CLINICAL STUDY PROTOCOL

Protocol Number:	**16-OBE2109-008**
EudraCT Number:	**2016-004058-14**
Investigational Medicinal Product:	**OBE2109**
Study Title:	A Phase 3, multicentre, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of daily oral administration of OBE2109 alone and in combination with add-back therapy for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.
Short Study Title:	**A phase 3 study of OBE2109 in subjects with heavy menstrual bleeding associated with uterine fibroids.**
Study Name:	**PRIMROSE 1**
Version number:	Version 3.0
Date:	December 18, 2017
Replacing:	Amended Protocol Version 2.0 – June 26, 2017
Study Sponsor:	ObsEva S.A. 12, Chemin des Aulx 1228 Plan-Les-Ouates, Geneva / Switzerland Phone +41 22 552 38 40 Fax +41 22 743 29 21
Clinical Trial Director:	**Florence Jean** ObsEva S.A. 12, Chemin des Aulx 1228 Plan-Les-Ouates, Geneva / Switzerland Office phone +41 22 552 15 61 Mobile phone +41 79 102 65 71 Fax +41 22 743 29 21
Medical Responsible:	**Elke Bestel, MD** ObsEva S.A. 12, Chemin des Aulx 1228 Plan-Les-Ouates, Geneva / Switzerland Office phone +41 22 552 15 68 Mobile phone +41 78 863 31 30 Fax +41 22 743 29 21

CRO Project Manager:	**Lukasz Kubarek** Chiltern International Sp z o.o, Crown Tower, 2 Hrubieszowska str., 01-209 Warsaw, Poland Office phone : +48 22 395 7000 Mobile phone : +48 608 051 601
	Jean-François Louvion Cytel Inc. Clinical Research Services ICC, Bat. C, 2nd floor Route de Pré-Bois 20 C.P. 1839 1215 Geneva 15 / Switzerland Office phone +41 22 761 70 29

VERSION HISTORY			
Amendment Number	**Amendment Date**	**General / Country-Specific/ Site-Specific**	**Amended Protocol version and date**
01	26 June 2017	General	V.2.0 June 26, 2017
02	18 December 2017	General	V.3.0 December 18, 2017

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. 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 with the applicable regulatory requirements.

Sponsor:

ObsEva S.A., 12, Chemin des Aulx, 1228, Plan-les-Ouates, Geneva, Switzerland

CJL on behalf of — 18 Dec 2017

Signature — Date of signature

Florence Jean, MSc
(Clinical Trial Director)

EBestel — 18 Dec 2017

Signature — Date of signature

Elke Bestel, MD
(Medical Responsible)

Contract Research Organization(s):

Chiltern International Limited and Affiliates, 171 Bath Road, Slough, Berkshire, SL1 4AA, United Kingdom

Lukasz Kubarek
Global Project Manager
I approved this document
19 Dec 2017 10:43 AM +01:00

Signature — Date of signature

Lukasz Kubarek
(Lead Project Manager – Clinical CRO)

Vitaliy Solskyy
Global Project Manager
I approved this document
19 Dec 2017 8:46 AM +02:00

Signature — Date of signature

Vitaliy Solskyy, MD, PhD
(Project Oversight – Clinical CRO)

Cytel Inc, 675 Massachusetts Avenue, Cambridge, MA 02139, United States

18-DEC-2017

Signature — Date of signature

Jean-François Louvion, PhD
(Project Manager – Data management and statistics)

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 an adequate number of qualified staff and adequate facilities available 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.

PI Name:

Institution:

Signature	Date of signature

TABLE OF CONTENTS

ABBREVIATIONS

AB	Add-back
AE	Adverse Event
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BMD	Bone Mineral Density
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats Per Minute
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
cm	Centimeter(s)
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CV	Coefficient of Variation
CYP	Cytochrome P450
DMC	Data Monitoring Committee
DXA	Dual-energy X-ray Absorptiometry
E2	Estradiol
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EQ-5D	Health outcomes questionnaire from the EuroQol group
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIGO	International Federation of Gynaecology and Obstetrics

FSH	Follicle-Stimulating Hormone
g	Gram(s)
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practice
(h)GnRH	(human) Gonadotropin Releasing Hormone
HDL	High Density Lipoprotein
HIFUS	High Intensity Focused UltraSound
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	Institutional Review Board
IU	International Unit
IUD	Intra-Uterine Device
IWRS	Interactive Web Response System
Ki	Dissociation Constant
kg	Kilogram(s)
L	Liter(s)
LEEP	Loop Electrosurgical Excision Procedure
LDH	Lactate DeHydrogenase
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LH	Luteinizing Hormone

LOQ	Limit Of Quantification
M	Meter(s)
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
mg	Milligram(s)
min	Minute(s)
mL	Milliliter(s)
mmHg	Millimeters of mercury
MRgFUS	Magnetic Resonance-guided Focused UltraSound
NETA	Norethisterone acetate
nM	Nanomolar
NOAEL	No Observed Adverse Effect Level
NRS	Numerical Rating Scale
NSAID	NonSteroidal Anti-Inflammatory Drug
OAT3	Organic Anion Transporter 3
OBE2109	(2-Hydroxyethyl)trimethylammonium-3-[2-fluoro-5-(2,3-difluoro-6-methoxybenzyloxy)-4-methoxyphenyl]-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,4-d]pyrimidine-5-carboxylate
OC	Oral Contraceptive
P4	Progesterone
PAP	Papanicolaou test
PD	PharmacoDynamics
PDF	Portable Document Format
PGI-I	Patient Global Impression of Improvement
PK	PharmacoKinetics
PP	Per Protocol
PSF	Pregnancy Surveillance Form
PT	Prothrombin Time

PVC/Al	PolyVinyl Chloride/Aluminum
QoL	Quality of Life
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
SLE	Systemic Lupus Erythematosus
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE(s)	Treatment Emergent Adverse Event(s)
TSH	Thyroid-Stimulating Hormone
TVUS	TransVaginal UltraSound
UAE	Uterine Artery Embolization
UFS-QoL	Uterine Fibroid Symptom and health related Quality of Life questionnaire
ULN	Upper Limit of Normal
US/USA	United States/United States of America
WBC	White Blood Cell

SYNOPSIS

Study Title: A Phase 3, multicentre, randomized, double-blind, placebo-controlled study investigating the efficacy and safety of daily oral administration of OBE2109 alone and in combination with add-back therapy for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.

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

Objectives:

Efficacy objectives

– **Primary**

To demonstrate the superior efficacy versus placebo of OBE2109 alone and in combination with add-back therapy for the reduction of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.

– **Secondary**

To demonstrate the superior efficacy of OBE2109 alone and in combination with add-back therapy versus placebo on:

- Incidence of amenorrhea.
- Time to amenorrhea.
- Hemoglobin levels.
- Menstrual bleeding.

To evaluate the effect of OBE2109 alone and in combination with add-back therapy versus placebo on:

- Pain.
- Uterine fibroid symptom severity and health-related quality of life.
- Uterus volume.
- Myoma volume.

To evaluate the impact of submucosal fibroids (baseline FIGO classification of 0, 1 or 2) on the primary efficacy endpoint.

Safety objectives

- To assess the effect of OBE2109 alone and in combination with add-back therapy versus placebo on bone mineral density.
- To assess the overall safety of OBE2109 alone and in combination with add-back therapy in subjects with uterine fibroids.

Endpoints:

Efficacy endpoints

- **Primary**
  - Reduced menstrual blood loss at 24 weeks of treatment (last 28 days prior to Week 24 visit) defined as menstrual blood loss ≤ 80 mL and ≥ 50% reduction from baseline.
- **Secondary**
  - Amenorrhea up to Weeks 24 and 52.
  - Time to amenorrhea up to Weeks 24 and 52.
  - Time to reduced menstrual blood loss (i.e. ≤ 80 mL and ≥ 50% reduction from baseline) up to Weeks 24 and 52.
  - Number of days of uterine bleeding for each 28-day interval up to Week 52.
  - Hemoglobin levels at Weeks 12, 24, 36, 52 and 64.
- **Additional Secondary endpoints**
  - Pain measured with a numeric rating scale at Weeks 12, 24, 36, 52 and 64.
  - Actual blood loss (in mL) for each 28-day interval up to Week 52.
  - Reduced menstrual blood loss for each 28-day interval up to Week 52.
  - Symptom severity score (UFS QoL) at Weeks 12, 24, 36, 52 and 64.
  - Health-related questionnaire (UFS QoL) score at Weeks 12, 24, 36, 52 and 64.
  - Quality of life measured with the EQ-5D questionnaire at Weeks 12, 24, 36, 52 and 64.
  - Patient Global Impression of Improvement Scale (PGI-I) at Weeks 12, 24, 36, 52 and 64.
  - Myoma volume at Weeks 12, 24, 36, 52 and 64.
  - Uterus volume at Weeks 12, 24, 36, 52 and 64.
  - Impact of submucosal fibroids (baseline FIGO classification of 0, 1 or 2) on the primary efficacy endpoint.

Safety endpoints

- BMD assessed by dual-energy X-ray absorptiometry (DXA) for femoral neck, hip and spine at Weeks 24, 52 and 76.
- Frequency and severity of Treatment-Emergent Adverse Events (TEAEs).
- Any clinically significant changes from baseline in clinical laboratory assessments: hematology, coagulation parameters, chemistry, lipids and serum hormones.
- Any pathological changes from baseline in the endometrium as assessed by histology from endometrial biopsies performed at Weeks 24 and 52.

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

Study Design:

The study is a prospective, randomized, parallel group, double-blind, placebo-controlled phase 3 study investigating the efficacy and safety of OBE2109 alone and in combination with add-back therapy for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.

The study duration will be approximately 85 weeks per subject. If a washout is required for Oral Contraceptive (OC) pill or other non-depot sex hormones, an additional period of up to 6 weeks is allowed between signing the informed consent and Screening.

The study starts with a screening period which must include at least two complete menstrual cycles but could include a third menstrual cycle if the menstrual blood loss volume measured by the Alkaline Hematin Method for the first eight days of the first menstrual period is ≤80mL due to missed collection of sanitary protection. Screening will therefore last between 6 and up to a maximum of 17 weeks, excluding washout. During this period, the subject will receive no study drug.

Once the screening central lab and menstrual blood loss volume measured by Alkaline Hematin Method are received, all inclusion and exclusion criteria will be reviewed. If the eligibility is confirmed, the site will contact the subject to confirm her willingness to continue in the study. If the subject confirms, she will be randomized in a 1:1:1:1:1 ratio to one of five treatment groups:

1. Placebo OBE2109 + Placebo E2/NETA
2. OBE2109 100 mg + Placebo E2/NETA
3. OBE2109 100 mg + E2 1 mg/NETA 0.5 mg
4. OBE2109 200 mg + Placebo E2/NETA
5. OBE2109 200 mg + E2 1 mg/NETA 0.5 mg

An Interactive Web Response System (IWRS) will be used to allocate the appropriate treatment. In order to maintain the blind, all subjects not receiving add-back therapy will receive a matching placebo.

At Week 24 visit, half of the subjects from the Placebo OBE2109 + Placebo E2/NETA arm will be switched to OBE2109 200 mg with add-back (E2 1 mg/NETA 0.5 mg) group while the other half will remain on placebo. This allocation will be pre-determined as part of the randomization and treatment will be continued up to Week 52.

From the Week 24 visit, all subjects in the OBE2109 200 mg without add-back group will receive add-back.

All subjects will be followed up for 24 weeks after end of treatment.

An analysis will be performed after all subjects have completed Week 24. A full analysis will be performed after all subjects have completed Week 52 and will be reported in an integrated Clinical Study Report. The follow up period will be reported in an addendum to the integrated Clinical Study Report. Treatment allocation, individual P4 and E2 levels, Alkaline Hematin results (as of Study Day 1) and the Week 24 study results will remain blinded up to the final Week 76 database lock for the Investigator and the subject.

Study Population:

Five hundred (500) premenopausal women aged 18 or above with symptomatic uterine fibroid(s) characterized by heavy menstrual bleeding will be randomized in approximately 100 sites in the USA.

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 premenopausal woman aged 18 years or above at screening.
3. The subject has a Body Mass Index $\geq$ 18 kg/m^2.
4. The subject has FSH $\leq$ 20 IU/L at screening.
5. The subject has a myomatous uterus < 20 weeks or < 20 cm from cervix to fundus as measured by ultrasound.
6. The subject has a largest uterine myoma of at least 3 cm and at most 12 cm diameter.
7. The subject has menstrual cycles $\geq$ 21 days and $\leq$ 40 days prior to screening.
8. The subject recalls having experienced abnormal heavy menstrual bleeding (heavy or lasting more than 5 days) in a majority of menstrual periods over the last 6 months. Examples of heavy bleeding may include, but are not limited to the following:
    a. Need for double protection to manage menstrual bleeding;
    b. Menstrual bleeding accompanied by the sensation of "gushing" or "flooding";
    c. Soaking one pad and/or tampon or more per hour for three or more consecutive hours;
    d. Regularly needing to change the tampon or sanitary pad at night or regularly soiling bedclothes;
    e. Heavy bleeding which affects work, school, or social activities.
9. The subject has menstrual blood loss > 80 mL for the first eight days of two menstrual periods assessed at screening using the alkaline hematin method. A third menstrual cycle can be assessed if the menstrual blood loss for the first eight days of the first cycle is $\leq$ 80mL.
10. The subject is willing to use and collect sanitary protection (pads or tampons) provided by the Sponsor and compatible with the alkaline hematin method.
11. If of childbearing potential, the subject agrees to use contraception until the end of the study. One of the following non-hormonal birth control methods must be used until 12 weeks after end of treatment (Week 64):
    a. Sexual abstinence (routinely and consistently practiced) from heterosexual intercourse.

b. Partner with a vasectomy performed at least 6 months prior to the study and confirmed azoospermia.

c. Double non-hormonal barrier contraception such as condom or diaphragm each combined with spermicide.

12. If of non-childbearing potential, the subject must have had tubal ligation sterilisation or ESSURE at least two months before the screening visit.

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 study.
2. The subject has a history of uterus surgery that would interfere with the study:
   a. Hysterectomy or total ovariectomy.
   b. Myomectomy or endometrial ablation, uterine artery embolization or MRgFUS/HIFUS in the past 6 months.
3. The subject has only subserosal myoma(s) (FIGO classification type 7).
4. The subject's condition is so severe that she will require surgery within 6 months regardless of the treatment provided.
5. The subject has a significant finding at breast examination at the screening visit, which would preclude inclusion and need follow-up treatment.
6. The subject has had a significant finding on Papanicolaou test (PAP) smear within the past 12 months or at the screening visit, which will require surgical intervention (e.g. Loop Electrosurgical Excision Procedure (LEEP) or cervical conization).
7. The subject has a history of or current uterine, cervical, ovarian, breast cancer or any estrogen-dependent neoplasia.
8. The subject has a history of endometrium atypical hyperplasia or adenocarcinoma prior to screening or similar lesions in the screening biopsy.
9. The subject has a large uterine polyp (> 2 cm), or another clinically significant gynecological condition identified on screening transvaginal ultrasound or endometrial biopsy which might interfere with the study efficacy and safety objectives. Subjects who have had a uterine polypectomy in the 6 months before screening with no recurrence may be included**.**
10. The subject has significantly calcified myomas and/or calcified uterus, which in the opinion of the investigator would affect treatment response.
11. The subject has undiagnosed abnormal uterine bleeding.
12. The subject has a documented severe coagulation disorder (e.g. hemophilia or Von Willebrand disease).
13. The subject has a hemoglobin level < 6 g/dL.
14. The subject has an in-situ copper intra-uterine device (IUD) or an IUD with progestogen. Subjects can be included one month after IUD removal.

15. The subject has a history of known failed treatment for uterine fibroids with GnRH agonists or GnRH antagonists.
16. The subject is likely to require treatment during the study OR has received treatment within the 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. Combined contraceptives and progestins	1 month
d. Depot contraceptives	10 months
e. Selective Progesterone Receptor Modulators (SPRMs) and Selective Estrogen Receptor Modulators (SERMs)	3 months
f. Systemic glucocorticoid treatments for acute diseases (not depot)	1 month
g. Acetylsalicylic acid, mefenamic acid, anticoagulants such as cumarins and/or antifibrinolytic drugs such as tranexemic acid	1 week
h. Strong CYP 3A4 inducers or inhibitors that (might potentially) interact with the add-back (APPENDIX H)	4 weeks

17. The subject is not willing to stop oral contraceptives or other sex hormones during the study. These drugs can be stopped following signature of the informed consent. Baseline assessments will be performed at least 4 weeks after last dose of OC or sex hormone.
18. The subject has a history of or current systemic glucocorticoid therapy for treatment of chronic diseases (e.g. Systemic Lupus Erythematosus (SLE), rheumatoid arthritis).
19. The subject is at significant risk of osteoporosis or has a history of, or known osteoporosis or other metabolic bone disease.
20. The subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) or total bilirubin $\geq$ 2 times the upper limit of normal at screening.
21. The subject has a known positive HIV or viral hepatitis serology prior to screening.
22. 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 for the participation of the subject in the trial or that could interfere with the trial objectives, conduct or evaluation.
23. The subject has a mental condition rendering her unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.
24. The subject has a history of, or known current (within twelve months) problems with alcohol or drug abuse (including painkiller abuse).
25. The subject has a contra-indication to E2 / NETA add-back therapy including:

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

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

c. Known hypersensitivity to the ingredients.

26. The subject is currently taking part in a clinical trial or has been administered any experimental drug in the 12 weeks before dosing.

Investigational Medicinal Product(s) (IMP):

OBE2109 100 mg tablets or placebo tablets for oral administration.

Add-back therapy: E2 1 mg / NETA 0.5 mg or placebo capsules for oral administration.

Data Analysis and Statistics:

1. Efficacy analysis methodology

Individual OBE2109 treatment group versus placebo comparisons will be made for superiority with an overall two-sided Type I error (alpha) of 0.05. In order to account for multiplicity given four different OBE2109 treatment groups, each primary endpoint comparison versus placebo will be conducted at the 0.0125 level of significance, i.e. 0.05 divided by 4. In addition, a sequential testing procedure within each OBE2109 treatment group will be used for the comparison of the secondary endpoints versus placebo, for those where a formal statement of efficacy may be made, thus continuing to protect the overall type I error. An endpoint will only be claimed to be statistically significant if the resulting p-value for that endpoint and all endpoints higher up the testing order (for a given treatment arm) are less than 0.0125. The additional efficacy endpoints will be tested at the 0.0125 significance level with no further adjustments for multiplicity.

The primary analyses of reduced menstrual blood loss at 24 weeks of treatment (last 28 days prior to week 24 visit) will be analysed as a categorical variable (yes / no response) and will be conducted as follows: Cochran-Mantel-Haenszel (CMH) tests with adjustment for the stratification factor race will be used to test the null hypothesis of no treatment effect for each OBE2109 group vs. placebo with regards to the proportion of subjects with a reduced menstrual blood loss at 24 weeks. The odds ratios will be estimated from the CMH test together with the associated 95% CI and corresponding p-values. The proportion per treatment arm will be displayed together with exact Clopper-Pearson 95% CIs. The differences in percentages with corresponding 95% Newcombe-Wilson confidence intervals will also be presented. The homogeneity of the odds ratios will be explored using the Breslow-Day test.

The analysis of amenorrhea will be conducted using the same methods as for the primary endpoint. Time to amenorrhea and time to reduced menstrual blood loss will be analyzed using Kaplan-Meier methodology (estimates and plots will be produced) and each OBE2109 group vs. placebo will be compared using a two-sided log-rank test stratified by race.

In general, between group comparisons for continuous endpoints will be analyzed via repeated measures analysis of covariance, including the baseline and stratification factor race as a covariate, with each treatment group compared versus placebo using contrasts.

Mean hemoglobin will be compared between treatment groups and categorical analyses may also be performed.

Fibroid volume and uterine volume are expected to be log-normally distributed and so will be log-transformed prior to analysis, with the subsequent results (mean differences and corresponding confidence intervals) back transformed and hence reported in terms of ratios. The underlying distributions will be checked, and if deemed necessary alternative analyses may also be conducted. The number of days of uterine bleeding (assessed via the alkaline hematin method) will be analyzed using a negative binomial model or zero-inflated negative binomial, depending on model fit. The PGI-I will be analysed using Mantel-Haenszel methodology.

Impact of submucosal fibroids (baseline FIGO classification of 0, 1 or 2) on the primary efficacy endpoint will be evaluated.

2. Safety analysis methodology

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

Bone mineral density loss will be compared between the OBE2109 treatment groups and placebo in terms of percent change from baseline. In addition, a confidence interval for the percent change from baseline within each group will be produced.

Effect of the add-back therapy versus placebo will be assessed by comparing the OBE2109 200 mg + E2 1 mg/NETA 0.5 mg versus the OBE2109 200 mg group alone, and the OBE2109 100 mg + E2 1 mg/NETA 0.5 mg versus the OBE2109 100 mg group alone on bone mineral density loss.

An analysis of covariance model including the baseline BMD and stratification factor race as a covariate will be used.

Extent of exposure and compliance will be evaluated.

1. BACKGROUND INFORMATION

1.1. INTRODUCTION TO OBE2109

OBE2109 is a new orally active, non-peptide GnRH antagonist. It has been shown to suppress luteinizing hormone (LH) and estradiol (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. Among endometriosis patients who also presented uterine fibroids, the 100 mg and 200 mg doses efficiently controlled uterine bleeding during treatment. It is being developed for the treatment of endometriosis-associated pelvic pain and for uterine myoma-associated heavy menstrual bleeding.

1.2. UTERINE MYOMA

Uterine myomas are benign, monoclonal, hormone-sensitive, smooth muscle tumors of the uterus. They are the most common tumor of the female reproductive tract in premenopausal women and are mostly asymptomatic, affecting approximately 40% of women between 35 and 55 years. By the time they reach 50 years of age, nearly 70% of white women and more than 80% of black women will have had at least one fibroid; severe symptoms develop in 15 to 30% of these women (Bulun *et al.*, 2013). When symptomatic, the main symptoms are heavy menstrual bleeding, abdominal pressure, abdominal pain, increased urinary frequency and infertility. Anemia may occur as a consequence of heavy bleeding. Besides causing physical morbidity, uterine myomas are a frequent cause of significant impairment of Quality of Life (QoL) (Spies *et al*., 2002). They are also a leading cause of hysterectomy (Jacobson *et al*., 2006).

1.3. CONVENTIONAL TREATMENT OF UTERINE MYOMA

The current mainstay of symptomatic myoma treatment is surgery. The most common procedure is hysterectomy, but less invasive procedures have been developed for use when the patient wishes to preserve fertility (e.g. myomectomy by laparoscopy, hysteroscopy or laparotomy) or her uterus (e.g. Uterine Artery Embolization (UAE), endometrial ablation). Short-term complications and long-term consequences of a hysterectomy can be significant, e.g. in the long term a significant increase of moderate and severe urinary incontinence has been reported (Brown *et al.*, 2000).

Myomectomy maintains fertility but does not prevent the reoccurrence of fibroids.

Endometrial ablation is a treatment option for patients who do not wish to maintain fertility, if the dominant symptom is bleeding and the uterus volume is relatively small.

UAE is a lighter procedure than hysterectomy and requires a shorter hospital stay, however there is a risk that myomas will reoccur and require further intervention to control symptoms. Pregnancies after UAE have been reported, however careful counseling of patients is needed as fertility may be seriously impacted.

Gonadotropin-Releasing Hormone (GnRH) agonists have been shown to be effective in reducing myoma-related bleeding, correcting anemia when given concomitantly with iron therapy, reducing abdominal symptoms and reducing myoma as well as uterine volume ((Lethaby *et al.*, 2001), (Stovall *et al.*, 1995)). Although they are registered for the pre-operative treatment of symptomatic myomas, the

use of GnRH agonists has been relatively limited due to their sub-optimal side effect profile caused by suppression of estrogen to castration levels, resulting in florid symptoms of menopause such as hot flushes, depression, mood swings, loss of libido, nervousness and vaginitis (see Lupron label at http://www.lupron.com/). In addition, GnRH agonists have a negative impact on bone mineralization, with an estimated loss of 2.7% in bone mineral density (BMD) after three months of treatment. The loss of BMD is only partially and slowly reversible. As a consequence of the adverse safety profile, the use of GnRH agonists is limited to 3 to 6 months.

Ulipristal acetate, a selective progesterone receptor modulator, is licensed in the European Union and Switzerland for the repeated intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

1.4. SUMMARY OF NON-CLINICAL STUDIES

1.4.1. Non-Clinical Pharmacology

OBE2109 showed potent affinity for the GnRH receptors in different species, particularly the human GnRH (hGnRH) receptor, and acted as an antagonist in vitro (hGnRH dissociation constant (Ki)=27.4 nM). The affinity of KP017, the main metabolite of OBE2109, for the hGnRH receptor was shown to be 4.4-fold lower (Ki=121 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 was 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 did not exhibit partitioning into blood cells.

Tissue distribution of radiolabeled OBE2109 was widespread and 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 in human hepatocytes was 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 roughly 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 (NonSteroidal Anti-Inflammatory Drugs (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 (see results of further clinical testing in section 1.5.1). Transporter substrate assessments showed that OBE2109 is a substrate for OATP1B1, OATP1B3, and to a lesser extend for OAT3. OBE2109 may have direct and time-dependent inhibitory action on CYP2C8 activity and could inhibit the organic anion transporter 3 (OAT3) uptake transporter at clinically relevant concentrations.

1.4.2.2. *Toxicology*

Overall, the toxicological profile of OBE2109 from repeated-dose toxicity studies was dominated by the consequences of its pharmacological activity as a GnRH receptor antagonist. During pivotal toxicology studies, dose levels of 200 and 10 mg/kg/day OBE2109 were shown to be the No Observed Adverse Effect Level (NOAEL) in the main toxicology species rat (26-week daily oral administration) and monkey (39-week daily oral administration), respectively, and resulted in therapeutic indices (based on total / unbound exposure) for a human dose of 200 mg/day of 6.7 / 4.6 and 0.8 / 3.6, respectively.

Reproductive toxicity studies, especially fertility studies and embryo-fetal 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-fetal 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 supports clinical dosing regimens of up to 200 mg OBE2109 per day.

1.5. SUMMARY OF CLINICAL STUDIES

OBE2109 efficacy, safety, pharmacokinetics (PK) and drug-drug interaction with CYP3A4 substrate midazolam were investigated in two Phase 1 studies (Study KLH1101 and Study 16-OBE2109-005) in Japanese and Caucasian volunteers at 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.

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 (standard fat meal). 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 a dose-dependent suppression of LH, FSH and E2.

A drug-drug interaction study (Study 16-OBE2109-005) in healthy Caucasian women of child bearing potential showed that administration of 200 mg OBE2109 did not induce CYP3A4 isoenzyme as demonstrated by the absence of effects on the pharmacokinetics of midazolam. In the same study, concomitant administration of OBE2109 with food (high fat meal) indicated that peak plasma concentrations (Cmax) were decreased while the extent of exposure (AUC) remained unchanged. This decrease in exposure is not clinically significant in the context of a chronic administration and therefore OBE2109 could be taken without regards to meals.

A phase 1 PK/PD study was performed to evaluate the pharmacodynamics, safety, tolerability and pharmacokinetics of the oral GnRH receptor antagonist OBE2109 alone or co-administered with E2/NETA add-back therapy. This was a prospective, randomized, parallel group study involving 76 healthy women of child-bearing potential. Subjects were randomized to one of five arms for a period of six weeks to receive either 100 mg of OBE2109 alone or with one of two add-back doses (E2/NETA: 0.5mg/0.1mg or 1mg/0.5mg), or 200 mg of OBE2109 alone or with the higher dose of add-back (E2/NETA: 1mg/0.5mg).

It was observed that within a week OBE2109 at 100 mg and 200 mg doses reduced E2 to levels that are expected to treat symptoms of Uterine Fibroids. The marked E2 reduction seen with stand-alone dosing supports the need for add-back therapy to minimize bone mineral density loss in the 200 mg group. The median E2 trough level of 18 pg/mL following six weeks of dosing with 100 mg of OBE2109 suggests that approximately 50% of patients may not require add-back therapy. The addition of add-back therapy doses in the study to subjects treated with 100 mg and 200 mg of OBE2109 restored E2 levels to the target range that is expected to treat symptoms of uterine fibroids whilst minimizing BMD loss (i.e. 20-50 pg/ml).

1.5.2. Efficacy

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. Approximately half of the 107 subjects presented with uterine fibroids as detailed in the table below. Post-hoc analyses were performed on this subgroup of subjects.

Treatment group	50 mg	100 mg	200 mg	Placebo
N	29	26	28	24
With Uterine Fibroids (N)	12	12	13	14
Fibroids diameter ≥ 30mm (N)	4	4	7	5

The bleeding profile of the uterine fibroid subgroup was assessed and compared to the same data in the entire study population to establish the right dose for further clinical studies in uterine fibroid subjects. The 50 mg dose of OBE2109 suppressed the menstrual bleeding insufficiently in the full subject population and even less in the fibroid subgroup, as bleeding suppression was achieved in only 1 of 12 subjects of the 50 mg dose in the uterine fibroid subgroup. In the subgroup of uterine fibroid subjects,

the 100 mg and the 200 mg dose suppressed menstruation in 8 of 12 and in all 13 subjects, respectively. Similarly, assessment of the proportion of bleeding days indicated that for uterine fibroid subjects and especially for fibroid subjects with bigger fibroids (≥ 30mm of diameter) higher doses of OBE2109 are needed to control the menstrual bleeding. Consequently, it was decided that the 50 mg dose insufficiently controls uterine bleeding, and that for subjects with heavy menstrual bleeding due to fibroids the lowest dose to be tested should be the 100 mg dose.

1.5.3. Safety

Overall, 42 subjects have been exposed to single doses and 187 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.

The most frequent side effects were disturbances of the menstrual cycle (Metrorrhagia) and hypoestrogenic adverse events (hot flushes).

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

The vast majority of Adverse Events (AEs) were reported as being of "mild" severity; only a 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

Orally active GnRH antagonists have been shown to significantly reduce myoma-related heavy menstrual bleeding (AbbVie 2016). OBE2109 is a GnRH-Antagonist that dose-dependently decreases estradiol levels. To date, subjects have been exposed to OBE2109 in a Phase 1 healthy volunteer study and in three Phase 2a endometriosis studies. One endometriosis study (KLH1202) in Japanese endometriosis subjects included 107 subjects who were exposed to 50 mg, 100 mg, 200 mg or placebo for 3 months. Approximately half of these subjects were also diagnosed with uterine fibroids. Post-hoc analyses on this subgroup of subjects have been performed looking at the control of bleeding as well as estradiol levels for the 50, 100 and 200 mg dose. It has been concluded that the 50 mg dose does not allow for a satisfactory control of bleeding and should not be further studied in this indication. On the other hand, 100 mg and 200 mg were effective and are therefore investigated in the proposed studies. These doses have been shown to significantly decrease estradiol levels in some Japanese subjects. Despite US and European subjects having a higher weight, it is expected that in some subjects these doses may lead to hypoestrogenic side effects such as hot flushes and BMD loss.

To minimize or prevent the hypoestrogenic side effects of GnRH agonists, add-back therapy is frequently used and is known to improve quality of life, BMD and adherence rates to treatment. It is therefore proposed to use an add-back therapy in addition to OBE2109. Various add-back therapy regimens are available on the market and there is no clear guidance regarding which add-back therapy is optimal. Combined add-back therapies with conjugated estrogens and Norethisterone acetate (NETA) appear to be more effective for increasing total BMD than NETA monotherapy; NETA, combined with conjugated estrogens or alone, is generally preferable over MPA add-back therapy as NETA has both

estrogenic and androgenic properties and through its estrogenic activity, may exert beneficial effects on BMD and vasomotor symptoms in women treated with GnRH-agonists. As per a recent publication (Lee *et al*, 2016), the proposed add-back (estradiol + NETA) appears to have the best efficacy in terms of quality of life, reduction of hypoestrogenism-associated symptoms, and prevention of BMD loss.

A phase 1 PK/PD study was performed to evaluate the pharmacodynamics, safety, tolerability and pharmacokinetics of the oral GnRH receptor antagonist OBE2109 alone or co-administered with E2/NETA add-back therapy. Based on estradiol concentrations, bleeding pattern and bone turnover markers, the higher dose of add-back therapy (E2/NETA: 1mg/0.5mg) best balanced the intended therapeutic effect with deleterious side effects.

1.7. SUMMARY OF OVERALL RISKS AND BENEFITS

OBE2109 is a new oral GnRH antagonist which has been shown to control uterine bleeding in Japanese subjects with endometriosis, half of whom presented with uterine fibroids. It has a half-life consistent with once daily dosing. Efficacy was demonstrated at daily doses of 100 and 200 mg for 3 months.

OBE2109 was well-tolerated at the doses proposed for this study. The most commonly reported AEs in the Phase 2 studies were metrorrhagia and hot flushes, which are related to the pharmacological activity of OBE2109.

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

The hypoestrogenic side effects of GnRH agonists will be mitigated by the combination with an add-back regimen, at the latest after 6 months of treatment with the highest dose of OBE2109.

The suggested add-back (E2 1mg /NETA 0.5 mg) therapy is registered for the treatment of postmenopausal symptoms in the USA. The most frequently reported adverse events in postmenopausal women were vaginal bleeding, breast pain/tenderness, vaginitis, fluid retention, depression, headache, nausea, breast edema, aggravation of uterine fibroids, peripheral edema and weight gain. Evidence regarding the risks associated with hormone replacement therapy in the treatment of premature menopause symptoms is limited. The risk to subjects in this study from treatment with OBE2109 and add-back therapy is considered low owing to the good safety profile of the drugs being used. The BMD density loss will be monitored during the study and subjects who present with more than 8% BMD loss at either femoral neck, hip or spine or a Z-score $\leq$-2.5 at the Week 24 scan will be required to stop treatment.

In conclusion, OBE2109 has a favorable benefit/risk ratio and represents a potentially useful therapy for treating heavy menstrual bleeding associated with uterine fibroids.

2. OBJECTIVES

2.1. EFFICACY OBJECTIVES

2.1.1. Primary

To demonstrate the superior efficacy versus placebo of OBE2109 alone and in combination with add-back therapy for the reduction of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.

2.1.2. Secondary

To demonstrate the superior efficacy of OBE2109 alone and in combination with add-back therapy versus placebo on:

- Incidence of amenorrhea.
- Time to amenorrhea.
- Hemoglobin levels.
- Menstrual bleeding.

To evaluate the effect of OBE2109 alone and in combination with add-back therapy versus placebo on:

- Pain.
- Uterine fibroid symptom severity and health-related quality of life.
- Uterus volume.
- Myoma volume.

To evaluate the impact of submucosal fibroids (baseline FIGO classification of 0, 1 or 2) on the primary efficacy endpoint.

2.2. SAFETY OBJECTIVES

- To assess the effect of OBE2109 alone and in combination with add-back therapy versus placebo on bone mineral density.
- To assess the overall safety of OBE2109 alone and in combination with add-back therapy in subjects with uterine fibroids.

3. ENDPOINTS

3.1. EFFICACY ENDPOINTS

3.1.1. Primary

- Reduced menstrual blood loss at 24 weeks of treatment (last 28 days prior to Week 24 visit) defined as menstrual blood loss ≤ 80 mL and ≥ 50% reduction from baseline.

3.1.2. Secondary

- Amenorrhea up to Weeks 24 and 52.
- Time to amenorrhea up to Weeks 24 and 52.

- Time to reduced menstrual blood loss (i.e. ≤ 80 mL and ≥ 50% reduction from baseline) up to Weeks 24 and 52.
- Number of days of uterine bleeding for each 28-day interval up to Week 52.
- Hemoglobin levels at Weeks 12, 24, 36, 52 and 64.

3.1.3. Additional Secondary endpoints

- Pain measured with a numeric rating scale at Weeks 12, 24, 36, 52 and 64.
- Actual blood loss (in mL) for each 28-day interval up to Week 52.
- Reduced menstrual blood loss for each 28-day interval up to Week 52.
- Symptom severity score (UFS QoL) at Weeks 12, 24, 36, 52 and 64.
- Health-related questionnaire (UFS QoL) score at Weeks 12, 24, 36, 52 and 64.
- Quality of life measured with the EQ-5D questionnaire at Weeks 12, 24, 36, 52 and 64.
- Patient Global Impression of Improvement Scale (PGI-I) at Weeks 12, 24, 36, 52 and 64.
- Myoma volume at Weeks 12, 24, 36, 52 and 64.
- Uterus Volume at Weeks 12, 24, 36, 52 and 64.
- Impact of submucosal fibroids (baseline FIGO classification of 0, 1 or 2) on the primary efficacy endpoint.

3.2. SAFETY ENDPOINTS

- BMD assessed by dual-energy X-ray absorptiometry (DXA) for femoral neck, hip and spine at Weeks 24, 52 and 76.
- Frequency and severity of treatment-emergent adverse events (TEAEs).
- Any clinically significant changes from baseline in clinical laboratory assessments: hematology, coagulation parameters, chemistry, lipids and serum hormones.
- Any pathological changes from baseline in the endometrium as assessed by histology from endometrial biopsies performed at Weeks 24 and 52.
- Change from baseline in any other safety parameter including weight, vital signs, gynecological assessment, breast assessment and endometrial thickness.

4. STUDY DESIGN

The study is a prospective, randomized, parallel group, double-blind, placebo-controlled phase 3 study investigating the efficacy and safety of OBE2109 alone and in combination with add-back therapy for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women.

The study duration will be approximately 85 weeks per subject. If a washout is required for OC pill or other non-depot sex hormones, an additional period of up to 6 weeks is allowed between signing the informed consent and Screening. A schematic of the study design is shown in Figure 1.

The study starts with a screening period which must include at least two complete menstrual cycles but could include a third menstrual cycle if the menstrual blood loss volume measured by the Alkaline Hematin Method for the first eight days of the first menstrual period is ≤80mL due to missed collection of sanitary protection. Screening will therefore last between 6 and up to a maximum of 17 weeks, excluding washout. During this period, the subject will receive no study drug.

Once the screening central lab and menstrual blood loss volume measured by Alkaline Hematin Method are received, all inclusion and exclusion criteria will be reviewed. If the eligibility is confirmed, the site will contact the subject to confirm her willingness to continue in the study. If the subject confirms, she will be randomized in a 1:1:1:1:1 ratio to one of five treatment groups:

1. Placebo OBE2109 + Placebo E2/NETA
2. OBE2109 100 mg + Placebo E2/NETA
3. OBE2109 100 mg + E2 1 mg/NETA 0.5 mg
4. OBE2109 200 mg + Placebo E2/NETA
5. OBE2109 200 mg + E2 1 mg/NETA 0.5 mg

An Interactive Web Response System (IWRS) will be used to allocate the appropriate treatment. In order to maintain the blind, all subjects not receiving add-back therapy will receive a matching placebo.

At Week 24 visit, half of the subjects from the Placebo OBE2109 + Placebo E2/NETA arm will be switched to OBE2109 200 mg with add-back (E2 1 mg/NETA 0.5 mg) group while the other half will remain on placebo. This allocation will be determined as part of the randomization and treatment will be continued up to Week 52.

From the Week 24 visit, all subjects in the OBE2109 200 mg without add-back group will receive add-back.

All subjects will be followed up for 24 weeks after end of treatment.

An analysis will be performed after all subjects have completed Week 24. A full analysis will be performed after all subjects have completed Week 52 and will be reported in an integrated Clinical Study Report. The follow up period will be reported in an addendum to the integrated Clinical Study Report. Treatment allocation, individual P4 and E2 levels, Alkaline Hematin results (as of Study Day 1) and the Week 24 study results will remain blinded up to the final Week 76 database lock for the Investigator and the subject.

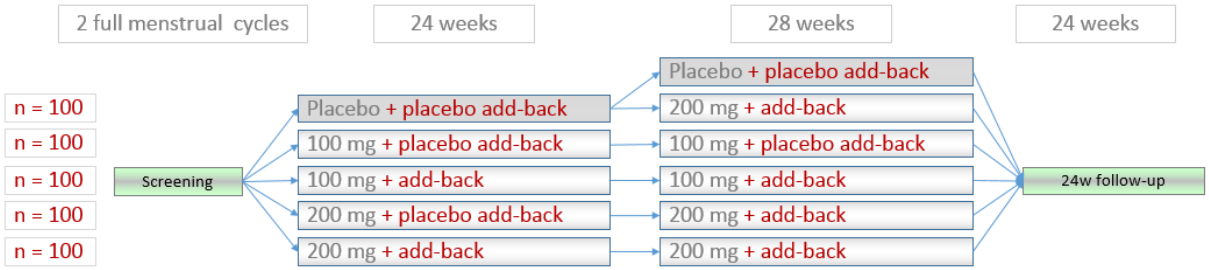


Figure 1: Study Design

5. STUDY POPULATION

5.1. SUBJECTS

5.1.1. Description of the target population

The target population will be premenopausal women aged 18 years or above with symptomatic uterine fibroid(s) characterized by heavy menstrual bleeding defined by a menstrual blood loss volume > 80 mL for two screening menstrual periods assessed by the Alkaline Hematin Method.

Subjects must not be planning to become pregnant until the end of the study and must agree to use double non-hormonal barrier contraception from screening to 12 weeks after end of treatment in case of heterosexual intercourse.

Due to a high incidence in fibroid prevalence and more severe symptoms in black women, a stratification will ensure equal distribution of black subjects within each treatment arm. The stratification will be managed via the IWRS.

5.1.2. Number of subjects

It is planned to randomize five hundred (500) subjects in a 1:1:1:1:1 ratio in order to obtain the following initial treatment allocation:

- Placebo OBE2109 + Placebo E2/NETA – 100 subjects
- OBE2109 100 mg + Placebo E2/NETA – 100 subjects
- OBE2109 100 mg + E2 1 mg/NETA 0.5 mg – 100 subjects
- OBE2109 200 mg + Placebo E2/NETA – 100 subjects
- OBE2109 200 mg + E2 1 mg/NETA 0.5 mg – 100 subjects

5.1.3. Study region/location

Approximately 100 investigational sites in the USA will conduct the study. Potential back-up sites will be identified and qualified and will be activated in case of recruitment issues. Recruitment will be competitive between 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 premenopausal woman aged 18 years or above at screening.
3. The subject has a Body Mass Index ≥ 18 kg/m^2.
4. The subject has FSH ≤ 20 IU/L at screening.
5. The subject has a myomatous uterus < 20 weeks or < 20 cm from cervix to fundus as measured by ultrasound.
6. The subject has a largest uterine myoma of at least 3 cm and at most 12 cm diameter.
7. The subject has menstrual cycles ≥ 21 days and ≤ 40 days prior to screening.
8. The subject recalls having experienced abnormal heavy menstrual bleeding (heavy or lasting more than 5 days) in a majority of menstrual periods over the last 6 months. Examples of heavy bleeding may include, but are not limited to the following:
    a. Need for double protection to manage menstrual bleeding;
    b. Menstrual bleeding accompanied by the sensation of "gushing" or "flooding";
    c. Soaking one pad and/or tampon or more per hour for three or more consecutive hours;
    d. Regularly needing to change the tampon or sanitary pad at night or regularly soiling bedclothes;
    e. Heavy bleeding which affects work, school, or social activities.
9. The subject has menstrual blood loss > 80 mL for the first eight days of two menstrual periods assessed at screening using the alkaline hematin method. A third menstrual cycle can be assessed if the menstrual blood loss for the first eight days of the first cycle is $\leq$ 80mL.
10. The subject is willing to use and collect sanitary protection (pads or tampons) provided by the Sponsor and compatible with the alkaline hematin method.
11. If of childbearing potential, the subject agrees to use contraception until the end of the study. One of the following non-hormonal birth control methods must be used until 12 weeks after end of treatment (Week 64):
    a. Sexual abstinence (routinely and consistently practiced) from heterosexual intercourse.

b. Partner with a vasectomy performed at least 6 months prior to the study and confirmed azoospermia.

c. Double non-hormonal barrier contraception such as condom or diaphragm each combined with spermicide.

12. If of non-childbearing potential, subject must have had tubal ligation sterilization or ESSURE at least two months before the screening visit.

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 study.
2. The subject has a history of uterus surgery that would interfere with the study:
    a. Hysterectomy or total ovariectomy,
    b. Myomectomy or endometrial ablation, uterine artery embolization or MRgFUS/HIFUS in the past 6 months.
3. The subject has only subserosal myoma(s) (FIGO classification type 7).
4. The subject's condition is so severe that she will require surgery within 6 months regardless of the treatment provided.
5. The subject has a significant finding at breast examination at the screening visit, which would preclude inclusion and need follow-up treatment.
6. The subject has had a significant finding on Papanicolaou test (PAP) smear within the past 12 months or at the screening visit, which will require surgical intervention (e.g. Loop electrosurgical excision procedure (LEEP) or cervical conization).
7. The subject has a history of or current uterine, cervical, ovarian, breast cancer or any estrogen-dependent neoplasia.
8. The subject has a history of endometrium atypical hyperplasia or adenocarcinoma prior to screening or similar lesions in the screening biopsy.
9. The subject has a large uterine polyp (> 2 cm), or another clinically significant gynecological condition identified on screening transvaginal ultrasound or endometrial biopsy which might interfere with the study efficacy and safety objectives. Subjects who have had a uterine polypectomy in the 6 months before screening with no recurrence may be included**.**
10. The subject has significantly calcified myomas and/or calcified uterus, which in the opinion of the investigator would affect treatment response.
11. The subject has undiagnosed abnormal uterine bleeding.
12. The subject has a documented severe coagulation disorder (e.g. hemophilia or Von Willebrand disease).
13. The subject has a hemoglobin level < 6 g/dL.
14. The subject has an in-situ copper intra-uterine device (IUD) or an IUD with progestogen. Subjects can be included one month after IUD removal.

15. The subject has a history of known failed treatment for uterine fibroids with GnRH agonists or GnRH antagonists.
16. The subject is likely to require treatment during the study OR has received treatment within the 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. Combined contraceptives and progestins	1 month
d. Depot contraceptives	10 months
e. Selective Progesterone Receptor Modulators (SPRMs) and Selective Estrogen Receptor Modulators (SERMs)	3 months
f. Systemic glucocorticoid treatments for acute diseases (not depot)	1 month
g. Acetylsalicylic acid, mefenamic acid, anticoagulants such as cumarins and/or antifibrinolytic drugs such as tranexemic acid	1 week
h. Strong CYP 3A4 inducers or inhibitors that (might potentially) interact with the add-back (APPENDIX H)	4 weeks

17. The subject is not willing to stop oral contraceptives or other sex hormones during the study. These drugs can be stopped following signature of the informed consent. Baseline assessments will be performed at least 4 weeks after last dose of OC or sex hormone.
18. The subject has a history of or current systemic glucocorticoid therapy for treatment of chronic diseases (e.g. Systemic Lupus Erythematosus (SLE), rheumatoid arthritis).
19. The subject is at significant risk of osteoporosis or has a history of, or known osteoporosis or other metabolic bone disease.
20. The subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) or total bilirubin $\geq$ 2 times the upper limit of normal at screening.
21. The subject has a known positive HIV or viral hepatitis serology prior to screening.
22. 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 for the participation of the subject in the trial or that could interfere with the trial objectives, conduct or evaluation.
23. The subject has a mental condition rendering her unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.
24. The subject has a history of, or known current (within twelve months) problems with alcohol or drug abuse (including painkiller abuse).
25. The subject has a contra-indication to E2 / NETA add-back therapy including:
    a. Active deep vein thrombosis, pulmonary embolism, or history of these conditions.

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

c. Known hypersensitivity to the ingredients.

26. The subject is currently taking part in a clinical trial or has been administered 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-specific screening procedures after being given sufficient time to consider her participation and the opportunity to ask for further details. One original copy of the consent form will be signed and personally dated by both the subject and the Investigator or medical delegate. The original signed copy will be kept by the Investigator in the confidential investigator file and a 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 whether 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:

- First 3 digits: site identifier (001 to 999)
- 4^{th} and 5^{th} digits: subject number (01 to 99)

During the entire 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 randomized in the study, the reason 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 5 treatment groups in a 1:1:1:1:1 ratio as shown in Figure 1. The randomization will determine the full treatment allocation up to Week 52.

Randomization will be done according to a computer-generated list at the Randomization Call (R) . Treatment assignments will be obtained via the IWRS according to the randomization list. The subject will be allocated a randomization number and corresponding treatment kit numbers via the IWRS.The randomization number allocated to the subject will allow any unblinded study personnel to identify the treatment group to which the subject is randomized. Each subject will receive two kits at each dispensing, one for OBE2109 and one for the add-back therapy. The treatment kit numbers will refer to unique kits present at site and corresponding to the randomization allocation. The OBE2109 kit number will start with the letter B and be 5 characters long: B0001, B0002, B0003 etc. The add-back therapy kit numbers will begin with the letter N and be 5 characters long: N0001, N0002, etc.

Treatment allocation will remain blinded up to the final Week 76 database lock for the Investigator and the subject.

Screen failures may be re-screened at a later date with the Sponsor's approval if it is believed that the reason for excluding them initially is no longer applicable. Any subject re-screened will be assigned a new Subject Identification Number in the eCRF and all the screening information will be collected again.

For screen failed subjects, the following information will be collected at a minimum: Informed Consent, Demographics, Adverse Events, Concomitant Medications/Procedures for Adverse Events, and reason for screen failure.

6.2. OUTLINE OF STUDY PROCEDURES AND ASSESSMENTS

The visit schedule is illustrated in Figure 2 below:

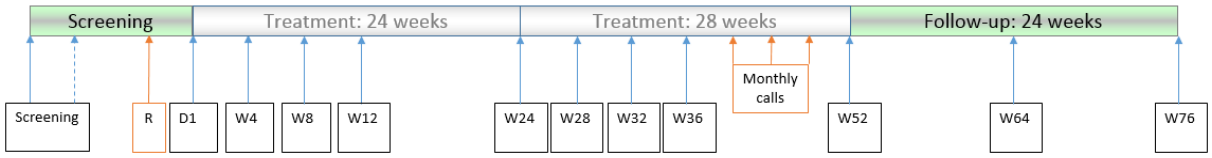


Figure 2: Schedule of Visits

6.2.1. Screening Period

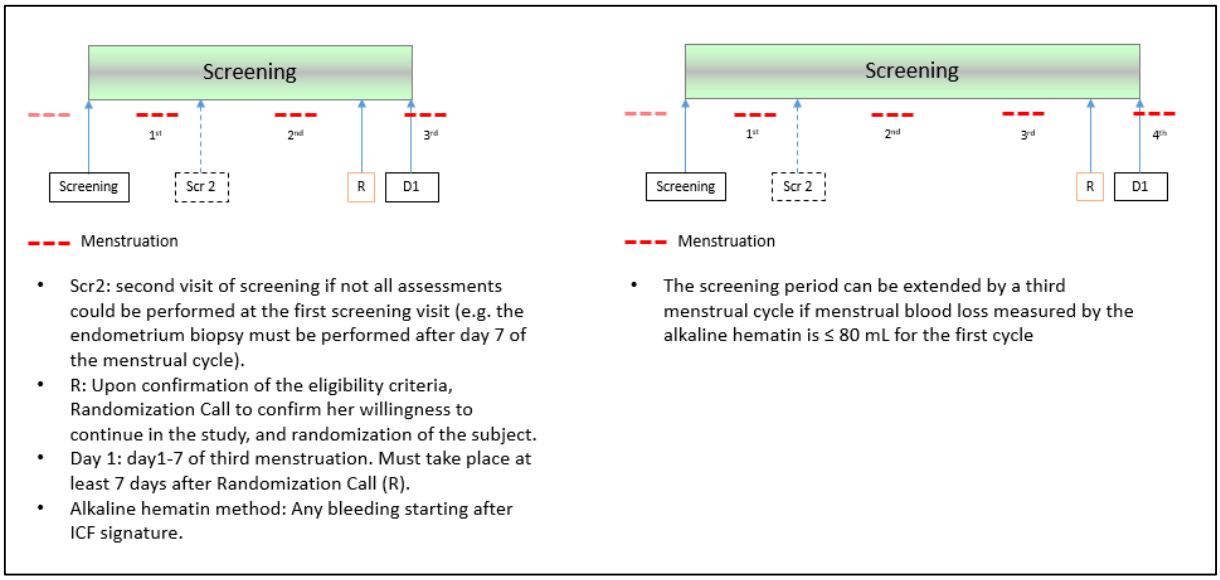
The subject will be informed of the study objectives and overall requirements, and written informed consent will be obtained before performing any study-specific procedures that are not standard of care.

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.

If required for wash-out of oral contraceptives or other non-depot sex hormones, an additional period of up to 6 weeks is allowed between signing the informed consent and the first screening visit.

The screening period will last between 6 and 17 weeks (excluding washout). In general, the screening must cover two full menstrual cycles and should end on the 1st day of menstruation for the 3rd cycle. However, if the menstrual blood loss measured by the Alkaline Hematin Method for the first cycle is ≤80mL, due to missed collection of sanitary protection, a third cycle may be added as this will give the

subject more time to become familiar with the Alkaline Hematin Method and give the site the opportunity to re-train the subject if required. During screening, the subject will be seen up to three times. Screening assessments may be performed over one visit if the timing of the visit is suitable for all assessments. The screening ultrasound must be prioritized and performed as soon as the subject starts screening to confirm that her heavy menstrual bleeding is due to Uterine Fibroids (inclusion criteria 5 and 6). The endometrium biopsy must be performed after day 7 of the menstrual cycle or following bleeding cessation for subjects whose heavy menstrual bleeding exceeds 7 days.



- Scr2: second visit of screening if not all assessments could be performed at the first screening visit (e.g. the endometrium biopsy must be performed after day 7 of the menstrual cycle).
- R: Upon confirmation of the eligibility criteria, Randomization Call to confirm her willingness to continue in the study, and randomization of the subject.
- Day 1: day1-7 of third menstruation. Must take place at least 7 days after Randomization Call (R).
- Alkaline hematin method: Any bleeding starting after ICF signature.

- The screening period can be extended by a third menstrual cycle if menstrual blood loss measured by the alkaline hematin is ≤ 80 mL for the first cycle

Figure 3: Screening Schedule

During this time the following study screening assessments will be completed (see schedule of assessments in APPENDIX A):

- Demographic data, height
- Medical history including concomitant diseases, obstetric/gynecological including uterine fibroid diagnosis
- Previous and current treatment or surgery for uterine fibroids and eligibility for future surgery
- Physical examination (including weight)
- Vital signs (blood pressure and heart rate)
- Gynecological examination, including manual breast examination (by palpation) and recording of previous menstrual cycle duration and strength (incl criteria 7)
- TVUS of uterus and ovaries to measure the uterus dimensions (incl criteria 5) and myoma dimensions (incl criteria 6), 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 does not have a large uterine polyp >2cm or a calcified

myoma or uterus. The ultrasound assessment must be performed at the beginning of the screening period to ensure that only subjects who suffer from heavy menstrual bleeding due to Uterine Fibroids (meet incl. criteria 5 and 6) undergo all other screening procedures.

- Endometrium biopsy should be performed after day 7 of the menstrual cycle. If heavy menstrual bleeding exceeds 7 days, the endometrial biopsy should be done following bleeding cessation. 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 report is available in source documents and slides are available to be provided if requested for current study assessment through retrospective central laboratory reading.

If the result of the endometrium biopsy is not available at the time of randomization, the subject can be randomized. If there is a subsequent clinically significant finding in the biopsy, the subject will be withdrawn immediately.

In case of multiple (at least two) unsuccessful attempts to get sufficient endometrial tissue, the subject is allowed to be randomized without any screening endometrial biopsy under the following conditions:

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

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

c) The medical monitor of the study approves the randomization of the subject.

- PAP smear

A screening PAP smear is not required if the subject has had a PAP test within the last 12 months indicating no clinically significant abnormalities requiring surgical intervention (e.g. LEEP or cervical conization) and the results are available for source document verification.

- Blood samples for hematology, coagulation parameters, chemistry, FSH and TSH. In case of unexpected high FSH result, a redraw of the blood for FSH is allowed but must be performed in the first five days of the subject's menstrual cycle to avoid the mid-cycle FSH peak.
- Urinary protein dipstick
- Urine pregnancy test
- Return of sanitary protection (if relevant and not already returned)
- Diary completion check (if applicable)
- Contraception counseling (not applicable in case of tubal ligation)

The eDiary should be completed:

- Daily, in the evening at approximately the same time: uterine bleeding

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

The subject will be advised on a suitable non-hormonal double barrier contraceptive method to be used up to 12 weeks after the end of treatment (Week 64). The subject will receive double barrier contraception (condoms and spermicide) if necessary. It will be provided upon need at each subsequent visit over the duration of the study. Between Week 64 and Week 76, the subject must continue to use contraception, however hormonal or non-hormonal methods are acceptable.

If the subject is eligible for continued screening based on completed assessments, she 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 daily bleeding status. Subject diary completion should be started on the first day of Screening.

In addition, she will be given sanitary protection and containers and will be trained on correct collection of any sanitary protection from the first day of menstruation onwards. Sanitary protection will be provided throughout the study.

On the first day of the menstruation after ICF signature, the subject will start collecting any soiled sanitary protection and storing it in the provided daily containers as per instructions. She will be informed about the different options to return the soiled sanitary products for analysis.

The subject should not send a container for the current day if she is still bleeding. Where possible, she should send all sanitary protection from a particular day in the same shipment. She must continue throughout the study to collect the sanitary material for any day she experiences bleeding.

The sanitary products must be received by the laboratory within 3 weeks of collection. The subject must be instructed to return the transportation box to the investigator's site either once it is full or after a collection period of a maximum of 12 days. During the second screening menstrual period (or third if the first period was $\leq$ 80mL), the box should be returned by the subject after the first eight days of collection.

During screening, the site will receive the results of the Alkaline Hematin Method on a regular basis. If menstrual blood loss is $\leq$ 80mL for the first eight days of the first menstrual period due to missed collection of sanitary protection, the subject can be offered the possibility to measure menstrual blood loss over two further cycles. The subject should be re-trained on the alkaline hematin method prior to starting the second cycle.

Subjects will be provided with iron supplements if Hemoglobin (Hb) levels are below 10 g/dL.

6.2.1.1. *Randomization*

Upon receipt of the menstrual blood loss volume measured by the Alkaline Hematin Method for the first eight days of the second menstrual cycle (or third if applicable) and central lab results, eligibility requirements will be checked. If the subject is eligible, the site staff will call her to confirm her willingness to continue in the study (Randomization Call (R)).
If the subject agrees, she will be randomized. The IWRS will provide the kit numbers and the necessary kits will be ordered via the IWRS for their availability at the Day 1 visit.

Randomization will not be postponed if the results of the endometrium biopsy done during the screening period are not available.

The randomization number of a subject who has withdrawn from the study after randomization will not be re-allocated irrespective of whether the subject has subsequently been treated or not.

Upon the start of the next menstruation (third if the screening lasted for two cycles or fourth if screening lasted three cycles) (Figure 3), the subject must contact the site to schedule the Day 1 visit, which should occur between the first and seventh day (inclusive) of the menstrual cycle. The visit should be scheduled at least 7 days after randomization in the IWRS to guarantee the availability of the treatment kits at the clinical site. Note that in exceptional cases, Day 1 visit may occur between Day 8 and Day 12 of the third or fourth cycle but only upon prior approval and instructions by the Sponsor.

If for logistical reasons or 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 may be allowed to start Day 1 in the following cycle. In this case, the eligibility will be assessed on the already completed cycles. However, the eDiary recording should be continued daily during the additional cycle.

6.2.2. Treatment period

During the whole study until Week 64, the subject will be asked to record in her eDiary:

- Daily, at approximately the same time each evening, her IMP intake and uterine bleeding.
- At site, at visits Day 1, Week 12, Week 24, Week 36, Week 52 and Week 64, the UFS-QoL, EQ-5D and pain Numerical Rating Scale (NRS) questionnaires.
- At site, at visits Week 12, Week 24, Week 36, Week 52 and Week 64, the Patient Global Impression of Improvement Questionnaire.

6.2.2.1. *Baseline visit – Study Day 1 visit*

The subject will come to the investigational site between Day 1 and Day 7 of her menstrual cycle to receive the treatment kit. Note that in exceptional cases, Day 1 visit may occur between Day 8 and Day 12 of the third or fourth cycle but only upon prior approval and instructions by the Sponsor. At the Day 1 visit, she will undergo the following evaluations before drug administration:

- Previous and concomitant treatments recording
- AE recording
- Physical examination (including weight)
- Vital signs (blood pressure and heart rate)
- Contraception counseling (not applicable in case of tubal ligation)
- Urine pregnancy test
- Urinary protein dipstick
- Return of soiled sanitary protection (if relevant and not already returned)
- eDiary check for good completion
- Assess iron intake (if applicable)

- Pain NRS, UFS QoL and EQ-5D questionnaires will be completed in the diary at site

The following assessments must be performed after confirmation that the subject is not pregnant. Blood samples should be taken prior to first administration of study drug as part of baseline assessments:

- Blood samples for hematology, coagulation parameters, chemistry, lipids, hormones (E2, P4) assessments. The subject must be fasting for the lipid blood sample. The blood sampling can be done prior to confirming eligibility to prevent the subject from remaining in a fasting state longer than necessary.
- BMD assessed by DXA for femoral neck, hip and spine. DXA can be performed up to 10 days after Day 1.

The subject will be provided with enough supplies for 14 weeks of treatment. Subjects will be provided with iron supplements if Hemoglobin (Hb) levels are below 10 g/dL. The subject will be instructed on how to take the study medication, and, if required, the iron supplementation. Iron supplements should be taken at least 4 hours apart from IMP intake.

From Day 1 up to the next scheduled study visit, the subject will also record her IMP intake in her eDiary.

The subject will take her first dose of study medication at the study site. She will be instructed to take one tablet from each blister and one capsule daily.

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 the Week 4 Study Visit and Week 8 Study Visit:

- Previous and concomitant treatments recording
- AE recording
- Vital signs (blood pressure and heart rate)
- Blood samples for hematology, chemistry, hormones (E2, P4)
- Contraception counseling (not applicable in case of tubal ligation)
- Urinary protein dipstick
- Urine pregnancy test
- Return of soiled sanitary protection (if relevant and not already returned)
- eDiary check for good completion
- Assess iron intake (if applicable)

6.2.2.3. *Study Visit Week 12 (Day 85 ± 3 days)*

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

- Previous and concomitant treatments recording
- AE recording
- Physical examination (including weight)
- Vital signs (blood pressure and heart rate)
- Gynecological examination
- TVUS of uterus and ovaries including: uterus dimensions, myoma dimensions, endometrium thickness and assessment of ovaries
- Blood samples for hematology, coagulation parameters, chemistry, lipids, hormones (E2, P4). The subject must be fasting for the lipid blood sample
- Contraception counseling (not applicable in case of tubal ligation)
- Urinary protein dipstick
- Urine pregnancy test
- Return of soiled sanitary protection (if relevant and not already returned)
- eDiary check for good completion
- Assess iron intake (if applicable)
- Pain NRS, PGI-I, UFS QoL and EQ-5D questionnaires will be completed in the diary at site

At this visit, the subjects will be given new kits for the next 14 weeks of treatment. The kit numbers will be provided by the IWRS. The subject will be reminded to take one tablet from each blister and one capsule daily.

6.2.2.4. *Study Visit Week 24 (Day 169 ± 3 days)*

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

- Previous and concomitant treatments recording
- AE recording
- Physical examination (including weight)
- Vital signs (blood pressure and heart rate)
- Gynecological examination
- TVUS of uterus and ovaries including: uterus dimensions, myoma dimensions, endometrium thickness and assessment of ovaries

- 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. If the subject is menstruating at the time of the visit, the biopsy can be performed at another time
- Blood samples for hematology, coagulation parameters, chemistry, lipids, hormones (E2, P4). The subject must be fasting for the lipid blood sample
- Contraception counseling (not applicable in case of tubal ligation)
- Urinary protein dipstick
- Urine pregnancy test
- Return of soiled sanitary protection (if relevant and not already returned)
- eDiary check for good completion
- Assess iron intake (if applicable)
- Pain NRS, PGI-I, UFS QoL and EQ-5D questionnaires will be completed in the diary at site
- BMD assessed by DXA for femoral neck, hip and spine. DXA can be performed ±10 days from Week 24 visit

At this visit, the subjects will be given new kits for the next 14 weeks of treatment. The kit numbers will be provided by the IWRS. The subject will be reminded to take one tablet from each blister and one capsule daily.

6.2.2.5. *Study Visit Week 28 ± 7 days and Week 32 ± 7 days*

The following tests and evaluations will be performed at the Week 28 and Week 32 Study Visits:

- Previous and concomitant treatments recording
- AE recording
- Vital signs (blood pressure and heart rate)
- Blood samples for hematology and chemistry
- Contraception counseling (not applicable in case of tubal ligation)
- Urinary protein dipstick
- Urine pregnancy test
- Return of soiled sanitary protection (if relevant and not already returned)
- eDiary check for good completion
- Assess iron intake (if applicable)

6.2.2.6. *Study Visit Week 36 ± 7 days*

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

- Previous and concomitant treatments recording
- AE recording
- Physical examination (including weight)
- Vital signs (blood pressure and heart rate)
- Gynecological examination
- TVUS of uterus and ovaries including: uterus dimensions, myoma dimensions, endometrium thickness and assessment of ovaries
- Blood samples for hematology, coagulation parameters, chemistry, lipids, hormones (E2, P4). The subject must be fasting for the lipid blood sample
- Contraception counseling (not applicable in case of tubal ligation)
- Urinary protein dipstick
- Urine pregnancy test
- Return of soiled sanitary protection (if relevant and not already returned)
- eDiary check for good completion
- Assess iron intake (if applicable)
- Pain NRS, PGI-I, UFS QoL and EQ-5D questionnaires will be completed in the diary at site

At the Week 36 visit, the subjects will be given additional 14-week kits for the rest of the treatment period. The kit numbers will be provided by the IWRS. The subject will be reminded to take one tablet from each blister and one capsule daily and must be instructed to finish the kits she already has before starting the new kits so that she has enough up to the Week 52 visit.

6.2.2.7. *Phone calls*

Between the Week 36 and Week 52 visits, the site will call the subject monthly to check her wellbeing and remind her about study procedures (diary, alkaline hematin, medication intake, contraception). Prior to the call, the site will monitor the subject's electronic diary data.

6.2.2.8. *Study Visit Week 52 – End of Treatment Visit*

This visit must occur prior to last IMP intake (i.e. no longer than 28 weeks after the Week 24 visit). The following tests and evaluations will be performed at the Week 52 Study Visit:

- Previous and concomitant treatments recording
- AE recording

- Physical examination (including weight)
- Vital signs (blood pressure and heart rate)
- Gynecological examination, including manual breast examination (by palpation)
- PAP smear
- TVUS of uterus and ovaries including: uterus dimensions, myoma dimensions, endometrium thickness and assessment of ovaries
- 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 or week 24 biopsy has provided assessable results. Appropriate photo documentation of the endometrium thickness is mandatory and will be kept in the source documents. If the subject is menstruating at the time of the visit, the biopsy can be performed at another time
- Blood samples for hematology, coagulation parameters, chemistry, lipids, hormones (E2, P4). The subject must be fasting for the lipid blood sample
- Contraception counseling (not applicable in case of tubal ligation). Non-hormonal contraception should be continued up to 12 weeks after last day of treatment (Week 64), however contraception (hormonal or non-hormonal) must be maintained up to the end of the study (Week 76).
- Urinary protein dipstick
- Urine pregnancy test
- Return of soiled sanitary protection (if relevant and not already returned)
- eDiary check for good completion
- Assess iron intake (if applicable)
- Pain NRS, PGI-I, UFS QoL and EQ-5D questionnaires will be completed in the diary at site
- BMD assessed by DXA for femoral neck, hip and spine. DXA can be performed ± 10 days from Week 52 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

The subject will return all used and unused blisters and continue in the treatment-free follow-up period.

6.2.3. Follow-up period without treatment

Up to the Week 64 study visit, the subject will be asked to record her uterine bleeding pattern daily in her eDiary at approximately the same time each evening.

6.2.3.1. *Study Visit Week 64 ± 7 days*

The following tests and evaluations will be performed at the Week 64 Study Visit:

- Previous and concomitant treatments recording
- AE recording
- Physical examination (including weight)
- Vital signs (blood pressure and heart rate)
- Gynecological examination
- TVUS of uterus and ovaries including: uterus dimensions, myoma dimensions, endometrium thickness and assessment of ovaries
- Endometrium biopsy if the Week 52 biopsy was not assessable, not done or diagnosis was not benign. If no tissue is available, the biopsy should be repeated as soon as possible in the following days
- Blood samples for hematology, coagulation parameters, chemistry, lipids, hormones (E2, P4, FSH (if menstruations have not returned)). The subject must be fasting for the lipid blood sample
- Contraception counseling (not applicable in case of tubal ligation)
- Urinary protein dipstick
- Urine pregnancy test
- eDiary check for good completion
- Pain NRS, PGI-I, UFS QoL and EQ-5D questionnaires will be completed in the diary at site

6.2.3.2. *Study Visit Week 76 ± 7 days – End of Follow-up Visit*

The following evaluation will be performed at Week 76 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
- Urine pregnancy test
- Completion of the eCRF exit form

6.2.4. Planned extension of the study

Not applicable.

6.3. EFFICACY OBSERVATIONS AND MEASUREMENTS

All endpoints relating to bleeding, including amenorrhea and time to amenorrhea will be based on the alkaline hematin data.

6.3.1. Menstrual blood loss

6.3.1.1. *Menstrual blood loss volume - Alkaline hematin method*

Menstrual bleeding encompasses any bleeding experienced during a menstrual cycle. Menstrual blood loss volume will be measured using the alkaline hematin method throughout the study up to Week 52. During this timeframe, all soiled sanitary protection will be collected and sent to a laboratory for analysis. For eligibility, menstrual blood loss during the first eight days of two screening menstrual periods must be > 80 mL. If menstrual blood loss during the first eight days of the first cycle is ≤ 80mL due to missed collection of sanitary products, the subject can be retrained, menstrual blood loss at screening would then be evaluated on the next two menstrual cycles.

The return of soiled sanitary protection will be arranged between the site and the subject. Soiled sanitary protection must be shipped to the laboratory within no more than 3 weeks. The sanitary products must be received by the laboratory within 3 weeks of collection. The subject must be instructed to return the transportation box to the investigator's site either once it is full or after a collection period of a maximum of 12 days. During the second menstrual period (or third if applicable), the box should be returned by the subject after the first 8 days of collection. Containers with materials collected during the same day of bleeding should always be returned together and not split over two shipments.

6.3.1.2. *Amenorrhea*

Amenorrhea will be determined using the alkaline hematin method and is defined as having no sanitary material returned or volume < lower limit of quantification within at least a 35-day interval. Amenorrhea will be assessed using data up to Week 24, i.e. at least a 35-day interval up to Week 24 and again using all data up to Week 52.

6.3.1.3. *Uterine bleeding scale*

The subject will complete a daily questionnaire in the eDiary assessing the incidence and amount of uterine/vaginal bleeding in the last 24 hours. The primary purpose of this eDiary is to monitor the subject's compliance with shipping soiled sanitary products for the alkaline hematin method. The incidence and strength of uterine bleeding will be assessed using the following scale:

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

6.3.2. Quality of life

6.3.2.1. *Uterine Fibroid symptom severity and health-related quality of life*

Symptom severity and quality of life will be assessed by the subject at Day 1, Week 12, Week 24, Week 36, Week 52 and Week 64 visits.

Subjects will complete the UFS-QoL questionnaire (APPENDIX B) at site in the eDiary. At the appropriate visits, the site staff will set up the device so that the questionnaire appears.

6.3.2.2. *EQ-5D*

Subjects will complete the EQ-5D-5L questionnaire (APPENDIX C) at Day 1, Week 12, Week 24, Week 36, Week 52 and Week 64 visits. Subjects will complete the questionnaire at site in the eDiary. At the appropriate visits, the site staff will set up the device so the questionnaire appears.

6.3.3. Pain NRS

Subjects will record pain on a Numeric Rating Scale (NRS) (APPENDIX D) at Day 1, Week 12, Week 24, Week 36, Week 52 and Week 64 visits. Subjects will complete the questionnaire at site in the eDiary. At the appropriate visits, the site staff will set up the device so the questionnaire appears.

6.3.4. Patient Global Impression of Improvement (PGI-I)

The Patient Global Impression of Improvement questionnaire (APPENDIX E) will be completed at Week 12, Week 24, Week 36, Week 52 and Week 64 visits. Subjects will complete the questionnaire at

site in the eDiary. At the appropriate visits, the site staff will set up the device so the questionnaire appears.

6.3.5. Myoma and uterus volume

Total volume of the three largest myomas and uterus volume will be measured using transvaginal ultrasound at Screening and at Week 12, Week 24, Week 36, Week 52 and Week 64. If transvaginal ultrasound is not possible, abdominal ultrasound can be used.

For the myomas, the operator should measure the three dimensions of each of the largest three myomas visible at the visit, even if these are not the ones that were previously measured. For correct volume assessment, the operator will be requested to record the myomas in three dimensions and to photodocument the measurements in the source data.

For the uterus volume, the operator should measure in three dimensions the length (from Cervix to outer fundus) and width and thickness and photodocument each measurement.

If possible, the transvaginal ultrasound should be performed by the same operator at each visit.

6.4. SAFETY OBSERVATIONS AND MEASUREMENTS

6.4.1. Adverse Events

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 unfavorable 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.

For screening failure subjects, adverse events and updates must be recorded in the eCRFs using the AE or SAE forms (as appropriate) until the date the subject is determined to be a screening failure. Beyond that date, only serious or medically relevant events will be followed up.

6.4.2. Vital signs

Blood pressure (BP) and heart rate will be measured in sitting position at Screening and from Day 1 at each visit up to the Week 64 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 the abnormality is 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. Physical examination

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 at the Week 12, 24, 36, 52 and 64 visits.

A gynecological exam will be performed at Screening, Week 12, 24, 36, 52 and 64 visits. In addition, a manual breast examination (by palpation) will be performed at Screening and Week 52 visits. Results of the examinations will be recorded on in the source subject data file and in the eCRF.

6.4.4. Transvaginal ultrasound and endometrial biopsies

In addition to the efficacy assessments (myoma and uterus volume) a number of safety measurements will be made during the TVUS. At the Screening, Week 12, 24, 36, 52 and 64 visits, the operator will measure endometrium thickness, assess ovaries and report any abnormality (adenomyosis, polyp, etc). The print-outs of the ultrasound will be interpreted and commented and kept as source data. Results of the examination will be recorded on source data forms and in the eCRF. If transvaginal ultrasound is not possible, abdominal ultrasound can be used.

Endometrial biopsies will be performed for histological assessment during Screening, at Weeks 24 and 52. At Week 64, an endometrial biopsy will only be taken if no endometrial biopsy was obtained at Week 52 or diagnosis at Week 52 was different from "benign endometrium". For subjects who demonstrate significant bleeding irregularities that differ from their typical pattern or the expected pattern due to study drug, unscheduled biopsies are to be taken. Endometrial biopsy samples will be collected with the Pipelle de Cornier® or equivalent (APPENDIX F), as will be described in the manual provided by the central laboratory. Endometrial biopsies will be centrally assessed by pathologists in the selected central laboratory blinded to treatment group.

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 report is available in source documents and slides are available to be provided if requested for current study assessment through retrospective central laboratory reading.

If the result of the endometrium biopsy is not yet available at the time of randomization, the subject can be randomized. If there is a subsequent clinically significant finding in the biopsy, the subject will be withdrawn immediately.

In case of multiple (at least two) and unsuccessful attempts to get sufficient endometrial tissue, the subject is allowed to be randomized without any screening endometrial biopsy under the following conditions:

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

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

c) The medical monitor of the study approves the randomization of the subject.

If biopsy samples collected during the study are inadequate and cannot be analysed by the laboratory they must be repeated as follows:

- Week 24 biopsy must be repeated at Week 36
- Week 52 biopsy must be repeated as soon as possible

- Week 64 biopsy must be repeated as soon as possible

In case of endometrial hyperplasia without atypia, the biopsies taken at Weeks 24, 52 and 64 must be repeated. In case of endometrial hyperplasia with atypia or in case of neoplasma, the laboratory will send an alert and the medical monitor will contact the sites to discuss the proceeding in line with local practice.

In case of dilatation and curettage during the study, which will be by definition a SAE, pathology results will be requested as part of the SAE follow-up information.

6.4.5. Bone mineral density and DXA

Bone mineral density (BMD) of femoral neck, hip and spine will be assessed by DXA at Day 1 and Weeks 24, 52 and 76.

All DXA scans will be read by a central imaging laboratory. Each site will use the same machine for the duration of the study under the supervision of a nominated primary technologist at the site. There will also be centralized monitoring of DXA scan quality for each site including a pre-qualification phantom scan, cross-calibration phantom scan and a monthly review of daily QC data.

In the event a scan does not meet quality standards a repeat scan request will be sent to the site. There will be predefined stopping rules for subjects.

Subjects presenting with a Z-score ≤ -2 assessed on the DXA at Day 1 will have to discontinue study treatment.

If there is more than 5% BMD loss on any one parameter a repeat DXA scan will be requested. If the Week 24 repeat scan shows more than 8% loss on any one parameter (femoral neck, hip or spine) or a Z-score ≤ -2.5, the subject will be required to stop treatment.

Detailed information on the centralized reading and QC and the stopping rules will be included in the Imaging Acquisition Guidelines and Imaging Reference Manual.

6.4.6. Laboratory parameters

- Serum levels of TSH will be assessed at Screening.
- Serum levels of FSH will be assessed at Screening and at Week 64 if menstruations have not returned.
- Serum levels of E2 and progesterone [P4] will be assessed from blood samples taken at Day 1 and Weeks 4, 8, 12, 24, 36, 52 and 64. These results will not be communicated to the site or study team.
- Hematology and chemistry (see APPENDIX G) will be assessed from blood samples taken at Screening, Day 1 and Weeks 4, 8, 12, 24, 28, 32, 36, 52 and 64.
- Fasting lipids will be assessed from blood samples taken at Day 1 and Weeks 12, 24, 36, 52 and 64.

- Coagulation parameters (see APPENDIX G) will be assessed from blood samples taken at Screening, Day 1 and Weeks 12, 24, 36, 52 and 64.

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.

The laboratory parameters are listed in APPENDIX G.

6.5. 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 30 days prior to the date of signature of informed consent and for the duration of the reporting period as defined in section 8.5. From Week 64 onwards, only concomitant medication with potential impact on BMD will be recorded in the eCRF.

6.5.1. Permitted Medicines

Any medications other than those excluded by the protocol (see section 5.2.2 or 6.5.2), 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.

Contraceptive use:

For subjects of childbearing potential and requiring contraception, non-hormonal contraception is required from the beginning of the screening period until 12 weeks after the end of treatment. Two forms of non-hormonal contraception will be required, e.g. condom with spermicide. Suitable condoms with spermicide (or condoms and spermicide separately) will be provided free of charge to subjects over the duration of the study.

Hormonal contraception including hormonal IUD must be stopped following ICF signature until 12 weeks after end of treatment. A washout period of 1 month must be allowed prior to screening assessments.

Between Week 64 and Week 76, the subject must continue to use contraception, however hormonal and non-hormonal methods are acceptable.

Iron supplementation:

Iron supplementation will be provided to the sites.

If at any visit (including screening) the subject's hemoglobin levels are below 10 g/dL (but higher than 6 g/dL at screening), iron supplementation should be given until the subject's hemoglobin levels increase by at least 2 g/dL and are above the lower limit of central lab normal range (12 g/dL). Once normal levels are reached, iron supplementation is to be stopped.

Iron supplements are reported to decrease absorption of concomitantly administered drugs – in the absence of drug interaction data with OBE2109, iron supplements will be taken at least four hours apart from OBE2109 intake. It is recommended to take the study IMP in the morning and the iron

supplementation with the lunch or evening meal but at least 30 minutes before going to bed. The iron supplement tablets should be taken with a glass of water.

While under iron supplementation, the subject must bring the used and unused blisters to the site at every visit so that the iron intake can be assessed.

6.5.2. Prohibited Medicines

Medication listed in the exclusion criteria (see Section 5.2.2) will be prohibited up to Week 52.

To consider a subject who is currently taking any prohibited therapies for potential inclusion in this study, the Investigator must ensure that the subject has sufficient washout time prior to screening (see Section 5.2.2).

Strong CYP3A inhibitors or inducers are prohibited up to 4 weeks after end of treatment in view of the add-back treatment (APPENDIX H).

OATP1B1/1B3 inhibitors (e.g. clarithromycin, erythromycin, gemfibrozil, telithromycin) are prohibited during the treatment period only (APPENDIX I).

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.

6.5.3. Non-Drug Therapies

Not applicable.

6.6. SUBJECT COMPLETION AND WITHDRAWAL

6.6.1. Subject Completion

For the first treatment period (primary endpoint), a subject will be considered as a "completer" when she has completed all study procedures at the Week 24 visit as described in the protocol.

For the second treatment period, a subject will be considered as a "completer" when she has completed all study procedures at the Week 52 visit as described in the protocol.

6.6.2. 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, except the DXA in case of premature discontinuation occurring during the first four weeks of treatment. Subjects discontinuing participation in the study between Week 24 and Week 52 visits should undergo the procedures required at Week 52 visit, except the DXA in case of premature discontinuation occurring less than four weeks after Week 24. Subjects discontinuing participation in the study between Week 52 and Week 64 visits should undergo the procedures required at Week 64 and Week 76 visits if more than one month since the last BMD measurement.

Subjects who withdraw from the study before receiving the study drug will not require any further study procedures to be performed. The eCRF exit form should be completed.

6.6.2.1. *Discontinuation criteria*

During the course of the study, the subject may be discontinued for the following reasons to be reported in the eCRF Study Termination Form:

- **Lack of Efficacy:** Investigator's judgment only. If subject's opinion only, check subject's Request. Explain in the specify field.

- **Adverse Event:** Includes clinically significant new or worsening existing condition as judged by the Investigator. Document also 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/or started before the Week 64 visit or **in case of early withdrawal** up to 4 weeks after treatment discontinuation 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 presenting with alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) or total bilirubin ≥ 2 times the upper limit of normal at Day 1 will have to discontinue study treatment once these results are received by the study site.

Subjects presenting with a Z-score ≤ -2 assessed on the DXA at Day 1 will have to discontinue study treatment.

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

Subjects who have an elevation of hepatic enzymes suggesting drug induced liver toxicity according to the Food and Drug Administration (FDA) guidance on drug-induced liver injury, i.e. LFT increase > 3 x ULN associated with increased total bilirubin > 2 x ULN or INR >1.5, will be immediately withdrawn from treatment and followed up until return to normal of hepatic parameters.

At the central reading of the DXA scan at Week 24, if there is more than a 5% BMD loss on any one parameter a repeat DXA scan will be requested. If the repeat shows more than 8% loss at either femoral neck, hip or spine or a Z-score ≤ -2.5, the subject will be required to stop treatment (see section 6.4.5).

All subjects withdrawn from treatment due to loss of BMD will have to complete the Week 76 assessments (urine pregnancy test, DXA scan and related AE follow-up) 6 months after treatment cessation.

6.6.2.2. *Follow-up for discontinued subjects*

For discontinued subjects, follow up data will be collected if the subject is willing to perform the follow up visits.

6.6.3. 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.

Discontinued subjects who had an exclusionary criterion, such as a Z-score ≤ 2, or ALT, AST, GGT or total bilirubin ≥ 2 times the upper limit of normal, or a clinically significant biopsy finding, at Day 1 (treatment start) may be replaced.

7. INVESTIGATIONAL MEDICINAL PRODUCT

7.1. DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCTS

The term "Investigational Medicinal Product" (IMP) will refer to the ObsEva investigational drug OBE2109, the add-back (E2 1 mg/NETA 0.5 mg) or their matching placebo.

	Investigational Medicinal Product	**Placebo**	**Add-back**	**Add-back Placebo**
International nonproprietary name (INN)	NA	NA	Estradiol and Norethisterone Acetate	NA
Name of active ingredient	OBE2109	NA	E2 and NETA	NA
Form	Film-coated tablet	Film-coated tablet	Capsules	Capsules
Strength	100 mg	Placebo	1.0/0.5 mg	Placebo
Dose or concentration of active treatment	100 mg and 200 mg	0 mg	1.0/0.5 mg	0 mg
Route of administration	Oral			
Frequency of administration	Once daily for up to 52 weeks			
Manufacturer (Name and address)	Catalent Germany Schorndorf GmbH Steinbeisstrasse 1-2 D-73614 Schorndorf, Germany		Sharp Clinical Services Inc. 300 Kimberton Road PA 19460 Phoenixville US	
Packaging (primary and secondary)	PVC/Al blister with 7 tablets per blister Aluminum pouch		PVC/Al blister with 7 capsules per blister Carton box	
Storage Requirements	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.

Add-back and placebo add-back will be supplied as capsules.

On Day 1, Week 12, Week 24 and Week 36, the subject will be given sufficient kits for 14 weeks (i.e. including two extra weeks).

At the Week 12, 24 and 52 visits, unused medication will be returned to the site. At Week 36, the subject will keep the kits that were provided at Week 24 as they will be needed to complete the treatment.

IMP treatment will start on Day 1 between the first and the seventh day of menstruation and will be administered once daily, up to about 52 weeks. The subjects will take 2 tablets(OBE2109/placebo), one from each blister, and 1 capsule (Add-back/placebo) ideally in the morning of each day as follows:

Treatment group	Daily dose Day 1 to Week 24	Daily dose Week 24 to Week 52
Placebo OBE2109 +placebo add-back	OBE2109 Placebo OBE2109 Placebo Add-back Placebo	OBE2109 Placebo OBE2109 Placebo Add-back Placebo
		OBE2109 100 mg OBE2109 100 mg Add-back E2/NETA
100 mg + placebo add-back	OBE2109 100 mg OBE2109 Placebo Add-back Placebo	OBE2109 100 mg OBE2109 Placebo Add-back Placebo
100 mg + add-back	OBE2109 100 mg OBE2109 Placebo Add-back E2/NETA	OBE2109 100 mg OBE2109 Placebo Add-back E2/NETA
200 mg + placebo add-back	OBE2109 100 mg OBE2109 100 mg Add-back Placebo	OBE2109 100 mg OBE2109 100 mg Add-back E2/NETA
200 mg + add-back	OBE2109 100 mg OBE2109 100 mg Add-back E2/NETA	OBE2109 100 mg OBE2109 100 mg Add-back E2/NETA

Add-back: E2 1 mg / NETA 0.5 mg

7.3. PACKAGING AND LABELLING

The study drug will be provided by the Sponsor (or delegate) as two separate 14-week kits to be dispensed at each time point: 1x OBE2109 or placebo kit and 1x add-back/placebo kit.

Each OBE2109 kit will contain 14 Aluminum (Al) pouches, each containing two PVC/Al blisters, i.e. sufficient to cover treatment for 14 weeks for each subject. All the 14 pouches and their corresponding blisters will be labeled with the same kit number, to be provided to a given subject. OBE2109 kit numbers will start with the letter B followed by 4 digits (B0001, B0002, etc).

The add-back kit will contain 14 blisters, i.e. sufficient to cover treatment for 14 weeks for each subject. All the 14 blisters will be labeled with the same kit number (different from the OBE2109 kit number), to be provided to a given subject. All add-back kits will begin with the letter N followed by 4 digits (N0001, N0002, etc)

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

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 and carton box.

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

OBE2109 and add-back must be stored at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59 °F and 86°F). 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.

1. 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.
2. 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.
3. IMP accountability records will include:
    a. Confirmation of IMP delivery to the trial site
    b. The inventory at the site of IMP delivered
    c. The use of each dose by each subject
    d. The return to the Sponsor (or delegate) or alternative disposition of unused IMP
    e. Dates, quantities, batch numbers and kit numbers assigned to the subject
4. The Investigator should maintain records that adequately document:
    a. The subjects were provided with the doses specified by the protocol/amendment(s)
    b. 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

Subjects will be randomized to one of five treatment groups in a 1:1:1:1:1 ratio, using a permuted block randomization stratified by race to ensure that black subjects are evenly represented in all treatment arms. The randomization will determine which subjects from the placebo arm will be switched at Week 24 to the OBE2109 200 mg + add-back and which will remain in the placebo arm.

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 labeling and for the set up of the IWRS.

Upon randomization in the IWRS, the site will be provided with the appropriate kits in time for the Day 1 visit which should take place at the earliest 7 days after randomization. The IWRS will provide the kit numbers, which will correspond to the OBE2109/placebo and add-back therapy/placebo kit

numbers. OBE2109 kit numbers will start from B0001, B0002, B0003 etc. (5-characters), while the add-back kit numbers will start with N0001, N0002, etc.

7.7. ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT COMPLIANCE

Each subject must be instructed to take one tablet from each blister and one capsule daily. In addition, she must 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 labeling and handling the study medication until the study database is locked and ready to be unblinded.

An analysis of Week 24 data, including the primary endpoint and bone mineral density endpoint will be performed after all subjects have completed Week 24 or terminated the study. The analysis will be performed by an unblinded statistician. The analysis will be restricted so that identification of individual patients is prevented as far as possible.

Every effort will be made to keep the Investigator and the subject fully blinded. Treatment allocation, individual P4 and E2 levels, Alkaline Hematin results (as of Study Day 1) will not be communicated up to the final Week 76 database lock.

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

The following items will be provided by the Sponsor free of charge to the subject:

- Iron supplementation (if applicable).
- Tampons and sanitary pads that are validated for the alkaline hematin method as well as a styrofoam box and containers to store used sanitary protection.
- Electronic Diaries will be used to record uterine bleeding IMP intake, UFS QoL, EQ-5D, pain NRS and PGI-I.
- Condoms with spermicide (or condoms and spermicide).
- Study bag to contain the items above

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, and 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 unfavorable 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.

For screening failure subjects, adverse events and updates must be recorded in the eCRFs using the AE or SAE forms (as appropriate) until the date the subject is determined to be a screening failure. Beyond that date, only serious or medically relevant events will be followed up.

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:

Drug (study drug) interrupted	Study drug is being temporarily interrupted due to AE.
Drug (study drug) withdrawn	Decision was made to withdraw the study drug due to AE.
Unknown	Unknown, not observed, not recorded, or refused.
Not applicable	AE started before dosing or after dosing finalized.

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 printouts and note directly on the report 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, if 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, "anemia" 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 Screening visit(s), including results of the study screening assessments, are defined as Baseline Medical Conditions. These medical conditions should be adequately documented on the "Medical History" page of the eCRF. Baseline Medical Conditions that worsen in severity or frequency during the study should be recorded and reported as AEs.

8.1.4. Exacerbation of symptoms

In this protocol, symptoms and signs of exacerbation or worsening of heavy menstrual bleeding will usually be captured in the context of efficacy assessment. Therefore, symptoms, exacerbation or worsening of bleeding 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 with 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 an 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 another situation. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize 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 64, with the exception of a SAE related to BMD loss which will be reported up to Week 76, 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 is to report such an SAE as follows:

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 concerning 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 section 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 INSTITUTIONAL REVIEW BOARDS AND REGULATORY AUTHORITIES

The Investigator must comply with any applicable requirements related to the reporting of SAEs involving the study subjects to the IRB that approved the study.

ObsEva will comply with the applicable regulatory requirements related to the expedited reporting of suspected unexpected serious adverse reactions (SUSARs) to the regulatory authorities (e.g. Health Authority, Central IRB). 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 accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of "findings that could affect adversely the safety of subjects, impact the conduct of the trial or alter the IRB's approval/favorable 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 SmPC for the Add-back) and are considered by the Investigator or the Sponsor, to have a reasonable possibility causal relationship between the administered IMP and the AE (i.e. SUSAR). The Investigator will keep copies of these safety reports in the investigator's file. National regulations with regards to safety reports notifications to Investigators will be taken into account.

Unless clearly defined otherwise by national or site-specific regulations, and duly documented, the responsible Investigator will promptly notify the concerned IRB of any safety reports provided by the Sponsor and provide copies of all related correspondence to the Sponsor. Only when specifically required by regulations, the Sponsor (or delegate) will provide appropriate safety reports directly to the concerned IRB 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 64, with the exception of an AE related to BMD loss which will be reported up to Week 76.

A last batch of queries will be sent after the subject's 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 the 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

Subjects who have been exposed to study treatment and who become pregnant during the treatment period will be immediately withdrawn from treatment. Pregnancies that have been exposed to study treatment and/or started before the Week 64 visit or - **in case of early withdrawal** - up to 4 weeks after treatment discontinuation will be followed up for pregnancy and neonatal outcomes at birth. Any pregnancy must be reported with the Pregnancy Surveillance Form (PSF; see below).

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 for 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-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). An SAE Report form must be completed when the subject sustains an event while PSF-part III must be completed when the child/fetus sustains an event. Abnormal outcomes are defined as:
    - Abnormality of the baby (birth defect): in this case, an 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 fulfill criteria of SAEs (e.g. prolongation of hospitalization due to caesarean section complications): in this case please complete an SAE form for the mother in addition to the PSF-III.

9. DATA ANALYSIS AND STATISTICS

9.1. TEST OF HYPOTHESES

The primary endpoint of the study will be assessed as the percentage of subjects with reduced menstrual blood loss at 24 weeks of treatment (last 28 days prior to the Week 24 visit), defined as menstrual blood loss $\leq$ 80 mL and $\geq$ 50% reduction from baseline. The primary analysis of the primary endpoint will be conducted by testing the null hypothesis of no treatment effect for each OBE2109 group vs placebo against the two-sided alternative:

Null hypothesis (H0): "There is no difference in the percentage of subjects meeting the primary endpoint for OBE2109 vs placebo".

H0: p (OBE2109) = p (placebo)

Alternative hypothesis (H1): "There is a difference in the percentage of subjects meeting the primary endpoint for OBE2109 vs placebo".

H1: p (OBE2109) $\neq$ p (placebo)

Where p is the percentage of subjects with reduced menstrual blood loss at 24 weeks of treatment.

9.2. SAMPLE SIZE

The planned sample of 500 subjects is based primarily on the requirements for the total number of exposed subjects required for drug registration. In terms of the primary efficacy endpoint, under the assumption of a 30% response rate in placebo and 70% response rate in an active arm based on data from a similar study/compound (AbbVie 2016), a conservative 64 subjects per treatment group are

required for at least 90% power for rejecting all of the OBE2109 group vs placebo group comparisons, each tested separately using a Bonferroni corrected type I error of 0.0125 (0.05 divided by 4). An increased sample size beyond 64 subjects per arm will help ensure success over the overall clinical program given that superior efficacy has to be demonstrated in two independent studies and for potentially additional secondary endpoints, as well as adequately assess the safety endpoints for example the bone mineral density loss.

9.3. RANDOMIZATION

A computer - generated random list using the stratification method and created by FlexRandomizer software (Cytel Inc., Boston, MA, USA) will be used for randomization. Allocation of treatment will be performed via a centralized IWRS system. Subjects will be randomized to one of five treatment groups in a 1:1:1:1:1 ratio for OBE2109 placebo, OBE2109 100 mg without add-back, 100 mg with add-back, OBE2109 200 mg without add-back and OBE2109 200 mg with add-back, stratified by race in order to ensure an equal representation of black women between treatment groups.

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

At Week 24 visit, half of the subjects from the Placebo OBE2109 + Placebo E2/NETA arm will be switched to OBE2109 200 mg with add-back (E2 1 mg/NETA 0.5 mg) while the other half will remain on placebo. This allocation will be determined as part of the randomization at Randomization Call (R) and treatment will be continued up to Week 52.

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 24 Per Protocol (PP) set:** All subjects in the FAS excluding those identified as major protocol violators up to Week 24.

4. **Week 52 Per Protocol (PP) set:** All subjects in the FAS excluding those identified as major protocol violators up to Week 52.

As per the analysis set defined above, randomized subjects who withdraw from the study prior to treatment will not be included for the statistical analyses. As this is a double-blind study with a single centralized randomization list (stratified only by race) the decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment.

9.5. DATA ANALYSIS

More details of the proposed statistical analysis will be documented in the Statistical Analysis Plan (SAP), which will be finalized prior to the database lock and unblinding of the Week 24 data.

Categorical data will be presented using counts and percentages of subjects, while continuous variables will be presented using the mean, standard deviation, median, 1st and 3rd quartiles, minimum, maximum, and number observations. Raw data will be listed.

Individual OBE2109 treatment group versus placebo comparisons will be made for superiority with an overall two-sided Type I error (alpha) of 0.05. In order to account for multiplicity given four different OBE2109 treatment groups, each primary endpoint comparison versus placebo will be conducted at the 0.0125 level of significance, i.e. 0.05 divided by 4. In addition, a sequential testing procedure within each OBE2109 treatment group will be used for the comparison of the following secondary endpoints versus placebo, where a formal statement of efficacy may be made, thus continuing to protect the overall type I error. An endpoint will only be claimed to be statistically significant if the resulting p-value for that endpoint and all endpoints higher up the testing order (for a given treatment arm) are less than 0.0125:

1. Reduced menstrual blood loss at 24 weeks of treatment (primary endpoint)
2. Time to reduced menstrual blood loss (i.e. $\leq$ 80 mL and $\geq$ 50% reduction from baseline) up to Week 24
3. Amenorrhea up to Week 24
4. Time to amenorrhea up to Week 24
5. Number of days of uterine bleeding for the 28-day interval up to Week 24
6. Hemoglobin level at Week 24

The additional efficacy endpoints will be tested at the 0.0125 with no further adjustments for multiplicity.

Unadjusted, ninety five percent (95%) confidence intervals will be presented throughout. Hypothesis testing (as described above) will be used to formally establish an effect, prior to returning to the estimation framework.

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. There will be no formal comparison of baseline data, that is, no statistical hypothesis testing.

The baseline value for the primary endpoint will be the mean of the menstrual blood loss assessed during the two, complete menstrual cycles at screening, which may not be exactly 28 days each. In the case that screening lasts three full cycles, the baseline will be calculated on the second and third cycles, i.e. those assessed for inclusion.

9.5.2. Primary Efficacy Analysis

The primary analysis set for the efficacy analyses will be the Full Analysis Set.

The primary analyses of reduced menstrual blood loss at 24 weeks of treatment (last 28 days prior to week 24 visit) will be analysed as a categorical variable (yes / no response) and will be conducted as follows:

Cochran-Mantel-Haenszel (CMH) tests with adjustment for the stratification factor race will be used to test the null hypothesis of no treatment effect for each OBE2109 group vs. placebo with regards to the

proportion of subjects with a reduced menstrual blood loss at 24 weeks. The odds ratios will be estimated from the CMH test together with the associated 95% CI and corresponding p-values. The proportion per treatment arm will be displayed together with exact Clopper-Pearson 95% CIs. The differences in percentages with corresponding 95% Newcombe-Wilson confidence intervals will also be presented. The homogeneity of the odds ratios will be explored using the Breslow-Day test.

In addition to the CMH tests and to further explore a possible interaction between race and treatment, a logistic regression model with terms for treatment, stratification factor race and the interaction between treatment and race will be fitted to the binary response data. Contrast and estimate statements will provide separated tests for each OBE2109 group vs. placebo for each strata. In case of too many empty cells or non-convergence of the model, separated Fisher's exact tests will be used for each comparison versus placebo, within strata. Subjects who discontinue prematurely due to lack of efficacy or adverse events, or who undergo operative or radiological interventions for uterine fibroids, will be considered as non-responders.

In order to account for multiplicity given four different OBE2109 treatment groups, each primary endpoint comparison versus placebo will be conducted at the 0.0125 level of significance, i.e. 0.05 divided by 4.

9.5.3. Secondary Efficacy Analysis

The endpoints amenorrhea, time to amenorrhea, menstrual blood loss and time to reduced menstrual blood loss will be assessed using data up to Week 24 and again using all data up to Week 52. For the subjects on the placebo arm who were randomized to switch treatment to OBE2019 at Week 24, only data up to the time they switch treatment will be used.

The analysis of amenorrhea will be conducted using the same methods as for the primary endpoint.

A sequential testing procedure will be used within each treatment group. Amenorrhea up to Week 24 vs. placebo will be tested at the 0.0125 significance level only if the primary endpoint hypothesis test is rejected, and in the same way, time to amenorrhea up to Week 24 will only be tested (at 0.0125) if the amenorrhea hypothesis test is rejected (see also the ordering of the sequential testing procedure described in section 9.5). The additional efficacy endpoints will be tested at the 0.0125 with no further adjustments for multiplicity.

Time to amenorrhea is defined as the number of days from first dose to the first day for which the subject does not have bleeding (see Section 6.3.1.2) for at least 35 days. Time to amenorrhea will be analyzed using Kaplan-Meier methodology (estimates and plots will be produced) and each OBE2109 group vs. placebo will be compared using a two-sided log-rank test stratified by race. In addition, the treatment difference as measured by the Hazard Ratio and its corresponding 95% Confidence Interval will be estimated using a stratified Cox regression model with race as stratification factor. Time to reduced menstrual blood loss (as defined by the primary endpoint) will be analysed in the same way.

For the 24-Week analysis, subjects who do not have any amenorrhea within the 24-Week period from Study Day 1 up to Week 24 visit will be considered as right-censored data. The date of the last alkaline hematin method assessment reported from Study Day 1 up to the Week 24 visit will be used as time of censoring. Data from the "last alkaline hematin method assessment" form of external data will be used. If no alkaline hematin method assessment is performed after Study Day 1, the date of Study Day 1 will be used as time of censoring.

In general, between group comparisons for continuous endpoints will be analyzed via repeated measures analysis of covariance, including the baseline and stratification factor race as a covariate, with each treatment group compared versus placebo using contrasts.

Mean hemoglobin will be compared between treatment groups and categorical analyses may also be performed.

Fibroid volume and uterine volume are expected to be log-normally distributed and so will be log-transformed prior to analysis, with the subsequent results (mean differences and corresponding confidence intervals) back transformed and hence reported in terms of ratios. The underlying distributions will be checked, and if deemed necessary alternative analyses may also be conducted. The number of days of uterine bleeding (assessed via the alkaline hematin method) will be analyzed using a negative binomial model or zero-inflated negative binomial, depending on model fit. The PGI-I will be analysed using Mantel-Haenszel methodology.

In order to explore the impact of submucosal fibroids on the efficacy of OBE2109, an analysis of the primary efficacy endpoint will be performed on the subset of patients from the FAS analysis set with a baseline FIGO classification of 0, 1 or 2 in either one fibroid only or in any fibroid, depending on the number of available fibroid data.

9.5.4. Safety analysis methodology

Safety analyses will be based on the Safety Set.

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

Bone Mineral Density loss will be compared between the OBE2109 treatment groups and placebo in terms of percent change from baseline. In addition, a confidence interval for the percent change from baseline within each group will be produced.

Effect of the add-back therapy versus placebo will be assessed by comparing on one hand the OBE2109 200 mg + E2 1 mg/NETA 0.5 mg versus the OBE2109 200 mg group alone, and on the other hand, the OBE2109 100 mg + E2 1 mg/NETA 0.5 °mg versus the OBE2109 100 mg group alone on bone mineral density loss.

An analysis of covariance model including the baseline BMD and stratification factor race as a covariate will be used.

Extent of exposure and compliance will be evaluated.

9.5.5. Missing Data

In order to take into account all randomized subjects in the analysis, the assessment of the primary endpoint for subjects who do not have menstrual bleeding data up to Week 24 (and who did not discontinue prematurely due to lack of efficacy or adverse events, or undergo operative or radiological interventions for uterine fibroids) will be based on the results from the last 28 days prior to the last diary completion. Subjects who have less than 28 days of data will be treated as non-responders. The secondary endpoint of amenorrhea will be assessed in a similar way.

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.

Sensitivity analyses will 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 and planned sensitivity analyses will be defined in the SAP.

9.6. STUDY SPECIFIC DATA ANALYSIS

An interim analysis was not planned for this study. However, a final analysis of Week 24 data, including the primary endpoint and BMD assessments will be performed once all randomized subjects have completed Week 24 or withdrawn from the study. The analysis will be performed by an unblinded team that will not be affiliated with the conduct, randomization and interpretation of theresults and reporting of this study.

During the Blinded Data Review meetings which will take place prior to each database lock, the Sponsor and clinical team members will only have access to aggregated summary tables using dummy treatment groups as well as blinded listings for discussion.

For this final analysis at Week 24, the baseline characteristics will be described using the Full Analysis Set. Subject disposition will be summarized but the summary will not provide specific information which could unblind individual subjects, for example the description of discontinuation. The primary endpoint and bone mineral density endpoint will be analyzed using the Full Analysis Set and the Per Protocol Set using data up to the Week 24 visit (included). Unblinded treatment groups will be presented in the corresponding tables without reporting the minimum and maximum values to help preserve the blind. Information of unblinded treatment will be removed from listings and listings will not be sorted by treatment group.

To respect the blind in the Week 24 analysis, the unblinded statistician will check that all tables do not contain information which allow identification of the treatment assignment of any subject. If it is the case, the table will be updated or removed from the analysis. Only after this has been checked and completed will the tables be provided to the Sponsor.

The Sponsor and study team will be fully unblinded after all subjects have completed the treatment period (Week 52) and the database has been locked.

A complete analysis will then be performed and the results will be summarized and described in an integrated Clinical Study Report.

The 24-week follow-up period will be reported in an addendum to the integrated Clinical Study Report.

Treatment allocation, individual P4 and E2 levels, Alkaline Hematin results (as of Study Day 1) will not be communicated and remain blinded up to the end of the study (Week 76 database lock) for the Investigator and the subject.

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, the ICH Harmonized Tripartite Guideline for GCP (ICH E6(R1)), 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 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 (IRB). If any amendments to any of these documents occur during the study, notification or written approval as appropriate must be obtained prior to their implementation. The Investigator is responsible for ensuring that these actions occur.

Where required by local regulations, the Sponsor (or its delegate) is responsible for ensuring IRB 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 76 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 US Code of Federal Regulations 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 on 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 Committee (DMC)

The DMC is a group of independent experts external to the study that, collectively, has experience in the management of subjects with uterine fibroids 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 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. PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or International Conference on Harmonisation Good Clinical Practice (ICH GCP requirements. It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and reported to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

All Protocol Deviations will be reported to the Sponsor, documented in the monitoring report and captured in the CRO's Clinical Trial Management System. These will be classified as minor or major based on their effect on the right, safety or well-being of the subjects and/or the quality and integrity of the data, and the final rating of all deviations will be confirmed prior to database lock.

10.9. STUDY OR SITE DISCONTINUATION

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

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

10.10. RETENTION OF ESSENTIAL STUDY DOCUMENTS

Essential documents as defined by ICH GCP include the signed protocol and any amendment(s), copies of the completed eCRFs, signed ICFs from all subjects who consented, hospital records, diary cards and other source documents, IRB 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.

10.11. PUBLICATION POLICY

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

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

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

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

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

11. APPENDICES

APPENDIX A: SCHEDULE OF STUDY ASSESSMENTS

APPENDIX B: UTERINE FIBROID SYMPTOM SEVERITY AND HEALTH-RELATED QUALITY OF LIFE

APPENDIX C: EQ-5D QUESTIONNAIRE

APPENDIX D: PAIN NUMERICAL SCALE QUESTIONNAIRE

APPENDIX E: PATIENT GLOBAL IMPRESSION OF IMPROVEMENT (PGI-I)

APPENDIX F: PIPELLE DE CORNIER® OR EQUIVALENT

APPENDIX G: LABORATORY PARAMETERS

APPENDIX H: STRONG CYP3A INDUCERS AND INHIBITORS

APPENDIX I: OATP1B1/1B3 INHIBITORS

APPENDIX J: REFERENCE LIST

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS

	Screening	Randomization Call (R)	Day 1	W4 ± 3 days	W8 ± 3days	W12 ± 3days	W24 ± 3days	W28 ± 7 days	W32 ± 7 days	W36 ± 7 days	W52 - 7 days	W64 ± 7 days	W76 ± 7 days
Informed Consent	X												
Demography, medical history	X												
Previous/concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X[a]
Inclusion-Exclusion criteria	X		X										
Randomization		X											
Physical examination	X		X			X	X			X	X	X	

[a] Only if treatments with potential impact on BMD

	Screening	Randomization Call (R)	Day 1	W4 ± 3 days	W8 ± 3days	W12 ± 3days	W24 ± 3days	W28 ± 7 days	W32 ± 7 days	W36 ± 7 days	W52 - 7 days	W64 ± 7 days	W76 ± 7 days
Vital signs	X		X	X	X	X	X	X	X	X	X	X	
Gynecological examination	X					X	X			X	X	X	
Breast examination	X										X		
PAP smear	X[b]										X		
Uterus and myoma volume (US)	X[c]					X	X			X	X	X	

[b] Screening PAP smear is not required if the subject has had a PAP test within the last 12 months indicating no clinically significant abnormalities requiring surgical intervention (e.g. LEEP or cervical conization) and the results are available for source document verification

[c] The ultrasound assessment must be performed at the beginning of the screening period to ensure that only subjects who suffer from heavy menstrual bleeding due to Uterine Fibroids (meet incl. criteria 5 and 6) undergo all other screening procedures.

	Screening	**Randomization Call (R)**	**Day 1**	**W4** ± 3 days	**W8** ± 3days	**W12** ± 3days	**W24** ± 3days	**W28** ± 7 days	**W32** ± 7 days	**W36** ± 7 days	**W52** - 7 days	**W64** ± 7 days	**W76** ± 7 days
Ovarian US/ Endometrium TVUS	X[c]					X	X			X	X	X	
Endometrial biopsy	X[d]						X[e]			(X[f])	X[g]	X[h]	
TSH	X												
FSH	X[i]											X[j]	

[d] After day 7 of the menstrual cycle or following bleeding cessation. 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.

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

[f] Only if Week 24 biopsy sample was insufficient and could not be analyzed.

[g] If endometrium thickness in TVUS is ≤ 5 mm, no endometrium biopsy will be necessary, as far as the screening or Week 24 biopsy has provided assessable results.

[h] If no endometrial biopsy was obtained at week 52 or diagnosis at week 52 was different from "benign endometrium".

[i] In case of unexpected high FSH result, a redraw of the blood for FSH is allowed but must be performed in the first five days of the subject's menstrual cycle to avoid the mid-cycle FSH peak.

[j] Only if menstruations haven't returned since end of treatment.

	Screening	Randomization Call (R)	Day 1	W4 ± 3 days	W8 ± 3days	W12 ± 3days	W24 ± 3days	W28 ± 7 days	W32 ± 7 days	W36 ± 7 days	W52 - 7 days	W64 ± 7 days	W76 ± 7 days
Progesterone (P4)			X	X	X	X	X			X	X	X	
Estradiol assay (E2)			X	X	X	X	X			X	X	X	
Hematology, Chemistry	X		X	X	X	X	X	X	X	X	X	X	
Lipids (Fasting)			X			X	X			X	X	X	
Coagulation parameters	X		X			X	X			X	X	X	
Contraceptive counseling (if applicable)	X		X	X	X	X	X	X	X	X	X	X	
Urinary protein dipstick and pregnancy test	X		X	X	X	X	X	X	X	X	X	X	X[k]
Collect sanitary protection (if applicable)	X		X	X	X	X	X	X	X	X	X		

[k] Pregnancy test only

	Screening	Randomization Call (R)	Day 1	W4 ± 3 days	W8 ± 3days	W12 ± 3days	W24 ± 3days	W28 ± 7 days	W32 ± 7 days	W36 ± 7 days	W52 - 7 days	W64 ± 7 days	W76 ± 7 days
Check subject eDiary completion	X		X	X	X	X	X	X	X	X	X	X	
Assess iron intake (if applicable)			X	X	X	X	X	X	X	X	X	X	
Pain NRS			X			X	X			X	X	X	
PGI-I						X	X			X	X	X	
UFS QoL			X			X	X			X	X	X	
EQ-5D			X			X	X			X	X	X	
BMD by DXA			X[l]				X[m,n]				X[m]		X[m]
Adverse events	X		X	X	X	X	X	X	X	X	X	X	X[o]
Dispense drug			X			X	X			X			

Between Week 36 and 52 visits, the site will call the subject monthly.

[l] DXA can be performed up to 10 days after Day 1 study visit. Subjects presenting with a Z-score ≤ -2 will have to discontinue the study treatment.
[m] DXA can be performed ± 10 days from study visit.
[n] Patients discontinued at W24 due to BMD loss will have to complete the W76 assessments after 6 months.
[o] If related to BMD loss.

APPENDIX B UTERINE FIBROID SYMPTOM SEVERITY AND HEALTH-RELATED QUALITY OF LIFE

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE (UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response.

During the previous 3 months, how distressed were you by...	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Fluctuation in the duration of your menstrual period compared to your previous cycle	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Feeling tightness or pressure in your pelvic area	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Frequent urination during the daytime hours	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Frequent nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Feeling fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If the question does not apply to you, please check "none of the time" as your option.

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you feel anxious about the unpredictable onset or duration of your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Made you anxious about traveling?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Interfered with your physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. Caused you to feel tired or worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. Made you decrease the amount of time you spent on exercise or other physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Made you feel as if you are not in control of your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. Made you concerned about soiling underclothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. Made you feel less productive?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Made you feel self-conscious of weight gain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Made you feel that it was difficult to carry out your usual activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Interfered with your social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Made you feel conscious about the size and appearance of your stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Made you concerned about soiling bed linen?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23. Made you feel sad, discouraged, or hopeless?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Made you feel down hearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Made you feel wiped out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Caused you to be concerned or worried about your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Made you feel uncertain about your future?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Made you feel irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Made you concerned about soiling outer clothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Affected the size of clothing you wear during your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Made you feel that you are not in control of your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Made you feel weak as if energy was drained from your body?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Diminished your sexual desire?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
37. Caused you to avoid sexual relations?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

APPENDIX B

UFS-QoL Scoring Manual

To calculate a symptom score for symptom severity, create a summed score from the items listed below and then use the formula below the table to transform the value. This will provide symptom scores where higher score values are indicative of greater symptom severity or bother and lower scores will indicate minimal symptom severity (high scores = bad).

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Symptom Severity	Sum 1 – 8	8, 40	32

Transformation for Symptom Severity raw scores ONLY:

$$\text{Transformed Score} = \frac{(\textit{Actual} \text{ raw score} - \textit{lowest} \text{ possible raw score})}{\textit{Possible raw score range}} \times 100$$

For the HRQL subscales (concern, activities, energy/mood, control, self-conscious, and sexual function), create summed scores of the items listed below for each individual subscale. To calculate the HRQL total score, sum the value of each individual subscale (do not sum individual items). Use the formula below the table to transform all values. Higher scores will be indicative of better HRQL (high = good).

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Concern	9+15+22+28+32	5, 25	20
Activities	10+11+13+19+20+27+29	7, 35	28
Energy/mood	12+17+23+24+25+31+35	7, 35	28
Control	14+16+26+30+34	5, 25	20
Self-conscious	18+21+33	3, 15	12
Sexual function	36+37	2, 10	8
HRQL TOTAL	Sum of 6 Subscale Scores	29, 145	116

Formula for transformation of HRQL raw scores ONLY:

$$\text{Transformed Score} = \frac{(\textit{Highest} \text{ possible score} - \textit{Actual raw} \text{ score})}{\textit{Possible raw score range}} \times 100$$

Missing Items

For the subscale analyses, if < 50% of the scale items are missing, the scale should be retained with the mean scale score of the items present used to impute a score for the missing items. If ≥ 50% of the items are missing, no scale score should be calculated, the subscale score should be considered missing. If a subscale score is missing, the HRQL total cannot be calculated.

APPENDIX C EQ-5D QUESTIONNAIRE

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

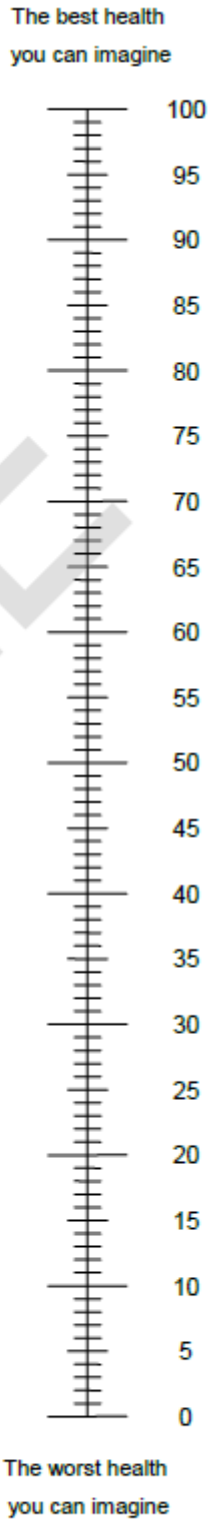
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

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

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX D PAIN NUMERICAL SCALE QUESTIONNAIRE

Please rate your pain related to your uterine fibroids during the last 4 weeks:

No pain

Worst possible pain

APPENDIX E PATIENT GLOBAL IMPRESSION OF IMPROVEMENT (PGI-I)

The PGI-I questionnaire is a simple, direct, and easy to use global index widely used to rate the response of a condition to a therapy. It consists of a scale that is a single question asking the subject to describe her menstrual bleeding status compared to before treatment. Subjects will rate their satisfaction with treatment at Week 12, Week 24, Week 36, Week 52 and Week 64 or upon early discontinuation from the study. The PGI-I will ask the question as follows:

During the last 4 weeks, how would you describe your menstrual/vaginal bleeding compared to before you started the study drug?

1 = Very much better

2 = Much better

3 = A little better

4 = No change

5 = A little worse

6 = Much worse

7 = Very much worse

APPENDIX F PIPELLE DE CORNIER® OR EQUIVALENT

Pipelle de Cornier® is given here as an example, other pipelles can be used to perform the biopsy as per the investigator's practice.

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

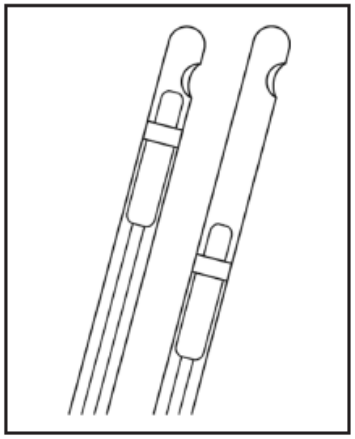
Imported by CCD International
88 Eliot Street,
NATICK, MA 01760

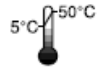
Distributed by SEPAL Reproductive Devices, Inc.
201 South Street, 6th Floor Boston MA 02111

www.ccd-international.com

C.C.D. International
Expertise in women's health

Pipelle de Cornier®





STERILE EO

C.C.D. International
Expertise in women's health

Made in France
X2998 Ed.: Mars 2007

APPENDIX G LABORATORY PARAMETERS

Routine Hematology	Blood Chemistry
	Ferritin
Hemoglobin	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	GGT
MCHC	Alkaline phosphatase
LDH	Creatine Kinase
	Urea and uric acid

Coagulation parameters	Lipids
APTT	HDL, LDL and total cholesterol, triglycerides
INR	
PT	

Urinary protein dipstick

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

Hormones

E2, P4, TSH, FSH.

All above listed blood tests will be performed by a central laboratory. Please consult the central laboratory instruction manual for the preparation and handling of the blood samples to be drawn to perform these tests.

APPENDIX H STRONG CYP3A INDUCERS AND INHIBITORS

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

Strong CYP3A inducers prohibited up to 4 weeks after end of treatment in view of the add-back treatment:

Carbamazepine
Enzalutamide
Mitotane
Phenytoin
Rifampin
St. John's Wort

Strong CYP3A inhibitors prohibited up to 4 weeks after end of treatment in view of the add-back treatment:

Boceprevir
Cobicistat
Conivaptan
danoprevir and ritonavir
elvitegravir and ritonavir
grapefruit juice
indinavir and ritonavir
itraconazole
ketoconazole
lopinavir and ritonavir
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
posaconazole
ritonavir
saquinavir and ritonavir
telaprevir
tipranavir and ritonavir
troleandomycin
voriconazole

clarithromycin
diltiazem
idelalisib
nefazodone
nelfinavir

APPENDIX I OATP1B1/1B3 INHIBITORS

The presented list is indicative and should not be considered exhaustive.

OATP1B1/1B3 inhibitors prohibited during the treatment period only:

Atazanavir (Reyataz®)
Clarithromycin (Biaxin®)
Cobicistat (part of Stribild®)
Cyclosporine (Neoral®, Gengraf®, Sandimmune®)
Daclatasvir (Daklinza™)
Eltrombopag (Promacta®)
Erythromycin (E-mycin®)
Gemfibrozil (Lopid®)
Lopinavir/Ritonavir (Kaletra®)
Paritaprevir (Viekira Pak™, Technivie™)
Ritonavir/Lopinavir (Kaletra®)
Sacubitril (Entresto®)
Saquinavir (Invirase®)
Simeprevir (Olysio®)
Telithromycin (Ketek®)
Tipranavir (Aptivus®)
Rifampin
Velpatasvir (Epclusa®)

APPENDIX J REFERENCE LIST

1. AbbVie 2016 R&D Day Presentation downloaded from http://www.abbvieinvestor.com/phoenix.zhtml?c=251551&p=irol-eventDetails&EventId=5223787 on 23 Nov 2016
2. Brown JS, Sawaya G, Thom DH, Grady D (2000) Hysterectomy and urinary incontinence: a systematic review. Lancet 356:535-539.
3. Bulun, S. E. Uterine Fibroids. N Engl J Med 2013; **369**(14):1344-1355.
4. Jacobson GF, Shaber RE, Armstrong MA, Hung YY (2006) Hysterectomy rates for benign indications. Obstet Gynecol 107:1278-1283.
5. Lee, D.Y., Park, H.G., Yoon, B.K., & Choi, D. (2016). Effects of different add-back regimens on hypoestrogenic problems by postoperative gonadotropin-releasing hormone agonist treatment in endometriosis. *Obstetrics & Gynecology Science, 59*(1), 32.
6. Lethaby A, Vollenhoven B, Sowter M (2001) Pre-operative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst RevCD000547.
7. Spies JB, Coyne K, Guaou GN, Boyle D, Skyrnarz-Murphy K, Gonzalves SM (2002) The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol 99:290-300.
8. Stovall TG, Muneyyirci-Delale O, Summitt RL, Jr., Scialli AR (1995) GnRH agonist and iron versus placebo and iron in the anemic patient before surgery for leiomyomas: a randomized controlled trial. Leuprolide Acetate Study Group. Obstet Gynecol 86:65-71.