CLINICAL STUDY PROTOCOL

Protocol Number:	**15-OBE2109-001**
EudraCT Number:	**2016-001736-35**
Investigational Medicinal Product:	**OBE2109**
Study Title:	**A randomized, double-blind, placebo-controlled, phase 2b dose-ranging study to assess the efficacy and safety of OBE2109 in subjects with endometriosis associated pain.**
Short Study Title:	**A phase 2b study to assess the efficacy and safety of OBE2109 in subjects with endometriosis.**
Study Name:	**EDELWEISS**
Version number:	Version 1.0
Final Protocol Date:	April 25, 2016
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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., 12, Chemin des Aulx, 1228, Plan-les-Ouates, Geneva, Switzerland

Signature
Véronique Lecomte, Pharm. D
(Clinical Trial Director)

25 April 2016.
Date of signature

Signature
Elke Bestel, MD
(Medical Responsible)

25 April 2016
Date of signature

Contract Research Organization(s):

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26 Apr 2016 11:38 AM +03:00

Signature
Vitaliy Solskyy, MD, PhD
(Lead Project Manager)

Date of signature

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 OBE2109, 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

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LIST OF ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism, Elimination
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
$AUC_{0-\infty}$	Are Under the Curve from time 0 to infinite time
AUC_{0-t}	Are Under the Curve from time 0 to the last measurable time
AUC_{τ}	Are Under the Curve to the end of the dosing period
mB&B	modified Biberoglu & Behrman
BMD	Bone Mineral Density
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats Per minute
°C	Degree Celsius
CK	Creatine Kinase
cm	Centimeter(s)
C_{max}	Maximum (peak) concentration of the drug
COC	Combined Oral Contraceptives
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CV	Coefficient of Variation
CYP	Cytochrome P
DMC	Data Monitoring Committee

DXA	Dual-energy X-ray Absorptiometry
E2	Estradiol
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EHP-30	Endometriosis Health Profile – 30
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
g	Gram(s)
GCP	Good Clinical Practice
γGT	Gamma-Glutamyl Transferase
GGT	Gamma-Glutamyl Transpeptidase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
(h)GnRH	(human) Gonadotropin Releasing Hormone
hERG	human Ether-a-go-go-Related Gene
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
hr	hour
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
INR	International Normalized Ratio
IRB/IEC	Institutional Review Board / Independent Ethics Committee

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
µmol	Micromole(s)
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
mmHg	Blood pressure in millimeter of mercury
MNT	MicroNucleus Test
nmol	Nanomole(s)
NOAEL	No Observed Adverse Effect level
NRS	Numerical Rating Scale
NSAID	NonSteroidal Anti-Inflammatory Drug
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
P4	Progesterone
PAP	Papanikolaou test
PD	PharmacoDynamics

PGIC	Patient Global Impression of Change
P-GP	Permeability-GlycoProtein
PK	PharmacoKinetics
PPB	Plasma Protein Binding
PSF	Pregnancy Surveillance Form
PT	Prothrombin Time
PVC/Al	PolyVinyl Chloride/Aluminum
RBC	Red Blood Cell
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Elimination half-life
TEAE(s)	Treatment Emergent Adverse Event(s)
TVUS	TransVaginal UltraSound
UDS	Unscheduled DNA Synthesis
ULN	Upper Limit of Normal
US/USA	United States/United States of America
VdSS	Volume of distribution at Steady State
VRS	Verbal Rating Scale
WBC	White Blood Cell

SYNOPSIS

Study Title: A randomized, double-blind, placebo-controlled, phase 2b dose-ranging study to assess the efficacy and safety of OBE2109 in subjects with endometriosis associated pain.

Code/Name ObsEva Investigational Drug: OBE2109	**Phase of Development:** 2

Objectives:

Efficacy objectives

- **Primary**

  To assess the efficacy of a range of oral doses of OBE2109 versus placebo, in reducing pelvic pain in subjects with moderate to severe endometriosis pain.

- **Secondary**

  To assess the efficacy of a range of oral doses of OBE2109 versus placebo in:

  - Reducing pelvic pain on days with uterine bleeding and pelvic pain on days with no uterine bleeding
  - Reducing pain associated with sexual intercourse (dyspareunia)
  - Reducing pain associated with defecation (dyschezia)
  - Reducing difficulty in performing daily activities
  - Reducing subject reported pain symptoms of endometriosis (dysmenorrhea, pelvic pain and dyspareunia) and physician assessed objective findings of endometriosis (pelvic tenderness and pelvic induration) according to the modified Biberoglu & Behrman (mB&B) scale
  - Reducing the use of analgesic medication to treat pelvic pain
  - Reducing incidence and intensity of uterine bleeding
  - Improving quality of life and subject perception of change and severity

Safety objectives

- To assess the safety and tolerability of OBE2109 in subjects with endometriosis.

Pharmacokinetic (PK)-pharmacodynamic (PD) objectives

To assess OBE2109 PK and establish the possible relationship between OBE2109 exposure and pain, estradiol (E2) level, luteinizing hormone (LH) level and bone mineral density (BMD).

Endpoints:

Efficacy endpoints

- **Primary**
  - Thirty percent or greater reduction from baseline to week 12 in the mean overall pelvic pain score defined as the mean of daily pain scores reported during the preceding 4-week period, assessed on a 0–3 Verbal Rating Scale (VRS) for pelvic pain.
- **Secondary**
  - Thirty percent or greater reduction from baseline to weeks 4, 8, 16, 20, 24, 28, 32 and 36 in the mean overall pelvic pain score defined as the mean of daily pain scores reported during the preceding 4-week period, assessed on a 0–3 VRS for pelvic pain.
  - Thirty percent or greater reduction from baseline to weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36 in the mean overall pelvic pain score defined as the mean of daily pain scores reported during the preceding 4-week period, assessed on a 0–10 Numerical Rating Scale (NRS).
  - Thirty percent or greater reduction from baseline to weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36 in the mean pelvic pain score for days with uterine bleeding/spotting and for days with no uterine bleeding during the preceding 4-week period, assessed on a 0–10 NRS and on a 0–3 VRS for pelvic pain.
  - The mean pelvic pain score for days with uterine bleeding/spotting, for days with no uterine bleeding and all days during the preceding 4-week period, assessed on a 0-10 NRS and on a 0–3 VRS for pelvic pain at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
  - The mean highest pelvic pain score defined as the mean of the 5 highest daily pain scores reported during the preceding 4-week period, assessed on a 0–10 NRS at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
  - The incidence of amenorrhea defined as no uterine bleeding or spotting only during the preceding 4-week period at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
  - The number of days with uterine bleeding (spotting excluded) during the preceding 4-week period at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.

- The mean of daily dyspareunia scores reported during the preceding 4-week period, assessed on a 0-10 NRS and a 0–3 VRS for dyspareunia at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The monthly dyschezia pain score defined as the mean of weekly dyschezia pain scores reported during the preceding 4-week period, assessed on a 0–10 NRS at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The use of analgesics for pelvic pain during the preceding 4-week period at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The number of days of analgesic use for pelvic pain during the preceding 4-week period at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The number of days with pelvic pain during the preceding 4-week period, assessed on a 0–3 VRS for pelvic pain at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The number of days with moderate to severe pelvic pain during the preceding 4-week period, assessed on a 0–3 VRS for pelvic pain at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The mean of scores for difficulty in performing daily activity reported during the preceding 4-week period, assessed on a 0-10 NRS scale at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The severity of subject assessed symptoms (dysmenorrhea, non-menstrual pelvic pain and dyspareunia) and physician assessed objective findings (pelvic tenderness and pelvic induration) according to the mB&B scale at screening and weeks 12, 24 and 36.
- The Endometriosis Health Profile-30 (EHP-30) score at weeks 12, 24 and 36.
- The Patient Global Impression of Change (PGIC) score at weeks 12, 24 and 36.
- The patient's impression of severity over the preceding 4-week period at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.

Safety endpoints

- Change from baseline to weeks 12, 24 and 48 in BMD assessed by dual-energy X-ray absorptiometry (DXA) for femoral neck, hip and spine.
- Treatment emergent adverse events (TEAEs) frequency and severity.
- Changes in clinical laboratory assessments (haematology, coagulation parameters, biochemistry, hormones, lipids and urinalysis) from baseline to weeks 4, 8, 12, 16, 20, 24, 28 and 36.
- Any pathological changes from baseline in the endometrium as assessed by histology from endometrial biopsies performed at weeks 12 and 24 (and week 36 only if no

endometrial biopsy was obtained at week 24 or diagnosis at week 24 was different from "benign endometrium").

- Change from baseline in any other safety parameter including weight, vital signs, gynecological assessment, breast assessment and endometrial thickness.

Pharmacokinetic-pharmacodynamic endpoints

- Plasma levels of OBE2109 and its metabolite KP017 measured pre-dose and 1.5–2 h post-dose on Day 1, pre-dose at weeks 4 and 16 visits, and post-dose at weeks 8, 12, 20 and 24 visits.

Study Design: The study is a prospective, dose-finding, randomized, parallel group, double-blind, placebo-controlled phase 2b study investigating the efficacy and safety of OBE2109 in the treatment of women with endometriosis-associated pain.

The study duration (from the Screening visit to the End-of-Study visit) will be up to 64 weeks per subject.

The study starts with an 11±5 week screening period evaluating the endometriosis pain over at least two full, spontaneous menstrual cycles. During this period, the subject will receive no study drug.

Eligibility will be confirmed on Day 1 based on data collected during the screening period. On Day 1, subject will be randomized to one of 6 treatment groups: placebo, fixed-dose groups at 50, 75, 100 and 200 mg daily and a titrated-dose group. After randomization, a 24-week active treatment period, composed of 2 periods of 12 weeks each (Part A and Part B) and a subsequent 24-week treatment-free period will follow.

In the placebo group, the placebo will be provided for 12 weeks (Part A) after which all placebo subjects will be crossed-over on to active treatment (100 mg daily) for a further 12 weeks (Part B).

In the titrated-dose arm, all subjects will start on 75 mg daily for 12 weeks (Part A) after which the dose will be titrated up or down to 100 or 50 mg, or remain at the same dose for the following 12 weeks (Part B). Up- or down-titration will depend on the mean of serum E2 assay results collected at weeks 4 and 8. Serum E2 levels will not be communicated to the investigational and the sponsor study teams to maintain the blind. Possible up- or down- titration will occur according to the following algorithm: subjects with a mean serum E2 level of <20pg/mL will be down-titrated to 50 mg daily whereas subjects with a mean serum E2 level of >50 pg/mL will be up-titrated to 100 mg daily. Subjects with a mean serum E2 level from 20 to 50 pg/mL inclusive will remain on 75 mg daily. Mean serum E2 level will be defined as the mean of the serum E2 assay results collected at week 4 and week 8.

After all subjects have completed the first 12-week period, an interim analysis of Part A data to assess efficacy and safety parameters will be performed. After all subjects have completed the Part B treatment period (week 24), and all data have been entered into the clinical database, cleaned and locked, an analysis of Part B data will be performed. The results for the study parts A and B will be summarized and described in an integrated Clinical Study Report.

A 24-week follow-up period without treatment is planned after Part B, or - for subjects willing to continue treatment with OBE2109 - an extension study will be proposed. The extension study will consist of a further 28 weeks of treatment and a 24-week follow-up period without treatment.

An analysis will be performed after week 48 on subjects entering the 24-week follow-up period after Part B and reported in an addendum to the integrated Clinical Study Report.

Treatment will remain blinded up to the end of the study for the Investigator and the subject.

The extension study will be described in a separate Protocol, and analyzed and reported in a separate Clinical Study Report.

Study Population: Three hundred and thirty (330) women aged 18 to 45 years inclusive with surgically, and – if available – histologically confirmed pelvic endometriosis and moderate to severe endometriosis-associated pain, will be randomized in approximately 60 sites in the USA and in Europe, to one of the six following treatment groups in a 1:1:1:1:1:1 ratio:

- OBE2109 50mg
- OBE2109 75mg
- OBE2109 100mg
- OBE2109 200mg
- OBE2109 75mg titration group
- OBE2109 placebo/100 mg

Main 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 initiation of any study related procedures.
2. The subject must be a female volunteer aged 18 to 45 years inclusive at screening.
3. The subject must have had surgically, and - if available - histologically confirmed pelvic endometriosis (laparoscopy, laparotomy, vaginal fornix or other biopsy) up to 7 years before screening.
4. The subject has moderate to severe endometriosis-associated pain during the screening period defined as:
    a. At the screening visit, a score of at least 2 for dysmenorrhea AND at least 2 for non-menstrual pelvic pain for the previous month assessed with the 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.

5. The subject is compliant with e-diary and has completed it on at least 80% of days during the two screening menstrual cycles.
6. The subject has regular menstrual cycles and the total length of the two screening menstrual cycles should be between 42 to 76 days.
7. The subject has a BMI ≥ 18 kg/m^2 and ≤ 39 kg/m^2 at the screening visit.
8. If of childbearing potential, the subject agrees to use one of the following birth control methods during the entire treatment period of the study:
    a. Sexual abstinence,
    b. Partner with a vasectomy with confirmed azoospermia,
    c. Double non-hormonal barrier contraception such as condom or diaphragm each combined with spermicide.
9. If of non-childbearing potential, the subject must have had tubal ligation sterilization at least two months before the screening visit.
10. 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 had an interventional surgery for endometriosis performed within a period of 60 days before screening.
4. The subject had a hysterectomy or bilateral ovariectomy.
5. The subject had a tubal sterilization which was performed with ESSURE™.
6. The subject has an in situ copper intra-uterine device (IUD) or an IUD with progestogen.
7. The subject had endometrial ablation resulting in amenorrhea.

8. The subject has at least one ovarian endometrioma with a diameter of 7 cm or greater.
9. 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 months/6 months
c. Danazol	3 months
d. Oral contraceptives and other sex hormones	1 month
e. Depot contraceptives	6 months
f. Selective Progesterone Receptor Modulators (SPRMs), Selective Estrogen Receptor Modulators (SERMs) and aromatase inhibitors	3 months
g. Long acting analgesics (i.e. requiring less than once daily dosing)	1 day
h. Systemic glucocorticoid treatments for acute diseases (not depot)	1 month

10. The subject has a history of or current systemic glucocorticoid therapy for treatment of chronic diseases (e.g. Systemic Lupus Erythematosus (SLE), rheumatic arthritis).
11. The subject did not respond to prior treatment with GnRH agonists or GnRH antagonists for endometriosis.
12. The subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥ 2 times the upper limit of normal OR gamma-glutamyl transpeptidase (GGT) level ≥ 3 times the upper limit of normal at screening.
13. The subject has a known positive HIV or viral Hepatitis serology.
14. The subject has abnormal uterine bleeding of undiagnosed cause.
15. The subject had/has clinically significant findings from a Papanikolaou (PAP) smear 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 conisation).
16. 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, or that would interfere with the assessment of endometriosis related pain.
17. The subject has any other clinically significant gynecological condition identified on screening transvaginal ultrasound (TVUS) or endometrial biopsy which might interfere with the study efficacy and safety objectives. However, uterine fibroids (as long as uterus size ≤ 12 weeks, i.e. equivalent gestational weeks) and adenomyosis are allowed.
18. The subject has a history of, or known osteoporosis or other metabolic bone disease.

19. 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.
20. 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.
21. The subject has current problem with alcohol or drug abuse (including painkiller abuse).
22. The subject has been administered with any experimental drug in the 12 weeks before dosing.

Investigational Medicinal Product(s) (IMP): OBE2109 50mg, 75mg and 100mg tablets or placebo tablets for oral administration.

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. The other parameters will be individually listed. All measured as well as derived efficacy and safety endpoints will be summarized by descriptive statistics for each treatment group and overall, and for each time point if applicable.

Data for the 75mg group and 75mg titrated group will be combined for the analyses of the Part A data. All statistical hypothesis tests and confidence intervals will be two sided, using a type I error rate of 0,05. No adjustment for multiple comparisons will be used for this study.

- Efficacy analysis methodology

Mean overall pelvic pain scores will be calculated separately for the VRS and NRS by adding up the daily pain scores during each successive 4-week periods and dividing by the actual number of days with non missing data (i.e. nominally 28 days if no missing data).

Mean pelvic pain scores on uterine bleeding days and non-uterine bleeding days will be calculated by adding up the pain scores on the relevant days during each successive 4-week periods (uterine bleeding days will be defined as those days on which the subject records any uterine bleeding or spotting in the subject eDiary) and dividing by the number of days with non missing data. Both the total number of non-missing days in the 4-week period (i.e. nominally 28 days if no missing data) and the number of non-missing uterine bleeding days/non-uterine bleeding days will be considered.

Comparisons between each individual active arm versus the placebo arm will be made for the analysis of Part A of the study (except the 75mg group and 75mg titrated group which will be combined). In addition, an overall test for dose response will be conducted using all treatment arms. The coefficients for this contrast will be defined assuming a linear response on a log (dose+1) scale. Analyses of Part B study data will be fully described in the statistical analysis plan.

The analysis of the primary endpoint will be conducted via a generalized linear model for binary data with repeated (correlated) measures, fitted using generalized estimating equations (a marginal model),

with the model including terms for treatment group, 4-week period, baseline and the interactions 4-week period*treatment, 4-week period*baseline.

In general, between-group comparisons for continuous endpoints will be analyzed via (repeated measures) analysis of (co)-variance (repeated measures mixed models) or Wilcoxon Rank Sum tests, subject to the underlying distribution of the data. Between-group comparisons for binary endpoints will be analyzed via generalized linear models (with repeated measures) and chi-squared tests. Between-group comparisons for count data (e.g. number of days) will also be analyzed via generalized linear models (with repeated measures).

It is not certain whether the continuous endpoints will be normally or log-normally distributed, and/or whether an absolute or proportional change in endpoints will be observed. If deemed necessary, the data will be log transformed prior to the analysis. The subsequent results (mean differences and corresponding confidence intervals) will be back transformed and hence reported in terms of ratios of geometric means.

- Safety analysis methodology

Extent of exposure and compliance will be evaluated.

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

- Pharmacokinetic analysis methodology

For descriptive statistics of plasma concentrations mean (arithmetic and geometric), standard deviation, median, first and third 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.

- Pharmacodynamic analysis methodology

Possible PK-PD relationships will be investigated graphically and through statistical modeling.

- Missing data handling

Summary statistics will be based primarily on non-missing values. For hypothesis tests, estimates and confidence intervals, missing values for continuous efficacy endpoints analyzed via likelihood methods (e.g. repeated measures mixed models) will not be directly imputed as they are handled within the analysis itself, under the assumption that the model specification is correct and that the data is missing at random. In addition, missing values for endpoints analyzed via generalized estimating equations will not be directly imputed as they are handled under the assumption that the model specification is correct and the data is missing completely at random. Sensitivity analyses may be conducted to check the robustness of the analysis results under alternative assumptions with regards to missing data.

Further details on the handling of missing values, including the rules applied to incomplete questionnaires (including incomplete diary entries) and any planned sensitivity analyses will be defined in the Statistical Analysis Plan.

o Interim analysis

After all subjects have completed the first 12-week period (Part A), an interim analysis of Part A data to assess the efficacy and safety parameters will be performed. The OBE2109 75mg group and OBE2109 75mg titrated group will be pooled for the analysis of the Part A data.

1. BACKGROUND INFORMATION

1.1. INTRODUCTION TO OBE2109

OBE2109 is a new orally active, non-peptide GnRH antagonist. It has been shown to suppress the LH and E2 and to significantly reduce endometriosis-associated pain in Japanese women at doses between 50 and 200 mg daily with a good safety and tolerability profile. It is being developed for the treatment of endometriosis-associated pelvic pain.

1.2. ENDOMETRIOSIS

Endometriosis is one of the most common gynecological diseases (1). It is defined as the presence of endometrial-like tissue outside the uterus. 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 infertility (2) and a variety of pain symptoms including dysmenorrhea, dyspareunia, chronic pelvic pain, dysuria and dyschezia (3, 4). Often the pain associated with endometriosis is cyclical in nature and reflects the response of the ectopic endometrial-like tissue to cycling reproductive hormones, particularly estrogens.

Endometriosis represents a significant economic burden (5). Indeed, the treatment of endometriosis-associated pain and infertility leads to significant direct costs. In addition, the endometriosis-associated signs and symptoms have a significant impact on health related quality of life and often lead to work absenteeism and productivity loss (6), especially as the diagnosis of endometriosis is often delayed (7, 8, 9).

Guidelines for the management of endometriosis have been published (10,11) and several medical and surgical therapies are available. However, an effective and well-tolerated treatment of endometriosis remains a largely unmet medical need.

1.3. CONVENTIONAL TREATMENT OF ENDOMETRIOSIS

The principal objective in treating endometriosis is symptom-relief management. Treatment options for women with endometriosis-associated pain are diverse and consist of analgesic therapies, hormonal therapies, conservative or minimal invasive surgery, or a combination of these (4). 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 (12, 13).

Combined oral contraceptives (COCs), although not approved for the treatment of endometriosis-associated pain, are often used as initial therapy. Their administration results in anovulation, reduction of menstrual blood flow, decidualization of endometriotic lesions, down regulation of cell proliferation and enhanced apoptosis in the endometrium (14). However, over time many women on COCs no longer have adequate pain relief and require second-line therapy (15).

Progestin monotherapy can be efficacious for the reduction in endometriosis-associated pain 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 (16). However, progestin monotherapy is often associated with breakthrough bleeding, alterations in mood, weight gain, and breast tenderness (17).

Other therapies with proven efficacy for the treatment of endometriosis-associated pain 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 a marked reduction of serum estrogen levels; thus their use is associated with significant hypoestrogenic side-effects. Short-term effects include menopausal symptoms such as hot flashes, vaginal dryness, loss of libido and emotional lability, and their long-term use is limited by substantial bone mineral density (BMD) reduction (18).

GnRH antagonists are a promising new potential treatment option that is hypothesized to allow dose-dependent control of E2 levels reducing endometriosis implants and endometriosis-associated pain without hypo-estrogenic side-effect including hot flashes and BMD loss (18).

1.4. SUMMARY OF NON-CLINICAL STUDIES

1.4.1. Non-Clinical Pharmacology

OBE2109 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 OBE2109, to hGnRH receptor was shown to be 5 fold lower (Ki=127 nM).

Specific effects on the endometrium were observed during in vivo studies, with OBE2109 acting through suppression of estrogen dependent endometrial proliferation in a rat autograft endometriosis model. It is noteworthy that clinical signs such as amenorrhea were also observed in toxicology work in the cynomolgus monkey.

Safety pharmacology studies 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.

1.4.2. Non-Clinical Pharmacokinetics and Toxicology

1.4.2.1. *Pharmacokinetics*

OBE2109 was rapidly and completely absorbed after oral dosing with exposures increasing in a generally dose-proportional manner. The volume of distribution and plasma clearance were low. OBE2109 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 OBE2109 was albumin. It does not exhibit blood partitioning.

Tissue distribution of radiolabeled OBE2109 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 OBE2109 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 OBE2109 in mice, rats and monkeys was comparable to the in vitro data.

Excretion of radioactivity from radiolabeled OBE2109 was predominantly via feces in both rats and monkeys.

Pharmacokinetic interaction studies in vitro indicated that drugs possibly co-administered in clinical settings (NSAIDs) did not affect the plasma protein binding of OBE2109. An in vitro CYP induction study indicated that OBE2109 could induce CYP3A4/5 expression at high concentrations unlikely to be reached in the current study. OBE2109 may have direct and time-dependent inhibitory action on CYP2C8 activity and could inhibit the OAT3 uptake transporter at clinically relevant concentrations.

1.4.2.2. *Toxicology*

Overall, the toxicological profile of OBE2109 from repeated-dose toxicity studies were 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 OBE2109 were shown to be the 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 OBE2109 preventing conception or leading to total litter loss. The effects of OBE2109 on conception were reversible, and rabbit embryo-foetal studies showed expected pharmacological activity and no adverse reprotoxic/teratogenic effect.

OBE2109 was not genotoxic or phototoxic.

Taken together, the data in this nonclinical package have shown OBE2109 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 confirms that OBE2109 supports clinical dosing regimens up to 200 mg per day.

1.5. SUMMARY OF CLINICAL STUDIES

The efficacy, safety and PK of OBE2109 were investigated by the originator company (Kissei Pharmaceutical Co., LTD. from Japan) in one Phase 1 study (Study KLH1101) in Japanese and Caucasian volunteers in single and multiple doses up to 400 mg, and in three Phase 2 studies (Studies KLH1201, KLH1202 and KLH1203) in Japanese endometriosis patients at doses up to 200 mg daily for 12 weeks.

To date, more than 150 subjects have been exposed to OBE2109 for a duration of up to 3 months.

1.5.1. PK/PD

OBE2109 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 OBE2109 from 12.5 to 400 mg and repeated doses of 100 to 400 mg once daily for 7 days under fed and fasted conditions. OBE2109

was safe and well-tolerated, showed linear pharmacokinetics, 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 no apparent effect of food on the extent of absorption and there was a dose-dependent suppression of LH, FSH and E2.

1.5.2. Efficacy

The clinical evidence for the efficacy of OBE2109 is derived from the results of three Phase 2 studies.

In a Phase 2 clinical study in patients with endometriosis (Study KLH1201), 50 or 200 mg OBE2109 was orally administered once daily for 8 weeks. OBE2109 improved endometriosis symptoms and continuously suppressed E2 in a dose-dependent manner.

In a Phase 2 clinical study in patients with endometriosis (Study KLH1202), 50, 100, or 200 mg OBE2109 or placebo was orally administered once daily after breakfast for 12 weeks. OBE2109 significantly reduced endometriosis pain symptoms compared with placebo.

In a Phase 2 clinical study in patients with endometriosis (Study KLH1203), 75 or 150 mg OBE2109 was orally administered once daily after breakfast for 8 weeks. OBE2109 improved endometriosis symptoms and continuously suppressed E2 in a dose-dependent manner.

1.5.3. Safety

Overall, 42 subjects have been exposed to single doses and 163 subjects to repeated doses of OBE2109.

Repeated dosing at up to 400 mg OBE2109 was safe and well-tolerated by premenopausal Caucasian and Japanese healthy volunteers. In endometriosis patients, doses up to 200 mg daily for up to 12 weeks of treatment were well tolerated.

Most frequent side effects were disturbances of the menstrual cycle (Metrorrhagia) and hypoestrogenic AEs (Hot flushes).

In some subjects, an increase in transaminase values was observed under treatment. However this increase was generally reversible under treatment, exceeded 3×ULN in only one single case and was never associated with any increase in bilirubin.

The vast majority of AEs were reported as being of “mild” severity, only few events were reported as being of “moderate” severity and only one AE (unrelated to study drug) was reported as of “severe” intensity.

1.6. RATIONALE FOR THE CURRENT STUDY

OBE2109 has been shown to suppress in a dose dependent manner LH and E2 and to significantly reduce endometriosis-associated pain in Japanese women at doses between 50 and 200 mg daily, with a good safety and tolerability profile. Furthermore, after administration of 50 or 75 mg per day, median E2 levels were in the range of 20–50 pg/mL, which is the range expected to provide relief from endometriosis symptoms while maintaining BMD (19, 20), suggesting 50 or 75 mg could be an optimal dose in Japanese patients. It is anticipated that the US/European population will have a higher average weight and therefore a dose range of 50–200 mg is planned for the current study.

In addition, a dose titration based on serum E2 levels will be explored in the current study. The rationale is to try to maximise the proportion of subjects with mean E2 levels in the range 20–50 pg/ml to see if this provides any clinical advantages over a fixed dose regimen.

The purpose of the current study is therefore to evaluate the safety and efficacy of OBE2109 in non-Japanese (primarily USA and European) women with surgically confirmed endometriosis and associated pelvic pain. It is a Phase 2b double-blind, placebo controlled dose ranging study with the aim of establishing doses, regimens and endpoints to be used in pivotal confirmatory Phase 3 studies.

1.7. SUMMARY OF OVERALL RISKS AND BENEFITS

OBE2109 is a new oral GnRH antagonist which has been shown to significantly reduce endometriosis related pain in Japanese patients via dose dependent suppression of LH, FSH and E2. It has a half-life consistent with once daily dosing. Efficacy was demonstrated at daily doses of 50–200 mg for 3 months and efficacy persisted 1 month after the end of treatment.

OBE2109 was well-tolerated at these doses. The most commonly reported AEs in the Phase 2 studies were metrorrhagia and hot flushes which are related to the biological activity of OBE2109.

There were no clinically relevant findings in laboratory measurements, vital signs or ECG recordings. The administration of OBE2109 results in infrequent, transient, moderate and not dose-related increases in transaminase levels which were not associated with any change in bilirubin levels.

In conclusion, OBE2109 has a favorable benefit/risk ratio and represents a potentially useful therapy for treating endometriosis related pain.

2. OBJECTIVES

2.1. EFFICACY OBJECTIVES

2.1.1. Primary

- To assess the efficacy of a range of oral doses of OBE2109 versus placebo, in reducing pelvic pain in subjects with moderate to severe endometriosis pain.

2.1.2. Secondary

To assess the efficacy of a range of oral doses of OBE2109 versus placebo in:

- Reducing pelvic pain on days with uterine bleeding and pelvic pain on days with no uterine bleeding
- Reducing pain associated with sexual intercourse (dyspareunia)
- Reducing pain associated with defecation (dyschezia)
- Reducing difficulty in performing daily activites
- Reducing subject reported pain symptoms of endometriosis (dysmenorrhea, pelvic pain and dyspareunia) and physician assessed objective findings of endometriosis (pelvic

tenderness and pelvic induration) according to the modified Biberoglu & Behrman (mB&B) scale (22, APPENDIX B)

- Reducing the use of analgesic medication to treat pelvic pain
- Reducing incidence and intensity of uterine bleeding
- Improving quality of life and subject perception of change and severity

2.2. SAFETY OBJECTIVES

- To assess the safety and tolerability of OBE2109 in subjects with endometriosis.

2.3. PHARMACOKINETIC-PHARMACODYNAMIC OBJECTIVES

- To assess OBE2109 PK and establish the possible relationship between OBE2109 exposure and pain, E2 level, LH level and bone mineral density (BMD).

3. ENDPOINTS

3.1. EFFICACY ENDPOINTS

3.1.1. Primary

- Thirty percent or greater reduction from baseline to week 12 in the mean overall pelvic pain score defined as the mean of daily pain scores reported during the preceding 4-week period assessed on a 0–3 Verbal Rating Scale (VRS) for pelvic pain.

3.1.2. Secondary

- Thirty percent or greater reduction from baseline to weeks 4, 8, 16, 20, 24, 28, 32 and 36 in the mean overall pelvic pain score defined as the mean of daily pain scores reported during the preceding 4-week period, assessed on a 0–3 VRS for pelvic pain.
- Thirty percent or greater reduction from baseline to weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36 in the mean overall pelvic pain score defined as the mean of daily pain scores reported during the preceding 4-week period, assessed on a 0–10 Numerical Rating Scale (NRS).
- Thirty percent or greater reduction from baseline to weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36 in the mean pelvic pain score for days with uterine bleeding/spotting and for days with no uterine bleeding during the preceding 4-week period, assessed on a 0–10 NRS and on a 0–3 VRS for pelvic pain.
- The mean pelvic pain score for days with uterine bleeding/spotting, for days with no uterine bleeding and all days during the preceding 4-week period, assessed on a 0–10 NRS and on a 0–3 VRS for pelvic pain at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.

- The mean highest pelvic pain score defined as the mean of the 5 highest daily pain scores reported during the preceding 4-week period, assessed on a 0–10 NRS at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The incidence of amenorrhea defined as no uterine bleeding or spotting only during the preceding 4-week period at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The number of days with uterine bleeding (spotting excluded) during the preceding 4-week period at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The mean of daily dyspareunia scores reported during the preceding 4-week period, assessed on a 0–10 NRS and a 0–3 VRS for dyspareunia at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The monthly dyschezia pain score defined as the mean of weekly dyschezia pain scores reported during the preceding 4-week period, assessed on a 0–10 NRS at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The use of analgesics for pelvic pain during the preceding 4-week period at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The number of days of analgesic use for pelvic pain during the preceding 4-week period at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The number of days with pelvic pain during the preceding 4-week period, assessed on a 0–3 VRS for pelvic pain at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The number of days with moderate to severe pelvic pain during the preceding 4-week period, assessed on a 0–3 VRS for pelvic pain at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.
- The mean of scores for difficulty in performing daily activity reported during the preceding 4-week period, assessed on a 0–10 NRS scale at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36
- The severity of subject assessed symptoms (dysmenorrhea, non-menstrual pelvic pain and dyspareunia) and physician assessed objective findings (pelvic tenderness and pelvic induration) according to the mB&B scale at screening and weeks 12, 24 and 36.
- The Endometriosis Health Profile-30 (EHP-30) score (23, APPENDIX C) at weeks 12, 24 and 36.
- The Patient Global Impression of Change (PGIC) score (24, 25, APPENDIX D) at weeks 12, 24 and 36.
- The patient's impression of severity over the preceding 4-week period at weeks 4, 8, 12, 16, 20, 24, 28, 32 and 36.

3.2. SAFETY ENDPOINTS

- Change from baseline to weeks 12, 24 and 48 in BMD assessed by dual-energy X-ray absorptiometry (DXA) for femoral neck, hip and spine.
- Treatment emergent adverse events (TEAEs) frequency and severity.

- Changes in clinical laboratory assessments (haematology, coagulation parameters, biochemistry, hormones, lipids and urinalysis) from baseline to weeks 4, 8, 12, 16, 20, 24, 28 and 36.
- Any pathological changes from baseline in the endometrium as assessed by histology from endometrial biopsies performed at weeks 12 and 24 (and week 36 only if no endometrial biopsy was obtained at week 24 or diagnosis at week 24 was different from "benign endometrium").

  Change from baseline in any other safety parameter including weight, vital signs, gynecological assessment, breast assessment and endometrial thickness.

3.3. PHARMACOKINETIC-PHARMACODYNAMIC ENDPOINTS

- Plasma levels of OBE2109 and its metabolite KP017 measured pre-dose and 1.5–2hrs post-dose on Day 1, pre-dose at weeks 4 and 16 visits, and post-dose at weeks 8, 12, 20 and 24 visits.

4. STUDY DESIGN

This is a prospective, dose-finding, randomized, parallel group, double-blind, placebo-controlled phase 2b study investigating the efficacy and safety of OBE2109 in the treatment of women with endometriosis-associated pain.

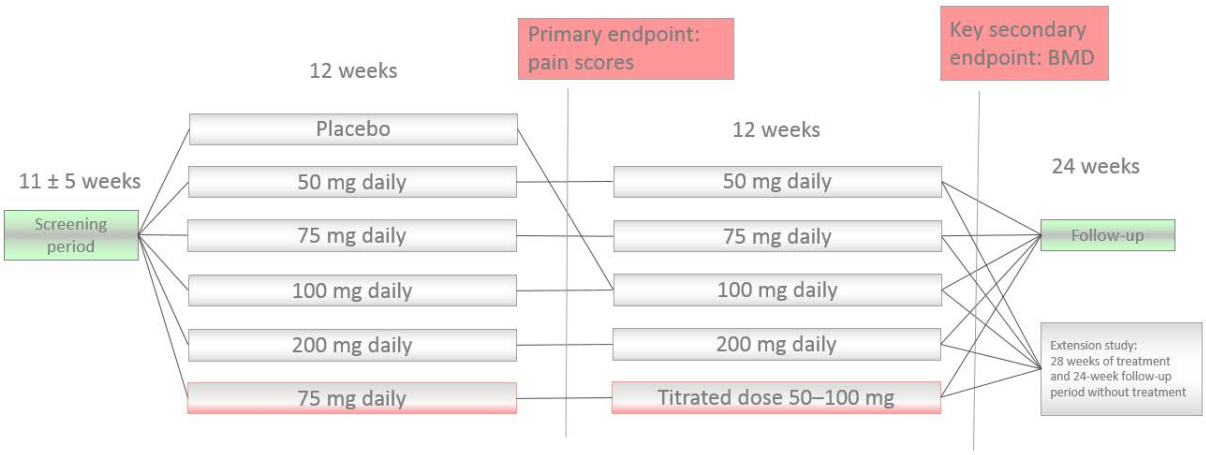
The study duration (from the Screening visit to the End-of-Study visit) will be up to 64 weeks per subject.

The study starts with an 11±5 week screening period evaluating the endometriosis pain over at least two full, spontaneous menstrual cycles. During this period, the subject will receive no study drug.

Eligibility will be confirmed on Day 1 based on data collected during the screening period. On Day 1, subject will be randomized to one of 6 treatment groups: placebo, fixed-dose groups at 50, 75, 100 and 200 mg daily and a titrated-dose group. After randomization, a 24-week active treatment period, composed of 2 periods of 12 weeks each (Part A and Part B), and a subsequent 24-week treatment-free period will follow.

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

Figure 1: Study design



In the placebo group, the placebo will be provided for 12 weeks (Part A) after which all placebo subjects will be crossed-over on to active treatment (100 mg daily) for a further 12 weeks (Part B).

In the titrated-dose arm, all subjects will start on 75 mg daily for 12 weeks (Part A) after which the dose will be titrated up or down to 100 or 50 mg, or remain at the same dose for the following 12 weeks (Part B). Up- or down-titration will depend on the mean of serum E2 assay results collected at weeks 4 and 8. Serum E2 levels will not be communicated to the investigational and the sponsor study teams to maintain the blind. Possible up- or down- titration will occur according to the following algorithm: subjects with a mean serum E2 level of <20pg/mL will be down-titrated to 50 mg daily whereas subjects with a mean serum E2 level of >50 pg/mL will be up-titrated to 100 mg daily. Subjects with a mean serum E2 level from 20 to 50 pg/mL inclusive will remain on 75 mg daily. Mean serum E2 level will be defined as the mean of the serum E2 assay results collected at week 4 and week 8.

An Interactive Web Response System (IWRS) will be used to allocate the appropriate treatment.

After all subjects have completed the first 12-week period, an interim analysis of Part A data to assess efficacy and safety parameters will be performed. After all subjects have completed the Part B treatment period (week 24), and all data have been entered into the clinical database, cleaned and locked, an analysis of Part B data will be performed. The results for the study parts A and B will be summarized and described in an integrated Clinical Study Report.

A 24-week follow-up period without treatment is planned after Part B, or - for subjects willing to continue treatment with OBE2109 - an extension study will be proposed. The extension study will consist of a further 28 weeks of treatment and a 24-week follow-up period without treatment.

An analysis will be performed after week 48 on subjects entering the 24-week follow-up period after Part B and reported in an addendum to the integrated Clinical Study Report.

Treatment will remain blinded up to the end of the study for the Investigator and the subject.

The extension study will be described in a separate Protocol, and analyzed and reported in a separate Clinical Study Report.

5. STUDY POPULATION

5.1. SUBJECTS

5.1.1. Description of the target population

The target population will be premenopausal women aged 18 to 45 years inclusive at screening, with surgically and, if available, histologically confirmed pelvic endometriosis and moderate to severe endometriosis-associated pain.

They must not be planning to become pregnant and must agree to non-hormonal barrier contraception from screening to the end of treatment period.

5.1.2. Number of subjects

Three hundred and thirty (330) randomized subjects are planned in total (approximately 55 subjects per group).

5.1.3. Study region/location

Approximately 60 investigational sites in the US and Europe will conduct the study. Potential back-up sites will be identified and qualified and will be activated in case of recruitment issue. Recruitment will be competitive beetwen sites.

5.2. ENTRY CRITERIA

5.2.1. 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 initiation of any study related procedures.
2. The subject must be a female volunteer aged 18 to 45 years inclusive at screening.
3. The subject must have had surgically and - if available - histologically confirmed pelvic endometriosis (laparoscopy, laparotomy, vaginal fornix or other biopsy) up to 7 years before screening.
4. The subject has moderate to severe endometriosis-associated pain during the screening period defined as:
    a. At the screening visit, a score of at least 2 for dysmenorrhea AND at least 2 for non-menstrual pelvic pain for the previous month assessed with the 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.

5. The subject is compliant with e-diary and has completed it on at least 80% of days during the two screening menstrual cycles.
6. The subject has regular menstrual cycles and the total length of the two screening menstrual cycles should be between 42 to 76 days.
7. The subject has a BMI $\geq$ 18 kg/m^2 and $\leq$ 39 kg/m^2 at the screening visit.
8. If of childbearing potential, the subject agrees to use one of the following birth control methods during the entire treatment period of the study:
    a. Sexual abstinence,
    b. Partner with a vasectomy with confirmed azoospermia,
    c. Double non-hormonal barrier contraception such as condom or diaphragm each combined with spermicide.
9. If of non-childbearing potential, the subject must have had tubal ligation sterilization at least two months before the screening visit.
10. The subject must be able to communicate well with the Investigator and research staff and to comply with the requirements of the study protocol.

5.2.2. 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 had an interventional surgery for endometriosis performed within a period of 60 days before screening.
4. The subject had a hysterectomy or bilateral ovariectomy.
5. The subject had a tubal sterilization which was performed with ESSURE™.
6. The subject has an in situ copper intra-uterine device (IUD) or an IUD with progestogen.

7. The subject had endometrial ablation resulting in amenorrhea.
8. The subject has at least one ovarian endometrioma with a diameter of 7 cm or greater.
9. 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 months/6 months
c. Danazol	3 months
d. Oral contraceptives and other sex hormones	1 month
e. Depot contraceptives	6 months
f. Selective Progesterone Receptor Modulators (SPRMs), Selective Estrogen Receptor Modulators (SERMs) and aromatase inhibitors	3 months
g. Long acting analgesics (i.e. requiring less than once daily dosing)	1 day
h. Systemic glucocorticoid treatments for acute diseases (not depot)	1 month

10. The subject has a history of or current systemic glucocorticoid therapy for treatment of chronic diseases (e.g. Systemic Lupus Erythematosus (SLE), rheumatic arthritis).
11. The subject did not respond to prior treatment with GnRH agonists or GnRH antagonists for endometriosis.
12. The subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels ≥ 2 times the upper limit of normal OR gamma-glutamyl transpeptidase (GGT) level ≥ 3 times the upper limit of normal at screening.
13. The subject has a known positive HIV or viral Hepatitis serology.
14. The subject has abnormal uterine bleeding of undiagnosed cause.
15. The subject had/has clinically significant findings from a PAP (Papanikolaou) smear 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 conisation).
16. 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, or that would interfere with the assessment of endometriosis related pain.
17. The subject has any other clinically significant gynecological condition identified on screening transvaginal ultrasound (TVUS) or endometrial biopsy, which might interfere with the study efficacy and safety objectives. However, uterine fibroids (as long as uterus size ≤ 12 weeks, i.e. equivalent gestational weeks) and adenomyosis are allowed.
18. The subject has a history of, or known osteoporosis or other metabolic bone disease.

19. 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.
20. 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.
21. The subject has current problem with alcohol or drug abuse (including painkiller abuse).
22. The subject has been administered with any experimental drug in the 12 weeks before dosing.

6. STUDY PROCEDURES AND ASSESSMENTS

6.1. 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 medical delegate 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. Two original copies of the consent form will be signed and personally dated by both the subject and the Investigator or medical delegate. One original signed copy will be kept by the Investigator in the confidential investigator file and the second original signed copy will be given to the subject. Although nursing staff may be involved in describing the trial to a subject, the Investigator/medical delegate must participate in discussions with the subject and personally sign and date the informed consent form (ICF).

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 ICF, each subject will be assigned a Subject Identification Number (SIN) in the electronic Case Report Form (eCRF). Subject Identification Numbers will be made of 5 digits, as follows:

- 1st digit: country identifier (1 to 4)
- 2nd and 3rd digits: site identifier (01 to 99)
- 4th and 5th digits: subject number (01 to 99)

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.

An eCRF will be completed for all subjects who signed the ICF. When a subject is subsequently not enrolled in the study, the reason for non enrollment will be recorded in the eCRF.

When a subject has been found to be eligible for the study, the subject will be randomized to one of the 6 treatment groups in a 1:1:1:1:1:1 ratio (approximately 55 subjects per treatment arm) as shown in Figure 1.

Randomization will be done according to a computer-generated list. Treatment assignments will be obtained via the IWRS according to the randomization list. The subject will be allocated a randomization number and a treatment kit number via the IWRS. The randomization number allocated to the subject will allow any unblinded study personal to identify the treatment group to which the subject is randomized. The treatment kit number will correspond to the kit number indicated on the label of the study drug. Kit numbers will start from K0001, K0002, K0003 etc. (5-characters).

At the end of Part A, to maintain the blind and prevent identification of the titrated subjects, all subjects will be allocated a new treatment kit number via IWRS for the 12-week Part B treatment period.

Treatment will remain blinded up to the end of the study for the Investigator and the subject.

6.2. OUTLINE OF STUDY PROCEDURES AND ASSESSMENTS

All post-baseline visits should take place at the end of the defined period (i.e. week 4 visit should be scheduled at the end of week 4, week 8 visit should be scheduled at the end of week 8, etc.). Post-baseline visits dates are calculated from Day 1 visit date.

6.2.1. Screening Period – Study Screening visit (11±5 weeks prior to Day 1 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 medical delegate.

The screening period will last up to 11±5 weeks during which the subject will be seen up to three times. During this time the following study screening assessments will be completed (see schedule of assessments in APPENDIX A):

- Demographic data, height and weight
- Medical history including concomitant diseases, obstetric/gynecological history and history of endometriosis including diagnosis and previous treatments
- Assessment of endometriosis pain with the mB&B scale (see APPENDIX B)
- Previous and current treatments recording
- Physical examination
- Vital signs (blood pressure and heart rate)
- Urine pregnancy test

- TVUS of uterus and ovaries to measure endometrium 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 B) clinical signs reporting (pelvic tenderness and pelvic induration)
- Endometrium 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.

The endometrium biopsy is not required at the screening visit for subjects having performed an endometrium biopsy within the past 6 months of the screening visit, which shows no endometrium atypical hyperplasia 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 conisation) and are available for source document verification.

- Manual breast examination (by palpation)
- Blood samples for haematology, coagulation parameters, chemistry, lipids and hormone assessments
- Urinary protein dipstick.
- Contraception counselling

The subject will receive double barrier contraception (condoms with spermicide) if necessary.

In addition, a limited quantity (as per Investigator's judgement) of ibuprofen and/or acetaminophen/paracetamol as standard rescue medication for endometriosis related pain will be given 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 correctly use and complete it: she will be asked to record her IMP intake, pelvic pain, dyspareunia, dyschezia, difficulty in performing daily activities, uterine bleeding, impression of severity and use of analgesic drug(s) including dose. These 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). Subject diary completion should be started on the day of screening visit.

The eDiary should be completed:

- Daily, in the evening at approximately the same time, for IMP intake, pelvic pain, dyspareunia, difficulty in performing daily activities, uterine bleeding and use of analgesic drug(s) including dose;
- Weekly, for dyschezia pain;

- 4-weekly, for patient's impression of severity.

Any concomitant medications taken after signature of informed consent will be recorded in the eCRF (excluding provided analgesics taken for endometriosis related pain 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 between the first and seventh day (inclusive) of her next menstrual period (the period after the 2 screening menstrual cycles) for the Day 1 visit. Final assessment of her eligibility will be performed including the minimum baseline scores for pelvic pain collected via the eDiary. The baseline mean pelvic pain scores will be calculated 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.

6.2.2. Part A treatment period

During the whole study Part A, the subject will be asked to record on her eDiary:

- Daily, at approximately the same time each evening, her IMP intake, pelvic pain, dyspareunia, difficulty in performing daily activities, uterine bleeding and use of analgesic drug(s) including dose;
- Weekly, her dyschezia pain;
- 4-weekly, the patient's impression of severity.

6.2.2.1. *Baseline visit – Study visit Day 1*

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

- Confirm inclusion/exclusion criteria (randomization will not be postponed if the results of the endometrium biopsy done during the screening period are not available on Day 1)
- Previous and concomitant treatments recording
- AE recording
- Physical examination
- Vital signs (blood pressure and heart rate)
- Urinary protein dipstick
- eDiary check for good completion

- EHP-30 questionnaire (see APPENDIX C) completion by the subject
- Urine pregnancy test
- Contraception counselling

The subject will receive double barrier contraception (condoms with spermicide) if necessary. It will be provided upon need at each subsequent visit over the duration of the study.

In view of the invasive nature of the following assessments it is recommended to perform these upon confirmation from the eDiary data that the subject meets the study entry requirement and upon receipt of the screening central laboratory results and confirmation that the values meet the study entry requirement. The following procedures will be performed and recorded as part of the screening/baseline assessments, prior to the first administration of study treatment:

- Fasting blood samples for haematology, coagulation parameters, chemistry, lipids, hormones and OBE2109 and KP017 pre-dose plasma levels assessments.
- BMD assessed by DXA for femoral neck, hip and spine. DXA can be performed up to 10 days after baseline.

The DXA scans will be read centrally.

The subject will then be randomized to one of the six treatment groups and will be provided with the study drug and analgesics. The subject will be instructed on how to take the study medication, analgesics, and on how to record the administration in the eDiary. The analgesics provided will be used only as rescue medication; no prophylactic use of analgesics is allowed during the whole study. The subject will be provided as necessary with analgesics at each subsequent visit to cover study period until Week 36.

From Day 1 up to the next scheduled study visit, the subject will be asked to record in the eDiary her IMP intake, pelvic pain, dyspareunia, difficulty in performing daily activities, uterine bleeding, dyschezia, impression of severity and use of analgesic drug(s) including dose.

The subject will take her first dose of study medication at the study site.

After **OBE2109/placebo administration,** the following procedure will be performed:

- Post-dose PK samples taken about 1.5 to 2.0 h after drug administration.

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

6.2.2.2. *Study visits Week 4 (Day 29 ± 3 days) and Week 8 (Day 57 ± 3 days)*

The following tests and evaluations will be performed at week 4 Study Visit and week 8 Study Visit:

- Previous and concomitant treatments recording
- AE recording
- Vital signs (blood pressure and heart rate)
- Urine pregnancy test

- eDiary check for good completion
- Blood samples for haematology, coagulation parameters, chemistry, lipids, hormones
- Urinary protein dipstick
- Contraception counselling

The following tests and evaluations will be performed at week 4 Study Visit only:

- Pre-dose PK samples (the approximate time of dose administration on previous day and time of taking of the PK sample will be recorded).
- The subject will take her daily dose of study medication at the study site. The time of taking the dose will be recorded.

The following tests and evaluations will be performed at week 8 Study Visit only:

- The subject will take her daily dose at the usual time in the morning at home.
- Post-dose PK samples same day during the site visit (the approximate time of dose administration at home and time of taking of the PK sample will be recorded)

6.2.2.3. *Study visit Week 12 (Day 85 ± 3 days) – End-of-Part A visit*

The subject will take her last daily dose of Part A study medication at the usual time in the morning at home. The approximate time of dose administration and time of taking of the blood sample will be recorded in the eCRF.

The following tests and evaluations will be performed at week 12 Study Visit:

- Assessment of endometriosis pain with the mB&B scale (see APPENDIX B)
- Previous and concomitant treatments recording
- AE recording
- Physical examination
- Vital signs (blood pressure and heart rate)
- Gynecological examination, including the mB&B scale (see APPENDIX B) clinical signs reporting (pelvic tenderness and pelvic induration)
- TVUS of uterus for measuring endometrium thickness and of ovaries for checking their normality.
- Urine pregnancy test
- Contraception counselling
- eDiary check for good completion

- EHP-30 (see APPENDIX C) and PGIC (see APPENDIX D) questionnaires completion by the subject
- Post-dose PK samples (the approximate time of dose administration at home and time of taking of the PK sample will be recorded)
- Blood samples for haematology, coagulation parameters, chemistry, lipids, hormones
- Urinary protein dipstick
- Endometrium biopsy, unless the endometrium thickness in TVUS is ≤ 5 mm, in which case no endometrium biopsy will be necessary, as far as the screening biopsy has provided assessable results. Appropriate photo documentation of the endometrium thickness is mandatory and will be kept in the source documents.
- BMD assessed by DXA for femoral neck, hip and spine. DXA can be performed ± 10 days from study visit.

The subject will be allocated a new treatment kit number via IWRS for the 12-week Part B treatment period. The subject will take her first daily dose of Part B study medication at home in the morning of the day following the Week 12 study visit.

Week 12 study visit constitutes the end of Part A visit.

6.2.3. Part B treatment period

During the whole study Part B, the subject will be asked to record on her eDiary:

- Daily, at approximately the same time each evening, her IMP intake, pelvic pain, dyspareunia, difficulty in performing daily activities, uterine bleeding and use of analgesic drug(s) including dose;
- Weekly, her dyschezia pain;
- 4-weekly, the patient's impression of severity.

6.2.3.1. *Study visits Week 16 (Day 113 ± 3 days) and Week 20 (Day 141 ± 3 days)*

The following tests and evaluations will be performed at week 16 Study Visit and week 20 Study Visit:

- Previous and concomitant treatments recording
- AE recording
- Vital signs (blood pressure and heart rate)
- Urine pregnancy test
- Contraception counselling
- eDiary check for good completion
- Blood samples for haematology, coagulation parameters, chemistry, lipids, hormones

- Urinary protein dipstick

The following tests and evaluations will be performed at week 16 Study Visit only:

- Pre-dose PK samples (the approximate time of dose administration on the previous day and time of taking of the PK sample will be recorded).
- The subject will take her daily dose of study medication at site in the morning. The time of taking the dose will be recorded.

The following tests and evaluations will be performed at week 20 Study Visit only:

- The subject will take her daily dose at the usual time in the morning at home.
- Post-dose PK samples (the approximate time of dose administration at home and time of taking of the PK sample will be recorded).

6.2.3.2. *Study visit Week 24 (Day 169 ± 3 days) – End-of-Part B visit*

The subject will take her daily dose at the usual time in the morning at home.

The following tests and evaluations will be performed at week 24 Study Visit:

- Weight
- Assessment of endometriosis pain with the mB&B scale (see APPENDIX B)
- Previous and concomitant treatments recording
- AE recording
- Physical examination
- Vital signs (blood pressure and heart rate)
- Gynecological examination, including the mB&B scale (see APPENDIX B) clinical signs reporting (pelvic tenderness and pelvic induration)
- TVUS of uterus for measuring endometrium thickness and of ovaries for checking their normality
- Urine pregnancy test
- Contraception counselling
- eDiary check for good completion
- EHP-30 (see APPENDIX C) and PGIC (see APPENDIX D) questionnaires completion by the subject
- Post-dose PK samples (the approximate time of dose administration at home and time of taking of the PK sample will be recorded)
- Blood samples for haematology, coagulation parameters, chemistry, lipids, hormones

- Urinary protein dipstick
- Endometrium biopsy, unless the endometrium thickness in TVUS is ≤ 5 mm, in which case no endometrium biopsy will be necessary, as far as the screening biopsy has provided assessable results. Appropriate photo documentation of the endometrium thickness is mandatory.
- BMD assessed by DXA for femoral neck, hip and spine. DXA can be performed ± 10 days from study visit.
- 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.

Study visit Week 24 constitutes the end of Part B visit.

The subject will be proposed to continue in an extension study. If the subject accepts, the eCRF exit form will be completed and the subject will stop the current study and continue in the extension study (see section 6.2.5).

Otherwise the subject will continue in the treatment-free follow-up period.

6.2.4. Follow-up period without treatment – Study visits Week 28 (Day 197 ± 3 days), Week 36 (Day 253 ± 3 days) and Week 48 (Day 309 ± 3 days)

Up to week 36 study visit, the subject will be asked to record on her eDiary:

- Daily, at approximately the same time each evening, her IMP intake, pelvic pain, dyspareunia, difficulty in performing daily activities, uterine bleeding and use of analgesic drug(s) including dose;
- Weekly, her dyschezia pain;
- 4-weekly, the patient's impression of severity.

6.2.4.1. *Study visit Week 28 (Day 197 ± 3 days)*

The following tests and evaluations will be performed at Week 28 Study Visit:

- Previous and concomitant treatments recording
- AE recording
- Vital signs (blood pressure and heart rate)
- Blood samples for haematology, coagulation parameters, chemistry, lipids, hormones
- Urinary protein dipstick
- eDiary check for good completion
- Urine pregnancy test
- Contraception counselling

6.2.4.2. *Study visit Week 36 (Day 253 ± 3 days)*

The following tests and evaluations will be performed at Week 36 Study Visit:

- Weight
- Assessment of endometriosis pain with the mB&B scale (see APPENDIX B)
- Previous and concomitant treatments recording
- AE recording
- Physical examination
- Vital signs (blood pressure and heart rate)
- Gynecological examination, including the mB&B scale (see APPENDIX B) clinical signs reporting (pelvic tenderness and pelvic induration)
- Manual breast examination (by palpation)
- TVUS for measuring endometrium thickness and of ovaries for checking their normality
- Urine pregnancy test
- Contraception counselling
- eDiary check for good completion
- EHP-30 (see APPENDIX C) and PGIC (see APPENDIX D) questionnaires completion by the subject
- Blood samples for haematology, coagulation parameters, chemistry, lipids, hormones
- Urinary protein dipstick
- Endometrium biopsy: will only be taken if no endometrial biopsy was obtained at week 24 or if diagnosis at week 24 was different from "benign endometrium"

6.2.4.3. *Study visit Week 48 (Day 309 ± 3 days) – End of Follow-up visit*

The following evaluation will be performed at Week 48 Study Visit:

- BMD assessed by DXA for femoral neck, hip and spine. DXA can be performed ± 10 days from study visit.
- AE recording if related to BMD loss
- Previous and concomitant treatments recording only if treatments with potential impact on BMD
- Completion of the eCRF exit form

6.2.5. Planned extension of the study

At the end of the treatment period (end of Part B), the subject will be offered the opportunity to continue on active treatment for 28 weeks. A separate specific ICF will have to be signed and dated by the subject and the Investigator or medical delegate. The design of this extension study will be described in a separate protocol.

6.3. EFFICACY OBSERVATIONS AND MEASUREMENTS

6.3.1. Pelvic pain

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

NRS: The subject will be asked to rate her worst endometriosis related 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 related pelvic pain or discomfort in the last 24 hours*:*

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

6.3.2. Daily activity

The subject will be asked in the eDiary if she had any difficulty doing her daily activities in the last 24 hours on a 0–10 scale with 0 representing no difficulty doing daily activities and 10 representing unable to do daily activities.

6.3.3. Uterine bleeding

The subject will answer in the eDiary a two-item questionnaire assessing the incidence and amount of uterine/vaginal bleeding in the last 24 hours. The amount of uterine bleeding will be assessed using the following VRS:

1 - Spotting	*A light amount of bleeding noted, no protection or panty shield only*
2 - Light	*1–2 regular tampons or pads required in 24 hours*
3 - Medium	*3–4 regular tampons or pads required in 24 hours*
4 - Heavy	*More than 4 tampons or pads required in 24 hours*

Subject will be asked additional questions to identify the first day of her menstrual periods for the screening period.

6.3.4. Analgesic use

The subject eDiary will include daily selection-boxes for ibuprofen (provided by site), acetaminophen/paracetamol (provided by site) or other. The subject will be asked to record the number of tablets taken and to confirm if the reason for use is her endometriosis related pain.

If the subject takes another pain medication and/or uses provided analgesics for pain other than her endometriosis related pain, she will be asked to record the details in a Pain Medication paper diary and bring this to her next site visit so that the details can be recorded in the eCRF.

6.3.5. Dyspareunia (pain associated with sexual intercourse)

The subject will be asked daily about dyspareunia via the eDiary using a VRS and a NRS:

VRS: The subject will be asked to rate how her endometriosis related pain interfered with any sexual intercourse in the last 24 hours*:*

	Not applicable*: I was not sexually active for reasons other than my endometriosis or did not have sexual intercourse.*
0	*No discomfort during sexual intercourse.*
1	*I was able to tolerate the discomfort during sexual intercourse.*
2	*Intercourse was interrupted due to pain.*
3	*I avoided sexual intercourse because of pain.*

NRS: If subject reported she had pain during intercourse, the subject will be asked to rate her worst endometriosis related pain experienced during or after sexual intercourse in the last 24 hours on a 0–10 scale with 0 representing no pain and 10 representing the worst pain imaginable.

6.3.6. Dyschezia (pain associated with defecation)

Dyschezia will be assessed weekly 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.

6.3.7. EHP-30, PGIC and question about severity of endometriosis condition

Subject will complete in addition two questionnaires in the eDiary: EHP-30 and PGIC (see APPENDIX C and APPENDIX D). EHP-30 will be completed at baseline and Weeks 12, 24 and 36 visits. PGIC will be completed at Weeks 12, 24 and 36 visits.

Subject will answer in the eDiary an additional question to describe the severity of her endometriosis condition over the preceding 4-week period, with following possible answers: no symptoms, very mild, mild, moderate, severe. This question will be asked every 28 days from day 1 up to week 36 included.

6.3.8. Modified Biberoglu and Behrman questionnaire

Endometriosis pain will be assessed by subject using the mB&B scale (see APPENDIX B) provided as paper questionnaire at screening visit and Weeks 12, 24 and 36 visits. This paper questionnaire will be kept as source data and corresponding scores recorded in eCRF by the Investigator.

On the same visits, a gynecological assessment including the assessment of the two clinical signs of the B&B - pelvic tenderness and pelvic induration (see APPENDIX B) - will be evaluated. Corresponding scores will be recorded in subject source data and in the eCRF by the Investigator.

6.4. SAFETY OBSERVATIONS AND MEASUREMENTS

6.4.1. Adverse Events

AE data will be collected continuously during the study as described in Section 8.

AE data will be obtained at scheduled study visits based on physical examination, vital signs 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, as defined in section 8, will be reported on an ongoing basis in the AE pages of the eCRF.

A complete physical examination, i.e. weight, 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 Screening, on Day 1 and Weeks 12, 24 and 36 visits. In addition, a manual breast examination (by palpation) will be performed at Screening and Week 36. Results of the examinations will be recorded on source subject data file and in the eCRF. Medical conditions present at screening that do worsen in severity and/or frequency during the study will be reported as AEs in the corresponding eCRF page.

6.4.2. Vital signs

Blood pressure (BP) and heart rate will be measured in sitting position at each monthly visit from the screening visit to the Week 36 visit. In case of abnormal vital signs (i.e. BP $\geq$ 150/100 mmHg or $\leq$ 90/50 mmHg and/or heart rate $\geq$ 100 bpm or $\leq$ 40 bpm) and if abnormality was not pre-existing, a repeat assessment after 5 min should be taken. In case of confirmed abnormality, 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.

6.4.3. Transvaginal ultrasound and endometrial biopsies

Endometrial thickness, uterus volume and abnormality (fibroids, adenomyosis, etc…) and left/right ovary abnormality status will be assessed by TVUS during screening, at weeks 12, 24 and 36. The print-

outs of the ultrasound will be interpreted and commented by the gynaecologist and kept as source data. Results of the examination will be recorded on source data forms and in the eCRF.

Endometrial biopsies will be performed for histological assessment during screening, at weeks 12 and 24. At week 36, endometrial biopsy will only be taken if no endometrial biopsy was obtained at week 24 or diagnosis at week 24 was different from "benign endometrium" . Endometrial biopsy samples will be performed with the Pipelle de Cornier® (APPENDIX E), as it will be described in the manual provided by the central laboratory. Endometrial biopsies will be centrally assessed by one single independent pathologist blinded to treatment group.

If at week 12 and week 24, the endometrium thickness in TVUS is ≤ 5 mm, no endometrium biopsy will be necessary, as far as the screening biopsy has provided assessable results. In this case the biopsy should be taken at week 36. However, if the week 24 biopsy result is available and indicated a benign endometrium then another biopsy is not required at week 36. Appropriate photo documentation of the endometrium thickness is mandatory and should be kept in the source documents at site.

6.4.4. Bone mineral density and DXA

Bone mineral density (BMD) of femoral neck, hip and spine will be assessed by DXA at baseline, weeks 12, 24 and 48. Instructions to measure the BMD and specific subject withdrawal criteria based on BMD will be provided in a specific imaging manual, which will be provided to the Investigator. The DXA scans will be transferred to a central reading unit who will assess the BMD blinded to treatment group.

6.4.5. Laboratory parameters

Haematology, coagulation parameters, chemistry, lipids and hormones (serum levels of E2, progesterone [P4] and LH) will be assessed from blood samples taken at screening, Day 1 and weeks 4, 8, 12, 16, 20, 24, 28 and 36. Serum levels of the anti-müllerian hormone (AMH) will be assessed on Day 1 and serum levels of the sex hormone-binding globulin (SHBG) will be assessed on Day 1 and weeks 12 and 24. 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, AMH, SHBG, P4 and LH 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, AMH, 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 F.

6.5. OBE2109 AND KP017 PLASMA LEVELS

PK blood samples will be collected from each subject for determining OBE2109 and KP017 plasma levels.

On Day 1, blood samples for PK assessment will be taken pre-first dose and 1.5 to 2 h post-first dose.

On the day of the site visits of weeks 8, 12, 20 and 24, the subject will take her daily dose of IMP at home at the usual time in the morning. The blood samples for PK will be taken at the site. The time of

dose administration in the morning and time of PK sampling on the same day will be recorded on the eCRF.

On weeks 4 and 16 visits, the subject will be asked to take the dose of IMP at site, after a pre-dose PK sampling. The time of dose administration on the previous day and time of taking of the PK sample will be recorded on the eCRF.

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

6.6. 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 duration of the reporting period as defined in section 8.5. From week 36 onwards, only concomitant medication with potential impact on BMD will be recorded in the eCRF.

The use of provided analgesics for endometriosis related pain will be recorded solely in the eDiary.

6.6.1. Permitted Medicines

Analgesics:

Subjects will be required to restrict if possible the use of analgesic to ibuprofen or acetaminophen/paracetamol for the duration of the study, from the screening to the Week 36 visit. Standard doses of ibuprofen and acetaminophen/paracetamol will be provided free of charge to the subject. The subject eDiary will include selection-boxes for ibuprofen, acetaminophen/paracetamol or other, including dosage. The analgesics provided will be used only as rescue medication; no prophylactic use of analgesics is allowed during the whole study.

Contraceptive use:

For subjects of childbearing potential and requiring contraception, non-hormonal contraception is required from beginning of screening period until end of treatment. Two forms of non-hormonal contraception will be required e.g. condom with spermicide. Suitable condoms with spermicide will be provided free of charge to subjects over the duration of the study.

After the end of treatment period (end of week 24) until the end of follow-up period, no contraception is required. For subjects wanting a contraceptive method, a single form of non-hormonal contraception is sufficient.

Hormonal contraception is prohibited from beginning of screening period until end of week 36.

OBE2109 could potentially induce CYP3A4 at high concentrations which are not expected with doses up to 200 mg daily. However, Investigators should note this potential induction of CYP3A4 in case that subjects taking drugs metabolised by CYP3A4 experience attenuation of their effects and should consider a dose adjustment of the CYP3A4 substrate or discontinuation of OBE2109 as appropriate.

Any medications other than those excluded by the protocol (see section 5.2.2 or 6.6.2), 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.

6.6.2. Prohibited Medicines

Medication listed in exclusion criteria (see Section 5.2.2) will be prohibited up to week 36.

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 enrolling the subject (see Section 5.2.2).

Substrates of cytochrome P450 2C8 (CYP2C8) (e.g. montelukast, repaglinide) and of organic anion transporter 3 (OAT3) (e.g. benzylpenicillin, sitagliptin, ciprofloxacin, pravastatin, rosuvastatin) are prohibited during the treatment period only.

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.

6.6.3. Non-Drug Therapies

Not applicable.

6.7. SUBJECT COMPLETION AND WITHDRAWAL

6.7.1. Subject Completion

A subject will be considered as a "completer" when she has completed all study procedures at visit Week 24 as described in the protocol. The end of Part B visit on Week 24 constitutes subject completion (see APPENDIX A).

Subjects who did not receive the study drug will be withdrawn from the study and no further study procedures will be performed. The eCRF exit form should be completed.

6.7.2. Subject Withdrawal from Study

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 and should be followed up by the Investigator.

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.

Subjects discontinuing participation in the study between Day 1 and Week 24 visits should undergo the procedures required at Week 24 visit. Subjects discontinuing participation in the study between Week 24 and Week 36 visits should undergo the procedures required at Week 36 and Week 48 visits. Subjects discontinuing participation in the study between Week 36 and Week 48 visits should undergo the procedures required at Week 48 visit.

6.7.2.1. *Discontinuation criteria*

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

- **Lack of Efficacy:** Investigator's judgment only. If subject's opinion only, check subject's Request. Explain in the comment section of the eCRF Exit Form.

- **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 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 week 36, 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 8.6).

- **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.

Subjects who have an elevation of hepatic enzymes suspicious of drug induced liver toxicity according to the Food and Drug Administration (FDA) guidance on drug-induced liver injury (26), i.e. LFT increase > 3 x ULN associated with increased bilirubin > 1 x ULN, will be immediately withdrawn from treatment and followed up to return to normal of hepatic parameters.

All subjects withdrawn from treatment will enter – if appropriate – a 24-week follow-up period without treatment and continue daily eDiary recording up to Week 36 visit in order to continue to collect efficacy data.

6.7.2.2. *Follow-up for discontinued subjects*

Not applicable.

6.7.3. Subject Replacement

Discontinued subjects who received the study drug will not be replaced.

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

7. INVESTIGATIONAL MEDICINAL PRODUCT

7.1. DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCTS

The term "Investigational Medicinal Product" (IMP) will refer to either the ObsEva investigational drug or the placebo.

	Investigational product	**Placebo**
International nonproprietary name **(INN)**	NA	NA
Name of active ingredient	OBE2109	NA
Form	Film-coated tablet	Film-coated tablet
Strength	50mg, 75mg and 100mg	placebo
Dose or concentration of active treatment	50mg, 75mg, 100mg and 200mg	0mg
Route of administration	Oral	
Frequency of administration	Once daily for up to 24 weeks	
Manufacturer (Name and address)	Catalent Pharma Solutions Steinbeisstrasse 1-2 D-73614 Schorndorf, Germany	
Packaging (primary and secondary)	PVC/Al blister with 7 tablets per blister, blister in two different colors (colored Al foil) for blinding purpose Aluminum pouch	PVC/Al blister with 7 tablets per blister, blister in two different colors (colored Al foil) for blinding purpose Aluminum pouch
Storage Requirements	As indicated on the study drug kit label	As indicated on the study drug kit label

7.2. DOSAGE AND ADMINISTRATION

Investigational Medicinal Products (IMPs)

OBE2109 and placebo treatments will be supplied as film-coated tablets for oral administration.

The subjects will be given 3-monthly treatment packs.

OBE2109 and placebo oral tablet treatments will start on Day 1 between the first and the seventh day of menstruation and will be administered once daily, up to about 24 weeks. The subjects will take 2 tablets in the morning of each day as follows :

Treatment arm	**Daily dose Part A** **Day 1 to Week 12**		**Daily dose Part B** **Week 12 to Week 24**	
	Active tablet	Placebo tablet	Active tablet	Placebo tablet
50 mg	1 × 50 mg	1 × placebo	1 × 50 mg	1 × placebo
75 mg	1 × 75 mg	1 × placebo	1 × 75 mg	1 × placebo
100 mg	1 × 100 mg	1 × placebo	1 × 100 mg	1 × placebo
200 mg	2 × 100 mg	None	2 × 100 mg	None
Titrated arm	1 × 75 mg	1 × placebo	Titrated dose*	1 × placebo
Placebo/100 mg	None	2 × placebo	1 × 100 mg	1 × placebo

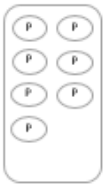
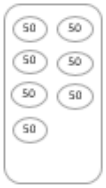
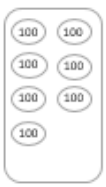
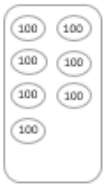
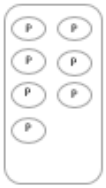
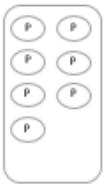
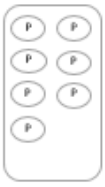
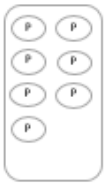
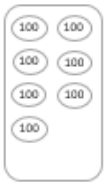
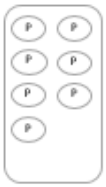
* Dose titrated after 12 weeks based on the mean E2 levels analyzed at weeks 4 and 8 as follows:

- If E2 < 20 pg/mL then reduce the dose to 50 mg daily
- If E2 > 50 pg/mL then increase the dose to 100 mg daily
- If 20 ≤ E2 ≤ 50 pg/mL then dose remains at 75 mg per day

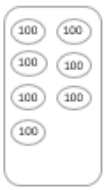
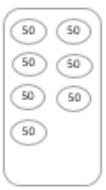
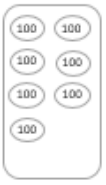
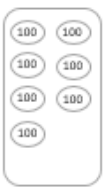
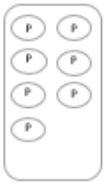
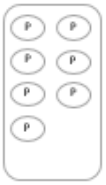
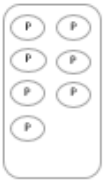
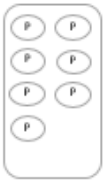
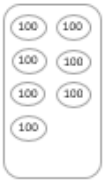
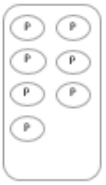
7.3. PACKAGING AND LABELLING

Study drug will be provided by the sponsor (or delegate) as 3-monthly kits. Each 3-monthly kit will contain 13 Aluminum (Al) pouches containing two PVC/Al blisters of two different colors (colored Al foil), i.e. sufficient to cover treatment for 13 weeks for each subject. All the 13 pouches and their corresponding blisters will be labelled with the same kit number, to be provided to a given subject.

Part A – 3-monthly treatment: 13 pouches/3-monthly kit – 26 blisters (13 blisters of each color) – 7 tablets/blister.

Population	55	55	55	55	55	55
Arm	Placebo	50mg	75mg	100mg	200mg	75mg
Blister with color A						
Blister with color B						

Part B – 3-monthly treatment: 13 pouches/3-monthly kit – 26 blisters (13 blisters of each color) – 7 tablets/blister.

Population	55	55	55	55	55	55
Arm	Placebo/100mg	50mg	75mg	100mg	200mg	50 or 75 or 100mg
Blister with color A						
Blister with color B						

On Day 1 and at Week 12 visit, the subject will be given one 3-monthly kit for a total of 13 weeks (i.e. including one extra week to cover the allowed time window for visit scheduling).

Each day, from Day 1 to the last day of Week 24 inclusive, the subject will have to swallow two tablets, one from each blister of different color and included in a same pouch.

In each 3-monthly kit, all 13 pouches will have a label including a tear-off part. The non-tear off part will remain affixed to the pouch and one of the 13 tear-off part containing the study number and the kit number will be placed into a drug accountability booklet 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 label on the secondary packaging will indicate at least the following items:

- Protocol number
- Kit number
- Batch number
- Storage conditions
- Sponsor name and address
- Expiry date (for EU only)

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

7.4. 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 pouch.

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

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).

7.5. 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 pharmacist) will check for accurate delivery and acknowledge receipt. 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 booklet provided by the sponsor (or delegate) 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
- The return to the sponsor (or delegate) or alternative disposition of unused IMP
- Dates, quantities, batch numbers and kit numbers assigned to the subject.

- 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 periodically check the IMP accountability booklet and check 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.

7.6. ASSIGNMENT TO TREATMENT GROUPS

Prior to the start of the study, a randomization list and a treatment kit list 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.

Kit numbers assigned by the IWRS will start from K0001, K0002, K0003 etc. (5-characters) and will correspond to the kit number indicated on the label of the study drug.

Complete blocks of treatment materials will be assigned to the investigational sites. However, the shipment of the treatment kits (as individual 3-monthly kits) to each site will be made on an as-needed basis depending on the site screening rate.

Subjects will be randomized to one of six treatment groups in a 1:1:1:1:1:1 ratio, stratified by site.

7.7. ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT COMPLIANCE

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

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

7.8. METHOD OF BLINDING

The study design is double blind. 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 and LH levels will not be communicated to them.

7.9. 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 and the complete Study Team.

If a Serious Adverse Event (SAE) is reported, the ObsEva (or delegate) Representative for Pharmacovigilance may unblind the treatment assignment for the affected subject. When applicable, an expedited report will be sent to all Investigators in accordance with regulations.

7.10. 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.

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 Section 8.2.

The effects of an overdose of OBE2109 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 1.5).

7.11. OTHER SUPPLIES TO BE USED IN THE STUDY

A limited quantity (as per Investigator’s judgement) of standard doses of ibuprofen and/or acetaminophen/paracetamol will be given to the subject as standard rescue medication for endometriosis pain. Ibuprofen and acetaminophen/paracetamol will be sourced by the investigational site and reimbursed by the sponsor.

The subject will have to record the intake of the analgesic rescue medication, including dose, in her eDiary.

Condoms with spermicide will also be provided by the sponsor free of charge to the subject.

8. 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 8.2.1, Eliciting Adverse Events).

The safety profile of OBE2109 will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, laboratory tests, BMD assessments.

The reporting period for AEs is described in section 8.5.

8.1. ADVERSE EVENTS

8.1.1. 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 in which the subject has been placed (i.e. withdrawal of a previous drug to enter the study or "protocol-related"). For monitoring purposes, any protocol-related event, as assessed by the Investigator, should be reported on an AE form or an SAE form, as appropriate.

Severity:

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

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

Causality assessment:

The causality assessment of an AE to the IMP 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, 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	Temporary interruption (termination) in the administration of study drug.
Drug (study drug) withdrawn	Administration of study drug is terminated (no further dosing).

Unknown	Unknown, not observed, not recorded, or refused.

8.1.2. 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.

8.1.3. Baseline Medical Conditions

Medical conditions present at the initial study visit 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.

8.1.4. 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.

8.1.5. Adverse Events of Special Interest

Not Applicable.

8.2. PROCEDURES FOR ELICITING, RECORDING AND REPORTING ADVERSE EVENTS

8.2.1. 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.

8.2.2. 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.

8.2.3. Reporting of Adverse Events

Complete and accurate data on all AEs experienced for the duration of the reporting period, as defined in section 8.5, 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.

8.3. SERIOUS ADVERSE EVENTS

8.3.1. 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 exercised 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.

8.3.2. SAE Urgent Reporting Procedure

If a SAE occurs from subject consent up to week 36, with the exception of a SAE related to BMD loss which will be reported up to week 48, 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 7.9. 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 **/ 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 8.3.1,
- 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).

8.4. REPORTING TO THE INDEPENDENT ETHICS COMMITTEES/ 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 IEC/IRB 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 Ethics Committee, Central IRB). In the US, 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; in the European Union (EU), the sponsor or designee is responsible for notifying the European Medicines Agency, IEC, and Competent Authorities. In regions/countries other than the US/EU, reporting of events to IECs or 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 IEC/IRB'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 OBE2109 Investigator Brochure) 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 IEC/IRB 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 IEC/IRB and maintain records of these notifications.

8.5. REPORTING PERIOD

Adverse Events (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 week 36, with the exception of an AE related to BMD loss which will be reported up to week 48.

Protocol-related 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 have been fully processed, eCRFs 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.

8.6. PREGNANCY AND IN UTERO DRUG EXPOSURE

Only pregnancies considered related to study treatment by the Investigator (i.e. resulting from a drug interaction) are considered as AEs.

However, **all pregnancies that are conceived up to week 36** 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 expedited AE reporting in section 8.3.2. 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 8.3.2. (within 24 hours of awareness of this outcome). A SAE Report form must be completed when the subject sustains an event while PSF-part III must be completed when the child/foetus sustains an event. Abnormal outcomes are defined as:
    - Abnormality of the baby (birth defect): in this case, a SAE form for the child should be completed in addition to the PSF-III.
    - Abnormality for the pregnancy (spontaneous abortion, stillbirth) or abnormality for the birth itself which could fulfil criteria of SAEs (e.g. prolongation of hospitalization due

to caesarean section complications): in this case please complete in supplement to the PSF-III a SAE form for the mother.

9. DATA ANALYSIS AND STATISTICS

9.1. TEST OF HYPOTHESES

The primary objective of the study is to assess the efficacy of a range of oral doses of OBE2109 versus placebo, in reducing overall pelvic pain in subjects with moderate to severe endometriosis pain. The corresponding primary endpoint is a 30% or greater reduction from baseline to week 12 in the mean overall pelvic pain score defined as the mean of daily pain scores reported during the preceding 4-week period assessed on a 0–3 VRS for pelvic pain.

The primary objective will be assessed by testing the following hypotheses for each active group separately:

Null hypothesis (H0): There is no difference in the proportion of subjects meeting the primary endpoint for the active treatment group compared to placebo.

H0: p (active) = p (placebo)

Alternative hypothesis (H1): There is a difference in the proportion of subjects meeting the primary endpoint for the active treatment group compared to placebo.

H1: p (active) ≠ p (placebo)

Where p is the proportion of subjects with a reduction equal to or above 30% from baseline to week 12 in the mean overall pelvic pain score reported during the preceding 4-week period.

Each comparison will be carried out at the two-sided 5% level of statistical significance. No adjustment will be made for the multiple active versus placebo group comparisons (four in total: 50mg versus placebo, 75mg versus placebo, 100mg versus placebo and 200mg versus placebo) with the understanding that this increase the overall type I error rate of the study.

In addition, an overall test for dose response will be conducted using all treatment arms. The coefficients for this contrast will be defined assuming a linear response on a log (dose+1) scale.

9.2. SAMPLE SIZE

The planned sample size for this study is 55 subjects per treatment arm (330 subjects in total). The sample size calculation is based on pairwise comparisons for each active dose versus placebo. A two-sided type I error of 0.05, not adjusted for multiple comparisons against placebo, will be used for this exploratory study. Fifty five (55) subjects per arm will provide a power of 90% assuming a placebo response rate of 45.5% and an active treatment response rate of 76.9% (based on data from Kissei's Phase 2 study KLH1202).

9.3. RANDOMIZATION

Randomization will be performed via a centralized IWRS. Subjects will be randomized on Day 1 to one of six treatment groups in a 1:1:1:1:1:1 ratio for OBE2109 placebo/100mg group, OBE2109 50mg fixed-dose group, OBE2109 75mg fixed-dose group, OBE2109 100mg fixed-dose group, OBE2109 200mg fixed-dose group, OBE2109 75mg titrated-dose group, stratified by site.

Subjects will be randomized into blocks of a pre-determined length, with complete blocks being assigned to the investigational sites.

9.4. 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. Subjects will be analyzed according to randomized treatment.
3. **Week 12 Per Protocol (PP) Set:** All subjects in the FAS excluding those identified as major protocol violators up to Week 12.
4. **Week 24 Per Protocol (PP) Set:** All subjects in the FAS excluding those identified as major protocol violators up to Week 24.
5. **Pharmacokinetic (PK) Set:** all subjects who received active study medication and had no major protocol deviations.

Any pre-planned sub-group analyses will be described in the statistical analysis plan (SAP).

9.5. DATA ANALYSIS

More details of the proposed statistical analysis will be documented in the SAP, which will be written following finalization of the protocol and prior to the interim analysis of the Part A data.

Analyses of Part B study data will be fully described in the SAP.

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.

For ordered categorical data and nominal data, absolute counts and relative frequencies (in %) will be calculated.

Data for the 75mg group and 75mg titrated group will be combined for the analyses of the Part A data.

All statistical hypothesis tests and confidence intervals will be two sided, using a type I error rate of 0.05. No adjustment for multiple comparisons will be used for this study.

Raw data will be listed.

9.5.1. 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.

9.5.2. Primary Efficacy Analysis

Mean overall pelvic pain scores will be calculated separately for the VRS and NRS by adding up the daily pain scores during each successive 4-week (28 day) periods and dividing by the actual number of days with non missing data (i.e. nominally 28 days if no missing data). The baseline mean overall pelvic pain score will be calculated as the mean over the two complete menstrual cycles during screening, which may not be exactly 28 days each.

The percentage of subjects with a 30% or greater reduction from baseline to week 12 (i.e. during the 4 weeks preceding week 12 time point) in the mean overall pelvic pain score will be summarized by descriptive statistics for each treatment group and overall.

The analysis of the primary endpoint will be conducted via a generalized linear model for binary data with repeated (correlated) measures, fitted using generalized estimating equations (a marginal model), with the model including terms for treatment group, 4-week period, baseline and the interactions 4-week period*treatment, 4-week period*baseline.

9.5.3. Secondary Efficacy Analysis

Mean overall pelvic pain scores will also be calculated separately for the NRS in the same way as for the VRS.

Mean pelvic pain scores on uterine bleeding days and non-uterine bleeding days will be calculated by adding up the pain scores on the relevant days (uterine bleeding days will be defined as those days on which the subject records any uterine bleeding or spotting in the subject eDiary) and dividing by the number of days with non missing data. Both the total number of non-missing days in the 4-week period (i.e. nominally 28 days if no missing data) and the number of non-missing uterine bleeding days/non-uterine bleeding days will be considered.

All secondary efficacy endpoints will be summarized by descriptive statistics for each treatment group and overall, for each time point, including summaries or change from baseline when applicable. The definition of baseline for each endpoint will be defined in the SAP. As with the primary analysis, individual active versus placebo arm comparisons will be made. In addition, an overall test for dose response will be conducted using all treatment arms.

In general, between group comparisons for continuous endpoints will be analyzed via (repeated measures) analysis of (co)-variance (repeated measures mixed models) or Wilcoxon Rank Sum tests, subject to the underlying distribution of the data. Between group comparisons for binary endpoints will be analyzed via generalized linear models (with repeated measures) and chi-squared tests. Between-group comparisons for count data (e.g. number of days) will also be analyzed via generalized linear models (with repeated measures).

It is not certain whether the continuous endpoints will be normally or log-normally distributed, and/or whether an absolute or proportional change in endpoints will be observed. If deemed necessary, the data will be log transformed prior to the analysis. The subsequent results (mean differences and corresponding confidence intervals) will be back transformed and hence reported in terms of ratios of geometric means.

Potential responder definitions for future studies will be explored. These are likely to incorporate use of rescue analgesics and reduction in difficulty of pain with daily activities, in addition to pain. A responder threshold that constitutes a meaningful reduction in symptomatology will also be explored, potentially by exploring a cumulative distribution and/or via an anchor based method using the PGIC and other appropriate endpoints and methods.

9.5.4. Safety analysis methodology

The safety and tolerability profile will be assessed versus baseline conditions and differences between treatment groups and descriptive statistics will be produced, where applicable. No formal hypothesis testing of safety data will be undertaken.

A treatment-emergent analysis will be done for AEs. AEs will be tabulated by MedDRA preferred term and system organ class. Tabulations by severity and drug-relatedness will also be made.

Extent of exposure and compliance will be evaluated.

The Safety Analysis Set shall be used when summarizing safety data.

9.5.5. Pharmacokinetic analysis methodology

PK Analysis will be performed by SGS Laboratories. 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.

9.5.6. Pharmacodynamic analysis methodology

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

9.5.7. Missing Data

Summary statistics will be based primarily on non-missing values. For hypothesis tests, estimates and confidence intervals, missing values for continuous efficacy endpoints analyzed via likelihood methods (e.g. repeated measures mixed models) will not be directly imputed as they are handled within the analysis itself, under the assumption that the model specification is correct and that the data is missing at random. In addition, missing values for endpoints analyzed via generalized estimating equations will not be directly imputed as they are handled under the assumption that the model specification is correct and the data is missing completely at random. Sensitivity analyses may be conducted to check the

robustness of the analysis results under alternative assumptions with regards to missing data. Further details on the handling of missing values, including rules applied to incomplete questionnaires (including incomplete diary entries) and any planned sensitivity analyses will be defined in the SAP.

9.6. STUDY SPECIFIC DATA ANALYSIS

9.6.1. Interim Analysis

An un-blinded interim analysis of Part A data to assess efficacy and safety parameters will be performed by an unblinded statistician after all subjects have completed the first 12-week period. The OBE2109 75mg group and OBE2109 75mg titrated group will be pooled for the analysis of the Part A data. The results will be made available to the sponsor for the purpose of planning future studies.

Every effort will be done to maintain the Investigator, the subject and the study personel fully blinded.

9.6.2. Final Analysis

After all subjects have completed the Part B treatment period (week 24), a complete analysis of Part A and Part B data will be performed. The results for the study parts A and B will be summarized and described in an integrated Clinical Study Report.

A 24-week follow-up period without treatment is planned after Part B.

An analysis will be performed after week 48 on subjects entering the 24-week follow-up period after Part B and reported in an addendum to the integrated Clinical Study Report.

Treatment will remain blinded up to the end of the study for the Investigator and the subject.

The extension study will be described in a separate protocol, and analyzed and reported in a separate Clinical Study Report

10. STUDY ADMINISTRATION

10.1. 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 (27), the ICH Harmonized Tripartite Guideline for GCP, and all applicable local regulatory requirements.

10.1.1. 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.

10.1.2. 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.

10.1.3. Institutional Review Board/ Independent Ethics Committee Requirements

Before initiation of the study at a given site, written approval of the protocol, ICF and any information presented to potential subjects must be obtained from the appropriate Institutional Review Board or Independent Ethics Committee (IRB/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 IEC/IRB approval of the study.

10.1.4. 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 Week 48 visit. This provides a single and conservative definition across all study sites.

10.2. 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.

10.2.1. Coordinating Investigator

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

10.3. 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.

10.4. 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.

10.5. REVIEW COMMITTEE(S)

10.5.1. Data Monitoring Committe (DMC)

The 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.

10.6. 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.

10.7. 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/IECs 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.

10.8. 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 IEC/IRB.

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

10.9. 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, 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.

11. APPENDICES

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS

Timing[1]	Screening	Part A				Part B			Follow-Up		
	11±5 weeks	Day 1	W4	W8	W12	W16	W20	W24	W28	W36	W48
Informed Consent	X										
Demography, height, weight, medical history	X							X[6]		X[6]	
Previous/concomitant medication	X	X	X	X	X	X	X	X	X	X	X[7]
Inclusion-Exclusion criteria	X	X									
Physical examination	X	X			X			X		X	
Vital signs	X	X	X	X	X	X	X	X	X	X	
Gynecological examination and mB&B	X				X			X		X	
Breast manual examination	X									X	
Pap test	X										
Endometrium TVUS	X				X			X		X	
Endometrial biopsy	X				X[2]			X[2]		X[3]	
Clinical laboratory & urinary protein dipstick	X	X	X	X	X	X	X	X	X	X	
Blood sample for PK[4]		X[4]	X[4]	X	X	X[4]	X	X			
OBE2109/Placebo taken daily		←	—	—	—	—	—	→			
Subject eDiary completion training/check[5]	X	X	X	X	X	X	X	X	X	X	
EHP-30		X			X			X		X	
PGIC					X			X		X	
BMD by DXA		X			X			X			X
Urine pregnancy test and contraceptive counselling	X	X	X	X	X	X	X	X	X	X	
Question regarding treatment received during study								X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X[7]

[1] All post-baseline visits should take place at the end of the defined period (i.e. week 4 visit should be scheduled at the end of week 4, week 8 visit should be scheduled at the end of week 8, etc.). Post-baseline visits dates are calculated from Day 1 visit date.

[2] If endometrium thickness in TVUS is ≤ 5 mm, no endometrium biopsy will be necessary, as far as the screening biopsy has provided assessable results.

[3] If diagnosis at week 24 was different from "benign endometrium" or if no endometrial biopsy was obtained at week 24, then endometrial biopsy must be performed.

[4] PK blood samples should be taken after dosing except on Day 1 when taken before and 1.5 to 2 h after dosing, and at week 4 and 16, when taken prior to dosing.

[5] eDiary completion includes daily record of pelvic pain scores, uterine bleeding, dyspareunia symptoms, analgesic use, study treatment, difficulty in performing daily activities, weekly record of dyschezia pain score and 4-weekly record of patient's impression of severity.

[6] Only weight will be recorded.[7] Record in eCRF only if related to BMD (any medications with potential impact on BMD or any AEs related to BMD loss).

APPENDIX B 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
Moderate	4 - 6
Severe	7 - 9

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

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
Moderate	3 - 4
Severe	5 - 6

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 C ENDOMETRIOSIS HEALTH PROFILE QUESTIONNAIRE (EHP-30)

PART 1: CORE QUESTIONNAIRE

DURING THE LAST 4 WEEKS,
HOW OFTEN, BECAUSE OF YOUR ENDOMETRIOSIS, 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 home 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?	☐	☐	☐	☐	☐

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

		Never	Rarely	Sometimes	Often	Always
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 to do 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?	☐	☐	☐	☐	☐

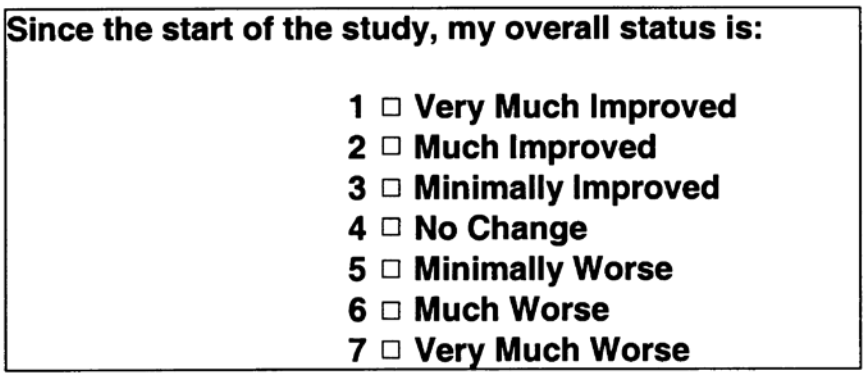
DURING THE LAST 4 WEEKS,
HOW OFTEN, BECAUSE OF YOUR ENDOMETRIOSIS, HAVE YOU...

		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,
HOW OFTEN, BECAUSE OF YOUR ENDOMETRIOSIS, HAVE YOU...

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

APPENDIX D PATIENT GLOBAL IMPRESSION OF CHANGE



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APPENDIX E PIPELLE DE CORNIER®

Pipelle de Cornier®

I - DESCRIPTION

the Pipelle de Cornier® includes:

- A flexible, transparent polypropylene sheath, 3.10 mm in external diameter, 2.6 mm in internal diameter and 23.5 cm long, with a lateral orifice 2.1 mm in diameter in its distal portion and four markings 4, 7, 8 and 10 cm from this extremity. Its proximal end is indented to stop the plunger.
- An internal EVA plunger, which slides up and down when pushed by a flexible acetal resin shaft.

- Single use.
- Latex free.
- Individual packaging.
- Sterilized with ethylene oxide.

II - INDICATIONS

The Pipelle de Cornier® generally requires no local anesthesia or cervical dilatation. As the sampling procedure is painless, the Pipelle de Cornier® can be used for systematic screening programs in women at risk.

The Pipelle de Cornier® is indicated for the following procedures:

- Systematic screening for endometrial cancer and hyperplasia
- Detection of luteal phase insufficiency
- Monitoring endometrial effects of hormone treatments
- Menometrorrhagia with or without HRT
- Screening in premopausal or postmenopausal women
- Investigate endometrial hypertrophy detected by ultrasonography
- Investigate polyps
- Monitor Tamoxifen treatment
- Bacteriological culture to identify pathogens.

III - CONTRAINDICATIONS

Suspected pregnancy:

Evidence of an on-going pregnancy provided by an ultrasound examination or serum hCG levels is an absolute contraindication to using the Pipelle de Cornier®. As a precautionary measure, it is therefore advisable to rule out a pregnancy in women with childbearing potential and not using an effective method of contraception, by performing a serum hCG assay and an ultrasound examination less than 15 days prior to the endometrial biopsy.

Suspected infection of the upper genital tract:

In patients with an infection of the upper genital tract, the Pipelle de Cornier® may be used to sample endometrial tissue, to diagnose a secondary infection of neoplastic tissue, or just to collect pus for bacteriological culture. In this case, special care is warranted to avoid, even more than usual, any risk of perforation of the uterus. Ultrasound examination before or during the procedure is strongly recommended. No force must be applied if unusual resistance is met when introducing the Pipelle de Cornier®.

Cervical stenosis:

In many women on HRT the cervix is stenosed. In women bleeding on SERM therapy or with abnormal or atrophic endometrium, local anesthesia using a small dilator (up to CH 4) can be helpful. In most cases, the sampling procedure will cause no discomfort provided it is performed gently and slowly to allow enough time for adequate dilation.

Very large uterus:

If the uterus is very large (over 15 cm by hysterometry, or corpus uteri length over 10 cm), the screening procedure is less reliable. In this case, ultrasonographic examination of the uterus to determine its position, shape, and size prior to the attempt is recommended, when available.

IV - INSTRUCTIONS FOR USE

- The Pipelle de Cornier® can be shaped before taking it out of its sterile packaging. The resilience of the material helps the device retain a given convexity to fit a uterine anteflexion or retroflexion.
- Disinfect the cervix thoroughly.
- In most cases, Pozzi forceps are not necessary. In post-menopausal women, a local anesthesia with xylocaine

Pipelle de Cornier®

helps to clear a stenosed cervix.

- Slide the Pipelle de Cornier® gently through the cervix up to the uterine fundus. The 4 guide-mark indicates the beginning of the uterine cavity. The 7 guide-mark will generally indicate that the fundus has been reached.
- Draw back the piston to the end of the biopsy cannula until it self locks to create a negative pressure.
- Sweep the uterine fundus slowly several times up to the internal orifice of the cervix, using regular to-and-fro movements while rotating the sampler to include the whole uterine cavity in the specimen.
- Continue until fragments of uterine mucosa appear within the sheath, which generally takes 30 seconds. If the Pipelle de Cornier® "slips" before the end of the procedure, it means the sheath is full. In this case, a second Pipelle de Cornier® must be used to explore the rest of the cavity.
- Remove the Pipelle de Cornier® fully.
- To recover the histology specimen, push the plunger to release the whole content in a vial containing the fixative solution.

V - REFERENCE

REF 1.103.000 PIPELLE DE CORNIER® box of 25 units

Manufactured by PRODIMED
60530 – Neuilly-en-Thelle – FRANCE

Imported by CCD International
88 Eliot Street,
NATICK, MA 01760

Distributed by SEPAL Reproductive Devices, Inc.
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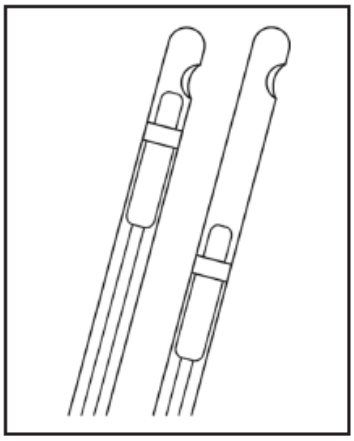
Pipelle de Cornier®



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APPENDIX F 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 and total cholesterol, triglycerides
	Urea and uric acid

Urinary protein dipstick

All the above listed tests are to be performed at the frequencies indicated in APPENDIX A.

Hormones

E2, LH, P4, SHBG, AMH

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.

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