CLINICAL STUDY PROTOCOL

OBSEVA
obstetrics & beyond

Protocol Number:	**18-OBE2109-003**
EudraCT Number:	**2019-000283-26**
Investigational Medicinal Product:	**Linzagolix (OBE2109)**
Study Title:	**A Phase 3 multicenter, randomized, double-blind, placebo-controlled, clinical study to assess the efficacy and safety of linzagolix in subjects with moderate to severe endometriosis-associated pain.**
Short Study Title:	**A phase 3 study to confirm the efficacy and safety of linzagolix to treat endometriosis-associated pain.**
Study Name:	**Edelweiss 3**
Version number:	Version 4.0
Date:	27 July20
Replacing:	Version 3.0 – 25 June 2019
Study Sponsor:	**ObsEva S.A.** [redacted]
Clinical Trial Director:	[redacted]
Medical Responsible:	[redacted]
CRO	[redacted]
CRO Project Director:	[redacted]

[redacted]

VERSION HISTORY			
Amendment Number	**Amendment Date**	**General / Country-Specific/ Site-Specific**	**Amended Protocol version and date**
01	March 28, 2019	General	V2.0 – March 28, 2019
02	June 25, 2019	General	V3.0 – June 25, 2019
03	July 27, 2020	General	V4.0 – July 27, 2020

CONFIDENTIAL AND PROPRIETARY

This protocol contains confidential and proprietary information about an investigational drug and is provided by ObsEva S.A., Plan-les-Ouates, Geneva, Switzerland, for the exclusive use of the Investigators of this clinical study and their Health Authorities/IRBs/IECs. This confidential information may not be disclosed to any other person without prior written consent of ObsEva S.A.

*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]

Signature [redacted] of signature

[redacted]

(Clinical Trial Director)

Signature [redacted] signature

[redacted]

(Medical Responsible)

Contract Research Organization(s):

[redacted]

Signature [redacted] 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
Al	Aluminum
ALT	ALanine amino Transferase
APTT	Activated Partial Thromboplastin Time
AMH	Anti-Müllerian Hormone
AST	ASpartate amino Transferase
AUC	Area Under the Curve
AUC (24hr)	Area Under the plasma concentration time Curve from time 0 to 24hr post-dose
$AUC_{0-\infty}$	Area Under the Curve from time 0 to infinite time
AUC_{0-t}	Area Under the Curve from time 0 to the last measurable time
AUCτ	Area Under the Curve to the end of the dosing period
BMD	Bone Mineral Density
BMI	Body Mass Index
BP	Blood Pressure
Bpm	Beats Per minute
°C	Degree Celsius
CDF	Cumulative Distribution Function
CK	Creatine Kinase
ClinRO	Clinician Reported Outcome
Cm	Centimeter(s)
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
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow-Up
FSH	Follicle-Stimulating Hormone
G	Gram(s)
GCP	Good Clinical Practice
γGT	Gamma-Glutamyl Transferase
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practice
hGnRH	human Gonadotropin Releasing Hormone
HDL	High Density Lipoprotein

HIV	Human Immunodeficiency Virus
Hr	hour
HRPQ	Health Related Productivity Questionnaire
HRUQ	Health Resource Utilization Questionnaire
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
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
Kg	Kilogram(s)
L	Liter(s)
LDH	Lactate DeHydrogenase
LDL	Low Density Lipoprotein
LEEP	Loop Electrosurgical Excision Procedure
LFT	Liver Function Test
LH	Luteinizing Hormone
LOQ	Limit Of Quantification
mB&B	Modified Biberoglu & Behrman
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
Mg	Milligram(s)

Min	Minute(s)
mL	Milliliter(s)
MME	Morphine Milligram Equivalent
mPGIS	Patient Global Impression of Severity – monthly recall
mmHg	millimeter of mercury
msec	Millisecond
nmol	Nanomole(s)
NETA	NorEThisterone Acetate
NMPP	Non-Menstrual Pelvic Pain
NOAEL	No Observed Adverse Effect level
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	PharmacoDynamics
PDF	Probability Density Function
PGIC	Patient Global Impression of Change
PPGIC	Post-treatment Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic
PP	Per Protocol
PSF	Pregnancy Surveillance Form
PSIQ	Pysician Surgery Intention Question

PT	Prothrombin Time
PVC/Al	PolyVinyl Chloride/Aluminum
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
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SERM	Selective Estrogen Receptor Modulator
SIN	Subject Identification Number
SPRM	Selective Progesterone Receptor Modulator
SHBG	Sex Hormone-Binding Globulin
SLE	Systemic Lupus Erythematosus
SSIQ	Subject Surgery Intention Question
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Elimination half-life
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
WHO	World Health Organization

4 SYNOPSIS

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

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

Objectives:

The primary objective of this study is to demonstrate the efficacy and safety of linzagolix administered orally once daily for up to 3 months at a dose of 75 mg alone or of 200 mg in combination with add-back hormone replacement therapy (ABT: estradiol (E2) 1 mg / norethisterone acetate (NETA) 0.5 mg) versus placebo, while under randomized treatment, 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 3 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 persistence of efficacy over the last 28 days of randomized treatment up to the Month 6 visit, evaluation of pain associated with sexual intercourse (dyspareunia) and defecation (dyschezia), difficulty of doing daily activities, analgesic use, assessment of subject perception of severity, change in uterine bleeding, Quality of Life (QoL) questionnaires, pharmacoeconomic burden of endometriosis by assessing changes in patient productivity, assessment of endometriosis related number of non-study health visits, number of days in hospital and type of medical procedures performed during the Treatment Period.

Safety and tolerability objectives 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) 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 3 visit (the 4-week period preceding Month 3 visit) or, for subjects who discontinue randomized treatment prior to the Month 3 visit, to the last 28 days of randomized treatment, , 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:**
  - **Ranked secondary efficacy endpoints** (in the order of the endpoints to be tested):
    - Change from baseline to Month 6 in DYS (VRS)
    - Change from baseline to Month 6 in NMPP (VRS)
    - Change from baseline to Month 6 in dyschezia (Numeric Rating Scale - NRS)
    - Change from baseline to Month 6 in overall pelvic pain (NRS)
    - Change from baseline to Month 6 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 6 in dyspareunia (VRS)
    - No analgesics use for EAP during the preceding 4-week period at Month 6
    - No opiate use for EAP during the preceding 4-week period at Month 6
  - **Additional secondary efficacy endpoints** :
    - Clinically meaningful reduction at scheduled visits other than Month 3 for DYS and NMPP
    - 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, placebo-controlled study to demonstrate the efficacy and safety of linzagolix administered orally once daily at doses of 75 mg alone and 200 mg in combination with low dose ABT (E2 1 mg/NETA 0.5 mg) versus placebo in the management of moderate to severe EAP in women with surgically confirmed endometriosis.

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

1. Linzagolix 75 mg
2. Linzagolix 200 mg combined with ABT
3. Placebo

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

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

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

The main analysis will be performed after 6 months of treatment and will include all of the subjects' data up to Month 6.

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

All subjects will receive once daily either linzagolix 75 mg alone or 200 mg combined with ABT or placebo for 6 months. Linzagolix or its corresponding placebo will be supplied as tablets for oral administration. ABT or its corresponding placebo will be supplied as capsules for oral administration.

Linzagolix/placebo treatments 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. Blinded treatment kit numbers corresponding to each subject's randomized treatment will be provided through an IWRS.

Study Population: The target population will be premenopausal women aged 18 to 49 years inclusive at screening, with surgically and, if available, histologically confirmed pelvic endometriosis and with moderate to severe EAP. They must not be planning to become pregnant and must agree to use double non-hormonal barrier contraception from screening until 3 months after the end of treatment. From 3 months after the end of treatment to the end of the drug-free follow-up period, contraception is still mandatory but hormonal contraception is allowed.

Four hundred and fifty (450) randomized subjects are planned in total (approximately 150 subjects per group). It is expected that the screen failure rate will be around 60%. Therefore, approximately 1125 subjects will be screened in order to randomize 450 subjects into the study.

The study will be conducted in approximately 100 investigational sites in the Unites States (US) and Europe. Additional sites will be identified, qualified and activated in case of recruitment issues. Recruitment will be competitive between countries and sites.

Eligibility Criteria:

Inclusion Criteria

To be eligible for inclusion into this study, the subject must **fulfill all** of the following criteria:

1. The subject must provide written informed consent prior to any study related procedures.
2. The subject must be a female subject aged 18 years to 49 years inclusive.
3. The subject must have had her most recent surgical and – if available – histological diagnosis of pelvic endometriosis (laparoscopy, laparotomy, vaginal fornix or other biopsy) up to 10 years before screening.
4. The subject must agree to the washout intervals for prohibited therapies (if applicable).
5. The subject must agree to switch from her usual analgesic rescue medication to only those permitted by the protocol during the Screening, Treatment and Follow-up Period.
6. The subject has moderate to severe EAP during the screening period defined as:
    a. At the screening visit, a score of at least 2 for DYS and at least 2 for NMPP for the previous month assessed with the modified Biberoglu & Behrman (mB&B) scale.
    b. Over two full menstrual cycles (i.e. from day 1 of the first menstruation going over two spontaneous menstrual cycles up to the day before the next menstruation i.e. the third menstruation) finishing just before the baseline visit:
        i. Mean overall pelvic pain scores of at least 4 on the 0–10 NRS over the 5 days with the highest score for each cycle separately, i.e. required for both cycles;
        ii. At least two days with “moderate” or “severe” pain on the 0–3 VRS for pelvic pain over the days with uterine bleeding for each cycle separately, i.e. required for both cycles;
        iii. At least two days with “moderate” or “severe” pain on the 0–3 VRS for pelvic pain over the days without uterine bleeding for each cycle separately, i.e. required for both cycles.
7. The subject is compliant with eDiary completion i.e. has completed at least 75% of days during the screening period.
8. The subject has regular menstrual cycles and the total length of the two screening menstrual cycles should be between 42 and 76 days inclusive.
9. The subject has a Body Mass Index (BMI) $\geq$ 18 kg/m^2 at the screening visit.
10. If of childbearing potential, the subject agrees to use one of the following birth control methods during the Screening Period, 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.

11. If of non-childbearing potential, the subject must have had tubal ligation sterilization at least two months before the screening visit.
12. The subject is ≥ 40 years of age at the screening visit has a normal mammogram within 1 year before randomization.
13. The subject must be able to communicate well with the Investigator and research staff and to comply with the requirements of the study protocol.

Exclusion Criteria

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

1. The subject is pregnant or breast feeding or is planning a pregnancy within the duration of the Treatment Period of the study.
2. The subject is less than 6 months postpartum or 3 months post-abortion/miscarriage at the time of entry into the screening period.
3. The subject has a surgical history of:
    a. Hysterectomy,
    b. Bilateral oophorectomy,
    c. Vagotomy, bowel resection or any surgical procedure (including gastric surgery) that might interfere with gastrointestinal motility, pH, or absorption,
    d. Any major abdominal surgery (including laparotomy for endometriosis) within 6 months or any interventional surgery for endometriosis performed within a period of 2 months before screening, or the subject is scheduled for a surgical abdominal procedure during the course of the study.
4. The subject had a tubal sterilization which was performed with ESSURE™.
5. The subject had endometrial ablation resulting in amenorrhea.
6. The subject has at least one ovarian endometrioma with a diameter of 7 cm or greater.
7. The subject is likely to require treatment during the study OR received treatment within a specified period prior to screening with any of the medications listed below:

a.	Gonadotropin releasing hormone (GnRH) antagonists	3 months
b.	GnRH agonist injections/3-month depot injections	3/6 months
c.	Danazol	3 months
d.	Oral contraceptives and other sex hormones	1 month
e.	Depot contraceptives	10 months
f.	Selective Progesterone Receptor Modulators (SPRMs), Selective Estrogen Receptor Modulators (SERMs) and aromatase inhibitors	3 months
g.	Long acting narcotics (i.e. requiring less than once daily dosing)	1 day
h.	Systemic glucocorticoid treatments for acute diseases (not depot)	1 month

i.	Medical (prescribed) marijuana	1 week
j.	In situ copper intra-uterine device (IUD)	1 day
k.	In situ IUD with progestogen	1 month

8. The subject is likely to use cannabinoids during the study washout, screening or treatment period.
9. The subject has required more than 2 weeks of continuous use of a narcotic analgesics for treatment of EAP within 6 months prior to Screening.
10. The subject received strong CYP3A4 inducers or inhibitors that (might potentially) interact with ABT within 1 month prior to randomization.
11. The subject has a contra-indication to ABT including:
    a. Active deep vein thrombosis, pulmonary embolism, or history of these conditions;
    b. Active or recent (e.g. within the past year) arterial thromboembolic disease (e.g. stroke, myocardial infarction);
    c. Known, suspected, or history of breast cancer;
    d. Known or suspected estrogen-dependent neoplasia;
    e. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    f. Migraine with aura;
    g. History of porphyria;
    h. Known hypersensitivity to the ingredients.
12. The subject has a history of or current systemic glucocorticoid therapy for treatment of chronic diseases (e.g. Systemic Lupus Erythematosus (SLE), rheumatic arthritis). Inhaled glucocorticoids for e.g. asthma are not considered systemic glucocorticoids.
13. The subject did not respond to prior treatment with GnRH agonists or GnRH antagonists for endometriosis.
14. The subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin levels or gamma-glutamyl transpeptidase (GGT) level ≥ 2 times the upper limit of normal and indicative of potential liver damage at Screening or Day 1 (subjects with abnormalities at Day 1 will be withdrawn from study at reception of the results).
15. The subject has clinically significant abnormal ECG, or ECG with QT interval corrected for heart rate (QTc) using Fridericia's correction formula (QTcF) > 450 msec at Screening or Day 1 (prior to dosing).
16. The subject has a known positive human immunodeficiency virus (HIV) or viral Hepatitis serology.
17. The subject has abnormal uterine bleeding of undiagnosed cause.

18. The subject had/has clinically significant findings from a Papanikolaou (PAP) smear test performed within the past 12 months or at the screening visit which will require surgical intervention (e.g. Loop electrosurgical excision procedure (LEEP) or cervical conization).
19. The subject has chronic pelvic pain that, in the opinion of the Investigator, is not caused by endometriosis and requires chronic analgesic or other chronic therapy which would interfere with the assessment of EAP (e.g., interstitial cystitis, presumptive adenomyosis, fibroids, non-endometriosis-related pelvic adhesive disease, post-tubal ligation or irritable bowel syndrome).
20. The subject has any other clinically significant gynecological condition identified during screening transvaginal ultrasound (TVUS) or endometrial biopsy which might interfere with the study efficacy and safety objectives (e.g. endometritis, endometrial hyperplasia). However, uterine fibroids (as long as uterus size ≤ 12 weeks, i.e. equivalent gestational weeks) and adenomyosis are allowed provided they do not interfere with the assessment of EAP (see previous criterion).
21. The subject has any known condition, including findings in the medical history or in the screening assessments, which in the opinion of the Investigator constitutes a risk or a contraindication to the participation of the subject in the trial or that could interfere with the trial objectives, conduct or evaluation.
22. The subject has a history of, or known, osteoporosis, hyperparathyroidism or other metabolic bone disease.
    a. Screening DXA results of the lumbar spine (L1–L4), femoral neck, or total hip BMD showing a Z-score ≤ –1.5
    b. Any condition that would interfere with obtaining adequate DXA measurements (e.g. weight [> 300 pounds or 136 kg], history of spinal surgery, spinal hardware, severe scoliosis)
    c. Intercurrent bone disease
    d. History of hip fracture
    e. History of pathologic or compression fractures
    f. History of bilateral hip replacement
23. The subject has a mental condition rendering her unable to understand the nature, scope and possible consequences of the study, or evidence of an uncooperative attitude.
24. The subject has current problem with alcohol or drug abuse (including painkiller abuse).
25. The subject has been administered with any experimental drug in the 12 weeks before screening.
26. The subject has calcium level above the upper limit of normal range at screening, which is confirmed on repeat fasting testing at Screening.
27. The subject has a history of, or active malignancy (with or without systemic chemotherapy) (except treated basal carcinoma of the skin which is not an exclusion criterion).
28. The subject has a history of attempted suicide and/or a history of, or known major psychiatric disorders that are not well controlled.

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

Descriptive statistics will be performed on relevant screening and baseline data (i.e. data collected prior to the treatment administration) and on demographic characteristics for each treatment group and overall. There will be no formal comparison of baseline data, that is, no statistical hypothesis testing.

All statistical hypothesis tests and confidence intervals will be two sided. To maintain an overall type I error rate of 0.05, as there are two linzagolix versus placebo comparisons, Bonferoni corrected p-values will be produced (raw p-values will be multiplied by two prior to comparing to 0.05), along with corresponding 97.5% confidence intervals.

Each linzagolix group will need to demonstrate a statistically significant difference for both co-primary endpoints in order for the group to be considered more efficacious than placebo, thus maintaining the overall type I error rate of 0.05.

For each linzagolix group that is statistically significantly more efficacious than placebo for the co-primary endpoints, a fixed-sequence testing strategy shall be used within the group to test the ranked secondary endpoints, so as to maintain the family-wise type I error rate.

Primary Efficacy Analysis

The primary efficacy analysis aims to estimate the effect of linzagolix versus placebo on DYS and NMPP over the last 28 days up to and including the Month 3 visit or, for subjects who discontinue randomized treatment prior to the Month 3 visit, over the last 28 days of randomized treatment. Use of analgesic medication for EAP will be included in the responder definition. A responder for the co-primary endpoints needs to demonstrate both a reduction in pain (DYS or NMPP, depending on the endpoint) and a stable or decreased use of analgesics for EAP. Anyone who does not meet both of these criteria will be defined as a non-responder.

For each of the co-primary endpoints, the criterion for defining a subject as a responder over the last 28 days of randomized treatment up to the Month 3 visit will include a reduction of X or greater from baseline in pain, where X will be determined using appropriate anchors as described below, as well as a stable or decreased use of analgesics for EAP.

Mean pelvic pain scores for DYS and for NMPP will be calculated by averaging over the corresponding 28 calendar days immediately prior to and including the day of the Month 3 visit. DYS will use days with uterine bleeding, defined as those days on which the subject records any uterine bleeding or spotting in the subject eDiary; NMPP will use days with no uterine bleeding. If a subject's mean score for DYS is undefined numerically because her daily eDiary reports indicate that she did not experience uterine bleeding on any days during the 28 calendar day time period, then the mean score for DYS will be set equal to zero (which reflects the absence of any DYS during that reporting time period). For subjects who discontinue treatment prior to Month 3, the last available observations prior to discontinuation will be used, in order to estimate the treatment effect of while under treatment, that is the 28 calendar days immediately prior to and including the last dose date. The baseline mean overall pelvic pain scores for DYS and NMPP will be calculated by averaging over the two complete

menstrual cycles during screening, which may not be exactly 28 days each. For both DYS and NMPP, responses of "No pain," "Mild pain," "Moderate pain," and "Severe pain" will be assigned a score of 0, 1, 2, and 3, respectively.

For the assessment of a stable or decreased use of analgesics for EAP, the analgesic use for any defined period will be based on the mean of the total pill count for each class of rescue analgesics (endometriosis-associated). The total pill count for each class of rescue analgesic is the sum of the pill count of the corresponding class of rescue analgesic, as reported in the eDiary during the time period of interest. The baseline analgesic use will be calculated as the mean of daily pill count of analgesics over the two complete menstrual cycles during screening. For purposes of determining a stable or decreased use of analgesics, the averaging will be done over the same calendar days as used for the pelvic pain scores. The evaluation of a stable or decreased use of analgesics will be done according to a pre-defined set of rules.

The analysis of each co-primary endpoint will be conducted using a logistic regression model, with treatment group as the main effect (three values) and including the baseline pain score as a covariate. Individual linzagolix versus placebo treatment group comparisons will be made using the same logistic regression model.

An additional analysis of the co-primary endpoints will be conducted to estimate the effect of treatment policy rather than that of while on treatment. A reference based multiple imputation approach will be used for subjects who discontinue the study prior to Month 3. Further details will be provided in the Statistical Analysis Plan (SAP).

Responder Thresholds analysis:

For each of the co-primary endpoints, the criterion for defining a subject as a responder over the last 28 days of randomized treatment up to the Month 3 visit will be a reduction of X or greater from baseline in pain. The threshold for response in the responder analysis (i.e., the value of X) will be chosen to represent a clinically meaningful reduction in pain and may not be the same for each endpoint. The threshold will be determined based on separate analyses of overall mean change using the mPGIS at Month 3 as an anchor. A 2-point improvement in the mPGIS will be used to define responders for the primary analysis. Response categories of “very mild” and “mild” will be collapsed into one category prior to the analyses. Monthly questions specific to DYS, NMPP, overall pelvic pain, dyschezia, dyspareunia and daily function will be used as separate anchors, PGIC as an anchor, Cumulative Distribution Function (CDF) and Probability Density Function (PDF) curves, and Receiver Operating Characteristic (ROC) analyses will be used as supportive analyses. The thresholds have been estimated in an analysis of DYS and NMPP data from the Phase 2b Edelweiss study and will be re-estimated in this study, calculated based on the blinded Month 3 data. The final responder thresholds, taking into account the previous estimates from phase 2b, will be included in the final SAP prior to breaking the blind after Month 6. Based on the results from the Phase 2b Edelweiss study, it is expected that the responder thresholds will be in the range of a 0.7 to 1.25 point (40% to 50%) reduction in pain in the 4-point VRS for a 2-point improvement, and of a 0.25 to 0.75 point (20% to 30%) reduction in pain in the 4-point VRS for a 1-point improvement. The numerical thresholds for DYS are expected to be larger than those for NMPP.

Secondary Efficacy Analysis

In order to estimate the treatment effect of while under treatment, endpoints that are collected daily using the eDiary will be based on the 28 calendar days immediately prior to and including the day of the corresponding visit, or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to the visit in question. Corresponding baseline values will be calculated based on the two complete menstrual cycles during screening, which may not be exactly 28 days each.

The value for other endpoints is defined as the value at the corresponding visit, or the last completed assessment prior to and including the last dose date for subjects who discontinue treatment prior to the visit in question.

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. As with the primary analysis, individual linzagolix versus placebo treatment group comparisons will be made.

In general, between-group comparisons for continuous endpoints will be analyzed via analysis of co-variance, with the baseline value as a covariate. Between-group comparisons for binary endpoints will be analyzed via logistic regression. Between-group comparisons for ordinal categorical data will be analyzed using a Mantel-Haenszel test, or using Koch's method when there is also a baseline covariate. Full details describing the derivation and analyses of each secondary endpoint will be provided in the SAP.

Safety analysis

The safety and tolerability profile will be assessed versus baseline conditions and differences between treatment groups and descriptive statistics will be produced for both values and change from baseline, where applicable.

Extent of exposure and compliance will be evaluated.

Concomitant medications will be summarized using the World Health Organization (WHO) Drug Dictionary with frequencies and percentages for each treatment group. All medications administered between the date of the first dose and the end of the study will be included.

An analysis of the TEAEs will be done. AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) tabulated by preferred term and system organ class. TEAEs will be summarized with frequencies and percentages for each treatment group. Tabulations by severity and drug-relatedness will also be made.

Laboratory parameters values will be summarized for each visit for each treatment group including within-group changes from baseline.

BMD values and corresponding Z-scores will be summarized at baseline and at Month 6 for each treatment group, using the observed data. The within-group percent changes from baseline for BMD values will also be summarized, including 2-sided 95% confidence intervals. Categorical summaries of percent change from baseline will also be produced. The percent changes from baseline to Month 6 will be compared between each of the linzagolix groups and the placebo group via analysis of co-variance with treatment group as the main effect (three values) and including the baseline as a covariate.

Pharmacokinetic and pharmacodynamic analyses

Plasma concentrations of linzagolix and 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. PK/PD analyses will be reported separately.

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 an estrogen-dependent gynecological condition, defined as the presence of endometrium-like tissue outside the uterus. It is one of the most common gynecological diseases (1). The condition is predominantly found in women in their reproductive years and disappears spontaneously after menopause. A chronic, inflammatory reaction, induced by the ectopic endometrial cells, results in a variety of pain symptoms including dysmenorrhea (DYS), dyspareunia, chronic pelvic pain, dysuria and dyschezia (2, 3).

5.3 CONVENTIONAL TREATMENT OF ENDOMETRIOSIS

The principal objective in treating endometriosis is symptom-relief management. Treatment options for women with EAP are diverse and consist of analgesic therapies, hormonal therapies, conservative or minimal invasive surgery, or a combination of these (3). Hormonal therapies aim at inhibition of ovulation, prevention of cyclic endometrium growth, and abolition of menstruation through achievement of a stable steroid hormone milieu, based on the concept that the response of the eutopic and ectopic endometrium is substantially similar (4, 5).

Combined oral contraceptives (COCs), although not approved for the treatment of EAP, are often used as initial therapy. Their intake results in anovulation, reduction of menstrual blood flow, decidualization of endometriotic lesions, down regulation of cell proliferation and enhanced apoptosis in the endometrium (6). However, over time many women on COCs no longer have adequate pain relief and require second-line therapy (7).

Progestin monotherapy can be efficacious for the reduction in EAP as it induces anovulation and a hypoestrogenic state via suppression of pituitary gonadotropin release. Progestins also have direct effects on the endometrium, causing decidualization of eutopic and ectopic endometrium leading to atrophy of the endometriotic implants (8). However, progestin monotherapy is often associated with breakthrough bleeding, alterations in mood, weight gain, and breast tenderness (9).

Other therapies with proven efficacy for the treatment of EAP are often limited by undesirable side effects. For example, GnRH agonists lead through a constant stimulation of the GnRH receptor at the pituitary level to its desensitization and ultimately to suppression of ovulation and reduced serum estrogen levels; thus their use is associated with significant hypoestrogenic side-effects. Short-term effects include menopausal symptoms such as hot flush, vaginal dryness, loss of libido and emotional lability and their long-term use is limited to 6 months without hormonal add-back therapy (ABT) by

substantial bone mineral density (BMD) reduction (10). In addition, GnRH-agonists are administered as depot products which lack flexibility in case of side effects.

For longer term use of GnRH-analogues, concurrent treatment with add-back (progestin and/or estrogen) hormone replacement therapy has been shown to be effective in reducing associated BMD loss (11). ABT is generally recommended as part of initial treatment with GnRH agonists to minimize side effects.

Randomized trial data comparing 12-month GnRH agonist treatment with and without ABT showed durable suppression of endometriosis symptoms and minimal impact on BMD with the addition of daily 5 mg norethisterone acetate (NETA) alone or in combination with estrogen (11). ABT is considered mandatory for women requiring GnRH agonist retreatment / treatment expected to go beyond 6 months. In a prospective cohort study comparing four different regimens of ABT, the add-back regimen containing 1 mg estradiol (E2) and 0.5 mg NETA demonstrated the best efficacy in terms of quality of life, hypoestrogenism-associated symptoms, and BMD (12).

GnRH antagonists are a new potential treatment option that is hypothesized to allow dose-dependent control of E2 levels reducing endometriosis implants and EAP (12). Partial or complete suppression of E2 is possible depending on the dose (13). Partial suppression with elagolix 150 mg once daily was demonstrated to reduce EAP significantly while having limited impact on BMD and therefore allowing for up to 2 years administration (14). A higher dose of elagolix 200 mg twice a day for 6 months led to nearly full suppression of E2, better reduction of EAP but significant reduction of BMD which limits treatment to 6 months (14).

Linzagolix is a new, orally active, non-peptide GnRH antagonist. In a Phase 2b placebo-controlled dose-ranging study, 75 mg linzagolix given once daily for 6 months partially suppressed E2 and significantly decreased EAP with limited effect on BMD. A dose of 200 mg given once daily for 6 months suppressed E2 to menopausal levels (< 20 pg/mL), significantly decreased EAP, with better efficacy for some symptoms such as DYS and dyspareunia, but as expected, significantly reduced BMD at 6 months.

Daily doses of 75 and 200 mg linzagolix have been chosen to be developed further for the treatment of EAP in order to provide dosing optionality to achieve both partial and complete E2 suppression. However, due to the significant BMD loss observed with 200 mg linzagolix, this dose will be developed in combination with concomitant estrogen/progestogen ABT.

The purpose of this study is to evaluate the safety, tolerability and efficacy of linzagolix in women with EAP. It is a Phase 3, randomized, double-blind, placebo-controlled study to demonstrate the superior efficacy of once daily oral 75 mg linzagolix and of once daily oral 200 mg linzagolix in combination with ABT on the reduction of EAP in women with surgically confirmed endometriosis.

5.4 SUMMARY OF NON-CLINICAL STUDIES

5.4.1 Non-Clinical Pharmacology

Linzagolix shows potent affinity for the GnRH receptors in different species particularly the human GnRH (hGnRH) receptor and acts as an antagonist *in vitro* (hGnRH Ki=27.4nM). The affinity of KP017, the main metabolite of linzagolix, to the hGnRH receptor was shown to be 4.4 fold lower (Ki=127 nM).

Specific effects on the endometrium were observed during in vivo studies, with linzagolix acting through suppression of estrogen dependent endometrial proliferation in a rat autograft endometriosis model.

Safety pharmacology studies, including a comprehensive set of cardiovascular ion channels, did not show any adverse effects on the central nervous, respiratory or cardiovascular system at exposures significantly exceeding those that would be used in a clinical setting.

5.4.2 Non-Clinical Pharmacokinetics and Toxicology

5.4.2.1 Pharmacokinetics

Linzagolix was rapidly and completely absorbed after oral dosing with exposures increasing in a generally dose-proportional manner. The volumes of distribution and plasma clearance were low. Linzagolix is highly bound to plasma proteins (>95%) across a range of species with no concentration dependent changes. In human plasma, the major binding protein for linzagolix was albumin. It does not exhibit blood partitioning.

Tissue distribution of radiolabeled linzagolix was widespread; there was no indication of unusual distribution or accumulation to tissues. Radioactivity was also detected in fetal tissues and milk.

The major route of biotransformation of linzagolix was the oxidative O-demethylation to KP017 (produced via CYP2C9 metabolism) which was observed in hepatocytes of all tested species. The in vivo metabolic pathway of linzagolix in mice, rats and monkeys was comparable to the in vitro data. Excretion of radioactivity from radiolabeled linzagolix was predominantly via feces in both rats and monkeys.

Pharmacokinetic (PK) interaction studies in vitro indicated that drugs possibly co-administered in clinical settings (non steroidal anti-inflammatory drugs - NSAIDs) did not affect the plasma protein binding of linzagolix.

5.4.2.2 Toxicology

Overall, the toxicological profile of linzagolix from repeated-dose toxicity studies was dominated by the consequences of its pharmacological activity as a GnRH receptor antagonist. During pivotal toxicology studies, dose levels of 200 and 10 mg/kg/day linzagolix were shown to be the no observed adverse effect level (NOAEL) in the main toxicology species rat (26-week daily oral administration) and monkey (39-week daily oral administration), respectively, and resulted in therapeutic indices (based on total / unbound exposure) for a human dose of 200 mg/day of 6.7 / 4.6 and 0.8 / 3.6, respectively.

Reproductive toxicity studies, especially fertility studies and embryo-foetal development studies in rabbits, were limited in dose by the anti-GnRH effects of linzagolix preventing conception or leading to total litter loss. The effects of linzagolix on conception were reversible, and rabbit embryo-foetal studies showed expected pharmacological activity and no adverse reprotoxic/teratogenic effect.

No effect on pre- and postnatal development of the offspring exposed during embryo-fetal development and lactation was recorded.

Linzagolix was not genotoxic nor phototoxic.

A 26-week carcinogenicity study in transgenic TgRasH2 mice showed no evidence of any linzagolix-induced carcinogenicity.

5.4.3 Non-clinical summary

Taken together, 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 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 PD of linzagolix have been further investigated in six 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 are being 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).

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. A total of 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 luteinizing hormone (LH), follicle-stimulating hormone (FSH) and E2.

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 heart rate corrected QT 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 pharmacodynamics (PD) and safety of linzagolix alone and combined with E2/ NETA add-back hormone replacement therapy 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. Additional drug-drug interaction studies (Studies 18-OBE2109-006 and 18-OBE2109-007) showed linzagolix to have no effect on OAT3 substrate benzylpenicillin and to increase the exposure to CYP2C8 substrate repaglinide. Linzagolix is considered 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 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 conducted in Japan in patients with endometriosis (Study KLH1201), 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 conducted in Japan in patients with endometriosis (Study KLH1202), 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 conducted in Japan in patients with endometriosis (Study KLH1203), 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 an ongoing Phase 2b study conducted in US and Europe in patients with endometriosis (Study 15-OBE2109-001, also known as Edelweiss), 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 24 weeks.

5.5.3 Safety

More than 1,500 subjects were exposed to different doses (25, 50, 75, 100, 200, 400 mg) of linzagolix from 12 completed and 3 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) (metrorrhagia and hot flush).

In the Phase 2b Edelweiss trial, 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 of the conditions in the majority of patients. As expected, full E2 suppression with linzagolix 200 mg lowers BMD by more than 2.5%, which indicates the need for a low dose ABT for use beyond 6 months.

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, a moderate proportion of patients reported a dose-dependent increase in hot flush (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 adverse events (AE) 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 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 under treatment up to normal. These increased transaminase values were not associated with increased bilirubin values.

A borderline effect of linzagolix on the heart rate corrected QT 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; only very few related events were reported as being of "severe" intensity.

5.6 RATIONALE FOR THE CURRENT STUDY

Linzagolix has been shown to suppress LH and E2 dose dependently and to significantly reduce EAP in women with moderate to severe EAP with a good safety and tolerability profile.

In the dose-ranging study (15-OBE2109-001), daily doses of 75, 100 and 200 mg linzagolix for 12 weeks significantly reduced EAP compared to placebo, whereas daily doses of 50 mg led to a reduction which was not significantly different than placebo. The effects of daily doses of 75, 100 and 200 mg were maintained or increased at 24 weeks. For overall pelvic pain, 49%, 62%, 56% and 56% of subjects responded (30% reduction in pelvic pain) to the doses of 50, 75, 100 and 200 mg linzagolix compared to 35% in placebo. For DYS, 43%, 68%, 69%, 79% of subjects responded to the dose of 50 mg, 75 mg, 100 mg and 200 mg, respectively, compared to 29% in placebo. For NMPP, 37%, 46%, 59%, 62% and 48% of subjects responded to the doses of 50, 75, 100 and 200 mg linzagolix, respectively, compared to 37% in placebo. Suppression of E2 was dose dependent with partial suppression achieved with once daily 75 mg dose and complete suppression with once daily 200 mg dose. Mean percent (95% CI, *P* value) BMD changes for lumbar spine from baseline to week 24 in the 50, 75, 100 and 200 mg dose groups were 0.137% (-0.83, -1.11, *P*=.777), 0.798% (-1.57, -0.03, *P*=.042), -1.365% (-2.14, -0.59, *P*<.001), -2.602% (-3.56, -1.65, *P*<.001). BMD of femoral neck and total hip showed a similar pattern but with generally smaller changes from baseline.

Based on the clinically and statistically very significant results of the dose-ranging study, two doses have been chosen for Phase 3 confirmatory registration studies: 75 mg alone and 200 mg in combination with hormone ABT (E2 1 mg/NETA 0.5 mg).

The two doses are chosen to provide two different long-term treatment options for women suffering from endometriosis: one dose providing a significant pain control for the majority of patients whilst maintaining E2 at levels above 20 pg/mL, which will mitigate a major impact on bone mineral density and one high dose requiring administration with hormone ABT (E2 1 mg/NETA 0.5 mg) achieving a better symptom control for some patients by providing complete E2 suppression but limiting the impact on bone mineral density due to the addition of ABT.

The study is double-blind and placebo-controlled which is considered the gold standard to prove efficacy of new medicines, in particular if potential advantages over alternative therapies lie in areas other than efficacy (15). For this reason, a placebo-controlled study is required by some regulatory authorities to support the registration of a product. In this study, the placebo control is restricted to 6 months after which all subjects will be offered active treatment (while maintaining the double-blind) for a further 6 months in a separate extension study. Of note, all subjects are allowed to use rescue analgesics for endometriosis-associated pain during the study. All subjects will enter a 6-month post-treatment follow-up, except for subjects who discontinued treatment prior to completing 3 months of treatment; those subjects will be directly discontinued from the study.

5.7 SUMMARY OF OVERALL RISKS AND BENEFITS

Endometriosis is an underserved gynecologic condition and one of the most common gynecological diseases (1). It is characterized by pain symptoms including DYS, dyspareunia, chronic pelvic pain, dysuria and dyschezia. Medical options are still limited and new treatment options are warranted.

Linzagolix is a new oral GnRH antagonist which has been shown significantly to reduce EAP via dose dependent suppression of LH, FSH and E2. This has included clinically meaningful improvements in DYS, NMPP, dyschezia and dyspareunia. 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 have been observed in the Phase 2 studies. No fetal or newborn abnormalities were reported in any of these 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 not dose-related increases in transaminase levels which were not associated with any change 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 ABT to mitigate BMD loss. The BMD loss will be monitored during the study and subjects who experience more than 8% confirmed BMD loss or a Z-score $\leq$ -2.5 will be

discontinued from treatment and will not be eligible to enter the extension study. In addition, subjects will be provided with vitamin D and calcium supplements which they will be recommended to take.

In conclusion, linzagolix has a favorable benefit/risk ratio and represents a potentially useful 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.

The trial was not completely stopped; rather, ObsEva implemented a temporary hold on recruitment in order to ensure patient safety. Therefore, ObsEva believes the hold had no potential effect on the benefit/risk balance for subjects.

Respecting national recommendations, as the COVID-19 pandemic situation improves and after careful assessment of risks and benefits, the Sponsor will decide on a site by site basis, when to resume screening and randomization for this study.

For randomized subject who could not attend her 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 study is to demonstrate the efficacy and safety of linzagolix administered orally once daily for up to 3 months at a dose of 75 mg alone or of 200 mg in combination with ABT (E2 1 mg / NETA 0.5 mg) versus placebo, while under randomized treatment, in the management of moderate to severe EAP in women with surgically confirmed endometriosis. The two co-primary efficacy endpoints will be clinically meaningful reduction over the last 28 days of randomized treatment up to the Month 3 visit along with a stable or decreased use of analgesics for EAP for 1) DYS and for 2) NMPP.

6.1.2 Secondary

Secondary objectives include evaluation of persistence of efficacy over the last 28 days of randomized treatment up to the Month 6 visit, evaluation of pain associated with sexual intercourse (dyspareunia) and defecation (dyschezia), difficulty of doing daily activities, analgesic use, assessment of subject perception of severity, change in uterine bleeding, Quality of Life (QoL) questionnaires, pharmacoeconomic burden of endometriosis by assessing changes in patient productivity, assessment

of endometriosis related number of non-study health visits, number of days in hospital and type of medical procedures performed during the Treatment Period.

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 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 3 visit (the 4-week period preceding Month 3 visit) or, for subjects who discontinue randomized treatment prior to the Month 3 visit, to the last 28 days of randomized treatment, 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

7.1.2.1 Ranked secondary efficacy endpoints

Ranked secondary efficacy endpoints (in the order of the endpoints to be tested) are:

- Change from baseline to Month 6 in DYS (VRS)
- Change from baseline to Month 6 in NMPP (VRS)
- Change from baseline to Month 6 in dyschezia (Numeric Rating Scale - NRS)
- Change from baseline to Month 6 in overall pelvic pain (NRS)
- Change from baseline to Month 6 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 6 in dyspareunia (VRS)
- No analgesics use for EAP during the preceding 4-week period at Month 6

- No opiate use for EAP during the preceding 4-week period at Month 6

7.1.2.2 Additional secondary efficacy endpoints

Additional secondary efficacy endpoints include:

- Clinically meaningful reduction at scheduled visits other than Month 3 for DYS and NMPP
- 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, placebo-controlled study to demonstrate the efficacy and safety of linzagolix administered orally once daily at doses of 75 mg alone and 200 mg in combination with low dose ABT (E2 1 mg/NETA 0.5 mg) versus placebo in the management of moderate to severe EAP in women with surgically confirmed endometriosis.

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

1. Linzagolix 75 mg
2. Linzagolix 200 mg combined with ABT
3. Placebo

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

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

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

The main analysis will be performed after 6 months of treatment and will include all of the subjects' data up to Month 6.

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

It is expected that only few subjects will have to enter the second 6-month follow-up period to have a DXA scan.

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

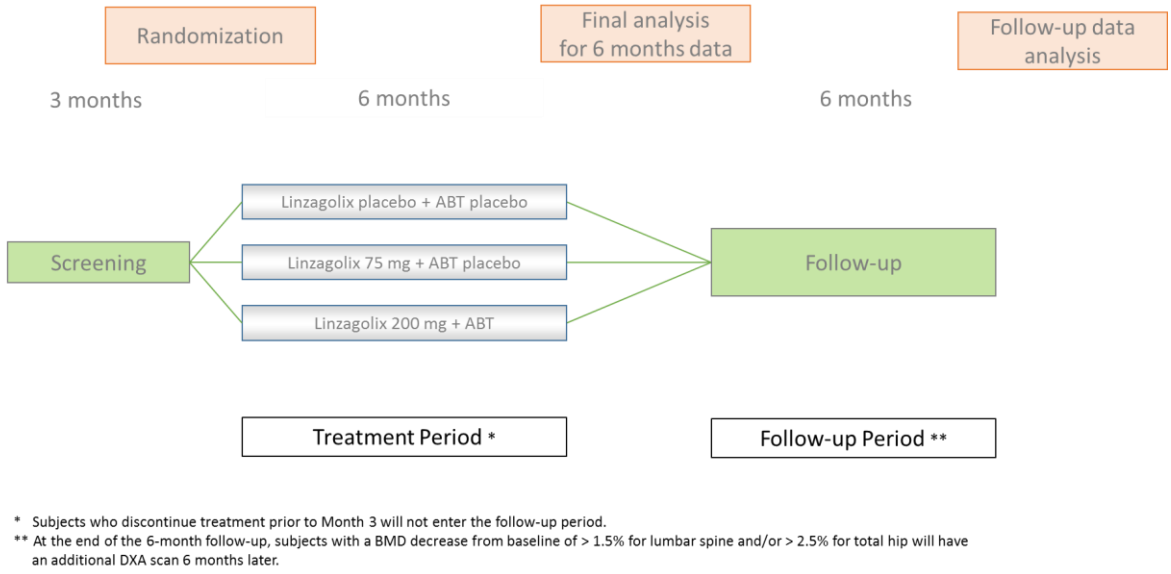


Figure 1 : Study design

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

Linzagolix/placebo treatments 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.

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

9 STUDY POPULATION

9.1 SUBJECTS

9.1.1 Description of the target population

The target population will be premenopausal women aged 18 to 49 years inclusive at screening, with surgically and, if available, histologically confirmed pelvic endometriosis and with moderate to severe EAP.

They must not be planning to become pregnant and must agree to use double non-hormonal barrier contraception from screening until 3 months after the end of treatment. From 3 months after the end of treatment to the end of the drug-free follow-up period, contraception is still mandatory but hormonal contraception is allowed.

9.1.2 Number of subjects

Four hundred and fifty (450) randomized subjects are planned in total (approximately 150 subjects per group). It is expected that the screen failure rate will be around 60%. Therefore, approximately 1125 subjects will be screened in order to randomize 450 subjects into the study.

9.1.3 Study region/location

The study will be conducted in approximately 100 investigational sites in the Unites States (US) and Europe. Additional sites will be identified, qualified and activated in case of recruitment issues. Recruitment will be competitive between countries and sites.

9.2 ENTRY CRITERIA

9.2.1 Inclusion Criteria

1. The subject must provide written informed consent prior to any study related procedures.
2. The subject must be a female subject aged 18 years to 49 years inclusive.
3. The subject must have had her most recent surgical and – if available – histological diagnosis of pelvic endometriosis (laparoscopy, laparotomy, vaginal fornix or other biopsy) up to 10 years before screening.
4. The subject must agree to the washout intervals for prohibited therapies (if applicable).
5. The subject must agree to switch from her usual analgesic rescue medication to only those permitted by the protocol during the Screening, Treatment and Follow-up Period.
6. The subject has moderate to severe EAP during the screening period defined as:
    a. At the screening visit, a score of at least 2 for DYS and at least 2 for NMPP for the previous month assessed with the modified Biberoglu & Behrman (mB&B) scale.

b. Over two full menstrual cycles (i.e. from day 1 of the first menstruation going over two spontaneous menstrual cycles up to the day before the next menstruation i.e. the third menstruation) finishing just before the baseline visit:

i. Mean overall pelvic pain scores of at least 4 on the 0–10 NRS over the 5 days with the highest score for each cycle separately, i.e. required for both cycles;

ii. At least two days with "moderate" or "severe" pain on the 0–3 VRS for pelvic pain over the days with uterine bleeding for each cycle separately, i.e. required for both cycles;

iii. At least two days with "moderate" or "severe" pain on the 0–3 VRS for pelvic pain over the days without uterine bleeding for each cycle separately, i.e. required for both cycles.

7. The subject is compliant with eDiary completion i.e. has completed at least 75% of days during the screening period.
8. The subject has regular menstrual cycles and the total length of the two screening menstrual cycles should be between 42 and 76 days inclusive.
9. The subject has a Body Mass Index (BMI) $\geq$ 18 kg/m^2 at the screening visit.
10. If of childbearing potential, the subject agrees to use one of the following birth control methods during the Screening Period, 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.

11. If of non-childbearing potential, the subject must have had tubal ligation sterilization at least two months before the screening visit.
12. The subject is $\geq$ 40 years of age at the screening visit has a normal mammogram within 1 year before randomization.
13. The subject must be able to communicate well with the Investigator and research staff and to comply with the requirements of the study protocol.

9.2.2 Exclusion Criteria

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

1. The subject is pregnant or breast feeding or is planning a pregnancy within the duration of the Treatment Period of the study.
2. The subject is less than 6 months postpartum or 3 months post-abortion/miscarriage at the time of entry into the screening period.
3. The subject has a surgical history of:

a. Hysterectomy,

b. Bilateral oophorectomy,

c. Vagotomy, bowel resection or any surgical procedure (including gastric surgery) that might interfere with gastrointestinal motility, pH, or absorption,

d. Any major abdominal surgery (including laparotomy for endometriosis) within 6 months or any interventional surgery for endometriosis performed within a period of 2 months before screening, or the subject is scheduled for a surgical abdominal procedure during the course of the study.

4. The subject had a tubal sterilization which was performed with ESSURE™.
5. The subject had endometrial ablation resulting in amenorrhea.
6. The subject has at least one ovarian endometrioma with a diameter of 7 cm or greater.
7. The subject is likely to require treatment during the study OR received treatment within a specified period prior to screening with any of the medications listed below:

a.	GnRH antagonists	3 months
b.	GnRH agonist injections/3-month depot injections	3/6 months
c.	Danazol	3 months
d.	Oral contraceptives and other sex hormones	1 month
e.	Depot contraceptives	10 months
f.	Selective Progesterone Receptor Modulators (SPRMs), Selective Estrogen Receptor Modulators (SERMs) and aromatase inhibitors	3 months
g.	Long acting narcotics (i.e. requiring less than once daily dosing)	1 day
h.	Systemic glucocorticoid treatments for acute diseases (not depot)	1 month
i.	Medical (prescribed) marijuana	1 week
j.	In situ copper intra-uterine device (IUD)	1 day
k.	In situ IUD with progestogen	1 month

8. The subject is likely to use cannabinoids during the study washout, screening or treatment period.
9. The subject has required more than 2 weeks of continuous use of a narcotic analgesics for treatment of EAP within 6 months prior to Screening.
10. The subject received strong CYP3A4 inducers or inhibitors that (might potentially) interact with ABT within 1 month prior to randomization.
11. The subject has a contra-indication to ABT including:

a. Active deep vein thrombosis, pulmonary embolism, or history of these conditions;

b. Active or recent (e.g. within the past year) arterial thromboembolic disease (e.g. stroke, myocardial infarction);

c. Known, suspected, or history of breast cancer;

d. Known or suspected estrogen-dependent neoplasia;

e. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;

f. Migraine with aura;

g. History of porphyria;

h. Known hypersensitivity to the ingredients.

12. The subject has a history of or current systemic glucocorticoid therapy for treatment of chronic diseases (e.g. Systemic Lupus Erythematosus (SLE), rheumatic arthritis). Inhaled glucocorticoids for e.g. asthma are not considered systemic glucocorticoids.
13. The subject did not respond to prior treatment with GnRH agonists or GnRH antagonists for endometriosis.
14. The subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin levels or gamma-glutamyl transpeptidase (GGT) level ≥ 2 times the upper limit of normal and indicative of potential liver damage at Screening or Day 1 (subjects with abnormalities at Day 1 will be withdrawn from study at reception of the results).
15. The subject has clinically significant abnormal ECG, or ECG with QTc using Fridericia's correction formula (QTcF) > 450 msec at Screening or Day 1 (prior to dosing).
16. The subject has a known positive human immunodeficiency virus (HIV) or viral Hepatitis serology.
17. The subject has abnormal uterine bleeding of undiagnosed cause.
18. The subject had/has clinically significant findings from a Papanikolaou (PAP) smear test performed within the past 12 months or at the screening visit which will require surgical intervention (e.g. Loop electrosurgical excision procedure (LEEP) or cervical conization).
19. The subject has chronic pelvic pain that, in the opinion of the Investigator, is not caused by endometriosis and requires chronic analgesic or other chronic therapy which would interfere with the assessment of EAP (e.g., interstitial cystitis, presumptive adenomyosis, fibroids, non-endometriosis-related pelvic adhesive disease, post-tubal ligation or irritable bowel syndrome).
20. The subject has any other clinically significant gynecological condition identified during screening transvaginal ultrasound (TVUS) or endometrial biopsy which might interfere with the study efficacy and safety objectives (e.g. endometritis, endometrial hyperplasia). However, uterine fibroids (as long as uterus size ≤ 12 weeks, i.e. equivalent gestational weeks) and adenomyosis are allowed provided they do not interfere with the assessment of EAP (see previous criterion).
21. The subject has any known condition, including findings in the medical history or in the screening assessments, which in the opinion of the Investigator constitutes a risk or a

contraindication to the participation of the subject in the trial or that could interfere with the trial objectives, conduct or evaluation.

22. The subject has a history of, or known, osteoporosis, hyperparathyroidism or other metabolic bone disease.
    a. Screening DXA results of the lumbar spine (L1–L4), femoral neck, or total hip BMD showing a Z-score ≤ –1.5
    b. Any condition that would interfere with obtaining adequate DXA measurements (e.g. weight [> 300 pounds or 136 kg], history of spinal surgery, spinal hardware, severe scoliosis)
    c. Intercurrent bone disease
    d. History of hip fracture
    e. History of pathologic or compression fractures
    f. History of bilateral hip replacement
23. The subject has a mental condition rendering her unable to understand the nature, scope and possible consequences of the study, or evidence of an uncooperative attitude.
24. The subject has current problem with alcohol or drug abuse (including painkiller abuse).
25. The subject has been administered with any experimental drug in the 12 weeks before screening.
26. The subject has calcium level above the upper limit of normal range at screening, which is confirmed on repeat fasting testing at Screening.
27. The subject has a history of, or active malignancy (with or without systemic chemotherapy) (except treated basal carcinoma of the skin which is not an exclusion criterion).
28. The subject has a history of attempted suicide and/or a history of, or known major psychiatric disorders that are not well controlled.

10 STUDY PROCEDURES AND ASSESSMENTS

10.1 GENERAL INSTRUCTIONS

Before the start of the study, each subject will be provided with a subject information leaflet giving details on the Investigational Medicinal Product (IMP), study procedures and potential risks and they will also be informed verbally by the Investigator or legally acceptable designee of the overall requirements of the study. They will be instructed that they can obtain further information from the Investigator at any time and that they are free to withdraw their consent and to discontinue their participation in the project at any time without prejudice.

If the subject is willing to participate in the study, she will be requested to give written informed consent prior to conducting any of the study screening procedures, after being given sufficient time to consider her participation and the opportunity to ask for further details. One original copy of the consent form 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.

The subject will be asked if she authorizes the Investigator to notify her general practitioner of her participation in the trial.

Upon signature of the Informed Consent Form (ICF), each subject will be assigned a Subject Identification Number (SIN) through an IWRS. 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)

During the whole study, the subject will be identified using the SIN for all documentation and discussion. The SIN assigned to a subject in this way must only be used for that subject.

Should a subject drop out from the study, the SIN will not be re-allocated.

Screen failures may be re-screened at a later date with the Sponsor's approval if it is believed that the reason for excluding them initially is no longer applicable. Any re-screened subject will be assigned a new SIN through an IWRS and all the screening information will be collected again. All screening procedures should be repeated except endometrial biopsy collection (if done during the preceding 6 months of re-screening), PAP smear (if done during the preceding 12 months of re-screening), DXA (if done during the preceding 3 months of randomization) and mammogram (if done during the preceding 12 months of randomization).

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

For screen failed subjects, the following information will be collected at a minimum: Informed Consent, Demographics, AEs and reason for screen failure.

When a subject has been found to be eligible for the study, she will be randomized to one of the three treatment groups in a 1:1:1 ratio (approximately 150 subjects per treatment group) as shown in Figure 1.

Randomization will be done according to a computer-generated list. Treatment assignments will be obtained via IWRS according to the randomization list. The subject will be allocated a randomization number and treatment kit numbers via IWRS. The randomization number allocated to the subject will allow any unblinded study personnel to identify the treatment group to which the subject is randomized.

Treatment kits will be dispensed to the subjects as follows:

- on Day 1 and Month 3 visits, subject will receive two kits, one for linzagolix/placebo (monthly kit) and one for the ABT/placebo (3-monthly kit).
- On Month 1, Month 2, Month 4 and Month 5 visits, subject will receive one kit only, for linzagolix/placebo.

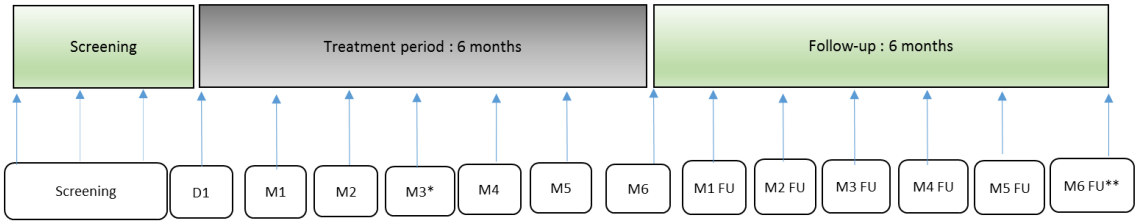
The treatment kit numbers for linzagolix/placebo and ABT/placebo will refer to unique kits present at site and corresponding to the randomization allocation.

10.2 OUTLINE OF STUDY PROCEDURES AND ASSESSMENTS

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

- Month 1 (Day 29), Month 2 (Day 57), Month 3 (Day 85), Month 4 (Day 113), Month 5 (Day 141) and Month 6 (Day 169) for the Treatment Period,
- Month 1 FU (Day 197), Month 2 FU (Day 225), Month 3 FU (Day 253), Month 4 FU (Day 281), Month 5 FU (Day 309) and Month 6 FU (Day 337) for the Follow-up Period.

A window of ± 3 days is allowed for each visit scheduled during the treatment period. A window of ± 7 days/1 week is allowed for each visit scheduled during the follow-up period. The visit schedule is illustrated in Figure 2 below:



* Subjects who discontinue treatment prior to Month 3 will not enter the follow-up period.
** At the end of the 6-month follow-up, subjects with a BMD decrease from baseline of > 1.5% for lumbar spine and/or > 2.5% for total hip will have an additional DXA scan 6 months later.

Figure 2 : Schedule of Visits

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

10.2.1 Screening Period – Screening visit

The subject will be informed of the study objectives and overall requirements, and written informed consent will be obtained before performing any study-specific procedures that are not standard of care.

The subject will be considered as included into the study after the ICF is signed and dated by the subject and the Investigator or legally acceptable designee.

For subjects who require washout for oral contraceptives, or other sex hormones, or GnRH antagonists/agonists (provided that the reason for discontinuing the previous GnRH-antagonist is not lack of efficacy), a period of up to 3 months will be allowed between signing the ICF and starting the collection of pain assessments in eDiary during the screening period. The screening period must cover

two full menstrual cycles and will last about 3 months. During the screening period, the subject will be seen up to three times if not all screening assessments could be performed at the first screening visit (e.g. the endometrial biopsy must be performed after day 7 of the menstrual cycle).

During the screening period the following study screening assessments will be completed (see Schedule of Assessments in Appendix A):

- Demographic data, height and weight
- Medical and surgical history including concomitant diseases (and especially presence of rectovaginal endometriosis and adenomyosis), previous medication, obstetric/gynecological history and history of endometriosis including diagnosis and previous treatments for endometriosis.
- Assessment of DYS, dyspareunia and NMPP with the mB&B scale (see Appendix C). Answers will be captured in eCRF.
- Completion of the paper C-SSRS questionnaire "Baseline" version specific for subjects under screening (see Appendix R)
- ECG
- Physical examination
- Vital signs (blood pressure (BP) and heart rate)
- Urine pregnancy test
- TVUS of uterus and ovaries to measure endometrial thickness, to rule out any clinically significant gynecological conditions which might interfere with the study efficacy and safety objectives and to confirm that the subject has no ovarian endometrioma ≥ 7 cm in diameter
- Gynecological examination, including the mB&B scale (see Appendix C) clinical signs reporting (pelvic tenderness and pelvic induration)
- Endometrial biopsy (should be performed at least 7 days after the first day of menstruation and sent for central assessment). If no tissue is available, the biopsy should be repeated as soon as possible in the following days. In case of multiple (at least two including the initial one) and unsuccessful attempts to get sufficient endometrial tissue, the subject is allowed to be randomized without any screening endometrial biopsy under the following conditions:

    a. the investigator confirms and documents in source that the subject has no signs of suspected endometrium malignancy (e.g. abnormal bleeding profile).

    b. The investigator and subject agree that at end of treatment all necessary actions will be taken to get a sufficient endometrium sample (e.g. short anaesthesia, if necessary).

    c. The medical monitor of the study approves the inclusion of the subject.

    The endometrial biopsy is not required for subjects having performed an endometrial biopsy within the past 6 months of the screening visit, which shows no endometrium hyperplasia of any type or adenocarcinoma and for which slides are available for current study assessment through retrospective central laboratory reading.

- PAP smear

  A screening PAP smear is not required for subjects in whom a PAP smear was performed within the 12 months prior to the screening visit and which results indicate no clinically significant abnormalities requiring surgical intervention (e.g. LEEP or cervical conization) and are available for source document verification.

- Manual breast examination by palpation (and mammography if applicable: subject ≥ 40 years of age at screening should have performed a mammogram within 12 months before randomization)

- Blood samples for haematology, coagulation parameters, chemistry and lipids assessments

- Urinary protein dipstick.

- Contraception dispensing and counselling

- BMD assessed by DXA for femoral neck, hip and spine. The DXA scans will be read centrally. To avoid unnecessary exposure to X-ray it is recommended to perform this procedure towards the end of the screening period (when all other Inclusion/Exclusion criteria are already met), but at least 2 weeks prior to the baseline visit to allow enough time to get the DXA results for eligibility confirmation at the time of the baseline visit at the latest.

The subject will receive double barrier contraception (condoms with spermicide) if requested. If the subject is at risk for acquiring HIV, she must be instructed to use double non-hormonal barrier contraception without spermicides (eg: condoms and diaphragms).

In addition, a limited quantity (as per Investigator's judgement) of permitted analgesics will be provided/prescribed to the subject at the screening visit to cover the screening period.

The subject will be given an eDiary with a user manual to take home and will be trained by the Investigator or delegate on how to use and complete it correctly. Subject eDiary completion should be started on the day of screening visit (after completion of washout period when applicable). The eDiary should be completed daily, in the evening at approximately the same time, for use of provided/prescribed analgesics, uterine bleeding (including start of menstruation), pelvic pain, dyspareunia, dyschezia and daily function. The eDiary screening assessments should cover at least two full menstrual cycles (from day 1 of the first menstruation going over two spontaneous menstrual cycles up to the day before the next menstruation i.e. the third menstruation).

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 the operational team.

Any concomitant medications taken after signature of informed consent will be recorded in the eCRF (excluding any provided/prescribed analgesics used for EAP which will be recorded daily in the eDiary).

Any AE occurring after signature of informed consent will be recorded in the eCRF.

The subject will be asked to return to the site and bring her eDiary between the first and seventh day (inclusive) of her next menstrual period (the period after the 2 screening full menstrual cycles) for the Day 1 visit. Final assessment of her eligibility will be performed, including calculation of the baseline

scores for pelvic pain collected via the eDiary. The baseline mean pelvic pain scores will be calculated using the data collected during the screening period over two full, spontaneous menstrual cycles.

If for logistical reasons beyond her control, the subject is unable to come to the clinic for Day 1 within the acceptable time window (1st to 7th day inclusive of the cycle) then the subject will be allowed to start Day 1 in the following cycle (again on the 1st to 7th day of the cycle). In this case, the eligibility assessments should be assessed based on the first two cycles only. However, the eDiary recording should be continued daily during the third cycle.

Note that in exceptional cases, the Day 1 visit may occur between Day 8 and Day 12 of the third or fourth cycle but only upon prior approval by the sponsor. In that case, the subject should do a urine pregnancy test at her home 1 week after the Day 1 visit to ensure she is not pregnant. The subject should communicate (e.g., via phone) results of the test to the site for recording into the source medical file.

10.2.2 Treatment period

From Day 1 to Month 6, the subject should record daily in her eDiary, at approximately the same time each evening, the following questionnaires: IMP intake, use of provided/prescribed analgesics, uterine bleeding, pelvic pain, dyspareunia, dyschezia and daily function.

During the entire treatment period, the subject will be asked to bring her eDiary and her IMP kits at each visit to the site.

10.2.2.1 Baseline visit: Day 1

If the subject has successfully completed all screening assessments and is between the first and seventh day (inclusive) of her menstruation, she will go to the investigational site for the following evaluations and tests **before drug administration**:

- eDiary eligibility data review
- ePRO and ClinRO completion, ideally before any other procedures or assessments: EHP-30, HRPQ, HRUQ, PSIQ, SSIQ, PROMIS, EQ-5D-5L, specific monthly severity questions, mPGIS (anchors must be completed last)
- Completion of the paper C-SSRS questionnaire “Baseline” version, if not already completed during screening period (see Appendix R)
- Screening DXA results review
- Screening lab results review
- Screening endometrial biopsy results review (randomization will not be postponed if the results of the endometrial biopsy performed during the screening period are not available on Day 1)
- Previous and concomitant treatments recording
- AE recording
- ECG

- Vital signs (BP and heart rate)
- Urine pregnancy test
- Urinary protein dipstick
- Fasting (overnight) blood samples for haematology, coagulation parameters, chemistry, lipids, glucose, hormones and bone biomarkers, prior to the first administration of study treatment, and after confirmation of the subject's eligibility (considering the invasive nature of this procedure).

Upon confirmation of inclusion/exclusion criteria, the subject will be randomized to one of the three treatment groups and will be provided with the study drugs (1 kit of linzagolix/placebo and 1 kit of ABT/placebo) and provided/prescribed with permitted analgesics as well as vitamin D and calcium supplements. The subject will be instructed on how to take the study drugs and analgesics, and advised to take the provided vitamin D and calcium daily. The subject will be provided/prescribed as necessary with analgesics and vitamin D/calcium supplements at each subsequent visit to cover requirements until the end of the follow-up period.

The subject will take her first dose of study medication at the study site. The exact time of dosing (hour/minute) will be recorded in eCRF.

After drug administration, the following procedures will be performed:

- ECG at about the same time as but before the post-dose PK sample
- Post-dose PK sample taken at least 1.5 h after treatment administration. The exact time of dosing and of PK sampling (hour/minute) will be recorded in the eCRF.
- Contraception dispensing (if applicable) and counselling

The subject will receive double barrier contraception (condoms with spermicide) if requested. If the subject is at risk for acquiring HIV, she will be instructed to use double non-hormonal barrier contraception without spermicides (condoms and diaphragms).

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

For the whole duration of the treatment period, 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.

10.2.2.2 Study visits: Month 1 (Day 29 -3/+2 days) and Month 2 (Day 57 ± 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 1 visit: EHP-30, HRPQ, HRUQ, PROMIS, EQ-5D-5L, mPGIS, PGIC
  - at Month 2 visit: HRPQ, HRUQ, mPGIS, PGIC

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 S) for patients responding to the C-SSRS for the first time during the study, or version "since last study visit" (see Appendix T) 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 for haematology, coagulation parameters, chemistry, lipids, hormones (overnight fasting required at Month 1 visit only)
- 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
- 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 baseline visit.

10.2.2.3 Study visit: Month 3 (day 85 ± 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, HRPQ, HRUQ, PROMIS, EQ-5D-5L, specific monthly severity questions, mPGIS, PGIC completion (anchors must be completed last)
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire (version for "already enrolled subjects" (see Appendix S) for patients responding to the C-SSRS for the first time during the study, or version "since last study visit" (see Appendix T) 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
- 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 and bone biomarkers
- Pre-dose PK samples (the time of dose administration on previous 4 days and time of PK sampling will be recorded)
- Contraception dispensing (if applicable) and counselling
- 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.

10.2.2.4 Study visits: Month 4 (day 113 ± 3 days) and Month 5 (day 141 ± 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: HRPQ, HRUQ, mPGIS, PGIC completion (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 S) for patients responding to the C-SSRS for the first time during the study, or version "since last study visit" (see Appendix T) 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 for haematology, coagulation parameters, chemistry, lipids, hormones

- Pre-dose PK samples (the time of dose administration on previous 4 days and time of PK sampling will be recorded)
- Contraception dispensing (if applicable) and counselling
- 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 3 visit.

At Month 5 visit, the subject will be informed of the possibility to enter the extension study at Month 6 (if eligible) and will be provided with a copy of the subject information sheet to read prior to the Month 6 visit.

10.2.2.5 Study visit: Month 6 (day 169 ± 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, HRPQ, HRUQ, PSIQ, SSIQ, PROMIS, EQ-5D-5L, specific monthly severity questions, mPGIS, PGIC completion (anchors must be completed last)
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire (version for “already enrolled subjects” (see Appendix S) for patients responding to the C-SSRS for the first time during the study, or version “since last study visit” (see Appendix T) 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 and bone biomarkers

- Pre-dose PK samples (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 6 study visit at the latest, knowing that subjects who experience more than 8% BMD loss or a Z-score ≤ -2.5 will not be eligible to enter the extension study.
- The subject will be verbally asked which treatment she believed she received during the blinded Treatment Period. The answer will be recorded in the eCRF.
- Contraception dispensing (if applicable) and counselling

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.

Study visit Month 6 constitutes the end of the Treatment Period.

The subject – if eligible - will be proposed to enter the extension study. If she is willing to participate, she will have to provide written consent. If she does not wish to enter the extension study or if she does not qualify for the extension, she will continue in the treatment-free follow-up period.

10.2.3 Follow-up period without treatment for subjects not entering the extension study

Up to Month 6 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.

10.2.3.1 Study visit: Month 1 FU

M1 FU visit should be scheduled on Day 197 ± 7 days after 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 FU visit:

- eDiary completion compliance check
- ePRO completion, ideally before any other procedures or assessments: mPGIS and PPGIC
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire (version for “already enrolled subjects” (see Appendix S) for patients responding to the C-SSRS for the first time during the study, or version

"since last study visit" (see Appendix T) 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 counselling
- Urinary protein dipstick
- Blood samples for haematology, coagulation parameters, chemistry, lipids, hormones
- Endometrial biopsy only if diagnosis at Month 6 was different than "benign endometrium" or if no endometrial biopsy was done at Month 6 (see section 10.4.5).

10.2.3.2 Study visits: Month 2 FU, Month 4 FU and Month 5 FU

Month 2 FU visit should be scheduled on Day 225 ± 7 days after Day 1 (or 56 days ± 7 days after last IMP intake for early discontinued subjects).

Month 4 FU visit should be scheduled on Day 281 ± 7 days after Day 1 (or 112 days ± 7 days after last IMP intake for early discontinued subjects).

Month 5 FU visit should be scheduled on Day 309 ± 7 days after Day 1 (or 140 days ± 7 days after last IMP intake for early discontinued subjects).

The following tests and evaluations will be performed at Month 2 FU, Month 4 FU and Month 5 FU visits:

- eDiary completion compliance check
- ePRO completion, ideally before any other procedures or assessments: mPGIS and PPGIC
- Concomitant treatments recording
- AE recording
- Completion of the paper C-SSRS questionnaire (version for "already enrolled subjects" (see) for patients responding to the C-SSRS for the first time during the study, or version "since last study visit" (see Appendix T) for patients for whom the C-SSRS was completed at the previous study visit)
- Urine pregnancy test and contraception counselling (at Month 2 FU visit only)
- Endometrial biopsy only if diagnosis at preceding biopsy was different than "benign endometrium" or if no endometrial biopsy was done at Month 6 nor at any visit since Month 6 (see section 10.4.5).

10.2.3.3 Study visit Month 3 FU

Month 3 FU visit should be scheduled on Day 253 ± 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 FU Visit:

- eDiary completion compliance check
- ePRO and ClinRO completion, ideally before any other procedures or assessments: EHP-30, HRPQ, HRUQ, PROMIS, EQ-5D-5L, mPGIS, PPGIC completion (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 S) for patients responding to the C-SSRS for the first time during the study, or version "since last study visit" (see Appendix T) for patients for whom the C-SSRS was completed at the previous study visit)
- ECG
- Physical examination
- 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 and bone markers. For subjects that do not resume menses at Month 3 FU visit, a FSH test should be performed at local laboratory and the subjects should be advised to consult for a gynaecological evaluation.
- Endometrial biopsy only if diagnosis at preceding biopsy was different than "benign endometrium" or if no endometrial biopsy was done at Month 6 nor at any visit since Month 6 (see section 10.4.5).

10.2.3.4 Study visit: Month 6 FU – End of Follow-up visit

Month 6 FU visit should be scheduled on Day 337 ± 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 FU Visit:

- ePRO and ClinRO completion, ideally before any other procedures or assessments: EHP-30, HRPQ, HRUQ, PROMIS, EQ-5D-5L, mPGIS, PPGIC completion (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 T) for patients for whom the C-SSRS was completed at the previous study visit.
- ECG
- Physical examination, including weight recording
- Urine pregnancy test
- TVUS of uterus
- Endometrialm biopsy if no endometrial biopsy was obtained at Month 6 nor at any visit since Month 6 (see section 10.4.5). If no tissue is available, 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 FU study visit.

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

10.2.3.5 Study visit: BMD Follow-up visit

BMD Follow-up visit should be scheduled on Day 505 ± 10 days after Day 1 (or 168 days ± 10 days after M6 FU visit).

This visit is applicable only to subjects with a BMD decrease from baseline > 1.5% for lumbar spine and/or > 2.5% for total hip at M6 FU visit.

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

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

10.3 EFFICACY OBSERVATIONS AND MEASUREMENTS

All the questionnaires described below except the mB&B scale 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 Modified Biberoglu and Behrman questionnaire

Endometriosis pain will be assessed at screening by subject using the mB&B scale (see Appendix C).

10.3.2 Daily diary

The subject will be given an eDiary with a user manual to take home and will be trained by the Investigator or delegate on how to use and complete it correctly. Subject eDiary completion should be started on the day of screening visit (after completion of washout period when applicable).

The eDiary should be completed daily, in the evening at approximately the same time. 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.

10.3.2.1 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.*

10.3.2.2 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.

10.3.2.3 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*

Subject will be asked additional questions to identify the first day of her menstrual periods during the Screening Period.

10.3.2.4 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.

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

10.3.2.6 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.

10.3.2.7 School or work missed

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

10.3.2.8 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 is removed in protocol version 4.0 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 implementation of protocol version 4.0.

10.3.2.9 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.

10.3.2.10 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 is removed in protocol version 4.0 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 implementation of protocol version 4.0.

10.3.2.11 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 J).

Following a request from the FDA, this assessment is removed in protocol version 4.0 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 implementation of protocol version 4.0.

10.3.3 Outcome rating scales assessed at site visits

ePROs are self-administered questionnaires completed by the subject. ePROs completed by the subject during the site visit include: specific monthly severity questions (i.e monthly dysmenorrhea question, monthly non-menstrual pelvic pain question, monthly overall pelvic pain question, monthly difficulty in doing daily activities question, monthly dyschezia question, monthly dyspareunia question), EHP-30, HRPQ, SSIQ, PROMIS, EQ-5D-5L, mPGIS and PGIC/PPGIC.

ClinROs are questionnaires administered by the site staff to the subject and completed by the site staff in the eDiary. ClinROs include monthly dyspareunia question, HRUQ and PSIQ.

Specific monthly severity questions (monthly dysmenorrhea question, monthly non-menstrual pelvic pain question, monthly overall pelvic pain question, monthly difficulty in doing daily activities question,

monthly dyschezia question, monthly dyspareunia question), mPGIS, and PGIC/PPGIC will be used as anchors to estimate meaningful change and deriving responder thresholds.

During site visits, ePROs and ClinROs should be completed ideally prior to any other study procedures, with the anchors being completed last.. Assessments will be performed at the visits as indicated in Appendix A and Appendix B.

Prior to the start of the study, site personnel will be trained on all rating scales (ePROs, ClinROs and scales of daily diary) used in this study. The training will be provided at the investigator meeting and/or site initiation visit. The objective of this training is to establish uniformity across subjects and sites in completion of these rating instruments.

10.3.3.1 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 D.

10.3.3.2 PROMIS Fatigue Short Form 6a14

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

10.3.3.3 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 F).

10.3.3.4 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 G).

10.3.3.5 Patient Global Impression of Change (PGIC)

The PGIC is used by the subjects to evaluate the change in their 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 H).

10.3.3.6 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 I).

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

At each study visit from Day 1 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 J).

10.3.3.8 Subject Surgery Intention Question (SSIQ)

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

10.3.3.9 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 L).

10.3.3.10 EQ-5D-5L

Subjects' health related quality of life will be measured using the EQ-5D-5L (see Appendix M). 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'.

10.3.3.11 Specific Monthly severity questions

The monthly severity questions specific to DYS, NMPP, overall pelvic pain, difficulty in doing daily activities, dyschezia and dyspareunia will be used as separate anchors to determine what constitutes a meaningful within-patient score change in the respective assessment.

10.3.3.11.1 Monthly dysmenorrhea question

At Day 1, Month 3 and Month 6 study visits, the subject will be asked to evaluate the severity of her dysmenorrhea over the past 28 days using a 5-point scale with the following possible answers: no pain, very mild, mild, moderate, severe.

Subject's answer to the question "How would you describe your **menstrual pelvic pain** (on any days of vaginal bleeding or spotting) over the past 28 days?" will be collected via the eDiary.

Not all subjects will have this assessment completed as it was added during the study course as a protocol amendment.

10.3.3.11.2 Monthly non-menstrual pelvic pain question

At Day 1, Month 3 and Month 6 study visits, the subject will be asked to evaluate the severity of her non-menstrual pelvic pain over the past 28 days using a 5-point scale with the following possible answers: no pain, very mild, mild, moderate, severe.

Subject's answer to the question "How would you describe your **non-menstrual pelvic pain** (on any days with no vaginal bleeding nor spotting) over the past 28 days?" will be collected via the eDiary.

Not all subjects will have this assessment completed as it was added during the study course as a protocol amendment.

10.3.3.11.3 Monthly overall pelvic pain question

At Day 1, Month 3 and Month 6 study visits, the subject will be asked to evaluate the severity of her overall pelvic pain over the past 28 days using a 5-point scale with the following possible answers: no pain, very mild, mild, moderate, severe.

Subject's answer to the question "How would you describe your **overall pelvic pain** (menstrual and non-menstrual) over the past 28 days?" will be collected via the eDiary.

Not all subjects will have this assessment completed as it was added during the study course as a protocol amendment.

10.3.3.11.4 Monthly difficulty in doing daily activities question

At Day 1, Month 3 and Month 6 study visits, the subject will be asked to evaluate how much has her endometriosis-related pain caused her difficulty in performing her daily activities over the past 28 days using a 5-point scale with the following possible answers: No difficulty, slight difficulty, mild difficulty, moderate difficulty, severe difficulty.

Subject's answer to the question "How much has your endometriosis-related pain caused you difficulty in performing your daily activities over the past 28 days?" will be collected via the eDiary.

Not all subjects will have this assessment completed as it was added during the study course as a protocol amendment.

10.3.3.11.5 Monthly dyschezia question

At Day 1, Month 3 and Month 6 study visits, the subject will be asked to evaluate the severity of her dyschezia over the past 28 days using a 5-point scale with the following possible answers: no pain, very mild, mild, moderate, severe.

Subject's answer to the question "Overall, how would you describe any endometriosis-related pain during defecation (bowel movement) over the past 28 days?" will be collected via the eDiary.

Not all subjects will have this assessment completed as it was added during the study course as a protocol amendment.

10.3.3.11.6 Monthly dyspareunia question

The question will be administered and completed in the eDiary using the mB&B scale for Deep Dyspareunia, at Day 1, Month 3 and Month 6 study visits.

The subject will first report, directly in the eDiary, if she had any sexual intercourse over the past 28 days.

If she didn't have any sexual intercourse over the past 28 days, she will report whether she avoided sexual intercourse mainly because of anticipation of pain during intercourse, with the following possible answers: Yes, No.

If she had any sexual intercourse over the past 28 days, her overall experience of pain with intercourse over the previous 28 days will be asked by the site staff and graded using the mB&B scale for Deep Dyspareunia:

None	0 = No symptoms
Mild	1 = Tolerated discomfort during intercourse
Moderate	2 = Interference of usual frequency of sexual intercourse due to pain
Severe	3 = Avoids, or wishes to avoid, intercourse because of pain

Not all subjects will have this assessment completed as it was added during the study course as a protocol amendment.

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). 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 at scheduled visits. In addition, a manual breast examination (by palpation) will be performed at Screening, Month 6 and Month 3 FU visits. Results of the examinations will be recorded on source subject data file and in the eCRF. Baseline medical conditions (see section 12.1.3) that do 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 of 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 print-outs 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 least two endometrial biopsies for histological assessment will have to be obtained for each subject:

- One at screening (unless an endometrial biopsy was performed within the past 6 months of the screening visit, which shows no endometrial hyperplasia of any type or adenocarcinoma and for which slides are available for current study assessment through retrospective central laboratory reading.
- One at Month 6 if endometrium thickness on TVUS is > 5 mm (see Figure 3)
- One at Month 1 FU, 2 FU, 3 FU, 4 FU, 5 FU or 6 FU if not obtained at Month 6 or if the preceding biopsy diagnosis is different than “benign endometrium” but is not “malignant” or not “hyperplasia” (see Figure 4)

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.

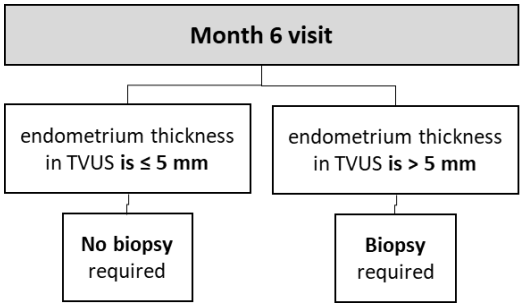


Figure 3 : Biopsy process for Month 6 study visit

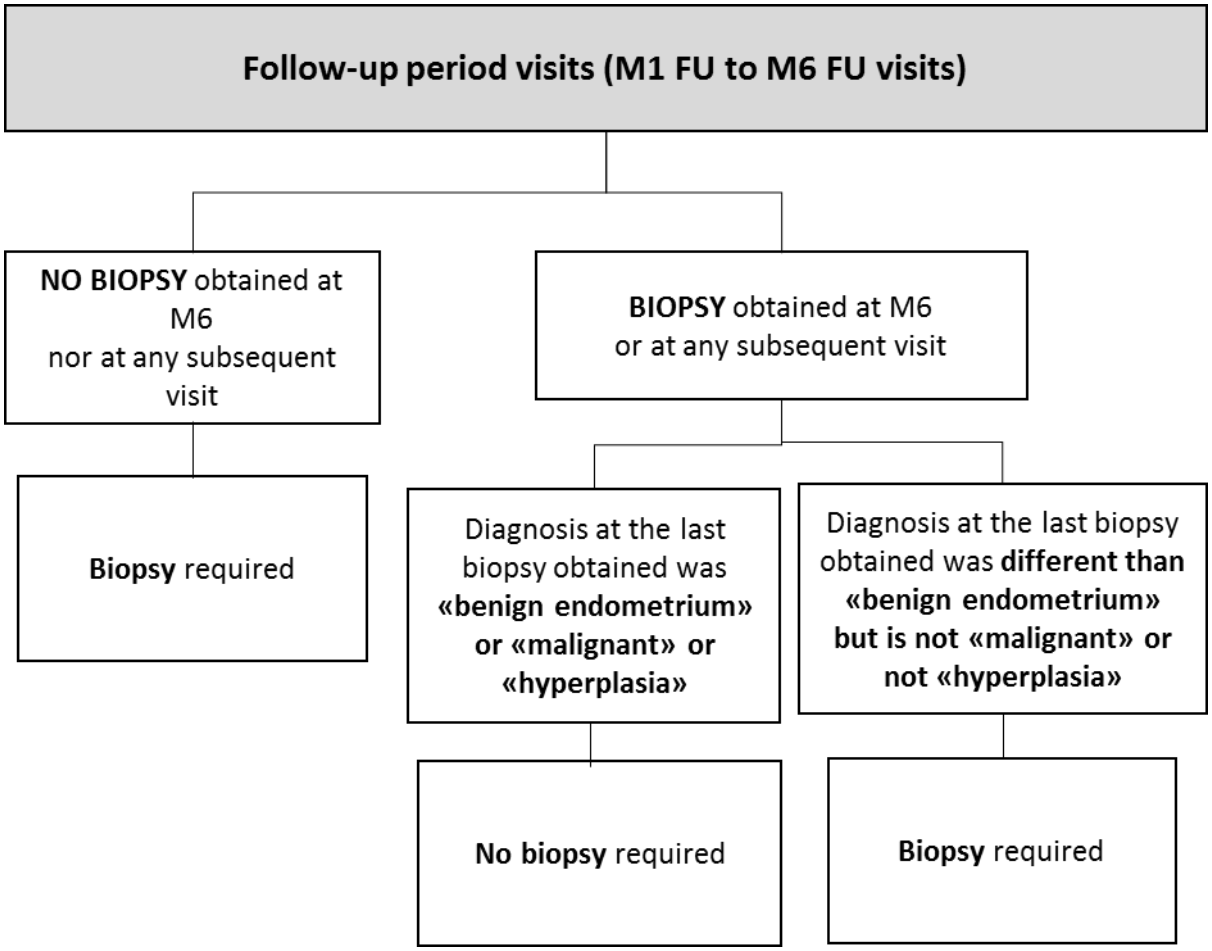


Figure 4 : Biopsy process for the follow-up period visits

Screening endometrial biopsy should be performed at least 7 days after the first day of menstruation and sent for central assessment. If no tissue is available, the biopsy should be repeated as soon as possible in the following days. In case of multiple (at least two including the initial one) and unsuccessful attempts to get sufficient endometrial tissue, the subject is allowed to be randomized without any screening endometrial biopsy under the following conditions:

a. The investigator confirms and documents in source that the subject has no signs of suspected endometrium malignancy (e.g. abnormal bleeding profile).

b. The investigator and subject agree that at end of treatment all necessary actions will be taken to get a sufficient endometrium sample (e.g. short anaesthesia, if necessary). However, it should be noted that for subjects who discontinue the study and complete less than 3 months of treatment an end-of-study biopsy is not required.

c. The medical monitor of the study approves the inclusion of the subject.

If there is a subsequent clinically significant finding in the biopsy, the subject will be withdrawn immediately

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 patients 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, (and will not be eligible to enter the extension study), will enter the follow-up period (unless she is discontinued prior to Month 3 visit) and will be advised to consult for a 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 femoral neck, total hip and lumbar spine will be assessed by DXA, under the supervision of a nominated primary technologist at the site.

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 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. 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, chemistry, lipids, glucose and hormones will be assessed from blood samples. Haematology, coagulation parameters, chemistry and lipids will be assessed at screening and at each visit during the treatment period, as well as at M1 FU and M3 FU visits. E2, progesterone (P4) and LH will be assessed at each visit during the treatment period (not at screening visit), as well as at M1 FU and M3 FU visits. Serum levels of the anti-müllerian hormone (AMH) and fasting glucose will be assessed on Day 1 only. Serum levels of the sex hormone-binding globulin (SHBG) will be assessed on Day 1 and Month 3 and Month 6 visits.

Overnight fasting is required for Day 1, Months 1, 3 and 6, and Month 3 FU 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, SHBG, P4, LH and bone marker levels will be assessed by the Investigator/sub-investigator and clinically significant abnormalities compared to screening/baseline status will be reported as AEs in the eCRF. E2, SHBG, P4 and LH levels will not be communicated to keep the operational team and the sites blinded to treatment administration.

The laboratory parameters are listed in Appendix N.

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 the scheduled visits.

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 assess 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 “Baseline” C-SSRS version, dedicated to subjects under screening, capturing lifetime history of suicidal ideation and behavior (see Appendix R)

- or the “already enrolled subjects” C-SSRS version, dedicated to randomized subjects who are providing answers to the C-SSRS for the first time during the study (see Appendix S)

- the “since last study visit” C-SSRS version (see Appendix T), 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 for determining linzagolix and KP017 plasma levels.

On Day 1, blood samples for PK assessment will be taken at least 1.5 h post-first dose.

During the treatment period, on days of site visits at Months 1, 2, 3, 4 and 5), the subject will be asked to take the dose of IMP at site, after a pre-dose PK sampling. 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 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 study, from the date of signature of informed consent and for the whole 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 Screening, Treatment and Follow-up Period. 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

Local equivalent Narcotic Analgesics:

Austria	tramadol 37.5mg + paracetamol 325mg
Bulgaria	tramadol 37.5mg + paracetamol 325mg
Czech Republic	codeine 30mg

	paracetamol 500 mg+ codeine 30 mg tramadol 37.5mg + paracetamol 325mg
France	paracetamol 500 mg+ codeine 30 mg tramadol 37.5mg + paracetamol 325mg
Hungary	paracetamol 500 mg+ codeine 30 mg codeine 30mg tramadol 37.5mg + paracetamol 325mg
Poland	tramadol 37.5mg + paracetamol 325mg
Romania	codeine 30mg paracetamol 500 mg+ codeine 30 mg
Spain	paracetamol 500 mg+ codeine 30 mg tramadol 37.5mg + paracetamol 325mg
Ukraine	N/A

Other:

In order to prevent or minimize possible impact on bone mineral density, 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 exclusion criteria (see section 9.2.2) will be prohibited up to Month 6.

To consider a subject who is currently taking any prohibited therapies for potential inclusion in this study, the Investigator must ensure that the subject has sufficient washout time prior to screening (see Section 10.2.1).

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

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 hormonal IUD must be stopped following ICF signature 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 from beginning of screening period 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.

After 3 months after the end of the Treatment Period until the end of the Follow-up Period, contraception is still required but 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 she is supposed to follow 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.

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

Withdrawal during treatment period:

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

Subjects discontinuing the study treatment between Month 3 and Month 6 should undergo the procedures required at Month 6. These subjects will enter a 6-month follow-up period and will continue daily eDiary recording for 6 months and up to Month 6 FU visit in order to continue to collect efficacy data.

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

Withdrawal during follow-up period:

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

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

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

Subjects who have a serum calcium level at Day 1 above 2.9 mmol/L and who have completed Day 1, should have calcium supplements interrupted. If serum calcium level at Day 1 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.

Discontinuation Rules during the Treatment Period:

Endometrial biopsies: in case of endometrial biopsy diagnosis being an endometrial hyperplasia of any type or worse, the subject will have to discontinue the treatment (and will not be eligible to enter the extension study) and will be advised to consult for a 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.

Bone mineral density 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 (they will not be eligible to enter the extension study).

Liver function tests: following the Food and Drug Administration (FDA) guidance on drug-induced liver injury (17), 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 first dose 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.

10.7.3 Subject Replacement

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

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

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 product	**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	Capsules	Capsules
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 and corresponding placebo treatments 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 start on Day 1 and will be administered once daily up to the day preceding the Month 6 visit . The subjects will have to swallow two tablets of linzagolix/placebo and one capsule of 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, after the PK blood sample collection, except on Day 1 visit where the study medication must be taken before the PK blood sample collection (at least 1.5 h before). 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 Day 1 and Month 3 visits, ABT/placebo capsules must be taken from the kits dispensed during these visits. On Month 1, 2, 4 and 5 visits, ABT/placebo capsules must be taken from the previously dispensed kits.

The treatment groups are described below:

Treatment group	**Daily dose Day 1 to Month 6**			
	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	1 □ 200 mg	1 □ placebo 75 mg	1 capsule	None
Placebo	None	1 □ placebo 75 mg AND 1 □ placebo 200 mg	None	1 capsule

11.3 PACKAGING AND LABELLING

Study drug (linzagolix/placebo) will be provided by the sponsor (or delegate) as monthly kits.

On Day 1, Month 1, Month 2, Month 3, Month 4 and Month 5 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.

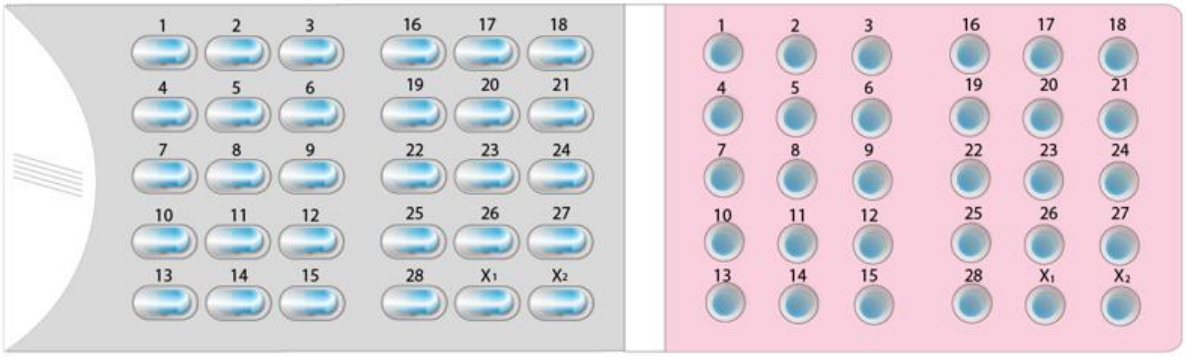


Figure 5 : Linzagolix/placebo kit design

Each linzagolix kit will be labeled with a unique kit number starting from B00001, B00002, B00003, etc. (6-characters). The blisters being attached into the wallet card, linzagolix 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 Day 1 and Month 3 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), starting from N00001, N00002, N00003 etc.

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
- Expiry date (for Europe only)
- 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.
- 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

Prior to the start of the study, a randomization list and 2 treatment kit lists (one for linzagolix/placebo, one for ABT/placebo) will be generated by a designated statistician from the sponsor or delegate to be transmitted to the assigned clinical packaging organization for labelling and to a fully integrated IWRS.

The IWRS will provide the kit numbers, which will correspond to the linzagolix/placebo and ABT/placebo kit numbers.

Subjects will be randomized to one of three treatment groups in a 1:1:1 ratio. There will be no stratification.

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 (linzagolix/placebo, ABT/placebo), 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. A blind review meeting will take place prior to unblinding. Subjects with poor compliance and other significant protocol violations may be excluded from the Per Protocol Analysis Set.

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. Linzagolix/placebo treatments 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.

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 subject and the sponsor study personnel fully blinded. Individual E2, SHBG, P4, LH, bone marker levels and PK data will not be communicated to them.

Post-randomization eDiary bleeding data will remain blinded to the Investigator, the operational team and to the sponsor study personnel.

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 single and repeated doses of up to 400 mg were shown to be safe in a Phase 1 single and multiple ascending dose study, 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. These will be provided by the sponsor free of charge to the subject or reimbursed.

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

Condoms with spermicide as well as calcium and vitamin D supplements will also be provided by the sponsor free of charge to the subject. If required, spermicide-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.

Events occurring prior to first IMP administration in the study are not considered AEs per se, but an event that could be due to the disease or specific circumstances. For monitoring purposes, any event occurring after signature of the informed consent form, as assessed by the Investigator, should be reported on an AE form or an SAE form, as appropriate. In case of AE reporting prior to IMP intake, an assessment should be performed whether an event constitutes rather a baseline medical condition (e.g. Gilbert's disease - to be reported on the "medical history page of the eCRF") or an AE.

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 screening visit or is assessed as having evolved since the screening 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), including results of the study screening assessments, are defined as Baseline Medical Conditions. These medical conditions should be 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 SAE 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 4 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 10.9. 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 1 working day after the receipt of the SAE form 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 1 working day for urgent queries or 5 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 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 IRB/IEC 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 IRB/IEC). 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 IRB/IEC. 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 IRB/IEC'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 IRB/IEC 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 IRB/IEC 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 M6 FU visit.

Events occurring during the screening period (i.e between ICF signature and Day 1 visit) must be recorded in the eCRFs using the AE form (and SAE form if appropriate) until the date the subject is determined to be a screening failure. Beyond that date, only serious or medically relevant protocol-related events will be followed-up.

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

However, **all pregnancies that are diagnosed up to M3 FU 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 criteria (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 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

All statistical hypothesis tests and confidence intervals will be two sided. To maintain an overall type I error rate of 0.05, as there are two linzagolix versus placebo comparisons, Bonferoni corrected p-values will be produced (raw p-values will be multiplied by two prior to comparing to 0.05), along with corresponding 97.5% confidence intervals.

The two co-primary efficacy endpoints will be clinically meaningful reduction (see section 13.5.2) over the last 28 days of randomized treatment up to the Month 3 visit (the 4-week period preceding Month 3 visit) from baseline in the mean daily assessment of DYS and of NMPP measured on a VRS, along with a stable or decreased use of analgesics for EAP.

The primary objective will be assessed by testing the following two-sided hypotheses for each co-primary endpoint, for each linzagolix group versus placebo separately:

Null hypothesis (H0): There is no difference in the odds of subjects meeting the primary endpoint for the active treatment group compared to placebo, that is, the odds ratio (OR) equals 1.

H0: OR =1

Alternative hypothesis (H1): There is a difference in the odds of subjects meeting the primary endpoint for the active treatment group compared to placebo, that is, the OR is not equal to 1.

H1: OR $\neq$ 1

Where odds are equal to the proportion of subjects meeting the endpoint divided by proportion of subjects not meeting the endpoint.

Each linzagolix group will need to demonstrate a statistically significant difference for both co-primary endpoints in order for the group to be considered more efficacious than placebo, thus maintaining an overall type I error rate of 0.05.

For each linzagolix group that is statistically significantly more efficacious than placebo for the co-primary endpoints, a fixed-sequence testing strategy shall be used within the group to test the ranked secondary endpoints as ordered in Section 7.1.2.1, so as to maintain the family-wise type I error rate. That is, the comparison for each linzagolix group versus placebo for each ranked endpoint will only be declared statistically significant different if the raw p-value multiplied by two is less than or equal to 0.05 for that endpoint and for all preceding endpoints for that dose versus placebo.

Response rates for DYS and NMPP pain at each visit will be analyzed to evaluate the changes in pain over time, with nominal bonferroni corrected p-values used in the comparisons of treatment groups at each visit. These are supportive analyses and will primarily be considered as descriptive. The analyses do not form part of the fixed-sequence strategy being used for the ranked secondary endpoints and will not be fully controlled for an overall type I error rate. However, to maintain consistency with the primary and secondary analyses, Bonferroni corrections will be used due to there being two linzagolix versus placebo comparisons for each endpoint / time point.

13.2 SAMPLE SIZE

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

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

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

The values used for the sample size calculations assume that this is what would be seen on average when under treatment including taking into account any subjects who might withdraw from treatment early and therefore the calculations do not need to be further adjusted for dropouts.

13.3 RANDOMIZATION

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

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

Subjects participating in the extension phase and who are in the placebo treatment group will be randomized at Month 6 visit to either linzagolix 75 mg or linzagolix 200 mg with ABT in a 1:1 ratio. Subjects participating in the extension phase and who are in the linzagolix treatment groups will remain on the same dose that they were taking at the end of Month 6 and will undergo a dummy randomization in order to maintain the blind.

13.4 ANALYSIS SETS

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

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

2. **Full Analysis Set (FAS):** All randomized subjects who received at least one dose of double-blind study drug irrespective of the treatment received. This is the same as the Safety Set, but for the FAS subjects will be analyzed according to randomized treatment.

3. **Per Protocol (PP) Set:** All randomized subjects who completed the six months of treatment excluding those identified as having major protocol deviations that could potentially affect the efficacy assessments up to Month 6. Subjects will be analyzed according to randomized treatment.

4. **Follow-up (FU) Set**: All randomized subjects who completed the six months of treatment and entered the drug free follow-up period. Subjects will be analyzed according to randomized treatment.

5. **Pharmacokinetic (PK) Set:** all subjects who received active study medication, had no major protocol deviations impacting PK and with available PK 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), including, where appropriate, time windows for various safety and efficacy analyses. In general, analyses of efficacy will be conducted using the FAS and PP sets, analyses of safety will be conducted using the Safety Set and analyses of PK will be conducted using the PK Set.

A sub-group analysis will be performed for the secondary endpoint of dyspareunia as described in Section 13.5.3.5. Additional pre-planned sub-group analyses will be described in the SAP.

13.5 DATA ANALYSIS

More details of the proposed statistical analyses will be documented in the SAP, which will be written following finalization of the protocol and prior to the blinded responder threshold analysis of the Month 3 data. The SAP will then be updated prior to unblinding and analysis of the data up to Month 6, in order to incorporate the results of the blinded responder threshold analysis.

For continuous data and for ordered categorical data, if appropriate, the number of non-missing observations, mean, standard deviation, median, first and third quartiles, minimum and maximum will be calculated, including for change from baseline when applicable. The baseline mean will be calculated for all subjects based on the FAS. A baseline mean will also be calculated for each visit using the baseline data for the subset of patients who attend that visit, such that the same subjects contribute to the mean for the visit and the mean for the corresponding baseline values. Summary statistics will be based primarily on non-missing values. For ordered categorical data and nominal data, absolute counts and relative frequencies (in %) will be calculated. As appropriate, time windows for various safety and efficacy analyses will be defined in the SAP.

This study will be conducted at approximately 100 study sites, resulting in only a few subjects per site on average. Subjects from all sites will be pooled and no adjustment for sites will be carried out in the statistical analyses.

The number of subjects randomized, who received at least one dose of study drug, who completed the study and who prematurely discontinued will be calculated overall and for each site by treatment group, as well as for all subjects combined. Premature discontinuation of study drug will be summarized for

each treatment group, as well as for all subjects combined, with frequencies and percentages overall and by reason for discontinuation for all randomized subjects.

Raw and derived data will be listed.

13.5.1 Baseline Assessment

Descriptive statistics will be performed on relevant screening and baseline data (i.e. data collected prior to the treatment administration) and on demographic characteristics for each treatment group and overall. There will be no formal comparison of baseline data, that is, no statistical hypothesis testing.

13.5.2 Primary Efficacy Analysis

The primary efficacy analysis aims to estimate the effect of linzagolix versus placebo on DYS and NMPP over the last 28 days up to and including the Month 3 visit or, for subjects who discontinue randomized treatment prior to the Month 3 visit, over the last 28 days of randomized treatment. Use of analgesic medication for EAP will be included in the responder definitions. A responder for each of the co-primary endpoints needs to demonstrate both a reduction in pain (DYS or NMPP, depending on the endpoint) and a stable or decreased use of analgesics for EAP. Anyone who does not meet both of these criteria will be defined as a non-responder.

The primary efficacy analysis will be conducted using the FAS.

For each of the co-primary endpoints, the criterion for defining a subject as a responder over the last 28 days of randomized treatment up to the Month 3 visit will include a reduction of X or greater from baseline in pain, where X will be determined using appropriate anchors as described below, as well as a stable or decreased use of analgesics for EAP.

Mean pelvic pain scores for DYS and for NMPP will be calculated by averaging over the corresponding 28 calendar days immediately prior to and including the day of the Month 3 visit. DYS will use days with uterine bleeding, defined as those days on which the subject records any uterine bleeding or spotting in the subject eDiary; NMPP will use days with no uterine bleeding. If a subject's mean score for DYS is undefined numerically because her daily eDiary reports indicate that she did not experience uterine bleeding on any days during the 28 calendar day time period, then the mean score for DYS will be set equal to zero (which reflects the absence of any DYS during that reporting time period). For subjects who discontinue treatment prior to Month 3, the last available observations prior to discontinuation will be used, in order to estimate the treatment effect of while under treatment, that is the 28 calendar days immediately prior to and including the last dose date (or fewer if treatment is stopped less than 4 weeks after randomization). The baseline mean overall pelvic pain scores for DYS and NMPP will be calculated by averaging over the two complete menstrual cycles during screening, which may not be exactly 28 days each. For both DYS and NMPP, responses of "None," "Mild," "Moderate," and "Severe" will be assigned a score of 0, 1, 2, and 3, respectively.

For the assessment of a stable or decreased use of analgesics for EAP, the analgesic use for any defined period will be based on the mean of the total pill count for each class of rescue analgesics (endometriosis-associated). The total pill count for each class of rescue analgesic is the sum of the pill count of the corresponding class of rescue analgesic, as reported in the eDiary during the time period of interest. The baseline analgesic use will be calculated as the mean of daily pill count of analgesics over the two complete menstrual cycles during screening. For purposes of determining a stable or decreased use of

analgesics, the averaging will be done over the same calendar days as used for the pelvic pain scores. The evaluation of a stable or decreased use of analgesics will be done per the specification in Appendix O.

The analysis of each co-primary endpoint will be conducted using a logistic regression model, with treatment group as the main effect (three values) and including the baseline pain score as a covariate. Individual linzagolix versus placebo treatment group comparisons will be made using the same logistic regression model.

Responder threshold analysis:

For each of the co-primary endpoints, the criterion for defining a subject as a responder over the last 28 days of randomized treatment up to the Month 3 visit will be a reduction of X or greater from baseline in pain. The threshold for response in the responder analysis (i.e., the value of X) will be chosen to represent a clinically meaningful reduction in pain and may not be the same for each endpoint. The threshold will be determined based on separate analyses of overall mean change using the mPGIS at Month 3 as an anchor. A 2-point improvement in the mPGIS will be used to define responders for the primary analysis. Response categories of "very mild" and "mild" will be collapsed into one category prior to the analyses. Monthly questions specific to DYS, NMPP, overall pelvic pain, dyschezia, dyspareunia and daily function will be used as separate anchors. PGIC as an anchor, Cumulative Distribution Function (CDF) and Probability Density Function (PDF) curves, and Receiver Operating Characteristic (ROC) analyses will be used as supportive analyses. The thresholds have been estimated in an analysis of DYS and NMPP data from the Phase 2b Edelweiss study and will be re-estimated in this study, calculated based on the blinded Month 3 data. As with the under treatment efficacy analysis, for subjects who discontinue treatment prior to Month 3, the 28 calendar days immediately prior to and including the last dose date will be used, along with the closest time matched PGIS and PGIC. The final response thresholds taking into account the previous estimates from phase 2b will be included in the final SAP prior to breaking the blind after Month 6. Based on the results from the Phase 2b Edelweiss study, it is expected that the responder threshold will be in the range of a 0.7 to 1.25 point (40% to 50%) reduction in pain in the 4-point VRS for a 2-point improvement and a 0.25 to 0.75 point (20% to 30%) reduction in pain in the 4-point VRS for a 1-point improvement. The numerical thresholds for DYS are expected to be larger than those for NMPP.

13.5.3 Secondary Efficacy Analysis

All secondary efficacy endpoints will be summarized by descriptive statistics for each treatment group, for each time point, including summaries of change from baseline when applicable. As with the primary analysis, individual linzagolix versus placebo treatment groups comparisons will be made.

13.5.3.1 Change from baseline to Month 6 in DYS (VRS) / NMPP (VRS)

Mean pelvic pain scores for DYS and for NMPP for each subject will be calculated in the same way as for the primary endpoints. The change from baseline to Month 6 (the last 28 days of randomized treatment up to the Month 6 visit, or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to Month 6) in DYS using the VRS, and the change from baseline to Month 6 (the last 28 days of randomized treatment up to the Month 6 visit, or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue

treatment prior to Month 6) in NMPP (VRS), will be analyzed via analysis of co-variance with treatment group as the main effect (three values) and including the baseline pain score as a covariate.

13.5.3.2 Change from baseline to Month 6 in dyschezia (NRS)

Mean dyschezia scores for each subject will be calculated by averaging over the corresponding 28 calendar days immediately prior to and including the day of the Month 6 visit (or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to Month 6). The baseline mean dyschezia score will be calculated by averaging over the two complete menstrual cycles during screening. The change from baseline to Month 6 in dyschezia using the NRS will be analyzed via analysis of co-variance with treatment group as the main effect (three values) and including the baseline pain score as a covariate.

13.5.3.3 Change from baseline to Month 6 in overall pelvic pain (NRS)

The change from baseline to Month 6 (the last 28 days of randomized treatment up to the Month 6 visit, or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to Month 6) in overall pelvic pain using the NRS will be analyzed the same way as for dyschezia.

13.5.3.4 Change from baseline to Month 6 in the interference of pain with the ability to perform daily activities, measured using the pain dimension of the EHP-30

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

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

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

It shall be scored as per the user manual, resulting in a score on a scale from 0 (best possible health status) to 100 (worst possible health status). The change from baseline to Month 6 (the last 28 days of randomized treatment up to the Month 6 visit) in ability to perform daily activities, measured using the pain dimension of the EHP-30 will be analyzed via analysis of co-variance with treatment group as the main effect (three values) and including the baseline pain score as a covariate.

13.5.3.5 Change from baseline to Month 6 in dyspareunia (VRS)

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

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

Mean dyspareunia scores for each subject will be calculated by averaging over the corresponding 28 calendar days immediately prior to and including the day of the Month 6 visit (or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to Month 6). The baseline mean dyspareunia score will be calculated by averaging over the two complete menstrual cycles during screening.

Dyspareunia scores will be summarized using the FAS and for the sub-group of subjects who have a mean dyspareunia score > 1 at baseline. The statistical analysis of dyspareunia will only use the sub-group of subjects in order to estimate the effect of treatment on such subjects. It is anticipated that this will be around 60% to 70% of the randomized subjects. This is a baseline assessment and does not influence the blinded, randomized treatment group. As per section 13.1, the type I error is maintained due to using fixed-sequence testing strategy. The change from baseline to Month 6 in dyspareunia will be analyzed via analysis of co-variance with treatment group as the main effect (three values) and including the baseline pain score as a covariate.

13.5.3.6 No analgesics use / no opiate use for EAP during the preceding 4-week period at 6 months

The analysis of the proportion of subjects reporting no analgesic use for EAP, and the proportion of subjects reporting no opiate use for EAP, during the preceding 4-week period at 6 months will be conducted using a logistic regression model, with treatment group as the main effect (three values).

In addition to analyzing the absence of analgesic use for EAP, the amount used for each 4-week period will be summarized, including the change from baseline. As it is likely that more than one opioid will be used (opioid analgesic may be different depending on countries), the amount of opioid used will be converted to morphine milligram equivalents (MME) in order to better quantify the actual amount of opioids used by subjects.

13.5.4 Additional Efficacy Analysis

Endpoints that are collected daily using the eDiary will be based on the 28 calendar days immediately prior to and including the day of the corresponding visit, or the 28 calendar days immediately prior to and including the last dose date for subjects who discontinue treatment prior to the visit in question (or fewer if treatment is stopped less than 4 weeks after randomization), in order to estimate the treatment effect of while under treatment. Corresponding baseline values will be calculated based on the two complete menstrual cycles during screening, which may not be exactly 28 days each.

The values for other endpoints are defined as the value at the corresponding visit, or the closest completed assessment to the last dose date for subjects who discontinue treatment prior to the visit in question.

An additional analysis of the co-primary endpoints will be conducted that considers all subjects who prematurely discontinue the study treatment before the Month 3 visit as non-responders. These are composite endpoints that estimate the proportion of subjects with clinically meaningful reduction in pain, a stable or decreased use of rescure medication and who complete 3 months of treatment.

An additional analysis of the co-primary endpoints will be also conducted to estimate the effect of treatment policy rather than that of while on treatment. A reference based multiple imputation approach will be used for subjects who discontinue the study prior to Month 3. Further details will be provided in the SAP.

All exploratory efficacy endpoints will be summarized by descriptive statistics for each treatment group, for each time point, including summaries of change from baseline when applicable. Individual linzagolix versus placebo treatment group comparisons will be made.

In general, between group comparisons for continuous endpoints will be analyzed via analysis of (co)-variance. Between-group comparisons for binary endpoints will be analyzed via logistic regression. Between-group comparisons for ordinal categorical data will be analyzed using a Mantel-Haenszel test, or using Koch's method when there is also a baseline covariate. Full details describing the derivation and analyses of each exploratory endpoint will be provided in the SAP.

Sub-group analyses based on demographic and baseline characteristics will be performed for each co-primary endpoint and select secondary endpoints, and will be specified in the SAP.

13.5.5 Safety Analysis

The safety and tolerability profile will be assessed versus baseline conditions and differences between treatment groups and descriptive statistics will be produced for both values and change from baseline, where applicable.

Extent of exposure and compliance to treatment will be evaluated.

Concomitant medications will be summarized using the World Health Organization (WHO) Drug Dictionary with frequencies and percentages for each treatment group. All medications administered between the date of the first dose of study drug and the date of the last dose of study drug, inclusive, (i.e., all medications starting or ongoing during the time interval) will be included. Thus, all medications with an end date prior to the first study drug dose will be excluded from the summary table.

An analysis of the TEAEs will be done. AEs will be summarized using the Medical Dictionary for Regulatory Activities tabulated by (MedDRA) dictionary preferred term and system organ class. TEAEs will be summarized with frequencies and percentages for each treatment group. TEAEs are defined as AEs with a start date on or after the first dose of study drug. Adverse events starting more than 30 days following discontinuation of study drug will not be included in summaries of TEAEs but will be summarized separately as post-treatment AEs. Tabulations by severity and drug-relatedness will also be made.

Laboratory parameters values will be summarized for each visit for each treatment group including within-group changes from baseline. Evaluation of shifts for changes from baseline according to the normal range will be provided.

BMD values and corresponding Z-scores will be summarized at baseline and at Month 6 for each treatment group, using the observed data. The within-group percent changes from baseline for BMD values will also be summarized, including 2-sided 95% confidence intervals. Categorical summaries of percent change from baseline will also be produced. The percent changes from baseline to Month 6 will be compared between each of the linzagolix groups and the placebo group via analysis of co-variance with treatment group as the main effect (three values) and including the baseline as a covariate. Sub-group analyses based on demographic and baseline characteristics will be performed for BMD, and will be specified in the SAP.The Safety Analysis Set shall be used when summarizing safety data.

13.5.6 Pharmacokinetic analysis methodology

PK sample analysis will be performed using a validated assay. The analyses have to be performed unblinded by the analytical laboratory. The analyst may be aware of the subject number, sampling time and dose group.

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

PK analyses will be based on the PK Set.

13.5.7 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. Possible PK-PD relationships may be investigated graphically and through statistical modeling, whilst also exploring possible covariates, and will be reported separately.

13.5.8 Missing Data

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

Subjects who cannot be assessed as a responders or not for the co-primary efficacy endpoints, e.g. due to lack of enough on treatment pain data will be considered as non-responders. In addition, for endpoints assessing the numeric change from baseline, such subjects will be assigned a change from baseline of zero. It is expected that very few subjects will be affected by these rules.

As additional analyses, in order to estimate the effect of treatment policy, a reference based multiple imputation approach will be used for the co-primary endpoints for subjects who discontinue the study early under the assumption that the efficacy of the linzagolix treated subjects gradually transitions to that observed in the placebo subjects.

There may be missing data during the screening period and whilst under treatment, for example, missed days of completing the eDiary. The primary analyses will use observed data only in such cases provided that a minimum number of completed daily edairy entries are available. This effectively assumes that the individual values such as daily eDiary assessments (observed or not) are independent of being missing.

Further details on the handling of missing values and the methods and planned sensitivity analyses to check the robustness of the analysis results under alternative assumptions with regards to missing data will be provided in the SAP.

13.6 STUDY SPECIFIC DATA ANALYSIS

13.6.1 Responder Threshold Analysis

An analysis will be performed using the blinded Month 3 data to determine the criterion for defining a subject as a responder for each co-primary and secondary endpoint, as described in section 13.5.2.

13.6.2 End-of-Treatment Period Analysis

After all subjects have completed the Treatment Period (Month 6), a complete analysis will be performed. This analysis will include all data up to the Month 6 visit. A database lock will be performed prior to unblinding of treatment, and any discrepant data will be clarified before the lock. Since this end-of-treatment-period analysis is the only and final analysis of the primary and ranked secondary endpoints, no additional adjustment of alpha-level is necessary beyond that described in section 13.1. The results for the Treatment Period will be summarized and described in an integrated Clinical Study Report.

13.6.3 Treatment Free Follow-Up Period Analysis

A 6 months follow-up period without treatment is planned after the 6 months Treatment Period, or after the optional extension study.

Analyses of the follow-up period data for subjects not entering the extension study will be reported in an addendum to the integrated Clinical Study Report.

After the Treatment period (Month 6), the Sponsor will be unblinded to the subject's treatment allocation but treatment allocation will remain blinded up to the end of the follow-up period for the Investigator, the subject and the CRAs.

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 (18), 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 written informed consent. 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 / Independent Ethics Committee

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 Institutional Review Board (IRB)/ Independent Ethics Committee (IEC). 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 IRB/IEC 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 drug-free 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 or the EU Clinical Trial Directive 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. 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 IRB/IEC 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 International Conference on Harmonization Good Clinical Practice (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 IRB/IEC per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB/IEC 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 IRB/IEC.

Where required by local regulations, the sponsor (or delegate) will be responsible for informing the IRB/IEC 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, IRB/IEC 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 – Screening and Treatment Periods

Schedule of study assessments – Screening and Treatment Periods								
Timing[1]	**Screening Period (up to 3 months[2])**	**Treatment Period**						
		Day 1	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Informed Consent	x							
Inclusion-Exclusion criteria	x	x						
Demography, height, weight, medical history	x							x[3]
mB&B	x							
Columbia-Suicide Severity Rating Scale	x	x	x	x	x	x	x	x

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

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

[3] Only weight will be recorded.

Schedule of study assessments – Screening and Treatment Periods								
Timing[1]	**Screening Period (up to 3 months[2])**	**Treatment Period**						
		Day 1	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
ECG	x	x[4]	x	x	x	x	x	x
Physical examination	x				x			x
Vital signs	x	x	x	x	x	x	x	x
Urine pregnancy test	x	x	x	x	x	x	x	x
TVUS of uterus	x				x			x
Gynecological examination	x				x			x
Endometrial biopsy	x							x[5]
Pap smear test	x							
Breast examination (mammogram if required)	x							x

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

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

Schedule of study assessments – Screening and Treatment Periods								
Timing[1]	**Screening Period (up to 3 months[2])**	**Treatment Period**						
		Day 1	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
Clinical laboratory & urinary protein dipstick	x	x[6]	x[6]	x	x[6]	x	x	x[6]
Blood sample for PK[7]		x	x	x	x	x	x	x
BMD by DXA	x							x
Adverse events	x	x	x	x	x	x	x	x
Previous/concomitant medication	x	x	x	x	x	x	x	x
Contraceptive dispensing and counselling	x	x	x	x	x	x	x	x
Permitted analgesic prescribing/dispensing	x	x	x	x	x	x	x	x
Vitamin D and calcium dispensing		x	x	x	x	x	x	x
Subject eDiary completion training/check	x	x	x	x	x	x	x	x

[6] Overnight fasting is required.

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

Schedule of study assessments – Screening and Treatment Periods								
Timing[1]	**Screening Period (up to 3 months[2])**	**Treatment Period**						
		Day 1	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**
IMP accountability			x	x	x	x	x	x
Dispense study drug		x	x	x	x	x	x	
Dispense ABT		x			x			
EHP-30, EQ-5D-5L and PROMIS[8]		x	x		x			x
mPGIS, PGIC, HRUQ and HRPQ		x[9]	x	x	x	x	x	x
Specific monthly severity questions[8]		x			x			x
SSIQ and PSIQ[8]		x						x
AMH		x						
E2, LH, P4		x	x	x	x	x	x	x
SHBG		x			x			x
Bone biomarkers		x			x			x

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

[9] PGIC not done at Day 1.

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

Appendix B. Schedule of study assessments – Follow-up Period

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

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

Schedule of study assessments – Follow-up Period						
Timing[1]	**M1 FU**	**M2 FU**	**M3 FU**	**M4 FU**	**M5 FU**	**M6 FU**
Breast manual examination			x			
Endometrium TVUS			x			x
Endometrial biopsy	x[2]	x[2]	x[2]	x[2]	x[2]	x[3]
Clinical laboratory & urinary protein dipstick	x		x[4]			
Subject eDiary completion check	x	x	x	x	x	x
Subject eDiary collection and deactivation						x
EHP-30, HRUQ, HRPQ, EQ-5D-5L and PROMIS			x			x
mPGIS and PPGIC	x	x	x	x	x	x
BMD by DXA						x[5]
E2, LH, P4	x		x			

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

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

[4] Overnight fasting is required.

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

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

Appendix C. Modified Biberoglu & Behrman symptom severity scale*

A. Dysmenorrhea

None 0 = No symptoms

Mild 1 = Some loss of ability to work or carry out normal activities

Moderate 2 = Unable to work or carry out normal daily activities for part of 1 or more days and/or moderately decreased work efficiency

Severe 3 = Unable to work or carry out normal daily activities for 1 or more full days and/or significantly decreased work efficiency

B. Deep Dyspareunia

None 0 = No symptoms

Mild 1 = Tolerated discomfort during intercourse

Moderate 2 = Interference of usual frequency of sexual intercourse due to pain

Severe 3 = Avoids, or wishes to avoid, intercourse because of pain

C. Non Menstrual Pelvic Pain

None 0 = No symptoms

Mild 1 = Occasional pelvic discomfort

Moderate 2 = Noticeable discomfort for most of cycle

Severe 3 = Pain persistent during cycle other than during menstruation

Total Pelvic Pain Score (A + B + C)	
None	0
Mild	1 - 3

D. Pelvic Tenderness *(assessed by the physician)*

None 0 = No findings
Mild 1 = Minimal tenderness on palpation
Moderate 2 = Moderate tenderness on palpation
Severe 3 = Exam limited due to tenderness

Total Physical Sign Score (D + E)	
None	0
Mild	1 - 2

E. Induration *(assessed by the physician)*

None 0 = No findings

Mild 1 = Uterus freely mobile, minimal induration in the cul-de-sac

Moderate 2 = Significant induration in the cul-de-sac, restricted uterine mobility

Severe 3 = Nodular adnexa and cul-de-sac, uterus fixed

Composite Pelvic Pain and Physical Sign Score (A + B + C + D + E)	
None	0

Mild	1 - 2
Moderate	3 - 5
Severe	6 - 10
Very Severe	11 – 15

** based on Biberoglu KO, Behrman SJ. Dosage aspects of danazol therapy in endometriosis: short term and long term effectiveness. Am J Obstet Gynecol. 1981;139:645.*

Appendix D. 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 E. 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 F. 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 G. Health Resource Utilization Questionnaire (HRUQ)

(To be completed by Site Staff)

Subject number: _____

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

Treatment period ☐ Day 1 ☐ Month 1 ☐ Month 2 ☐ Month 3
☐ Month 4 ☐ Month 5 ☐ Month 6

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

Date of Assessment: _____

Instructions to complete:

At each scheduled on-site visit in the Treatment Period (Day 1 through Month 6) and at Month 3 FU and Month 6 FU 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):	☐	

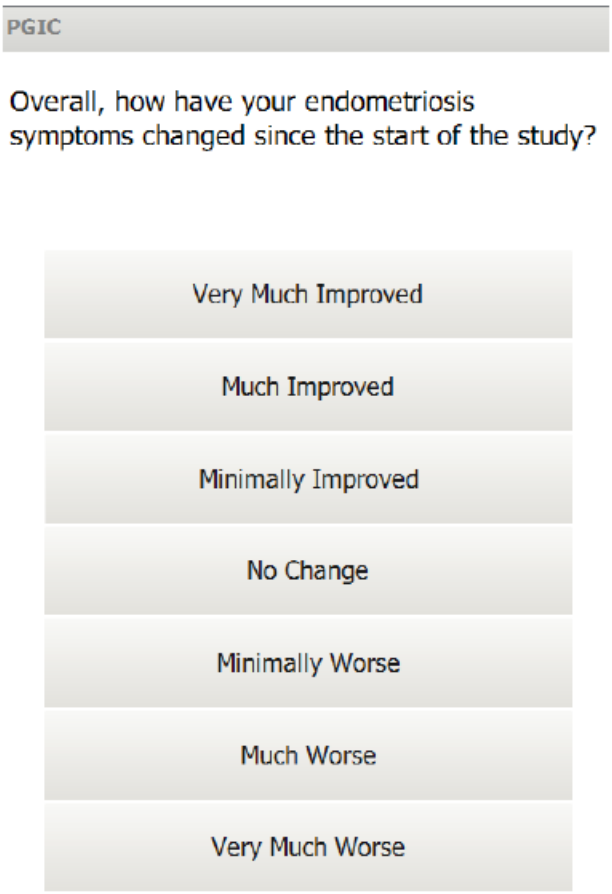
Question 5

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 H. Patient Global Impression of Change (PGIC)



Appendix I. 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 J. Patient Global Impression of Severity (PGIS)

Daily recall (dPGIS)

Overall, how would you describe your endometriosis symptoms **in the last 24 hours**?

- No symptoms
- Very mild
- Mild
- Moderate
- Severe

Monthly recall (mPGIS)

Overall, how would you describe your endometriosis symptoms **over the past 28 days**?

- No symptoms
- Very mild
- Mild
- Moderate
- Severe

Appendix K. 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 L. 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 M. 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 walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems 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

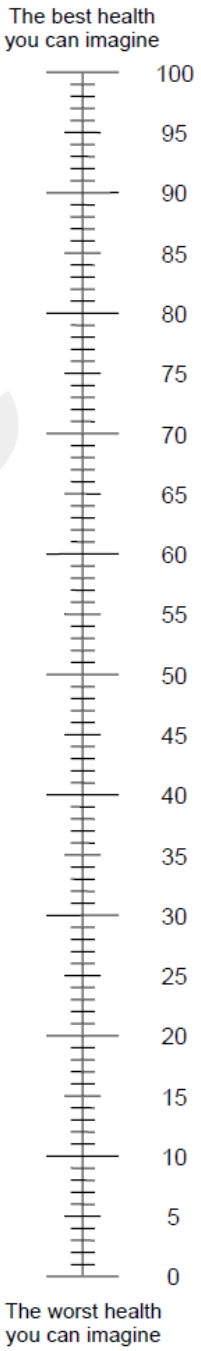
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 N. 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, AMH

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 O. Analgesic change during treatment period

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

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

**Stable =Dose is the same as the screening dose or increases by less than 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 P. 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

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Appendix R. Baseline C-SSRS

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

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.

Lifetime: Time He/She Felt Most Suicidal

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.
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). Ask about time he/she was feeling the most suicidal.

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

Most Severe

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
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
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 ☐

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* _____

 C-SSRS—Baseline (Version 1/14/09) Page 2 of 2

Appendix S. 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* _____

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

Appendix T. 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: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for this, 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