanosis').
- However, signs and symptoms that are not linked (as "co-manifestations") to an identified disease or syndrome, or for which an overall diagnosis is not available, should be reported as individual AEs in separate eCRF AE page(s).
- Provisional diagnosis (e.g. "suspected Myocardial Infarction") are acceptable but should be followed up to a definite diagnosis, if finally available.
- AEs occurring secondary to other events (e.g. sequelae or complications) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to record in the eCRF. The Investigator should be invited to provide his/her opinion of which is the primary AE.

12.2.3 Reporting of Adverse Events

Complete and accurate data on all AEs experienced for the duration of the reporting period, as defined in section 12.5, will be reported on an ongoing basis in the AE pages of the eCRF.

It is important that each AE report includes a description of the event, whether it is considered serious (and if so the criterion satisfied), its duration (onset and resolution dates), its severity, its relationship to the IMP(s), any other potential causality factors, any treatment given or other action taken (including dose modification or discontinuation of the IMP) and its outcome.

12.3 SERIOUS ADVERSE EVENTS

12.3.1 Definitions

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence or effect that at any dose:

- **results in death**,

  i.e. the AE causes or contributes to the death.

- **is life-threatening**,

  i.e. the AE places the subject at immediate risk of death; it does not refer to AE which hypothetically might have caused death if it were more severe.

- **requires inpatient hospitalization or prolongation of existing hospitalization**,

  i.e. the AE requires at least an overnight admission or prolongs a hospitalization beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons, for any elective surgery (i.e. plastic surgery) or for normal disease management (including treatment adjustment) are NOT to be considered as SAEs according to this criterion.

- **results in persistent or significant disability / incapacity**,

  i.e. the AE resulted in a substantial disruption of the subject's ability to conduct normal activities.

- **is a congenital anomaly / birth defect**,

  i.e. an adverse outcome in a child or fetus of a subject exposed to the IMP before conception or during pregnancy.

- **is an important medical event, i.e. is medically significant ;**

  Medical and scientific judgment should be exercized in deciding whether an AE is serious in other situation. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.3.2 SAE Urgent Reporting Procedure

If a SAE occurs from subject consent up to the end of the Follow-Up Period, or in case of study discontinuation, if the site becomes aware of an SAE up to four weeks post study treatment discontinuation, regardless of relationship and expectedness, the Investigator is to take prompt and appropriate therapeutic action, if necessary, to protect the safety of study subjects and report such SAE as following.

For blinded studies, refer to section 11.9. for instructions related to emergency unblinding.

The Investigator must notify **VOISIN CONSULTING** (acting on behalf of ObsEva Pharmacovigilance) **WITHIN 24 HOURS** of awareness of a new SAE or of new information on a previously reported SAE (= follow-up).

To do so, the Investigator must complete a SAE report and any specific eCRF pages if justified by the protocol e.g. AE, medical history, concomitant medication eCRF pages and blinded and anonymized

copies of any other supporting source documents such as lab reports, hospital discharge letter/report, etc.), sign it and send it directly to Voisin Consulting by e-mail using the dedicated e-mail address specified below:

Name/Title: Voisin Consulting Life Sciences / **ObsEva Pharmacovigilance**

E-mail: **obsevasafety@voisinconsulting.com**

VOISIN CONSULTING will notify ObsEva Pharmacovigilance within one working day after the receipt of the SAE report or follow-up information, using the same reporting forms.

The SAE follow-up observation period, for the concerned subjects, will be jointly decided by the Investigator or one of the co-Investigators (in case of Investigator's absence) and the Sponsor.

In addition, the Investigator must respond to any request for follow-up information or questions regarding the SAE the Sponsor may have, within one working day for urgent queries or five working days for normal queries. SAE will be followed until the Investigator and ObsEva agree that the event is satisfactorily documented and resolved/stabilized.

For any new SAE, the following minimum information is required as initial notification:

- Clear identification of the Investigator/Reporter with full contact information or site number,
- Subject identification details (study number, site number, subject's unique study identification number and date of birth),
- IMP(s) administration details (dose and dates),
- Diagnosis of the event (or a brief description of signs/symptoms/clinical course if the diagnosis is not available) and the date of onset,
- Seriousness criteria (see Section 12.3.1),
- Causal relationship (Investigator's opinion) of the event with the IMP(s) or with the trial procedure (e.g. the causality according to the Investigator during screening).

12.4 REPORTING TO THE INSTITUTIONAL REVIEW BOARDS AND REGULATORY AUTHORITIES

The Investigator must comply with any applicable requirements related to the reporting of SAEs involving the study subjects to the Institutional Review Board (IRB)Research Ethics Board) (REB) that approved the study.

ObsEva will comply with the applicable regulatory requirements related to the expedited reporting of suspected unexpected serious adverse reactions (SUSARs) to the regulatory authorities (e.g. Health Authority, Central IRBREB). The Sponsor will be responsible, through their US Agent, for notifying the FDA of any SUSAR, and the Sponsor or designee is responsible for notifying the Central IRBREB. In regions/countries other than the US, reporting of events to local authorities will be performed by the Investigator/Sponsor or designee and in accordance with local procedures/regulations.

In accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of "findings that could affect adversely the safety of subjects, impact the conduct of the trial or alter the IRBREB's

approval/favourable opinion to continue the trial". In particular and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and unexpected (i.e. as per the linzagolix Investigator Brochure, and SmPC for the ABT) and are considered by the Investigator or the Sponsor, to have a reasonably possibility of causal relationship between the administered IMP and the AE (i.e. SUSAR). The Investigator will keep copies of these safety reports in the investigator's file. National regulations with regards to safety reports notifications to Investigators will be taken into account.

Unless clearly defined otherwise by national or site-specific regulations, and duly documented, the responsible Investigator will promptly notify the concerned IRBREB of any safety reports provided by the Sponsor and provide copies of all related correspondence to the Sponsor. Only when specifically required by regulations, the Sponsor (or delegate) will provide appropriate safety reports directly to the concerned IRBREB and maintain records of these notifications.

12.5 REPORTING PERIOD

AEs are collected on an ongoing basis from the day of signed informed consent. All new AEs and updates on all ongoing AEs or AEs with an unknown outcome, must be recorded up to the Month 6 ExFU visit.

A last batch of queries will be sent after last study visit if remaining ongoing/unknown outcomes of reported AEs are pending. After the last batch of queries with all collected data has been fully processed, eCRF and database will no longer be updated. Only SAEs and medically relevant ongoing/unknown outcome AEs will be followed-up until resolution or stabilization, under Voisin Consulting responsibility.

12.6 PREGNANCY AND IN UTERO DRUG EXPOSURE

A**ll pregnancies that are diagnosed up to Month 3 ExFU visit** or up to 4 weeks after the last IMP administration for subjects prematurely terminating the study must be recorded using the **Pregnancy Surveillance Form (PSF) – Part I** (History and Start of Pregnancy; PSF-part I), provided by the Sponsor (or delegate) at the beginning of the study.

Initial reporting of pregnancies:

Subjects who become pregnant during the study Treatment Period will be immediately withdrawn from the IMP treatment.

The Investigator must notify the Sponsor in an expedited manner (same as SAE reporting) of any pregnancy occurring during the above-mentioned period, by completing the **PSF-part I**.

This form should be sent to ObsEva's Representative for Pharmacovigilance as per the same procedures and timelines described for SAE Urgent Reporting in section 12.3.2. This form should be accompanied, as needed, by copies of the eCRF Medical History, Previous and Concomitant Therapy and the Exit Form.

Follow-up of pregnancies:

The Investigator must actively follow-up, document and report to ObsEva's Representative for Pharmacovigilance the progress by **tri-monthly updates up to the final outcome of the pregnancy** using the **Pregnancy Surveillance Form – Part II**: (Course of Pregnancy; PSF-part II). If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with two phone calls and a letter (certified with return receipt) are required.

Pregnancy outcomes are not recorded in the eCRF unless considered AEs.

Pregnancy outcomes must be reported to ObsEva's Representative for Pharmacovigilance by completing the **Pregnancy Surveillance Form – Part III**: (Course and Outcome of Pregnancy; PSF-part III). Timelines vary according to the nature of the pregnancy outcome:

- For normal outcomes, ObsEva's Representative for Pharmacovigilance should be notified within 45 days of birth/delivery.
- For abnormal outcomes, the fully completed form must be sent to ObsEva's Representative for Pharmacovigilance according to the same procedures and timelines described for expedited AE reporting in section 12.3.2 (within 24 hours of awareness of this outcome). An SAE Report form should be completed in addition to the PSF-part III if the subject sustains an event meeting seriousness criterion (e.g. abnormality for the pregnancy (spontaneous abortion, stillbirth) or abnormality for the birth itself (e.g. prolongation of hospitalization due to caesarean section complications)). In case of congenital malformation or birth defect of the child, a SAE Report form for the child should be completed in addition to the PSF-part III (Subject identifier = Subject ID – 1 for a singleton neonate).

13 DATA ANALYSIS AND STATISTICS

13.1 TEST OF HYPOTHESES

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

13.2 SAMPLE SIZE

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

13.3 RANDOMIZATION

Subjects who previously received placebo will be 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 will be randomized into permutated blocks of a pre-determined length.

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

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

13.4 ANALYSIS SETS

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

1. **Treatment Extension Analysis Set**: All subjects from the main study who entered the extension study and received at least one dose of study drug with the exception of subjects whose Month 6 assessments subsequently met any of the discontinuation criteria listed in section 10.7.2.1. These subjects will be withdrawn from study treatment and will enter the Follow-Up Period. Subjects will be analyzed according to randomized treatment.

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

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

4. **Extension Pharmacokinetic (PK) Set**: all subjects who were randomized and received active study medication in the main study, had no major protocol deviations impacting PK throughout the main study or extension and with available PK data.

5. **Extension Pharmacodynamic (PD) Set:** all subjects who were randomized and received active study medication in the main study, had no major protocol deviations impacting PD throughout the main study or extension and with available PD data.

Individual data points may also be excluded from the analysis sets. Rules for such exclusions will be described in the statistical analysis plan (SAP).

13.5 DATA ANALYSIS

The primary objective of this extension study is 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 the subset of subjects who are treated with linzagolix up to the time point of interest. As such, the focus will be on subjects who received active treatment in the main study. The assessment of subjects who switched from placebo in the main study to active treatment in the extension study will be conducted as a secondary objective.

Subjects will be analyzed according to actual treatment received. The following four treatment groups will be analyzed: linzagolix 75 mg and linzagolix 200 mg with ABT fixed dose groups, linzagolix 75 mg and linzagolix 200 mg with ABT after 6 months placebo treatment. Only subjects with assessments at both baseline and the given time points will be included in the summaries. Baseline values are the same as in the main study (18-OBE2109-002 - Edelweiss 2), i.e. data collected prior to the treatment administration in the main study.

More details of the proposed statisical analyses will be described in the SAP, which will be written following finalization of the protocol and prior to database lock.

13.5.1 Baseline Assessment

Descriptive statistics will be performed on relevant baseline data and on demographic characteristics for each treatment group and overall. Baseline is defined as the data collected prior to the treatment administration in the main study. A second baseline is defined as the data collected prior to the treatment administration in the extension study for subjects who were in the placebo arm in the main study. There will be no formal comparison of baseline data, that is, no statistical hypothesis testing.

13.5.2 Efficacy Analysis

Summaries will be performed using the Treatment Extension Analysis Set and the Follow-up Extension Analysis Set. Data from both the main study and the extension study will be summarized.

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

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

13.5.3 Safety Analysis

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

Data from both the main study and the extension study will be summarized.

13.5.4 Pharmacokinetic analysis methodology

Descriptive statistics of plasma concentrations will include mean (arithmetic and geometric) and standard deviation, median, 1st and 3rd quartiles, minimum, maximum, coefficient of variation (CV%) and number of observations. Concentrations below the limit of quantification (LOQ) will be assigned a value of zero. Explorative analyses of correlations between plasma concentrations and intrinsic PK factors such as e.g. body weight/BMI, race, age may be performed, as appropriate, and will be reported separately.

PK analyses will be based on the Extension PK Set.

13.5.5 Pharmacodynamic analysis methodology

Pharmacodynamic parameters, such as for example estradiol and other hormones, will be summarized by time point for each treatment group, and listed for each subject by visit day and dose regimen. Where appropriate, changes from baseline will be presented. Potential PK-PD relationships may be investigated graphically and through statistical modeling, whilst also exploring possible covariates, and will be reported separately.

PD analyses will be based on the Extension PD Set.

13.5.6 Missing Data

Summary statistics will be based on non-missing values.

13.6 STUDY SPECIFIC DATA ANALYSIS

13.6.1 End-of-Treatment Period Analysis

After all subjects have completed the Treatment Period, a complete analysis will be performed. This analysis will include all data up to the end of treatment visit. A database lock will be performed, with any discrepant data clarified before the lock.

13.6.2 Post-Treatment Follow-Up Period Analysis

After all subjects have completed the Post-Treatment Follow-up Period, a final database lock will be performed, followed by a second analysis. This analysis will include all data collected during the Post-Treatment Follow-up Period.

14 STUDY ADMINISTRATION

14.1 REGULATORY AND ETHICAL CONSIDERATIONS

This study is to be performed in accordance with the protocol, with the ethical principles that have their origin in the Declaration of Helsinki (9), the ICH Harmonized Tripartite Guideline for GCP and all applicable local regulatory requirements.

14.1.1 Informed Consent

Before a subject can participate in the study, she must give a written informed consent specific to the extension study. The informed consent process will be in accordance with ICH GCP and local regulatory requirements.

14.1.2 Regulatory Authority Approval

Before the study is initiated at a site, the Sponsor (or its delegate) will obtain approval to conduct the study from the appropriate regulatory authority in accordance with any applicable country-specific regulatory requirements.

14.1.3 Institutional Review Board Requirements

Before initiation of the study at a given site, written approval of the protocol, ICF and any information presented to potential subjects must be obtained from the appropriate IRBREB. If any amendments to any of these documents occur during the study, notification or written approval as appropriate must be obtained prior to their implementation. The Investigator is responsible for ensuring that these actions occur.

Where required by local regulations, the Sponsor (or its delegate) is responsible for ensuring IRBREB approval of the study.

14.1.4 End of the study

For administrative and safety reporting purposes, the end of the study will be defined as the date of the final clinical database lock after the last subject has completed the Post-Treatment Follow-Up Period. This provides a single and conservative definition across all study sites.

14.2 INVESTIGATOR RESPONSIBILITIES

The Investigator must be familiar with and conduct the study according to ICH GCP guidelines, the FDA Code of Regulation and applicable local laws and regulations.

Where required by local regulations, national level coordinating Investigators may be appointed. Their responsibilities are outlined in a separate agreement with the Sponsor.

14.3 DATA MANAGEMENT

The Investigator or designee will be responsible for recording study data in the eCRF provided by the Sponsor. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs. The data will be entered into a validated database. The Sponsor or delegate will be responsible for data processing, in accordance with the Sponsor (or delegate) data management procedures. Database lock will occur once quality assurance procedures have been completed. The database will not be locked before all data clarifications have been resolved and monitored and the decision on subject evaluation has been completed. PDF files of the eCRFs will be sent to the Investigator at the completion of the study.

14.4 STUDY MONITORING

The Investigator must ensure that eCRFs are completed in a timely manner and must allow a Sponsor representative (e.g. Clinical Research Associate (CRA) or study monitor) periodical access to subject records and all study-related materials. The frequency of monitoring visits will be determined by factors

such as the design of the study, the frequency of subject visits and the site enrolment rate. In order to verify that the study is conducted in accordance with ICH GCP, regulatory requirements, and the study protocol and that the data are authentic, accurate and complete, the study monitor will review eCRFs and other study documents and will conduct source data verification.

Upon study completion, the Sponsor representative (e.g. CRA or study monitor) will visit the site to conduct a Study termination visit. This will involve collection of any outstanding documentation and study material if applicable.

14.5 DATA MONITORING COMMITTEE

The Data Monitoring Committee (DMC) is a group of independent experts external to the study that, collectively, has experience in the management of subjects with endometriosis and in the conduct and oversight of randomized clinical trials.

Composition, responsibilities, rules for decision and procedures of the DMC will be described in more details in the DMC charter.

The DMC will be responsible for:

- safeguarding the interests of trial participants,
- assessing the safety of the IMP during the trial (reviewing unblinded safety data and AEs and SAEs, on a regular basis, as per charter prepared for the study).

The DMC will provide advisory support to the Study Director, the trial team and any other Sponsor representative. The Study Director will be responsible for promptly reviewing the DMC recommendations and determine whether expedited reporting of any safety issues, amendments to the protocol or changes in study conduct are required.

14.6 SUBJECT CONFIDENTIALITY

The Investigator and the CRA (or study monitor) representing the Sponsor must ensure that the subject's anonymity is maintained. In the eCRFs or other documents submitted to the Sponsor, the subject should not be identified by her name, but by her assigned SIN. If a subject's name is included on copies of documents to be submitted to the Sponsor, the name (except for initials) must be obliterated and the assigned SIN added to the documents.

The Investigator should keep a separate log of SINs, names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for submission to the Sponsor, such as signed ICFs, should be maintained in strict confidentiality by the Investigator.

14.7 QUALITY ASSURANCE

In compliance with ICH GCP and regulatory requirements, the Sponsor, a third party acting on behalf of the Sponsor, regulatory agencies or IRBREB may conduct quality assurance audits at any time during or following a study. The Investigator must agree to allow auditors direct access to all study-related documents including source documents, and must agree to allocate his or her time and the time of his or her study staff to the auditors in order to discuss findings and issues.

14.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP requirements. It is the responsibility of the site Investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and reported to the reviewing IRBREB per their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRBREB requirements.

All Protocol Deviations will 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, and the final rating of all deviations will be confirmed prior to database lock.

14.9 STUDY OR SITE DISCONTINUATION

The Sponsor may temporarily or permanently discontinue the study for safety, ethical, compliance or other reasons. If this is necessary, the Sponsor will endeavour to provide advance notification to the site. If the site or study is suspended or discontinued, the Investigator will be responsible for promptly informing the IRBREB.

Where required by local regulations, the Sponsor (or delegate) will be responsible for informing the IRBREB of study or site discontinuation. In such cases, all study data and unused IMP must be returned to the Sponsor.

14.10 RETENTION OF ESSENTIAL STUDY DOCUMENTS

Essential documents as defined by ICH GCP include the signed protocol and any amendment(s), copies of the completed eCRFs, signed ICFs from all subjects who consented, hospital records, diary cards and other source documents, IRBREB approvals and all related correspondence including approved documents, drug accountability records, study correspondence and a list of the subjects' names and addresses.

The Investigator must retain copies of the essential documents for the period specified by ICH GCP and by applicable regulatory requirements.

The Investigator will inform the Sponsor of the storage location of the essential documents, and must contact the Sponsor for approval before disposing of any. The Investigator should take measures to prevent accidental or premature destruction of these documents.

14.11 PUBLICATION POLICY

ObsEva registers clinical trials (Phase I – IV) wherever and whenever mandatory on publicly accessible websites (e.g.: www.clinicaltrials.gov ; www.clinicaltrialsregister.eu), including posting the trial design, population, and study details as required.

ObsEva posts the outcome of clinical trials on the required medium(a), within required timelines, regardless of the nature of the outcome.

ObsEva shares information on the outcome of clinical trials with the Principal/Coordinating Investigators of trials in the form of a final report synopsis, regardless of the trial outcome.

ObsEva duly communicates to stakeholders all relevant information arising from research activities related to products developed by the company, at any point and during any phase of the development of a product and the entire life-cycle of an ObsEva product.

Registration, reporting and communication of clinical trial results, results and/or outcome of non-clinical research are subject to mandatory preliminary review and authorization by the relevant ObsEva functions, prior to disclosure.

15 APPENDICES

Appendix A. Schedule of study assessments – Treatment Period

Schedule of study assessments – 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
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

[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 – Treatment Period (cont'd)

Schedule of study assessments – Treatment Period							
Timing[1]	Treatment Period						
	M6[2]	M7	M8	M9	M10	M11	M12
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.

Appendix B. Schedule of study assessments – 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]
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] 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.

Appendix C. Endometriosis Health Profile questionnaire (EHP-30)

Final English (US) EHP-30 + Section C

PART 1: CORE QUESTIONNAIRE

DURING THE LAST 4 WEEKS,
BECAUSE OF YOUR ENDOMETRIOSIS, HOW OFTEN HAVE YOU...

		Never	Rarely	Sometimes	Often	Always
1.	Been unable to go to social events because of the pain?	☐	☐	☐	☐	☐
2.	Been unable to do jobs around the house because of the pain?	☐	☐	☐	☐	☐
3.	Found it difficult to stand because of the pain?	☐	☐	☐	☐	☐
4.	Found it difficult to sit because of the pain?	☐	☐	☐	☐	☐
5.	Found it difficult to walk because of the pain?	☐	☐	☐	☐	☐
6.	Found it difficult to exercise or do the leisure activities you would like to do because of the pain?	☐	☐	☐	☐	☐

DURING THE LAST 4 WEEKS,
BECAUSE OF YOUR ENDOMETRIOSIS, HOW OFTEN HAVE YOU…

		Never	Rarely	Sometimes	Often	Always
7.	Lost your appetite and/or been unable to eat because of the pain?	☐	☐	☐	☐	☐
8.	Been unable to sleep properly because of the pain?	☐	☐	☐	☐	☐
9.	Had to go to bed/lie down because of the pain?	☐	☐	☐	☐	☐
10.	Been unable to do the things you want because of the pain?	☐	☐	☐	☐	☐
11.	Felt unable to cope with the pain?	☐	☐	☐	☐	☐
12.	Generally felt unwell?	☐	☐	☐	☐	☐
13.	Felt frustrated because your symptoms are not getting better?	☐	☐	☐	☐	☐
14.	Felt frustrated because you are not able to control your symptoms?	☐	☐	☐	☐	☐

DURING THE LAST 4 WEEKS,
BECAUSE OF YOUR ENDOMETRIOSIS, HOW OFTEN HAVE YOU...

		Never	Rarely	Sometimes	Often	Always
15.	Felt unable to forget your symptoms?	☐	☐	☐	☐	☐
16.	Felt as though your symptoms are ruling your life?	☐	☐	☐	☐	☐
17.	Felt your symptoms are taking away your life?	☐	☐	☐	☐	☐
18.	Felt depressed?	☐	☐	☐	☐	☐
19.	Felt weepy/tearful?	☐	☐	☐	☐	☐
20.	Felt miserable?	☐	☐	☐	☐	☐
21.	Had mood swings?	☐	☐	☐	☐	☐
22.	Felt bad-tempered or short-tempered?	☐	☐	☐	☐	☐

DURING THE LAST 4 WEEKS,
BECAUSE OF YOUR ENDOMETRIOSIS, HOW OFTEN HAVE YOU...

		Never	Rarely	Sometimes	Often	Always
23.	Felt violent or aggressive?	☐	☐	☐	☐	☐
24.	Felt unable to tell others how you feel?	☐	☐	☐	☐	☐
25.	Felt others do not understand what you are going through?	☐	☐	☐	☐	☐
26.	Felt as though others think you are whining?	☐	☐	☐	☐	☐
27.	Felt alone?	☐	☐	☐	☐	☐
28.	Felt frustrated that you cannot always wear the clothes you would choose?	☐	☐	☐	☐	☐
29.	Felt your appearance has been affected?	☐	☐	☐	☐	☐
30.	Lacked confidence?	☐	☐	☐	☐	☐

PART 2: MODULAR QUESTIONNAIRE CORRESPONDING TO SEXUAL RELATIONSHIPS

DURING THE LAST 4 WEEKS,
BECAUSE OF YOUR ENDOMETRIOSIS, HOW OFTEN HAVE YOU...

		Never	Rarely	Sometimes	Often	Always
1.	Experienced pain during or after intercourse? *If not applicable, please check here* ☐	☐	☐	☐	☐	☐
2.	Felt worried about having intercourse because of the pain? *If not applicable, please check here* ☐	☐	☐	☐	☐	☐
3.	Avoided intercourse because of the pain? *If not applicable, please check here* ☐	☐	☐	☐	☐	☐
4.	Felt guilty about not wanting to have intercourse? *If not applicable, please check here* ☐	☐	☐	☐	☐	☐
5.	Felt frustrated because you cannot enjoy intercourse? *If not applicable, please check here* ☐	☐	☐	☐	☐	☐

Appendix D. PROMIS Fatigue – Short Form 6a

This scale is formally known as PROMIS Item Bank v1.0 – Fatigue – Short Form 6a. The questions and the response categories included in this scale are presented below.

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
1	I feel fatigued	☐	☐	☐	☐	☐
2	I have trouble starting things because I am tired	☐	☐	☐	☐	☐
	In the past 7 days…					
3	How run-down did you feel on average?	☐	☐	☐	☐	☐
4	How fatigued were you on average?	☐	☐	☐	☐	☐
5	How much were you bothered by your fatigue on average?	☐	☐	☐	☐	☐
6	To what degree did your fatigue interfere with your physical functioning?	☐	☐	☐	☐	☐

Scoring Rules:

The mapping of the response categories is as follows:

1 = Not at all; 2 = A little bit; 3 = Somewhat; 4 = Quite a bit; 5 = Very much

Assessment will be based on the sum of the individual scores across the six questions (possible scores 6 to 30, 6 = not at all, 30 = very much). Missing data will not be imputed.

Appendix E. Health-Related Productivity Questionnaire (HRPQ)

Health Related Productivity Questionnaire V2 (Generic)

These questions deal with how illnesses and their treatment have affected your ability to remain in the workforce and perform work and daily activities in your home. Your responses and those of other patients will help us to understand the impact of illnesses and their treatment on these aspects of your life.

1. What is your **current** employment status?
   - ☐ a Currently employed full-time → Please go to Question 2
   - ☐ b Currently employed part-time → Please go to Question 2
   - ☐ c Not currently employed → Please go to Question 5

2. How many hours were you scheduled to work at your job during the last **week**?
   (If none or you are not employed, put a "0" here and go to Question 5.)
   _____ Hours

3. Did **illnesses/treatments** keep you from working any of your scheduled hours during the last **week**?
   - ☐ a Yes → I missed _____ b hours of work because of **illnesses/treatments**.
   - ☐ c No, **illnesses/treatments** did not keep me from working my scheduled hours.

4. For the hours that you **did** work during the past week, how did **illnesses/treatments** impact your **work output**?

Write a number on the line below, based on this scale.	*0%* — *Illnesses/treatments had no impact on how much I accomplished*	*100%* — *Illnesses/treatments kept me from* accomplishing anything

_____ % impact on work output

5. How many hours of household chores (cooking, cleaning, gardening, repairs, etc.) did you plan to do during the last **week**?
   (If none, put a "0" here and go to Question 8.)
   _____ Hours

6. Did **illnesses/treatments** keep you from doing any of your planned hours of household chores last **week**?
   - ☐ a Yes → I worked _____ b hours less because of **illnesses/treatments**.
   - ☐ c No, **illnesses/treatments** did not keep me from working my planned hours.

7. For the hours of household chores you **did** during the past week, how did **illnesses/treatments** impact your **work output**?

Write a number on the line below, based on this scale.	*0%* — *Illnesses/treatments had no impact on how much I accomplished*	*100%* — *Illnesses/treatments kept me from* accomplishing anything

_____ % impact on work output

[This block of items deals with workforce participation and should be collected at study start]

8. How long has it been since [X] developed?
_____a Months _____b Years

9. Which of the following statements are true of your life **since** [X] **developed** (mark all that apply):

☐ [X] or its treatment(s) forced me to work part-time when I wanted to work **full-time**.
For how long was this true? _____a Months _____b Years
☐ [X] or its treatment(s) kept me from having a job when I wanted to work **full-time**.
For how long was this true? _____c Months _____d Years
☐ [X] or its treatment(s) kept me from having a job when I wanted to work **part-time**.
For how long was this true? _____e Months _____f Years
☐ None of the above

Health Related Productivity Questionnaire V2

Appendix F. Health Resource Utilization Questionnaire (HRUQ)

(To be completed by Site Staff)

Subject number: _____

Study Visit *(please ensure to tick 1 visit only)*:

Treatment period ☐ Month 7 ☐ Month 8 ☐ Month 9

☐ Month 10 ☐ Month 11 ☐ Month 12

Follow-up period ☐ Month 3 ExFU ☐ Month 6 ExFU

Date of Assessment: _____

Instructions to complete:

At each scheduled on-site visit in the Treatment Period (Month 6 through Month 12) and at Month 3 ExFU and Month 6 ExFU visits in the Follow-up period, please ask if the subject saw a **non-study** health care practitioner since her last scheduled on-site visit for a **routine/general health care visit that is not associated with an adverse event**.

Only record below the health care visits with non-study health care practitioners. Any visits associated with Adverse Events should be recorded on the AE eCRF form only (do not record below).

****

Question 1

Since the subject's last scheduled study on-site visit, has she seen a **non-study** health care practitioner (e.g., physician, nurse practitioner, physician assistant, dentist, physical therapist) for a **routine/general health care visit that is not associated with an adverse event?**

☐ **No** ☐ **Yes** *If Yes, please complete the questions 2 and 3 below.*

Question 2

a. Select the type of non-study health care practitioner who saw the subject.
b. Indicate if it was at an office or a clinic (includes a hospital outpatient visit)
c. Indicate the number of times the subject was seen by each practitioner.

Types of *non-study* health care practitioner who saw the subject (check all that apply)	Type of facility		Number of times subject was seen by this *non-study* health care practitioner	
	Office	Clinic	Office	Clinic
☐ AUDIOLOGIST	☐	☐		
☐ ALLERGIST	☐	☐		
☐ CARDIOLOGIST	☐	☐		
☐ DENTIST	☐	☐		
☐ DERMATOLOGIST	☐	☐		
☐ ENDOCRINOLOGIST	☐	☐		
☐ ENT	☐	☐		
☐ FAMILY PHYSICIAN	☐	☐		
☐ GASTROENTEROLOGIST	☐	☐		
☐ GYNECOLOGIST	☐	☐		
☐ HEMATOLOGIST	☐	☐		
☐ HEPATOLOGIST	☐	☐		
☐ IMMUNOLOGIST	☐	☐		
☐ INFECTIOUS DISEASE SPECIALIST	☐	☐		

☐ INTERNAL MEDICINE SPECIALIST	☐	☐
☐ INTERNIST	☐	☐
☐ MEDICAL GENETICIST	☐	☐
☐ NEPHROLOGIST	☐	☐
☐ NEUROSURGEON	☐	☐
☐ NURSE	☐	☐
☐ NURSE PRACTITIONER	☐	☐
☐ OCCUPATIONAL THERAPIST	☐	☐
☐ OPHTHALMOLOGIST	☐	☐
☐ ORTHOPEDIC SURGEON	☐	☐
☐ OPTOMETRIST	☐	☐
☐ PHYSIATRIST	☐	☐
☐ PHYSICAL THERAPIST	☐	☐
☐ PLASTIC SURGEON	☐	☐
☐ PODIATRIST	☐	☐
☐ PSYCHOLOGIST	☐	☐
☐ PULMONOLOGIST	☐	☐
☐ RADIOLOGIST	☐	☐
☐ REPRODUCTIVE ENDOCRINOLOGIST	☐	☐
☐ RHEUMATOLOGIST	☐	☐
☐ SURGEON	☐	☐
☐ UROLOGIST	☐	☐
☐ UNKNOWN	☐	☐
☐ OTHER HEALTH CARE PRACTITIONER (specify type):	☐	☐

Question 3

Did the Subject have any diagnostic or therapeutic procedures performed by a *non-study* health care practitioner since the last scheduled study on-site visit?

☐ **No** ☐ **Yes** *If Yes, complete question 4 below.*

Question 4

a. Select the type of diagnosis/therapeutic procedures performed by non-study health care practitioner who saw the subject.
b. Indicate the number of times the diagnosis/therapeutic procedures were performed.

Diagnostic/Therapeutic Procedure *(check all that apply)*		Number of times the procedure was performed
Ultrasound Scan	☐	
Physical Examination	☐	
Vital Signs	☐	
MRI	☐	
CT Scan	☐	
X-Ray	☐	
Biopsy and Histologic Examination	☐	
Pelvic Exam	☐	
Urine Test	☐	
Blood Test	☐	
Hysteroscopy	☐	
SIS (Saline infusion Sonohysterography)	☐	
Colposcopy	☐	
Other (specify):	☐	

Question 5

Has the patient spent any nights as a hospital in-patient since the last visit?

☐ **No** ☐ **Yes**

If Yes, how many nights did they spend in hospital?

Appendix G. Patient Global Impression of Change (PGIC)

PGIC

Overall, how have your endometriosis symptoms changed since the start of the study?

- Very Much Improved
- Much Improved
- Minimally Improved
- No Change
- Minimally Worse
- Much Worse
- Very Much Worse

Appendix H. Post-treatment Patient Global Impression of Change (PPGIC)

"Overall, how have your endometriosis symptoms changed since you stopped taking the study drug?"

- Very Much Improved
- Much Improved
- Minimally Improved
- No Change
- Minimally Worse
- Much Worse
- Very Much Worse

Appendix I. Patient Global Impression of Severity (PGIS)

Daily recall (dPGIS)	Monthly recall (mPGIS)
Overall, how would you describe your endometriosis symptoms in the last 24 hours?	Overall, how would you describe your endometriosis symptoms over the past 28 days?
No symptoms	No symptoms
Very mild	Very mild
Mild	Mild
Moderate	Moderate
Severe	Severe

Appendix J. Subject Surgery Intention Questionnaire (SSIQ)

1. How likely are you to consider having laparoscopic surgery to treat your endometriosis if your symptoms continue as they are now?

The SSIQ evaluates subject likelihood of considering endometriosis-related surgeries if current symptoms continue, with possible scores from 0 to 10,

0 = not at all, 10 = very likely.

Appendix K. Physician Surgery Intention Questionnaire (PSIQ)

1. How likely are you to recommend laparoscopic surgery to treat this patient's endometriosis if her symptoms continue as they are now?

The PSIQ evaluates physician likelihood of recommending endometriosis-related surgeries to the subject if current symptoms continue, with possible scores from 0 to 10,

0 = not at all, 10 = very likely.

Appendix L. EQ-5D-5L

EQ-5D-5L English US version

Please tap the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking ❑
I have slight problems in walking ❑
I have moderate problems in walking ❑
I have severe problems in walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

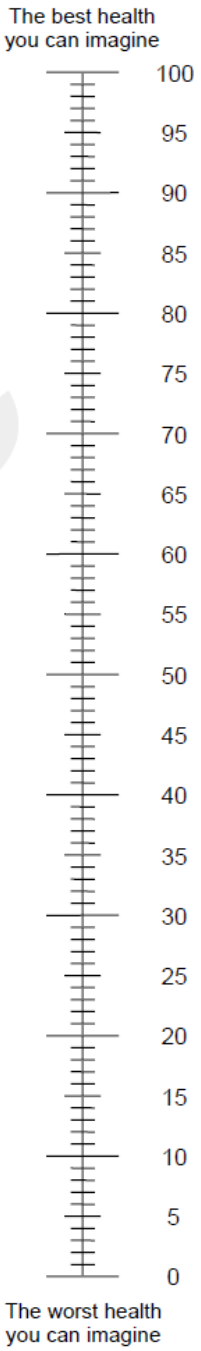
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please tap on the scale to indicate how your health is TODAY.

YOUR HEALTH TODAY = ☐



Appendix M. Laboratory parameters

Routine Haematology	Blood Chemistry
Haemoglobin	Sodium
Haematocrit	Potassium
RBC count	Calcium
WBC count	Phosphate
Neutrophils	Creatinine
Lymphocytes	Bilirubin total
Monocytes	Indirect Bilirubin
Eosinophils	Total protein
Basophils	Albumin
Thrombocytes	AST
MCV	ALT
MCH	γGT
MCHC	Alkaline phosphatase
APTT	Creatine Kinase
INR	LDH
PT	HDL, LDL, total cholesterol, and LDL/HDL ratio, triglycerides
	Glucose
	Urea and uric acid

Urinary protein dipstick

Hormones

E2, LH, P4, SHBG

All the above listed tests are to be performed at the frequencies indicated in Appendix A and Appendix B. All above listed blood tests will be performed by a central laboratory. Please consult the central laboratory instructions manual for the preparation and handling of the blood samples to be drawn to perform these tests.

Bone markers

Blood samples for exploratory bone biomarkers such as, but not limited to, collagen type 1 β-carboxy-telopeptide (CTx), procollagen 1 Intact N-Terminal (P1NP), bone-specific alkaline phosphatase (B-ALP) and osteocalcin will be collected as part of clinical chemistry.

Appendix N. Prohibited medicines

- GnRH antagonists
- GnRH agonist injections/3-month depot injections
- Danazol
- Oral contraceptives and other sex hormones
- Depot contraceptives
- Selective Progesterone Receptor Modulators (SPRMs), Selective Estrogen Receptor Modulators (SERMs) and aromatase inhibitors
- Long acting narcotics (i.e. requiring less than once daily dosing)
- Systemic glucocorticoid treatments for acute diseases (not depot)
- Medical (prescribed) marijuana
- In situ copper intra-uterine device (IUD)
- In situ IUD with progestogen

Appendix O. Strong CYP3A4 Inducers and Inhibitors

The presented lists are indicative and should not be considered exhaustive.

Strong CYP3A4 inducers prohibited up to end of treatment in view of the add-back treatment:

Carbamazepine

Enzalutamide

Mitotane

Phenytoin

Rifampin

St. John's Wort

Strong CYP3A4 inhibitors prohibited up to end of treatment in view of the add-back treatment:

Boceprevir

clarithromycin

Cobicistat

Conivaptan

danoprevir and ritonavir

diltiazem

elvitegravir and ritonavir

grapefruit juice

idelalisib

indinavir and ritonavir

itraconazole

ketoconazole

lopinavir and ritonavir

nefazodone

nelfinavir

paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)

posaconazole

ritonavir

saquinavir and ritonavir

telaprevir

tipranavir and ritonavir

troleandomycin

voriconazole

Appendix P. Analgesic change during Treatment Period

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

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

*Screening and Baseline are defined as the screening and baseline visits in the main study.

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

Appendix Q. Reference List

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Appendix R. C-SSRS Already Enrolled Subjects

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Already Enrolled Subjects

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103-130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

	Prior to Study Entry: Time He/ She Felt Most Suicidal	Since Study Start:
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. *Have you wished you were dead or wished you could go to sleep and not wake up?* If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. *Have you actually had any thoughts of killing yourself?* If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* *Have you been thinking about how you might do this?* If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* *Have you had these thoughts and had some intention of acting on them?* If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. *Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?* If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). For prior to study entry, ask about time he/she was feeling the most suicidal.

	Most Severe	Most Severe
Prior to Study Entry - *Most Severe Ideation:* ____ (Type # (1-5)) ____ (Description of Ideation)		
Since Study Start - *Most Severe Ideation:* ____ (Type # (1-5)) ____ (Description of Ideation)		
Frequency *How many times have you had these thoughts?* (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration *When you have the thoughts how long do they last?* (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability *Could/can you stop thinking about killing yourself or wanting to die if you want to?* (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents *Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?* (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation *What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?* (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

C-SSRS—Already Enrolled Subjects (Version 1/14/09) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Prior to Study Entry**	**Since Study Start**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. *There does not have to be any injury or harm*, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun), or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix S. C-SSRS Since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AUS.1_eng-USorl.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it"*.
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them"*.
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe

Most Severe Ideation: _____ _____
Type # (1-5) ***Description of Ideation***

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

 C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2