Cover page of the integrated protocol

A randomized, parallel-group, double-blind and open-label, placebo-controlled, multicenter study to assess the efficacy and safety of vilaprisan in subjects with uterine fibroids

This protocol version is an integration of the following documents / sections:

- **Original protocol**, Version 1.0, dated 01 SEP 2017
- **Amendment 02** (global amendment described in Section 15.1)
  forming integrated protocol Version 2.0, dated 15 NOV 2017

Local amendments not forming part of this integrated global protocol:

- **Amendment 01** (dated 25 SEP 2017)
  (local amendment, valid for South Africa only)

1. Title page

A randomized, parallel-group, double-blind and open-label, placebo-controlled, multicenter study to assess the efficacy and safety of vilaprisan in subjects with uterine fibroids

Short title: **A**ssess **S**afety and Efficacy of Vilaprisan in Subjects with U**ter**ine Fibr**oid**s

Acronym: ASTEROID 3

Test drug:	BAY 1002670 / Vilaprisan		
Clinical study phase:	3	Date:	15 NOV 2017
Registration:	EudraCT: 2017-002997-38	Version no.:	2.0
Sponsor's study no.:	15787		

Sponsor: Non-US territory: Bayer AG, D-51368 Leverkusen, Germany

US territory: Bayer HealthCare Pharmaceuticals, Inc.
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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: Christian Seitz, MD, PhD Role: Global Clinical Leader

Date: 20 Nov 2017 Signature:

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

In the protocol document, this page may remain unsigned.

2. Synopsis

This section was changed in Amendment 2, see Section 15.1.1

Title	A randomized, parallel-group, double-blind and open-label placebo-controlled, multicenter study to assess the efficacy and safety of vilaprisan in subjects with uterine fibroids
Short title	**A**ssess **S**afety and Efficacy of Vilaprisan in Subjects with U**ter**ine Fibr**oid**s
Acronym	ASTEROID 3
Clinical study phase	3
Study objective(s)	The primary objective of this study is to show superiority of vilaprisan in the treatment of heavy menstrual bleeding (HMB) in subjects with uterine fibroids compared to placebo. The secondary objectives of this study are to additionally evaluate the efficacy and safety of vilaprisan in subjects with uterine fibroids. The other objectives of this study are to evaluate the variability in exposure in relation to the efficacy and safety for vilaprisan and to collect patient-reported outcome (PRO) and clinician-reported outcome (ClinRO) data.
Test drug	Vilaprisan (BAY 1002670)
Name of active ingredient	Vilaprisan (BAY 1002670)
Dose	2 mg, once daily
Route of administration	Oral
Duration of treatment	Treatment Group A1: vilaprisan, 2 treatment periods of 12 weeks, separated by 1 bleeding episode Treatment Group A2: vilaprisan, 2 treatment periods of 12 weeks without a break Treatment Group B1: placebo, 1 treatment period of 12 weeks and vilaprisan, 1 treatment period of 12 weeks, separated by 1 bleeding episode Treatment Group B2: vilaprisan, 1 treatment period of 12 weeks and placebo, 1 treatment period of 12 weeks, separated by 1 bleeding episode
Reference drug	Placebo
Name of active ingredient	Not applicable
Dose	Dose not applicable, once daily
Route of administration	Oral
Duration of treatment	See Treatment Groups B1 and B2 above

Indication	Uterine fibroids
Diagnosis and main criteria for inclusion /exclusion	Women, 18 years or older, with at least 1 uterine fibroid documented by ultrasound at screening with largest diameter ≥30 mm and <120 mm and HMB in at least 2 bleeding periods during the screening period each with blood loss volume > 80.00 mL, documented by the alkaline hematin (AH) method, will be eligible for enrollment in the study. Women who are pregnant, lactating, or have any condition requiring immediate blood transfusion are not eligible.
Study design	This is a randomized, parallel-group, double-blind and open-label, placebo-controlled, multicenter study.
Methodology	Subjects will document the intensity of their daily menstrual bleeding in the Uterine Fibroid Daily Bleeding Diary (UF-DBD) and assess the intensity of their menstrual blood loss daily using a visual scoring system (MP) in an electronic diary (eDiary). Subjects will collect the sanitary products used during the study to analyze the volume of blood loss using the AH method. Uterine fibroids will be assessed during the study through ultrasound. Patient-reported outcome (PRO) data will also be collected using the Uterine Fibroid Daily Symptom Diary (UF-DSD), the Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QoL), the Patient Global Impression of Severity and Change (PGI-S; PGI-C), the Short Form 36 Health Survey Version 2 (SF-36v2), and the Treatment Satisfaction Questionnaire for Medication (TSQM-9). Clinician-reported outcome (ClinRO) data will be collected using the Clinical Global Impression Investigator (CGI_I). Safety will also be assessed by the evaluation of adverse events (AEs), laboratory parameters, endometrial biopsies, cervical smears, physical and gynecological examinations including ultrasound, and vital signs. The (population) pharmacokinetics (PK) and the effect of intrinsic and extrinsic factors on the variability in exposure will be assessed by population PK analysis using sparse vilaprisan concentration samples.
Type of control	Placebo
Number of subjects	Based upon the anticipated screen failures rates (60% in the US and 50% in China and the other countries), about 585 subjects will be enrolled to achieve the planned number of randomized subjects. A total of 260 subjects are planned to be randomized (65 subjects in each treatment group).
Primary variable	Amenorrhea (yes/no), defined as menstrual blood loss (MBL) <2 mL during the last 28 days of treatment
Time point/frame of measurement for primary variable	Presence of amenorrhea after 12 weeks of treatment in Treatment Period 1 and after 24 weeks of treatment in Treatment Period 2

Plan for statistical analysis	The primary efficacy will be assessed by testing the amenorrhea rates of vilaprisan after 12 weeks of treatment in Treatment Period 1 and after 24 weeks of treatment in Treatment Period 2 (with and without a break) versus placebo after 12 weeks of treatment using two-sided Cochran-Mantel-Haenszel test at a 0.05 significance level. A hierarchical (fixed sequence) testing procedure will be used, involving the primary efficacy variable amenorrhea and key secondary efficacy variables HMB response, time to onset of amenorrhea and time to onset of controlled bleeding. In addition, efficacy and safety variables will be summarized by descriptive statistics.

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List of abbreviations

AE	adverse event
AESI	adverse event of special safety interest
AG	*Aktiengesellschaft*, incorporated company
AH	alkaline hematin
ALT	alanine aminotransferase (also known as GPT)
AP	alkaline phosphate
aPTT	activated partial thromboplastin time
ASCUS	atypical squamous cells of undetermined significance
AST	aspartate aminotransferase (also known as GOT)
ATC	Anatomical Therapeutic Chemical
β-HCG	beta human chorionic gonadotropin
BMI	body mass index
CD	Compact disk
CDISC	Clinical Data Interchange Standards Consortium
CGI_I	Clinical Global Impression Investigator
ClinRO	clinician-reported outcome
CRA	Clinical research associate
CRO	contract research organization
CYP3A4	cytochrome P450 isoenzyme 3A4
dL	deciliter
E2	estradiol
EA	endometrial ablation
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic Diary
eg	*exempli gratia*, for example
EIN	endometrial intraepithelial neoplasia
EoT	end of treatment
ePRO	electronic patient-reported outcomes
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FUP	follow-up
g	gram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH(a)	gonadotropin-releasing hormone (agonist)
GOT	glutamic oxaloacetic transaminase (also known as AST)
GPT	glutamic pyruvic transaminase (also known as ALT)
Hb	hemoglobin
HbA_{1c}	glycosylated hemoglobin
HDL	high density lipoprotein
HMB	heavy menstrual bleeding
HPV	human papilloma virus
HRQoL	Health-related quality of life
IB	investigator's brochure

ICH	International Council on Harmonisation
ie	*id est*, that is
IEC	Independent Ethics Committee
INN	international nonproprietary names
INR	international normalized ratio
IRB	Institutional Review Board
IVRS/IWRS	interactive voice/web response system
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDL	low density lipoprotein
LH	luteinizing hormone
MBL	menstrual blood loss
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MD	doctor of medicine
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MP	menstrual pictogram
M&S	Modeling and Simulation
P	progesterone
PAEC	progesterone receptor modulator-associated endometrial changes
PASS	Power analysis and sample size
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
pH	negative logarithm of proton concentration
PK	pharmacokinetic(s)
PPS	per protocol set
PRM	progesterone receptor modulator
PROs	patient-reported outcomes
QA	quality assurance
QC	quality control
QoL	quality of life
QS	questionnaire
QSEVAL	Evaluator
RAVE	electronic data capturing system
RND	randomization
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	standard deviation
SDTM	Standard Data Tabulation Model
SESAC	Site Electronic Source Assessment Checklist
SF-36v2	Short Form 36 Health Survey Version 2
SID	subject identification
SS	Symptom Severity
SUSAR	suspected, unexpected serious adverse reaction
TEAE	Treatment emergent adverse event

THIN	The Health Improvement Network
TP	treatment period
TSH	thyroid-stimulating hormone
TSQM-9	Treatment Satisfaction Questionnaire for Medication
TVU	transvaginal ultrasound
UAE	uterine artery embolization
UF-DBD	Uterine Fibroid Daily Bleeding Diary
UF-DSD	Uterine Fibroid Daily Symptom Diary
UFS-QoL	Uterine Fibroid Symptom and Quality of Life questionnaire
ULN	upper limit of normal
UPA	ulipristal acetate
UPP	uterus-preserving procedures
US/USA	United States (of America)
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
wk	week

Definition of terms

3/1 regimen	3 months (ie, 3 x 28 days) of treatment with 1 bleeding episode between treatment periods
6/2 regimen	6 months (ie, 6 x 28 days) of treatment followed by 2 bleeding episodes
month	equals 28 days when referring to treatment (ie, 28 tablets per drug pack); equals 30 days when referring to the number of days in a month

3. Introduction

Uterine fibroids are benign tumors originating from smooth muscle cells of the myometrium. The pathophysiology of fibroids is not well understood. Genetic predisposition, exposure to steroid hormones, and growth factors play a role in formation and growth.

Based on ultrasound screening, the prevalence of uterine fibroids was found to be 40% in Caucasian and 60% in African-American women by the age of 35 years. In Japan, a cumulative incidence for uterine fibroids of 19% was reported (1). While women often remain asymptomatic, studies have shown that approximately 25% to 30% become symptomatic. Heavy menstrual bleeding (HMB) is a key symptom of uterine fibroids and can have a significant impact on patients' lives, but the majority of women presenting with symptomatic myomas experience multiple symptoms (2). A large survey (21,700 women in 8 countries) resulted in a self-reported prevalence of uterine fibroids of 6.8% in women aged 15 to 49 years, thereof 45% were symptomatic (3). According to the latest system review, the prevalence of uterine fibroids was 11.21% in 2011 in China (4). However, there is no nationwide epidemiological study available in China so far. The actual prevalence of uterine fibroids in China is assumed to be much higher (5).

Uterine fibroids typically appear and grow during reproductive years, but stabilize or regress after menopause. Therefore, they rarely require treatment after menopause. Clinically, fibroids and associated symptoms are most prominent in the late reproductive years. The most common symptoms of uterine fibroids are HMB and pelvic discomfort.

Uterine fibroids are the leading cause for hysterectomy. Hysterectomy is the only definitive treatment and eliminates the possibility of recurrence. In North America, 275,000 women per year undergo hysterectomy as uterine fibroid treatment.

The hysterectomy rate has decreased recently but still accounts for almost three quarters of all fibroid related surgical procedures. Increasingly more women desire to avoid hysterectomy, electing for a uterine preserving procedures, regardless of whether they desire to retain their fertility. The surgical treatment options are numerous, and each carries both the risks for surgery itself, as well as the possibility that the woman may require subsequent surgery as new fibroids often develop over time and become symptomatic.

In the United Kingdom, women with uterine fibroids aged 15–54 years were included in a retrospective observational study on the natural history of disease of uterine fibroids using the "The Health Improvement Network (THIN)". Analyses were done on the incidence of hysterectomy and uterus-preserving procedures (UPPs) including myomectomy, endometrial ablation (EA) and uterine artery embolization (UAE). The cumulative incidence of hysterectomy or UPPs was 23.6% at 1 year, and 40.9% after the follow-up period (median 3.6 years). At the end of the follow-up period of median 3.6 years, the cumulative incidences of hysterectomy, myomectomy, EA and UAE were 33.0%, 3.9%, 6.4% and 1.9%, respectively. For women initially treated with a UPP, the cumulative incidence of second procedures was 11.5% at 1 year. (6).

Not surprisingly, many women would prefer not to have surgery at all. A US based national survey revealed that 84% of women under the age of 40 with symptoms related to their uterine fibroids thought that it was important to have a leiomyoma treatment option that did

not involve invasive surgery (7). Therefore, there is a great medical need for effective pharmacological treatment suitable for long-term treatment of uterine fibroids. Unfortunately, there is no approved medical therapy in the United States that addresses this need for a prolonged treatment strategy that can serve as an acceptable alternative to surgery.

In China, treatment for uterine fibroids depends on the size/location, symptoms, age, and wish for pregnancy. However, surgery is also the major treatment for uterine fibroids, and medical treatment is just indicated for the patients whose symptoms are mild, or at peri-menopausal period, or who have contraindications of surgery. Gonadotropin-releasing hormone agonist (GnRHa) and mifepristone are the commonly used medical treatments for uterine fibroids in China, but mainly for short-term use (8).

The development of selective progesterone receptor modulators (PRMs) offers the potential for a novel, well tolerated medical treatment approach for women who are experiencing symptoms caused by their fibroids. Various studies have demonstrated the steroid-dependence of fibroid growth and that progesterone has a critical role.

The PRM ulipristal acetate (UPA) (Esmya® 5 mg tablets) is the first in class PRM to be approved for the treatment of fibroid-related symptoms. First, Esmya was approved in the European Union in FEB 2012 for pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age; the duration of treatment was limited to three months. In DEC 2013, the statement limiting treatment to a single 3 month course was removed and a change from single to two treatment courses (separated by a drug-free interval which requires 2 menstrual bleedings) was implemented. Since MAY 2015, Esmya is also indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age; a statement was added that repeated intermittent treatment has been studied up to 4 intermittent courses. In the US, China, and in Japan, ulipristal acetate is currently under development.

The PRM vilaprisan is being developed for the treatment of uterine fibroids and for the treatment of endometriosis. In Phase 1, vilaprisan has demonstrated dose-dependent induction of amenorrhea in healthy women. Two Phase 2 studies (15788 – ASTEROID 1 and 17541 – ASTEROID 2 [in reporting phase]) with a treatment duration of up to 24 weeks were conducted in women with uterine fibroids. The results of both studies demonstrated a clinically meaningful reduction of symptoms associated with uterine fibroids, especially of HMB, improvements of patients' health-related quality of life (HRQoL) and a reduction of fibroid size. Safety data also showed a favorable safety profile with no relevant safety concerns.

Further details can be found in the latest available version of the investigator's brochure (IB), which contains comprehensive information on the study drug.

4. Study objectives

The primary objective of this study is to show superiority in the treatment of HMB of vilaprisan in subjects with uterine fibroids compared to placebo.

The secondary objectives of this study are to additionally evaluate the efficacy and safety of vilaprisan in subjects with uterine fibroids.

The other objectives of this study are to evaluate the variability in exposure in relation to the efficacy and safety for vilaprisan and to collect patient-reported outcome (PRO) and clinician-reported outcome (ClinRO) data.

5. Study design

This section was changed in Amendment 2, see Section 15.1.1

This is a randomized, parallel-group, double-blind and open-label, placebo-controlled, multicenter study. Blinding will be applied to Treatment Groups A1, B1, and B2; Treatment Group A2 will be open-label.

The study is planned to be conducted in the US and China. Additional countries will be chosen in Europe, South Africa and Asia Pacific.

Overview of the study design is shown in Figure 5–1.

Figure 5–1 Design overview - amended

Treatment Group A1	Screening up to 120 days	RND	Vilaprisan 2 mg 12 week	*B*	Vilaprisan 2 mg 12 week	Follow-up Day 7 to 15 of the 2nd menstrual cycle after EoT
Treatment Group A2	Screening up to 120 days	RND	Vilaprisan 2 mg 12 week		Vilaprisan 2 mg 12 week	Follow-up Day 7 to 15 of the 2nd menstrual cycle after EoT
Treatment Group B1	Screening up to 120 days	RND	Placebo 12 week	*B*	Vilaprisan 2 mg 12 week	Follow-up Day 7 to 15 of the 2nd menstrual cycle after EoT
Treatment Group B2	Screening up to 120 days	RND	Vilaprisan 2 mg 12 week	*B*	Placebo 12 week	Follow-up Day 7 to 15 of the 2nd menstrual cycle after EoT

B = bleeding episode; RND = randomization.

During the screening period, subjects will have to demonstrate eligibility including the presence of at least 1 uterine fibroid ≥30 mm and <120 mm in largest diameter based on ultrasound, HMB in at least 2 bleeding periods, each with menstrual blood loss (MBL) >80.00 mL, documented by the alkaline hematin (AH) method, and endometrial biopsy results without significant histological disorder. The duration of the screening period should be kept to a minimum (maximum up to 120 days). In the event that the screening endometrial biopsy yielded an inadequate sample and needs to be repeated before randomization, the screening period interval is allowed to be extended in order to accommodate the endometrial sample analysis. In this case, the randomization visit (Visit 3) should take place: 1) after the biopsy results are available, 2) when all the eligibility criteria are confirmed, and 3) as close to the screening period interval as possible.

Eligible subjects will be randomized in 1:1:1:1 ratio to one of the four treatment groups (Group A1, A2, B1, or B2) and stratified by country/region (US, China, and other countries),

and will start treatment as described in Section 7.1. The time between randomization and start of treatment should not exceed 40 days.

After the end of the final treatment period, subjects will be followed up until day 7 to 15 of the 2nd menstrual cycle after end of treatment visit.

The **primary efficacy** variable is:

- Amenorrhea (yes/no), defined as MBL <2 mL during the last 28 days of treatment.

For the **secondary variables**, see Sections 10.3.1.2 and 10.3.2.2.

Justification of the design

Placebo control and blinding:

A double-blind placebo-controlled design (Treatment Groups A1, B1, and B2) is considered necessary to differentiate drug effects from the natural course of disease and background findings. To minimize subject burden due to randomization to placebo treatment, all subjects will receive active treatment during a part of the study. Treatment Group A2 will be open-label because the subjects and the investigators will know the treatment regimen since there is no break between the treatment periods.

Dose and regimen:

Ten Phase 1 studies with vilaprisan have been completed. Vilaprisan has been tested at a maximum oral dose of 30 mg for up to 28 days (Study 14721, Report A52153) in postmenopausal women and at oral doses of 0.1, 0.5, 1.0, 2.0 and 5.0 mg for up to 12 weeks (Study 14723, Report A56310) in healthy young women. In postmenopausal Japanese women, 5 mg once daily vilaprisan dose for 28 days was well tolerated (Study 14885, Report PH-27190). Furthermore, the pharmacokinetic (PK) results showed no ethnic difference in vilaprisan PK between the Asian and Caucasian populations. Vilaprisan has been studied in two Phase 2 studies in subjects with uterine fibroids using oral doses of 0.5, 1, 2, and 4 mg for a duration of 12 weeks (ASTEROID 1), and using a dose of 2 mg for up to 24 weeks (ASTEROID 2).

Based on the results of the Phase 2 dose finding study ASTEROID 1, the dose of 2 mg/day was chosen as the optimal dose for further development of vilaprisan, based on the following considerations:

- According to exposure-response analysis, a dose of 2 mg is required to achieve the exposure required for maximum efficacy on induction of amenorrhea in all subjects. There is no additional benefit of a higher dose.
- According to exposure-response analysis, the additional shrinkage in fibroid volume at end of treatment relative to baseline of approximately 6% on average for the 4 mg compared to the 2 mg dose is considered small compared to the considerable variability in the shrinkage of fibroid volume at these doses, which ranges from approximately 10% to 90%. Hence, the additional benefit of 4 mg compared to the 2 mg dose is considered limited.
- No safety findings were observed prohibitive to continue into Phase 3 for any dose up

to 4 mg tested in the dose finding study ASTEROID 1.

- The degree of ovarian suppression induced by the 2 mg dose seems to be optimally balanced. Maximum efficacy with respect to ovulation inhibition is accompanied with moderate suppression of estradiol production.
- Based on a population PK covariate analysis, it is concluded that the same dose can be used in all patients irrespective of age, body weight, fat free mass, and race.

Justification of regimens:

PRMs are applied either short-term or in an intermittent treatment regimen to avoid endometrial changes that may result in episodes of heavy menstrual bleeding (HMB) after cessation of treatment. A 3/2 regimen (3 months treatment followed by 2 menstrual bleeding episodes) has been established for a different compound in the PRM class. Currently available data indicate that this regimen is safe for repeated intermittent use.

Data from ASTEROID 1 show that efficacy of vilaprisan with regard to HMB is achieved rapidly after start of treatment and is maintained during treatment. However, ASTEROID 1 also shows that symptoms return quickly after cessation of treatment (ie, there is no relevant persistence of treatment effect during the treatment-free interval). This pattern was also observed for other efficacy parameters and is reflected in the assessment of quality of life (QoL) which improves during treatment and drops again during the treatment-free phase.

From these data, it is concluded that efficacy of long-term (ie, repeated-intermittent, treatment) will be more favorable if treatment phases are longer and treatment-free breaks are shorter, because this will result in fewer episodes of HMB per time interval and will reduce drops in QoL during the treatment-free phases.

Therefore, this study investigates the efficacy and safety of vilaprisan treatment over 3 months (followed by one menstrual bleeding episode) as well as over 6 months with the aim to develop a treatment regimen with a reduced number of days with HMB per time interval compared to the established treatment regimen for the class of PRMs. Such a reduction in the number of bleeding days is considered a clinically relevant benefit for patients with HMB.

In ASTEROID 2, vilaprisan was tested for a treatment duration of up to 24 weeks. In this study, a treatment duration of either 24 weeks or of two times 12 weeks (separated by one menstrual bleed), was chosen to evaluate safety and efficacy of vilaprisan against placebo.

Efficacy / pharmacodynamic assessments:

Menstrual bleeding and the impact uterine fibroids symptoms have on the subjects' daily life will be determined as efficacy parameters.

Fibroid size and uterus size (by ultrasound), endocrine hormone levels, and bleeding will be determined as pharmacodynamic (PD) parameters.

Safety monitoring:

Safety parameters will be regularly and closely monitored throughout the study (eg, questioning for adverse events (AEs), measurement of laboratory values, vital signs, endometrial thickness, abnormal menstrual bleeding, and size of follicle like structures

comprising follicles and functional ovarian cysts). Normal or clinically insignificant results for these parameters as well as from an endometrial biopsy are prerequisites for randomization to treatment. Criteria for withdrawal of individual subjects or termination of the entire study are described in Sections 6.4 and 12, respectively.

After treatment with PRMs histological changes in the endometrium are described in the literature that cannot be fully captured by using the conventional histological categories for endometrial tissues (9). A pathologist expert panel designated these changes as PRM associated endometrial changes (PAEC). PAEC are expected PD effects of PRM treatment and, according to current knowledge, do not constitute a safety concern by themselves. Data from ASTEROID 1 show that, as expected, PAEC that were observed during treatment with vilaprisan, resolved spontaneously after end of treatment and return to background level after the 2nd menstrual bleeding during follow-up in the majority of subjects. No treatment-emergent clinically relevant critical endometrial findings occurred in Phase 1 and Phase 2 studies.

A careful endometrial safety monitoring assessment will be applied in this study including regular ultrasound investigations during the treatment period, observation of bleeding patterns, and endometrial biopsies at defined time points. Clear decision trees are outlined as to when to perform an additional unscheduled endometrial biopsy in case of endometrial thickening and/or on the clinical management of endometrial thickening/HMB/abnormal menstrual bleeding pattern (see Section 9.7.2).

In addition to drug-related side effects, symptoms caused by the study conduct (eg, due to blood sampling, endometrial biopsy) are possible. However, possible risks are regarded as acceptable because the planned methods are used routinely in clinical studies, clinical and/or gynecological practice. Adverse effects will be monitored throughout the study, with systematic monitoring of parameters of special interest (eg, endometrial thickness and volume of menstrual bleeding).

The overall benefit-risk assessment for the present study is considered favorable based on the available data. It is expected that the information gained from the study will help in the development of better treatment for women with uterine fibroids in the future.

End of study

The end of the study as a whole will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (EU and non-EU).

Primary completion

The primary completion event for this study is the last visit of the last subject.

The primary completion date for this study according to the Food and Drug Administration (FDA) Amendment Act is specified in a separate document (not part of this study protocol).

6. Study population

Eligibility

Women with symptomatic uterine fibroids meeting all inclusion and presenting none of the exclusion criteria will be eligible for enrollment in the study.

6.1 Inclusion criteria

1. Signed and dated informed consent
2. Women, 18 years or older at the time of Visit 1
3. Diagnosis of uterine fibroid(s) documented by ultrasound at screening with at least 1 fibroid with largest diameter ≥30 mm
4. The largest diameter of any uterine fibroid is <120 mm
5. Heavy menstrual bleeding (HMB) in at least 2 bleeding periods during the screening period each with blood loss volume of >80.00 mL documented by the alkaline hematin (AH) method

   Women who did not suffer from perceived HMB during the 3 months prior to Visit 1 due to any effective medical treatment (eg, with a hormonal contraceptive) are not considered appropriate candidates and should not undergo further screening procedures.

   Women suffering from perceived HMB despite medical treatment (eg, with a hormonal contraceptive) are appropriate candidates for further screening, if rules on stopping prior medication (see exclusion criterion 8) are followed.

   Heavy menstrual bleeding >80.00 mL should be documented within 10 consecutive days. As guidance, the duration of a bleeding episode should not exceed 12 days.
6. Good general health (except for findings related to uterine fibroids) as proven by medical history, physical and gynecological examinations, and laboratory test results.
7. Normal or clinically insignificant cervical smear not requiring further follow-up. The cervical smear may be waived if a normal result has been documented in the subject's medical records within the previous 6 months.

   Human papilloma virus (HPV) testing in subjects with atypical squamous cells of undetermined significance (ASCUS) can be used as an adjunctive test. Subjects with ASCUS can be included if they are negative for high-risk HPV strains.
8. An endometrial biopsy performed during the screening period without significant histological disorder such as endometrial hyperplasia (including simple hyperplasia) or other significant endometrial pathology. If the sample is inadequate, the biopsy can be repeated once within the screening period and must be repeated within 6 weeks from the first biopsy in order for the subject to continue. No further repeated biopsies for inadequate samples are permitted.
9. Use of an acceptable non-hormonal method of contraception (ie, either male condom,

cap, diaphragm or sponge, each in combination with spermicide) starting at Visit 1 until the end of the study. (Short-acting hormonal contraception [oral, vaginal, or transdermal] are allowed up until the start of the menstrual cycle that follows Visit 1.) This is not required if contraception is achieved by a permanent method, such as bilateral fallopian tube blockage of the subject (including Essure®) or vasectomy of the partner(s).

6.2 Exclusion criteria

This section was changed in Amendment 2, see Section 15.1.1

1. Pregnancy or lactation (less than 3 months since delivery, abortion, or lactation before start of treatment)
2. Hypersensitivity to any ingredient of the study drug
3. Any condition requiring immediate blood transfusion
4. Laboratory values outside inclusion range [1] before randomization and considered as clinically relevant.
5. Any diseases, conditions, or medications that can compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study drug including, but not limited to:
    - Impaired function of the kidneys (laboratory values outside of inclusion range)
    - Elevated liver enzymes (presence of at least one of the following criteria):
        - 2 x upper limit of normal (ULN) for glutamic oxaloacetic transaminase (GOT) / aspartate aminotransferase (AST)
        - 2 x ULN for glutamic pyruvic transaminase (GPT) / alanine aminotransferase (ALT)
        - 2 x ULN for alkaline phosphatase (AP)
        - 1.5 x ULN for total bilirubin
    - Chronic bowel diseases, eg, M. Crohn and Colitis ulcerosa
    - Intake of strong cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors within the last 2 weeks before the randomization visit and during the treatment period including antivirals (eg, viekira pak, telaprevir, boceprevir), protease inhibitors (eg, ritonavir, lopinavir, indinavir, nelfinavir, saquinavir), antifungals (eg, itraconazole, voriconazole, posaconazole), antibiotics (eg, clarithromycin, telithromycin), grapefruit and any grapefruit containing food products (eg, grapefruit juice). Metronidazole, ketoconazole and other triazole antifungal drugs are allowed for topical/local use (including vaginal application) within

[1] As specified in the laboratory manual and in the reports from the central laboratory

the last 2 weeks before the randomization visit and during the treatment period. A detailed list is provided in Section 16.1.

- Intake of strong CYP3A4 inducers (eg, rifampicin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, St John´s wort, efavirenz, nevirapine, long term use of ritonavir) within the last 2 weeks before the randomization visit and during the treatment period. A detailed list is provided in Section 16.2.

6. Any diseases or conditions that might interfere with the conduct of the study or the interpretation of the results, including
    - Known severe coagulation disorder
    - Known anemia for reason other than HMB
    - Known hemoglobinopathy
    - History of or current uterine, cervical, ovarian, or breast cancer; except cervical cancer after curative treatment
    - One or more ovarian cysts >30 mm in diameter as measured by ultrasound
    - Any ovarian tumors or pelvic masses of unclear etiology requiring further diagnostic procedures
    - Known or suspected uterine polyp >15 mm
7. Abuse of alcohol, drugs, or medicines (eg, laxatives)
8. Use of other treatments that might interfere with the conduct of the study or the interpretation of the results including
    - Short-acting hormonal contraception (oral, vaginal, or transdermal), if not stopped at the start of the menstrual cycle that follows Visit 1
    - Long-acting hormonal contraception (injectable), if last application was performed less than 1 application interval before start of the menstrual cycle that follows Visit 1
    - Contraceptive devices with or without hormone release (implant, intra-uterine device), if not removed at Visit 1 (not applicable in cases of bilateral fallopian tube blockage of the subject (including Essure®))
    - Other hormonal treatments for HMB or fibroids, if not stopped before the start of the menstrual cycle that follows Visit 1 (eg, androgens, estrogen receptor antagonists, selective estrogen receptor modulators, and progesterone receptor modulators)
    - Gonadotropin-releasing hormone agonists (GnRHa), if not stopped at least one application interval before Visit 1
    - Tranexamic acid, traditional Chinese medicine for uterine fibroids or HMB, or other treatments for HMB, if not stopped at Visit 1

- Anticoagulants, if not stopped at Visit 1
- Previous use of vilaprisan (≥2 mg) without satisfactory result

9. Undiagnosed abnormal genital bleeding
10. Simultaneous participation in another clinical study with investigational medicinal product(s). Participation in another clinical trial prior to study entry (before Visit 1) that might have an impact on the study objectives.
11. Close affiliation with the investigational site (eg, a close relative of the investigator), dependent person (eg, employee or student of investigational site, or sponsor's staff)
12. Inability to cooperate with the study procedures for any reason, including the following examples: language comprehension, psychiatric illness, inability to get to the study site, eDiary compliance
13. Previous enrollment to the study (ie, rescreening is only allowed as described in Section 6.4.1)

6.3 Justification of selection criteria

The exclusion criteria are valid for known or suspected conditions and are chosen to ensure that subjects with specific risks for administration of the study drugs and/or subjects with conditions that may have an effect on the aims of the study are excluded.

6.4 Withdrawal of subjects from study

6.4.1 Withdrawal

Withdrawal criteria

Subjects *must* be withdrawn from the **study** if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- At the specific request of the sponsor and in liaison with the investigator (eg, obvious non-compliance, safety concerns)
- Pregnancy
- Surgical treatment of uterine fibroids

Subjects *must* be withdrawn from **study treatment** if any of the following occurs:

- If, in the investigator's opinion, continuation of the study treatment would be harmful to the subject's well-being
- GPT/ALT or GOT/AST >8 x ULN
- GPT/ALT or GOT/AST >5 x ULN for more than 2 weeks

- GPT/ALT or GOT/AST >3 x ULN **and** total bilirubin >2 x ULN **or** international normalized ratio (INR) >1.5
- GPT/ALT or GOT/AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash, and/or eosinophilia
- Atypical hyperplasia, endometrial intraepithelial neoplasia (EIN) or malignant neoplasm

Subjects *may* be withdrawn from study treatment if any of the inclusion criteria are no longer fulfilled or if any of the exclusion criteria apply during treatment.

Follow-up of subjects prematurely withdrawing from study treatment or during follow-up

For details of the premature discontinuation visit see Section 9.2.4.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "dropout" as specified below:

Screening failure

A subject who, for any reason (eg, failure to satisfy the selection criteria), terminates the study before randomization, is regarded a "screening failure".

Re-starting the defined set of screening procedures to enable the "screening failure" subject's participation at a later time point is only allowed if the in- / exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment). A subject can be rescreened only once. The investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk. The screening laboratory evaluations, cervical smear, and endometrial biopsy do not have to be repeated provided that the criteria for inclusion were previously met and are within an acceptable time frame (ie, within 4 weeks for laboratory parameters and within 6 months for the cervical smear and endometrial biopsy). In case endometrial thickness (double layer) >18 mm is detected during the ultrasound measurements at screening (ie, Visit 1 or 2), the subject should undergo an evaluation by endometrial biopsy. Rescreened subjects must re-sign the informed consent form and will be assigned a new subject identification (SID) number.

Dropout

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been randomized.

General procedures

In all cases, the reason for withdrawal must be recorded in the electronic Case Report Form (eCRF) and in the subject's medical records.

The subject may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12.

6.4.2 Replacement

Dropouts will not be replaced.

6.5 Subject identification

At screening upon signing the informed consent form and registering the subject in the interactive voice/web response system (IVRS/IWRS), each subject will be assigned a unique multi-digit SID number by the site for unambiguous identification. The SID number will be constructed as follows:

- Digits 1 to 2: unique country code
- Digits 3 to 5: center code (unique within each country)
- Digits 6 to 9: unique subject code (unique within each center); 6th digit will be "3" for this ASTEROID 3 study

Once allocated, the SID number will identify the subject throughout the study.

On random assignment to treatment, each subject will be assigned a unique randomization number.

7. Treatments

7.1 Treatments to be administered

Eligible subjects will be randomized to one of the following treatment groups:

A1: vilaprisan (2 mg), 2 treatment periods of 12 weeks, separated by 1 bleeding episode

A2: vilaprisan (2 mg), 2 treatment periods of 12 weeks without a break

B1: placebo, 1 treatment period of 12 weeks, and vilaprisan (2 mg), 1 treatment period of 12 weeks, separated by 1 bleeding episode

B2: vilaprisan (2 mg), 1 treatment period of 12 weeks, and placebo, 1 treatment period of 12 weeks, separated by 1 bleeding episode

Randomization will be 1:1:1:1 and stratified by country/region (US, China, and other countries) for Treatment Groups A1, A2, B1, and B2.

Each treatment period will consist of 12 weeks (84 days). One tablet (oral) will be taken daily during the treatment periods.

The tablets should be taken at about the same time every day. Exceptions to this rule may occur before visits with PK blood sampling (see Section 9.5.1).

Start of treatment

Treatment Period 1 for all subjects will start within Days 3 to 7 of the first bleeding episode following randomization visit. In case a bleeding episode is ongoing at randomization visit, the subject can already start with the intake of study medication during Days 3 to 7 of this bleeding episode. A negative pregnancy test is a prerequisite for starting the study drug

(applies to both treatment periods except the start of Treatment Period 2 in Treatment Group A2).

In Treatment Groups A1, B1, and B2, Treatment Period 2 will start within Days 3 to 7 of the first bleeding episode following the end of the Treatment Period 1. If no bleeding episode occurs within 7 weeks after end of the previous treatment period, proceed with the induction of bleeding according to Section 9.7.5.

For the start of treatment, subjects will judge based on their experience whether their bleeding episode has started. In case of unusual patterns (eg, start with some days of spotting) subjects should consult with the investigator.

For the statistical analysis, a bleeding episode is characterized by the following entries in the Uterine Fibroid Daily Bleeding Diary (UF-DBD):

- day(s) with bleeding / spotting of which at least one day is of intensity “mild” or higher
- preceded and followed by at least 2 bleed-free days (in case the first bleeding episode starts directly after Visit 1, the preceding 2 bleed-free days may not be recorded for this first bleeding episode).

Missed intake of study drug

If a subject misses a dose of study drug, she should take the tablet as soon as possible. If the dose of study drug was missed by more than 12 hours, she should not take the missed dose but simply resume the usual dosing schedule on the following day.

Diet

Subjects will be allowed to eat and drink as usual. However, grapefruit and grapefruit juice must be excluded from the subject's diet during treatment because these foods contain constituents that inhibit cytochrome P450 3A4.

7.2 Identity of study treatment

The investigational medicinal product vilaprisan and matching placebo are round immediate-release tablets, 6 mm in diameter and coated with a dark red coat (see Table 7—1).

Table 7—1: Identity of test drug/vilaprisan tablets and matching placebo

Sponsor's substance code	BAY 1002670
INN	Vilaprisan
Brand name	Not applicable
Formulation	Film-coated tablet
Tablet strength	2 mg
Composition	Active ingredient: Vilaprisan micronized Other ingredients: Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, dark red lacquer (containing hypromellose, macrogol 3350, talc, titanium dioxide, and red ferric oxide)
Packaging	28 tablets per package
Marketing Authorization Holder	Not applicable
Sponsor's substance code	Placebo (to BAY 1002670)
INN	Not applicable
Brand name	Not applicable
Formulation	Film-coated tablet
Tablet strength	Not applicable
Composition	Ingredients: Lactose monohydrate, microcrystalline cellulose, magnesium stearate, dark red lacquer (containing hypromellose, macrogol 3350, talc, titanium dioxide, and red ferric oxide)
Packaging	28 tablets per package
Marketing Authorization Holder	Not applicable

INN = International nonproprietary name.

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies QA group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file.

Study drugs need to be stored in accordance with the label text.

7.3 Treatment assignment

At Visit 3 (randomization), eligible subjects will be randomized via the IVRS/IWRS to one of the treatment groups (see Section 7.1).

The site will receive confirmation on the completion of the randomization procedure from the IVRS/IWRS. The confirmation will be considered as source documentation and should be maintained in the subject files. For additional details, refer to the separate IVRS/IWRS instructions.

7.4 Dosage and administration

See Section 7.1 for administration details.

7.5 Blinding

7.5.1 Blinding measures

Vilaprisan tablets and respective placebo tablets are identical in appearance (size, shape, color). The packaging and labeling will be designed to maintain the blinding of the investigator's team and the subjects for Treatment Groups A1, B1, and B2. Treatment Group A2 is open-label because the subjects and the investigators will know the treatment regimen since there is no break between the treatment periods.

The study data will remain blinded in the blinded treatment arms until database lock and authorization of data release according to Sponsor's standard operating procedures.

7.5.2 Unblinding

In compliance with applicable regulations, in the event of a suspected, unexpected serious adverse reaction (SUSAR) (see Section 9.6.1.5) related to the blinded treatment, the subject's treatment code will usually be unblinded by the sponsor's Pharmacovigilance department before reporting to the health authorities. Notifications of the ethics committees and investigators will be done according to all applicable regulations (see Section 9.6.1.4).

Study responsible PK and bioanalytical personnel will remain unblinded.

7.5.3 Emergency unblinding by the investigator

In case of emergency or any finding that requires unblinding, the investigator can break the blind for an individual subject via IVRS/IWRS consistent with the unblinding instructions provided. This will allow breaking the blind for an individual subject without impairing the study as a whole, unless safety findings required unblinding.

If it becomes necessary to know the individual treatment during the study and thus to break the code for that subject, the date, and reason are to be recorded in the relevant eCRF page. The investigator is required to promptly document and explain to the sponsor any premature unblinding (eg, unblinding because of a serious adverse event [SAE]) of the study drug. In case of unblinding, the subject will not be automatically withdrawn from study treatment.

7.6 Drug logistics and accountability

Study drug will be dispensed at the visits indicated in Table 9—1. For drug accountability, subjects will bring unused study drug and empty drug packs to each treatment visit. Drug accountability has to be determined for all tablets of study drug including placebo. Dispensation to the subject and return of the study drug will be documented in the drug accountability section of the eCRF and on the appropriate drug dispensing form by the investigator or designee. Any discrepancies between actual and expected amount of returned study drug must be discussed with the subject at the time of the visit, and any explanation must be documented in the source records and in the eCRF.

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/contract research organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. The responsible site personnel will confirm receipt of study drug via IVRS/IWRS. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

7.7 Treatment compliance

To monitor compliance, the subjects will be required to complete an electronic Diary (eDiary) daily throughout the study. The date of each study drug intake will be tracked via the eDiary. The eDiary will be dispensed at Visit 1 and the completeness of the eDiary data will be reviewed by the investigator or designee regularly between the visits, and together with the subject at every visit.

8. Non-study therapy

8.1 Prior and concomitant therapy

Information on prior medication for the treatment of uterine fibroids will be collected for the previous 6 months before Visit 1 (screening). Information on all other prior medication will be collected for the last 4 weeks before Visit 1.

All concomitant medications administered after signing of informed consent until the follow-up (FUP) visit, including topical (eg, vaginal) preparations and over the counter drugs will be recorded in the eCRF (trade name, dose, unit, frequency, route, start and stop dates, and indication).

For prohibited prior and concomitant medication, see Section 6.2. Prohibited strong CYP3A4 inhibitors are listed in Table 16—1 and strong inducers in Table 16—2.

Subjects who withdraw from study drug and subjects who withdraw during FUP should not receive hormonal treatments before the first menstruation after end of treatment (EoT) is completed and the EoT biopsy was performed.

Surgical and interventional treatment for fibroids must be documented in the eCRF if performed during the study period (ie, until the last visit of the subject) and should be regarded as AE if deemed appropriate by the investigator (see Section 9.6.1.1).

8.1.1 Iron supplementation

In subjects with hemoglobin ≤10.9 g/dL in blood, iron supplementation should be offered in a standardized regimen (see Section 9.7.1). Iron supplementation will not be considered a study

medication and will be documented as concomitant medication.

8.1.2 Progestin therapy for induction of bleeding

If required, subjects will be given an appropriate progestin therapy for induction of bleeding. Progestin therapy will not be considered as study medication and will be documented as concomitant medication (see Section 9.7.5 for details).

8.2 Post-study therapy

Subjects completing the treatment periods will participate in the post-treatment FUP without study drug treatment.

At the individual end of study, the investigator will decide in consultation with each subject which treatment is further required and will choose from available treatment options.

After completion of study the subjects will not be given free access to study drug, since alternative treatment options are available. Hormonal treatments for HMB should be started only after the first menstruation after the end of the study.

9. Procedures and variables

9.1 Tabular schedule of evaluations

This section was changed in Amendment 2, see Section 15.1.1

Significant time deviations from the given visit schedule will be documented as important deviations and/or validity findings. The definition of important deviations and validity findings will be provided in the Specification of assessment criteria and identification requirements document. Respective time windows are specified in Table 9—1.

Table 9—1: Schedule of procedures - amended

Study Phase	**Screening**			**TP 1** [a]		**TP 2** [b]		**FUP**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**EoT Visit** [c]	**FUP Visit** [d]
Timing		Day 7-15 (inclusive) of the 1st or 2nd menstrual cycle after Visit 1	RND	Day 22-42/ Wk 4-6 after start of TP1	Day 78-84/ Wk 12 after start of TP1	Day 22-42/ Wk 4-6 after start of TP2	Day 78-84/ Wk 12 after start of TP2	Day 7-15 (inclusive) of the 2nd menstrual cycle after EoT
Informed consent	X							
In-/exclusion criteria	X	X	X					
Demographics/smoking/alcohol consumption	X							
Medical/reproductive/menstrual/fibroids histories	X							
HMB questions	X							
Prior/ concomitant medications	X	X	X	X	X	X	X	X
AE assessments	X	X	X	X	X	X	X	X
Physical examination	X						X	X
Vital signs [e]/body weight/BMI/height at Visit 1 only	X		X				X	X
Gynecological/breast exam	X							X

Table 9—1: Schedule of procedures - amended

Study Phase	**Screening**			**TP 1** [a]		**TP 2** [b]		**FUP**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**EoT Visit** [c]	**FUP Visit** [d]
Timing		Day 7-15 (inclusive) of the 1st or 2nd menstrual cycle after Visit 1	RND	Day 22-42/ Wk 4-6 after start of TP1	Day 78-84/ Wk 12 after start of TP1	Day 22-42/ Wk 4-6 after start of TP2	Day 78-84/ Wk 12 after start of TP2	Day 7-15 (inclusive) of the 2nd menstrual cycle after EoT
Urine pregnancy test [f]	X	X	X	X	X	X	X	X
Cervical smear	X [g]							X
Ultrasound examination [h]	X	X [i]	X	X	X	X	X	X [b]
Instruct subject to contact site at start of next menstrual bleed	X						X at the 2nd bleed	
Endometrial biopsy [j]		X [k]					X [l]	X [b]
Laboratory (blood) [m]	X				X		X	X
PK sampling [n]					X	X		
Supervised study drug intake at site					X	X		
Urinalysis	X							
Barrier contraception/sanitary protection/home pregnancy test dispensed	X	X	X	X	X	X	X	
Alkaline hematin kit dispensed (as needed)	X	X	X	X	X	X	X	
Collect pads and tampons (as needed)		→	→	→	→	→	→	→
Randomization			X					
Study drug dispensed			X	X	X	X		
Unused study drug and empty drug packs collected/drug accountability				X	X	X	X	X if applicable
Return unused study drug to subject				X	X [o]	X	X [o]	
Assess subject's study drug compliance				→	→	→	→	→ if applicable
eDiary dispensed/collected	X							X
eDiary checked via web-report	→	→	→	→	→	→	→	→
PRO (eDiary/hand held device) [p]**:**								
UF-DSD	→	→	→	→	→	→	→	→
UF-DBD [q]	→	→	→	→	→	→	→	→
Menstrual pictogram	→	→	→	→	→	→	→	→
PRO (tablet computer) – completed at the site [r]**:**								
UFS-QoL			X		X		X	X
PGI-S			X		X		X	
PGI-C					X		X	
SF-36v2			X		X		X	X
TSQM-9					X		X	
ClinRO (RAVE): CGI_I			X				X	X

Treatment Day 1 is defined as the first day of study drug intake (ie, start of treatment).

a If no bleeding episode occurs within 7 weeks after the end of the TP, an ultrasound will be performed after which bleeding will be induced (Treatment Groups A1, B1, and B2).

b If spontaneous menstrual bleeding does not occur within 7 weeks after the EoT, the scheduled ultrasound will be performed as planned after which bleeding will be induced. The scheduled endometrial biopsy (ie, at FUP visit) will be performed thereafter at Day 7-15 (inclusive) of the first menstrual cycle after the induced bleeding episode. Ultrasound and pregnancy test will be performed before the endometrial biopsy as described in Section 9.6.3.2.

c EoT visit is also to be performed if a subject is prematurely withdrawn from the study during treatment phase.

d FUP visit is also to be performed, if a subject is prematurely withdrawn from the study during FUP phase.

e Vital signs after 5 minutes of rest in a sitting position.

f Instruct the subject to perform a home pregnancy test before the start of study drug treatment (all groups at TP 1, and all but Group A2 at TP 2), document it in the eDiary and only start study drug if the test is negative.
g The cervical smear may be waived if a normal result has been documented in the subject's medical records within the previous 6 months.
h 1. Ultrasound measurements do not have to be done on the same day as other assessment on that visit, but have to be performed as close to the specified visit as possible. On visits where a biopsy will be taken, the ultrasound must be done before the biopsy.
2. If endometrial thickness (double layer) >18 mm is detected after the start of treatment, the subject should undergo immediate evaluation by endometrial biopsy as described in Section 9.6.3.2. If cyst like structures >30 mm without suspicious appearance (ie, functional cysts) are visualized in the ovaries, unscheduled ultrasound examinations to document regression/outcome of these finding should be performed every 4 weeks or more frequently, if required due to symptoms.
i Ultrasound for safety only.
j For scheduling the visits, consider for subjects with menstrual cycles that biopsies should be taken between Day 7-15 (inclusive) of a menstrual cycle, which may require scheduling an additional visit. The EoT biopsy should be taken while under treatment; this biopsy may require to be scheduled before the EoT visit. A pregnancy test and ultrasound have to be performed before an endometrial biopsy is taken. See Section 9.6.3.2 for details.
k Check laboratory results prior to the biopsy at Visit 2 to ensure subject is still eligible for the study.
l For subjects with amenorrhea, biopsies are to be taken without considering any day in a cycle.
m Coagulation parameters will be determined at Visit 1 only.
n PK sampling. At Visit 5, one sample is to be taken pre-dose. At Visit 6, 1 sample is to be taken pre-dose, and 2 samples are to be taken after supervised study drug intake at the site (one between 0.5-1 hour after, and one between 2-4 hours after study drug intake). Document the following in the eCRF: the date and time of the last 2 study drug doses prior to the first PK sample at each visit, the time of the supervised drug intake at the study site (Visits 5 and 6), and the time of all blood samples. For China, a minimum of 30 subjects with PK samples from V5 and V6 are required from some centers. See Section 9.5.1.
o For subjects who have completed the TP, collect unused study drug and empty packaging. For subjects who have not completed TP, collect empty packaging and provide unused study drug back to the subject. Instruct the subject to complete the treatment period.
p PROs on the eDiary/electronic hand-held device will be responded by the subjects until the next visit at home as required.
q Check for any suspicious bleeding pattern and/or HMB at each visit except Visit 1.
r PROs on the tablet computer will be responded by the subjects at scheduled visits under standardized conditions in the same visit-relevant sequence and prior to other activities and evaluations.

→ = continuous collection of used sanitary products (pads or tampons), data (eg, daily or weekly questionnaire) or collection of data and used sanitary products in a schedule different to the visit time point;

AE = adverse event; BMI = body mass index; CGI_I = Clinical Global Impression - Investigator; ClinRO= Clinician-reported outcome; EoT = end of treatment; FUP = follow-up; HMB = heavy menstrual bleeding; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; PRO = patient-reported outcome; RND = randomization; SF-36v2 = Short Form 36 Health Survey Version 2; TP = Treatment Period; TSQM-9 = Treatment Satisfaction Questionnaire for Medication (9 items); UF-DBD = Uterine Fibroid Daily Bleeding Diary; UF-DSD = Uterine Fibroid Daily Symptom Diary; UFS-QoL = Uterine Fibroid Symptom and Quality of Life questionnaire; Wk = week.

9.2 Visit description

The measures listed in the following sections will be performed by the study site investigator or an appropriately qualified, trained and delegated individual of the investigational site.

9.2.1 Unscheduled visits

If deemed necessary for an individual subject, the investigator or designee, at his/her discretion, may arrange visits in addition to the scheduled study visits. Possible reasons for unscheduled visits include return of used sanitary protection items, suspicion of pregnancy and other safety concerns that will be documented in the eCRF.

9.2.2 Optional pre-screening phone contact

This section was changed in Amendment 2, see Section 15.1.1

Before Visit 1 (screening), an optional pre-screening contact can be arranged and will typically occur via telephone or as a response to an advertisement. During this contact, the study candidate may be interviewed for suitability to participate in the study consistent with the entry criteria of the study, including questions on HMB. The pre-screening contact may be performed by the investigator, study nurse, or other individuals trained for this task.

After the telephone discussion, the patient information and informed consent form may be sent to the subject for further information. Regardless of whether the patient information and informed consent form is sent to the subject, it must be thoroughly discussed and reviewed with her in person before obtaining the signed informed consent form.

If, based on the pre-screening contact, a study candidate is not interested in participating in the study or if she is not suitable for Screening Visit 1, she will be given advice about available treatment options for uterine fibroids, how they can be accessed, and where to contact for further information or, if applicable, directed to treatment consistent with standard care. Before the informed consent is signed by the subject, no modifications to the subject´s current treatment will be made for the purpose of entry into the trial.

9.2.3 Scheduled visits

This section was changed in Amendment 2, see Section 15.1.1

For timing of the visits see Table 9—1. Site personnel will determine the start of each treatment period from the eDiary provider web portal. For Scheduling Visit 6 and the EoT visit in Treatment Group A2, the Day 1 of the TP2 is the next day after Day 84 of TP1. Subjects must be contacted (eg, via phone call) after the first dose is taken in each treatment period to schedule the subsequent visits.

9.2.3.1 Visit 1 Screening

This section was changed in Amendment 2, see Section 15.1.1

The following procedures will be performed during this visit:

- Informative discussion about the study and distribute subject information and informed consent form. This must occur even if the subject information and informed consent form was sent to the subject following a pre-screening contact. (See Section 13.4).
- Obtain signed and dated informed consent.
- SID number assigned (see Section 6.5)
- Assess inclusion and exclusion criteria (see Sections 6.1 and 6.2)
- Demographic data, smoking history, and alcohol consumption (see Section 9.3.1)
- Medical, reproductive, menstrual, and fibroids histories (see Sections 9.3.2 and 9.3.3)
- HMB questions (see Section 9.3.4)

- Prior and concomitant medications (see Section 8.1)
- AE assessment (see Section 9.6.1)
- Blood pressure and heart rate after 5 minutes of rest in a sitting position; body weight, height, and body mass index (BMI)
- Physical examination
- Gynecological examination including breast palpation
- Cervical smear (may be waived if a normal result has been documented in the subject's medical records within the previous 6 months; see Section 9.6.3.3)
- Ultrasound examination (see Sections 9.4.4 and 9.6.3.6)
- Laboratory (blood and urine) evaluations including coagulation parameters (see Section 9.6.3.1)
- Urine pregnancy test (see Section 9.6.3.7)
- Dispense barrier contraception, (eg, condoms with spermicide) (see Section 9.6.3.7)
- Dispense AH kit and sanitary protection Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss
- Remind the subject to return all used sanitary protection items as soon as the bleeding episode has been completed (but no later than 12 days from the start of the collection of the first item).
- Dispense home pregnancy tests. Instruct the subject to contact the site immediately in case of a positive home pregnancy test.
- Explain and dispense eDiary device
- Instruct the subject to complete eDiary-based questionnaires until the next visit at home as required (UF-DSD, UF-DBD, and MP) (see Sections 9.4.1.1 and 9.4.1.2.1).
- Instruct the subject to call the study site at the start of her next menstrual bleeding to schedule Visit 2 on Day 7 to 15 (inclusive) of the 1st or 2nd menstrual cycle.

9.2.3.2 Visit 2 Screening

This section was changed in Amendment 2, see Section 15.1.1

Laboratory test results should be checked before performing the endometrial biopsy in order to determine if a retesting is needed and to confirm that the subject is still eligible for study participation. It is recommended that Visit 2 takes place after HMB has been shown in at least 1 bleeding period.

The following procedures will be performed during this visit:

- Check of eDiary entries via web; check for suspicious bleeding pattern and HMB (see Section 9.7.3)
- (Re-)assess inclusion and exclusion criteria (see Sections 6.1, 6.2, and 9.7.3)

- Concomitant medications (see Section 8.1)
- AE assessment (see Section 9.6.1)
- Urine pregnancy test (see Section 9.6.3.7) and ultrasound (safety only; see Section 9.6.3.6) before the endometrial biopsy
- Endometrial biopsy (see Section 9.6.3.2). If the endometrial biopsy sample is inadequate, the biopsy can be repeated once within the screening period and must be repeated within 6 weeks from the first biopsy in order for the subject to continue. No further repeated biopsies for inadequate samples are permitted.
- Dispense barrier contraception (eg, condoms with spermicide) (see Section 9.6.3.7)
- Dispense AH kit and sanitary protection. Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss.
- Collect used sanitary protection items, if they have not yet been provided to the site
- Dispense home pregnancy tests. Instruct the subject to contact the site immediately in case of a positive home pregnancy test.
- Remind the subject to complete eDiary-based questionnaires until the next visit at home as required (UF-DSD, UF-DBD, and MP) (see Sections 9.4.1.1 and 9.4.1.2.1)
- Remind the subject to return all used sanitary protection items as soon as a bleeding episode has been completed, (but no later than 12 days from the start of the collection of the first item).

Visit 3 should take place when the biopsy result is available and all eligibility criteria are confirmed.

In the event that the screening endometrial biopsy yielded an inadequate sample and needs to be repeated before randomization, the screening period interval is allowed to be extended in order to accommodate the endometrial sample analysis (as described above). In this case, Visit 3 should take place: 1) after the biopsy result is available, 2) when all the eligibility criteria are confirmed, and 3) as close to the screening period interval as possible.

9.2.3.3 Visit 3 Randomization

This section was changed in Amendment 2, see Section 15.1.1

The following procedures will be performed during this visit:

- Administer the Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QoL), Patient Global Impression of Severity (PGI-S), and the Short Form 36 Health Survey Version 2 (SF-36v2) on the tablet computer prior to any other assessments or examinations (see Sections 9.4.1.2.2 to 9.4.1.2.4)
- Check of eDiary entries via web; check for suspicious bleeding pattern and HMB (see Section 9.7.3)
- Re-assess inclusion and exclusion criteria (see Sections 6.1, 6.2, and 9.7.3)

- Concomitant medications (see Section 8.1)
- AE assessment (see Section 9.6.1)
- Blood pressure and heart rate after 5 minutes of rest in a sitting position, body weight, and BMI
- Urine pregnancy test (see Section 9.6.3.7)
- Ultrasound examination (see Sections 9.4.4 and 9.6.3.6)
- Dispense barrier contraception (eg, condoms with spermicide) (see Section 9.6.3.7)
- Dispense AH kit and sanitary protection. Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss
- Collect used sanitary protection items, if they have not yet been provided to the site
- Dispense home pregnancy tests. Instruct the subject to perform a home pregnancy test before the start of study drug treatment, document it in the eDiary and only start study drug if the test is negative. Remind the subject to inform the study site immediately of a positive home pregnancy test.
- Randomize to treatment group (see Section 7.3)
- Dispense study drug according to IVRS/IWRS assignment
- Instruct the subject to start the study drug within Days 3 to 7 of their next menstrual cycle, or of their current menstrual cycle, and to report the start date in their eDiary.
- Remind the subject to bring unused study drug and empty drug packs to the next visit
- Remind the subject to complete eDiary-based questionnaires until the next visit as required (UF-DSD, UF-DBD, and MP) (see Sections 9.4.1.1 and 9.4.1.2.1)
- Remind the subject to return all used sanitary protection items as soon as a bleeding episode has been completed (but no later than 12 days from the start of the collection of the first item).
- Complete ClinRO (RAVE): CGI_I (see Section 9.4.2)

9.2.3.4 Visits 4, 5, and 6

This section was changed in Amendment 2, see Section 15.1.1

The following procedures will be performed during these visits:

- Visit 5 only: Administer the UFS-QoL, the PGI-S, the PGI-C, the SF-36v2, and the Treatment Satisfaction Questionnaire for Medication (TSQM-9) on the tablet computer prior to any other assessments (see Sections 9.4.1.2.2, 9.4.1.2.3, 9.4.1.2.4, and 9.4.1.2.5)
- Concomitant medications (see Section 8.1)
- AE assessment (see Section 9.6.1)

- Urine pregnancy test (see Section 9.6.3.7)
- Ultrasound examination (see Sections 9.4.4 and 9.6.3.6)
- Visit 5 only: Laboratory evaluations excluding coagulation parameters and urinalysis (see Section 9.6.3.1)
- Visits 4 and 5 only: Remind the subject NOT to take the study drug at home on the day of Visits 5 and 6. Study drug intake should be supervised at the site at Visit 5 and 6. Remind the subject to report the date and time of the last 2 study drug intakes before the PK sampling is done.
- Visit 5 only: PK sampling, pre-dose only (see Section 9.5.1). Document the date and time of the last 2 doses of the study drug prior to the PK sample, the time of the supervised drug intake at the study site, and the time of the blood sample in the eCRF.
- Visit 6 only: 3 PK samples will be collected. The first PK sample should be taken pre-dose. Two additional PK samples should be collected after supervised study drug intake at site: 1 sample between 0.5 to 1 hour after study drug intake and 1 sample between 2 to 4 hours after study drug intake (see Section 9.5.1). Document the date and time of the last 2 doses of the study drug prior to the first PK sample, the time of the supervised drug intake at the study site, and the time of all blood samples in the eCRF.
- Dispense barrier contraception (eg, condoms with spermicide) (see Section 9.6.3.7)
- Dispense AH kit and sanitary protection. Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss
- Collect used sanitary protection items, if they have not yet been provided to the site.
- Dispense home pregnancy tests. At Visit 5, instruct the subject (Treatment Groups A1, B1, and B2) to perform a home pregnancy test before the start of Treatment Period 2, document it in the eDiary and only start study drug if the test is negative. Remind the subject to contact the site immediately in case of a positive home pregnancy test.
- Dispense study drug according to IVRS/IWRS assignment
- Visit 5 only: Instruct the subject to start study drug within Days 3 to 7 of the next menstrual cycle following the end of Treatment Period 1 (Treatment Groups A1, B1, and B2 only)
- Drug accountability and assessment of subject compliance, remind the subject to bring unused study drug and empty drug packs to the next visit
    - Visit 4 and 6 only: Collect unused study drug and empty drug packs and provide unused study drug back to subject
- Visit 5 only: For subjects who have completed Treatment Period 1, collect unused study drug and empty packaging. For subjects who have not completed Treatment

Period 1, collect empty packaging and provide unused study drug back to the subject and instruct the subject to complete Treatment Period 1.

- Visit 5 only: Instruct the subject to call the study site at the start of her next menstrual bleeding to schedule Visit 6
- Remind the subject to complete eDiary-based questionnaires until the next visit as required (UF-DSD, UF-DBD, and MP) (see Sections 9.4.1.1 and 9.4.1.2.2)
- Remind the subject to return all used sanitary protection items as soon as a bleeding episode has been completed, (but no later than 12 days from the start of the collection of the first item).
- Check of eDiary entries via web; check for suspicious bleeding pattern and HMB (see Section 9.7.3)

Visit 6 only: For scheduling the EoT biopsy for a subject with menstrual cycle, the EoT biopsy should be taken between Day 7 to 15 [2] (inclusive) of the last menstrual cycle during Treatment Period 2, which may require an unscheduled visit before the EoT visit. If the subject is in amenorrhea, the biopsy will be taken at the scheduled EoT visit without considering any day in a cycle.

9.2.3.5 EoT visit

This section was changed in Amendment 2, see Section 15.1.1

If a subject is prematurely withdrawn from the study during the treatment phase, all efforts should be made to perform the applicable assessments scheduled for the EoT visit before study withdrawal.

The following procedures will be performed during this visit:

- Administer the UFS-QoL, the PGI-S, the Patient Global Impression of Change (PGI-C), the SF-36v2, and the TSQM-9 on the tablet computer prior to any other assessments (see Sections 9.4.1.2.2, 9.4.1.2.3, 9.4.1.2.4, and 9.4.1.2.5)
- Concomitant medications (see Section 8.1)
- AE assessment (see Section 9.6.1)
- Physical examination
- Blood pressure and heart rate after 5 minutes of rest in a sitting position, body weight, and BMI
- Urine pregnancy test (see Section 9.6.3.7) and ultrasound (see Sections 9.4.4 and 9.6.3.6) before the endometrial biopsy
- Collect used sanitary protection items, if they have not yet been provided to the site.

[2] Day 1 of a menstrual cycle is defined as the first day of the first bleeding episode occurring in the specified time period.

- Remind the subject to continue collecting the used sanitary products during the follow-up.
- Remind the subject to return all used sanitary protection items as soon as a bleeding episode has been completed, (but no later than 12 days from the start of the collection of the first item).
- Endometrial biopsy (see Section 9.6.3.2)
- Laboratory evaluations excluding coagulation parameters and urinalysis (see Section 9.6.3.1)
- Dispense barrier contraception (eg, condoms with spermicide) (see Section 9.6.3.7)
- Dispense AH kit and sanitary protection. Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss.
- Dispense home pregnancy tests. Remind the subject to contact the site immediately in case of a positive home pregnancy test.
- For subjects who have completed the treatment period, collect unused study drug and empty packaging. For subjects who have not completed the treatment period: collect empty packaging and provide unused study drug back to subject. Instruct subject to complete the treatment period.
- Drug accountability and assessment of subject compliance; for subjects who have not completed the treatment period, remind subjects to bring unused study drug and empty drug packs to the next visit
- Complete ClinRO (RAVE): CGI_I (see Section 9.4.2)
- Remind the subject to complete eDiary-based questionnaires until the next visit at home as required (UF-DSD, UF-DBD, and the MP) (see Sections 9.4.1.1 and 9.4.1.2.2)
- Check of eDiary entries via web; check for suspicious bleeding pattern and HMB (see Section 9.7.3)
- Instruct the subject to call the site at the start of the 2nd menstrual bleed to schedule the endometrial FUP on Day 7 to 15 (inclusive) of the 2nd menstrual cycle.

9.2.3.6 FUP visit

If a subject is prematurely withdrawn from the study during FUP phase, all efforts should be made to perform all assessments scheduled for this visit before study withdrawal. In this case, an endometrial biopsy should be taken unless an endometrial biopsy with normal findings is available from this subject since EoT.

The following procedures will be performed during this visit:

- Administer the UFS-QoL and the SF-36v2 (see Sections 9.4.1.2.2 and 9.4.1.2.4) on the tablet computer prior to any other assessments or examinations

- Concomitant medications (see Section 8.1)
- AE assessment (see Section 9.6.1)
- Physical examination
- Blood pressure and heart rate after 5 minutes of rest in a sitting position, body weight, and BMI
- Gynecological examination including breast palpation
- Laboratory evaluations excluding coagulation parameters and urinalysis (see Section 9.6.3.1)
- Urine pregnancy test (see Section 9.6.3.7)
- Ultrasound examination (see Sections 9.4.4 and 9.6.3.6)
- Cervical smear (see Section 9.6.3.3)
- Endometrial biopsy (see Section 9.6.3.2)
- Collect used sanitary protection items, if they have not yet been provided to the site
- Check of eDiary entries via web; check for suspicious bleeding pattern and HMB (see Section 9.7.3)
- Complete ClinRO (RAVE): CGI_I (see Section 9.4.2)
- Collect eDiary (device)
- Collect unused study drug and empty drug packs and assess subject compliance (for subjects who completed the treatment period during FUP)
- Drug accountability (for subjects who completed the treatment period during FUP)

9.2.4 Premature discontinuation visit

Subjects who discontinue the study prematurely during a treatment period should have the EoT visit performed. In addition to the assessments scheduled for the EoT visit, a gynecological exam including breast palpation and a cervical smear should be done for the subjects prematurely withdrawing during the treatment phase.

Subjects who discontinue the study prematurely during the post-treatment FUP phase should have the FUP visit performed. An endometrial biopsy should be taken unless an endometrial biopsy with normal findings is already available from this subject since EoT.

9.3 Population characteristics

9.3.1 Demographic

Demographic data (eg, year of birth, age at Visit 1, race, ethnic group, educational level) and other population characteristics including smoking habits and alcohol consumption will be collected consistent with the schedule of procedures (see Table 9—1).

9.3.2 Medical history

Medical history findings (ie, previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant for the subject's study eligibility

Any condition that is being stabilized by medication at the time of signing the informed consent should also be documented in the eCRF. The medication being used should be recorded in the prior and concomitant medication eCRF.

All new or worsened findings after signing the informed consent should be documented on the Adverse Event (AE) eCRF.

Detailed instructions on the differentiation between medical history and AEs can be found in Section 9.6.1.1.

9.3.3 Reproductive, menstrual, and fibroids history

Reproductive and menstrual history includes information on menarche, births, other pregnancies, and inability to conceive.

Fibroids history includes information on family history, onset of symptoms, diagnosis, and previous medical treatments and procedures, if applicable.

9.3.4 Heavy menstrual bleeding questions

This set of questions has been developed as a tool to identify women with HMB. It will be used at Visit 1 and the responses can be entered directly into electronic data capturing system RAVE, which will be considered as primary source data. The questionnaire can also be used as a pre-screening tool. Print outs of the questionnaire can be provided to the sites as needed.

9.4 Efficacy

This section details the procedures for collecting efficacy variables. A concise listing of efficacy variables is given in Section 10.3.1. The complete list of variables to be analyzed for this study will be provided in the Statistical Analysis Plan (SAP).

9.4.1 Patient-reported outcomes

Patient-reported outcomes (PROs) are self-administered questionnaires completed by the subjects themselves. All questionnaires will be administered in the subject's local linguistically validated language versions. In this study PROs will be collected using electronic devices: an e-Diary/electronic hand-held device at home for daily entries and a tablet computer at the study site. The time window for data entry into the device is technically regulated.

Site staff will be trained regarding the use of the electronic devices. Standardized technical training for the subjects will be provided by the trained study site personnel. In addition, a

user manual will be provided and a 24-hour help desk in local language will be available. Following the training on the use of the electronic devices, the subjects will be asked to confirm their understanding on the use of the devices and completion of the questionnaires before the device is activated. Training on the use of the devices and ongoing technical support will minimize the failure in data entry or missing of data entry.

All questionnaires completed at home should be completed independently by the subject herself in a quiet, private area. The questionnaires answered at the site should also be completed independently by the subject herself in a quiet, private area, accessible only to the subject and study staff, and prior to any other study-related procedures. The subject should be seated comfortably, and allowed sufficient time to complete the questionnaires. Study personnel should allow the subject privacy while completing the questionnaires but should be available in the event the subject has technical questions. No help other than technical support should be given to the subjects regarding the completion of the PROs. To reduce the amount of missing data, site staff should be instructed to check the questionnaires for completeness.

Time for PRO completion is calculated based on the 12 second per item conservative assumption. For PROs completed daily on the hand-held device at home, the completion time will be 2 to 3 minutes. Completion of PROs on the tablet computer at the study site during the site visits will take 15 to 17 minutes.

Data from the electronic devices will be uploaded to a database at regular intervals. Completeness of eDiary and tablet entries will be monitored by the investigator or site personnel via password protected web access on a regular basis and at each study visit. Actions resulting from this review process (eg, contact with a subject in case of missing data) will be captured in the source data. In case of technical failure, the subject should immediately contact the help desk and contact the site if a replacement diary (new device) is needed. Paper questionnaires will not be used as replacement for the eDiary device.

The eDiary (device) will be returned to the site as indicated in Table 9—1.

PROs administered by the eDiary/electronic hand-held device at home

At Visit 1, an eDiary will be dispensed. The device is a small hand-held, touch-screen computer, similar in size and design to a smart-phone. The following PROs will be applied within the eDiary:

- UF-DBD (see Section 9.4.1.1.1)
- UF-DSD (see Section 9.4.1.2.1)
- MP (see Section 9.4.1.1.2)

All home pregnancy tests and study drug intake will also be documented within the eDiary (see Sections 9.6.3.7 and 7.7).

PROs administered by the tablet computer at the study site

Subjects must complete the following PRO on the tablet computer at the study site at scheduled visits:

- UFS-QoL (see Section 9.4.1.2.2).
- PGI-S and PGI-C (see Section 9.4.1.2.3)
- SF-36v2 (see Section 9.4.1.2.4)
- TSQM-9 (see Section 9.4.1.2.5)

9.4.1.1 PROs to assess HMB

9.4.1.1.1 Uterine Fibroid Daily Bleeding Diary (UF-DBD)

Subjects will be asked to rate any vaginal bleeding in the past 24 hours on a daily basis using the following question and scoring categories: "Rate the severity of any vaginal bleeding in the past 24 hours":

- No vaginal bleeding
- Spotting
- Mild
- Moderate
- Severe
- Very severe

The information will be collected in the eDiary.

9.4.1.1.2 Menstrual pictogram

During the study, subjects will be required to use selected types of sanitary products (pads and/or tampons), and to assess the intensity of their menstrual blood loss per sanitary product using a visual scoring system.

This will be documented in the eDiary whenever a sanitary product is changed or discarded.

9.4.1.2 Other PROs

9.4.1.2.1 Uterine Fibroid Daily Symptom Diary (UF-DSD)

The UF-DSD will be filled in daily using the eDiary.

The UF-DSD is a newly developed multi-item PRO instrument designed to assess cardinal symptoms of uterine fibroids using a 24-hour recall period.

The UF-DSD includes 2 items to assess swelling and bloating symptoms using a 5-graded Likert-type severity rating ('no symptom' to 'very severe symptom'), and 2 items using a 0 to 10 numerical rating scale to assess pain at its worst in the abdominal/pelvic and lower back areas with 0 indicating "no pain" and 10 "pain as bad as you can imagine". Additionally, intake of pain medication is investigated using a 4-point verbal rating scale (no;

yes, over the counter [non-prescription] pain medication; yes, prescription pain medication; or yes, both over the counter and prescription pain medication).[3]

9.4.1.2.2 Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QoL)

The UFS-QoL questionnaire will be filled in during site visits consistent with Table 9—1.

The UFS-QoL is a widely used disease-specific instrument that assesses symptom severity and HRQoL in subjects with uterine fibroids. It consists of 37 items including an 8-item Symptom Severity (SS) scale and 29 HRQoL questions, comprising 6 subscales: concern, activities, energy/mood, control, self-consciousness, and sexual function (10) using a recall period of 3 months.

All items are scored on a 5-point Likert scale, ranging from "not at all" to "a very great deal" for SS items and "none of the time" to "all of the time" for the HRQoL items. SS and HRQoL individual item scores are summed and transformed into a 0-100 point scale to form SS and HRQoL subscale scores respectively. The SS scale and the HRQoL subscale scores are inversely related with higher SS scores indicating greater symptoms while higher HRQoL subscale scores indicate better HRQoL.

9.4.1.2.3 Patient Global Impression (PGI)

The tablet computer-based Patient Global Impression of Severity (PGI-S) and the Patient Global Impression of Change (PGI-C) will be filled in consistent with Table 9—1.

The PGI-S is a single item that asks the subject to rate her uterine fibroids symptoms severity with the following verbal rating options "none", "very mild", "mild", "moderate", "severe" and "very severe". The PGI-S does not use a recall period. It is considered that the respondent assesses the actual severity of uterine fibroid related symptoms.

The PGI-C includes a single item that asks the subject to rate the change of her uterine fibroid symptoms since the start of study drug treatment. The verbal rating options are "very much better", "much better", "a little better", "no change", "a little worse", "much worse", and "very much worse".

All data of the PGI-S and the PGI-C will be reported in accordance with Clinical Data Interchange Standards Consortium (CDISC) Standard Data Tabulation Model (SDTM) using the questionnaire (QS)_CGI with study subject as the evaluator (QSEVAL) of the instrument.

9.4.1.2.4 Short Form 36 Health Survey Version 2 (SF-36v2)

The tablet computer-based SF-36v2 will be filled in consistent with Table 9—1.

The SF-36v2 is a widely used measure of health status with well-documented reliability, validity, and responsiveness in the general population as well as in various disease indications. Use of this instrument will enable to compare the impact of uterine fibroids on HRQoL with an age-matched normative sample (11). It consists of 36 items comprising

[3] It should be ensured that all concomitant medication is documented in the eCRF.

8 domains: physical function, role physical, bodily pain, general health, vitality, social functioning, role of emotional, and mental health. Descriptive analysis will base on: the single item level assessment, aggregation of single item scores to the 8 health domains respectively, and calculations of both: the psychometrically-based physical component summary and the mental component summary scores.

9.4.1.2.5 Treatment Satisfaction Questionnaire for Medication (TSQM-9)

The tablet computer-based TSQM-9 questionnaire will be filled in consistent with Table 9—1.

The TSQM-9 is a 9-item widely used generic measure to assess treatment satisfaction and has been psychometrically validated in a heterogeneous sample. (14) The 3 domains of the TSQM-9 include the effectiveness scale (items 1 to 3), the convenience scale (questions 4 to 7), and the global satisfaction scale (items 8 and 9) to be assessed over the previous 2 to 3 weeks (for assessments done during treatment period), or since the subject's last use of the medication (for assessments done after EoT). All items have 5 or 7 response options, scored from 1 (least satisfied) to 5 or 7 (most satisfied). The 7-item scales have a non-neutral midpoint in order to allow for precise information to be obtained at the upper end of the score distribution. Item scores are summed to give 3 domain scores, which are in turn transformed to a scale of 0 to 100, with higher scores representing higher satisfaction on that domain.

9.4.2 Clinician-reported outcome

The investigators will complete the Clinical Global Impression Investigator (CGI_I) at the time points indicated in Table 9—1. The responses to the CGI_I will be entered directly into RAVE, which will be considered as primary source data. The CGI_I asks the investigator to describe the subject's overall severity of uterine fibroids symptoms with the response options "none", "very mild", "mild", "moderate", "severe" and "very severe".

9.4.3 Alkaline hematin method to assess HMB

This section was changed in Amendment 2, see Section 15.1.1

During the duration of the study, subjects will be required to use selected types of sanitary products provided (pads and/or tampons). During the entire duration of the study, subjects need to collect their used sanitary products and return them to the study site as soon as the bleeding episode is completed to be sent to the central laboratory for analysis.

The AH method will be applied to measure MBL from Screening onwards during the entire study.

The AH method measures hemoglobin in a fixed amount of alkaline solution with the use of a spectrophotometer (15). The fixed amount of solution is taken from the solution pool in which the materials (ie, used sanitary protection) to be tested have been macerated for hemoglobin extraction. The blood loss volume will be reported by day and bleeding episode. This test will be performed at the central laboratory. For details refer to the laboratory manual.

9.4.4 Ultrasound (efficacy) to assess uterine fibroids

This section was changed in Amendment 2, see Section 15.1.1

If possible, the same examiner should conduct all ultrasound examinations of a subject throughout the study and the same ultrasound machine (per site) should be used throughout the study. For each subject, the most appropriate ultrasound method (transvaginal, abdominal or transrectal) should be used depending on fibroid location and this method should be used consistently throughout the study.

Ultrasound examinations will be performed consistent with the schedule of procedures (Table 9—1). The 3 largest fibroids will be identified during the screening period. The largest transverse, longitudinal, and antero-posterior diameters of these 3 fibroids will be documented at each efficacy ultrasound examination for volume calculation.

The dimensions of the uterus will also be documented at the same time points. This is of particular importance in subjects with multiple small fibroids.

The minimum source documentation will include printouts from the ultrasound machine showing the 3 largest fibroids. The printouts have to be labeled unambiguously, containing at least the study number, SID number, time point, and longest diameter of 3 largest fibroids. It is also possible that the site has a CD with the ultrasound images available, when in the source the evaluation of the ultrasound images from the CD is available as well. The CRA should be able to review the data on the CD and compare the images with the evaluations in the source during the onsite monitoring visits.

Furthermore, if the ultrasound machine is SESAC (Site Electronic Source Assessment Checklist) conform, ie, GCP conform electronic data storage is possible, then no print out is needed.

For safety ultrasound procedures, see Section 9.6.3.6.

9.5 Pharmacokinetics / pharmacodynamics

9.5.1 Drug measurements

Blood samples for measurement of vilaprisan in plasma for PK will be collected at the time points given in Table 9—1. At Visit 5, the PK sample will be taken predose. At Visit 6, 3 PK samples will be taken. The first sample will be taken before intake of study drug. After the predose sample is taken at Visits 5 and 6, the subject should take her study drug under supervision at the site. The second sample at Visit 6 will be taken 0.5 to 1 hour after drug intake and the third sample will be taken 2 to 4 hours after drug intake. The date and time of the last 2 doses of the study drug prior to the first PK sample at Visits 5 and 6, the time of the supervised drug intake at the study site, and the time of all blood samples should be documented in the eCRF.

If, for any reason, PK samples are taken outside of the pre-specified time window, the exact time that the sample was taken should be recorded and not the time of the time window. These time deviations will not be considered as important deviations.

In China, samples will be collected in some centers only, to achieve a minimum of least 30 Chinese subjects.

If a subject discontinues study treatment permanently, no blood sampling for PK is required. Pharmacokinetic analyses will be based on a population modeling approach (see Section 9.5.2). Blood samples will be considered valid for the population PK analysis under the following conditions:

1) The dose amount and time of drug intake prior to the blood sample is known

2) The time of the blood sample collection is known.

The samples will be collected and processed as described in detail in the respective Sample Handling Sheets as a part of a separate Laboratory manual.

Plasma concentrations of vilaprisan will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS). Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of calibration samples, QC samples, and study samples will be reported in the Bioanalytical Reports, which will be included in the Clinical Study Report for this study. A re-opening of the database may become necessary in order to include the results of the PK measurements.

The bioanalyst will be unblinded for analysis of study samples. Placebo samples will not be analyzed.

9.5.2 Population pharmacokinetic analysis of vilaprisan

Based on the plasma concentrations, the variability in vilaprisan PK will be analyzed using population PK modeling. This analysis might start prior to database lock (eg, at the moment that approximately 80% of the expected PK samples have been measured). Appropriate measures will be taken to maintain blinding of the study team (eg, data access will be restricted to specific people involved in the analysis and members of the study team will neither have access to the randomization list nor to individual data). The measures will be described in a Data Operations Plan, which will be provided to the study manager for adequate documentation.

Population or nonlinear mixed effects PK models describe the relationship between dose, time, and the vilaprisan plasma drug concentration. A previously developed population PK model for vilaprisan based on Phase 1 and 2 data will be applied to all valid PK samples to evaluate the relationship between variability in PK and covariates,(ie, intrinsic [eg, body weight, race] and extrinsic factors [eg, concomitant medication]) that are of clinical relevance. If necessary, the population PK model will be adapted to adequately fit the data. Individual PK parameters of vilaprisan will be calculated. A separate Modeling and Simulation (M&S) Plan, providing details of the model development and evaluation will be provided before the start of the population PK analysis. Evaluation of the data will be presented in a separate M&S Report.

9.5.3 Pharmacokinetic/pharmacodynamic relationship of vilaprisan

Optionally, a population PK/PD model could be used to describe the effect of vilaprisan

exposure on PD data related to efficacy and safety such as bleeding intensity and endocrine hormone levels. The final population PK model that will be applied to describe the PK of vilaprisan in the study population as outlined in Section 9.5.2 will be linked to relevant PD parameters (eg, fibroid size, uterus size, endocrine hormone levels, and bleeding) obtained in this study to investigate the relationship between vilaprisan exposure and response. Details of the model development and evaluation, if conducted, will be described in a separate M&S Analysis Plan and the results reported in a separate M&S Report.

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of AE

This section was changed in Amendment 2, see Section 15.1.1

In a clinical study, an AE is any untoward medical occurrence (ie, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Treatment emergent adverse event (TEAE) is defined as any event that occurred after the first study drug intake until the end of FUP.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term “condition” may include abnormal eg, physical examination findings, symptoms, diseases, and laboratory findings.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (eg, seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (eg, allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as AEs. This includes intercurrent illnesses (eg, increase in occurrences and/or severity of symptoms for seasonal allergy or allergic pollinosis).

Definition of SAE

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours
   - The admission is pre-planned (eg, elective or scheduled surgery arranged prior to the start of the study)
   - The admission is not associated with an AE (eg, social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence. Any fibroid surgery should always be reported as SAE, irrespective of associated hospitalization.

d. Results in persistent or significant disability / incapacity

   Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

The following types of events are excluded from SAE reporting:

- Elective abortion is considered as an 'abnormal pregnancy outcome' but is not considered an SAE. (However, abortions are to be documented as SAEs if they match one of the following terms: spontaneous abortion, missed abortion, infected abortion, or abortion induced incomplete. If no specification for the abortion is available, then one of these categories is assumed to have occurred and the 'abortion' is regarded as serious and must be recorded as an SAE.)
- Hospitalizations for the evaluation or treatment of pre-existing conditions that do not worsen in severity or frequency during the subject's participation in the study. Such

conditions must have been present before the subject's participation in the study and reported as such in the corresponding eCRF.

- Elective surgery performed for cosmetic reasons or because of pre-existing conditions as defined in Section 9.3.2.

Important medical event: Any AE may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events, refer to the "World Health Organization (WHO) Adverse Reaction Terminology – Critical Terms List". These terms either refer to or might be indicative of a serious disease state. Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

9.6.1.2 Classifications for AE assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild
- Moderate
- Severe

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the eCRF.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no"

An assessment of "no" would include:

1. The existence of a highly likely alternative explanation, eg, mechanical bleeding at surgical site.

or

2. Non-plausibility, eg, the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): subject's response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical
- The pharmacology and PK of the study treatment: The PK properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment as detailed in the eCRF.

- Drug withdrawn
- Drug interrupted
- Dose not changed
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of AEs

- None
- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessments and documentation of AEs

Attention is to be paid to the occurrence of AEs at all stages of the examination. Thus, the subject should be closely observed by the investigator.

AEs observed, mentioned on open questioning by a member of the investigator team or spontaneously reported by the subject will be documented. The observation period for AEs will start with signing the informed consent, and will end with the last visit (either after FUP phase or at any time point before, in case of a premature study termination). After the end of the FUP phase there is no requirement to actively collect AEs including deaths.

The outcome of recorded non-serious AEs should be followed up between the signing of the informed consent and the end of the FUP phase.

The investigator is responsible for the grading of each category listed in Section 9.6.1.2. An assessment of the **seriousness** of the event will be made by the investigator using the electronic reporting tool in RAVE. However, SAEs will also be recorded on the AE page of the eCRF.

For all SAEs the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

“Death” should not be recorded as an AE on the AE page. Instead, “death” is the outcome of underlying AE(s).

For details on monitoring algorithms see Section 9.7.

9.6.1.4 Reporting of SAEs

The definition of SAEs is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 using the electronic reporting tool in RAVE (see Section 11) according to the detailed instructions for SAE reporting included in the Investigator File.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the Independent Ethics Committees/Institutional Review Boards

Notification of the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) about all relevant events (eg, SAEs, SUSARs) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (eg, SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (eg, SUSARs) according to all applicable regulations.

9.6.1.5 Expected AEs

For this study, the applicable reference document is the most current version of the IB.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.1.6 Adverse events of special safety interest

The investigators will assess all AEs to determine if they are AEs of special interest (AESIs) and document this in the eCRF. An AESI is defined based on the following criteria:

- HMB (especially during a treatment break or after EoT) should be recorded as an AE (and then it automatically qualifies as an AESI) only if one or more of the following applies:
    - Leads to study discontinuation

- Leads to diagnostic procedures
- Requires any treatment
- Shows a clinically significant worsening during the study that, in the judgment of the investigator, is not consistent with the expected clinical course
- Meets any seriousness criterion and is to be recorded as an SAE.

HMB will be documented in detail throughout the study (see Sections 9.4.1.1 and 9.7.3).

- Liver enzymes:

  If the GPT/ALT or GOT/AST value increases to >3 x ULN after start of study drug treatment, a close observation has to be initiated. This should include repeating liver enzymes and serum bilirubin measurements 2 to 3 times per week, obtaining a more detailed history of the symptoms, obtaining a history of concomitant drug use, alcohol use, recreational drug use, and special diets, ruling out acute viral hepatitis, additional tests to evaluate liver function as appropriate, (eg, international normalized ratio [INR], direct bilirubin measurements). Any of these additional findings is to be recorded on the corresponding eCRF pages (eg, for concomitant medication, lab assessment) in RAVE.

  The subject has to be withdrawn from treatment in the following cases:

  - GPT/ALT or GOT/AST value increases to > 8 x ULN
  - GPT/ALT or GOT/AST > 5 x ULN for more than 2 weeks
  - GPT/ALT or GOT/AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia
  - GPT/ALT or GOT/AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** INR > 1.5

- Endometrial hyperplasia (all subcategories according to WHO 2014 [and WHO 1994] classification)
- Endometrial thickening >18 mm
  - If endometrial thickness (double layer) >18 mm is detected after the start of treatment, the subject should undergo immediate evaluation by endometrial biopsy as described in Section 9.7.4.

Progesterone receptor modulator-associated endometrial changes (PAEC) will be assessed and documented in a systematic way (see Section 9.6.3.2.4). The results of the PAEC assessment will only be reported back to the investigators if they trigger the request for a repeat biopsy. Apart from cases where such a repeat biopsy is necessary, no clinical action for an individual subject is required based on the PAEC assessment results. PAEC assessment results are systematically collected for all samples and will be reported in

aggregated form at the end of the study. They should therefore not be reported as AE for an individual subject.

A systematic approach of assessment and evaluation will also be applied to HMB (see Sections 9.4.1.1 and 9.7.3), endometrial hyperplasia and endometrial thickening (see Sections 9.7.2 and 9.7.4), and liver function test.

9.6.2 Pregnancies

An acceptable nonhormonal contraceptive method has to be used starting at Screening Visit 1 and continued until the end of the study. Barrier contraception (eg, condoms with spermicide) will be dispensed as required by the subject. This is not required if contraception is achieved by a permanent method such as bilateral fallopian tube blockage (including Essure) of the subject or vasectomy of her partner(s).

Pregnancy tests will be performed at site visits and at home before the start of study drug in each treatment period. Home pregnancy tests should also be performed in case the subject is concerned about being pregnant. All home pregnancy tests will be documented in the eDiary. In case of a positive pregnancy test, study drug must be discontinued and the investigator must be informed immediately.

Any planned pregnancy should be postponed until the end of the study. This is to be discussed with the subject at screening. If an investigator becomes aware that a subject wishes to conceive or plans an insemination directly after EoT (thereby deviating from study protocol), subject should be made aware that she is participating in a clinical study with a new drug in early clinical development. Therefore she should preferably complete the FUP phase (including endometrial biopsy) or should at least wait for 3 months/2 menstrual cycles after discontinuation of study drug treatment due to unknown effect of the study drug on the human embryo.

Pregnancies occurring during the study

The sponsor will closely monitor the occurrence of unintended pregnancies (based on the expedited reporting of pregnancies by the investigators) throughout the study. If a pregnancy is detected before initiation of study drug, the subject will not be enrolled into the study (see Section 6.2).

The investigator must report to the sponsor any pregnancy occurring in a study subject during the subject's participation in this study. The report should be submitted within the same timelines as an SAE (ie, no later than 24 hours of having gained knowledge of the event; see Section 9.6.1.4), although a pregnancy per se is not considered an AE or SAE. The subject will be instructed to contact the study site immediately if a pregnancy is suspected or detected. In such a case, an unscheduled visit should be arranged for the subject as soon as possible and the investigator or designee should confirm the pregnancy by a valid method (eg, ultrasound, serum human chorionic gonadotropin [β-HCG] test). If such confirmation cannot be achieved within **24 hours** of the subject contacting the study center, the investigator must still report the pregnancy to the sponsor and then follow-up with information once confirmation has been obtained. A pregnancy will be reported on the forms provided by the

sponsor. The investigator is required to document the date of confirmatory testing, whether the pregnancy was confirmed, the estimated date of conception, and the location of the pregnancy implantation at time of diagnosis.

The investigator is required to provide any additional information (eg, early termination) as soon as it becomes available.

All pregnancies occurring during the treatment and follow-up periods will be followed for the outcome for both the mother and fetus/child (in case of a life birth) until first birthday of the child. The outcome will be documented on a pregnancy outcome form and a follow-up report is requested upon the first birthday of the child.

Any abnormal outcome of the mother or the child should also be reported as an SAE (eg, spontaneous abortion, preterm birth, elective abortion triggered by medical concern).

For details on elective abortions, refer to Section 9.6.1.1.

For all reports, the forms provided are to be used.

9.6.3 Further safety

9.6.3.1 Laboratory evaluations

This section was changed in Amendment 2, see Section 15.1.1

Only blood samples analyzed at the central laboratory will be considered for analysis. The name and address for the central lab service provider can be found in the documentation supplied by the vendor. The safety laboratory tests may be repeated once during the screening period if laboratory values are outside the inclusion range and assessed as clinically relevant (this repeat is not considered rescreening). Time points for safety lab blood sampling are presented in Table 9—1. The following parameters will be assessed:

Hematology: leukocytes, erythrocytes, hematocrit[4], mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelets, neutrophils, eosinophils, basophils, lymphocytes, and monocytes.

Hemoglobin (Hb): Hb concentrations in blood will be measured within the safety laboratory in blood samples taken according to Table 9—1. [4]

Coagulation (at Visit 1 only): prothrombin time (Quick), INR, and activated partial thromboplastin time (aPTT).

Serum chemistry: creatinine, chloride, potassium, sodium, calcium, total protein, albumin, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase, alkaline phosphatase, and total bilirubin.

See Section 9.6.1.6 for procedure in case of elevated liver enzymes.

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[4] Hematocrit, hemoglobin and ferritin are also efficacy variables.

Biochemistry: glycosylated hemoglobin (HbA1c) and ferritin[4].

Additional parameters: hormones (follicle-stimulating hormone [FSH], luteinizing hormone [LH], estradiol [E2], progesterone [P], prolactin, and thyroid-stimulating hormone [TSH]).

Urinalysis (at Visit 1 only): pH, urobilinogen, blood/hemoglobin, total protein, ketone, bilirubin, nitrite, glucose, and leukocytes.

For **urine pregnancy test**, see Section 9.6.3.7.

9.6.3.2 Endometrial biopsies

9.6.3.2.1 Timing of endometrial biopsies

Subjects will undergo scheduled endometrial biopsies at the following visits during the study (for the timing of the visits and further details, see Table 9—1):

- Screening Visit 2
- EoT visit
- FUP visit

If no bleeding episode occurs within 7 weeks after EoT, bleeding should be induced (see Section 9.7.5 for the induction of bleeding) before performing the endometrial biopsy.

In certain situations, unscheduled endometrial biopsies should be performed in addition. See Sections 9.6.3.2.4 and 9.7.3 for details.

9.6.3.2.2 Sampling of endometrial biopsies

A negative pregnancy test is a prerequisite for performing an endometrial biopsy. In addition, an ultrasound should be performed before each biopsy.

If a cervical smear sample is collected at the same visit, those procedures have to be performed before performing the biopsy.

The sterilized, disposable device Pipelle de Cornier will be used – a flexible and transparent polypropylene sheath with an internal plunger for aspiration. This device allows for gentle tissue sampling, without hysteroscopy, and generally requires no local anesthesia or cervical dilatation.

A repeat endometrial biopsy will be requested, if sample is inadequate for evaluation.

The following contraindications have to be strictly adhered to: pregnancy (ie, positive urine pregnancy test), and local inflammation (eg, vaginitis, cervicitis).

Any procedure-related complaints will be documented as AEs. If necessary for pain prophylaxis or relief relating to the endometrial biopsy procedure, the use of an analgesic is permitted and will be documented as concomitant medication (investigator's choice; however, no intake of acetylsalicylic acid or any other medication substantially influencing bleeding).

9.6.3.2.3 Assessment of endometrial biopsies

Blinding and distribution of biopsy samples will be organized by the central laboratory.

Central assessment of endometrial biopsies will be performed in 2 steps:

Safety assessment

The safety assessment will be performed by one pathologist who will be blinded regarding treatment group. The results of the safety assessment need to be available in time to document

- Eligibility of the subject before randomization (biopsy at Visit 2)
- Any relevant pathology that requires further diagnostic or therapeutic measures according to local medical practice
- Absence of clinically relevant endometrial pathology before the subject leaves the study

Multi-reader assessment

The multi-reader assessment will be performed by a panel of pathologists who will be blinded regarding treatment group and time point of sample. This assessment will be performed as batch reads when a sufficient number of samples are available.

A majority consensus diagnosis of the multi-reader assessment needs to be obtained. In the absence of a majority consensus, the most severe diagnosis is used. The diagnosis resulting from this algorithm will be used for primary analysis of endometrial biopsy data. The individual diagnoses of each reader will be reported in addition. Besides standard criteria (eg, proliferative/secretory/atrophic endometrium, endometrial hyperplasia) the pathologists will document the presence of PAEC.

9.6.3.2.4 Follow-up of PAEC

Presence of PAEC will be analyzed in all endometrial biopsy samples. The diagnosis of PAEC is based on a constellation of histologic features that, taken together, are characteristic. None of the features is unique, and to some extent any may be seen in patients who have not been treated with PRMs. The common histologic features are endometrial glands showing cystic dilatation and an irregular architecture lined by inactive gland cells and compact, nondecidualized stroma. Beside standard criteria (eg, proliferative/secretory/atrophic endometrium, endometrial hyperplasia) endometrial biopsies will be assessed for presence of PAEC.

If PAECs have been detected in the biopsy at the FUP visit according to the majority diagnosis resulting from the multi-reader assessment, an additional FUP biopsy should be scheduled. In case PAEC findings are still present, the study site will be informed and an additional biopsy is to be taken to evaluate resolution. If needed, more than one repeated biopsy may be taken and analyzed, except for cases with PAEC already present in the pre-treatment biopsy.

The time point of this additional biopsy will be determined case-by-case.

9.6.3.3 Cervical smear

This section was changed in Amendment 2, see Section 15.1.1

The cervical smear should be obtained with the gynecological examination at the visits shown in Table 9—1. It may be repeated once during the screening period if the results are abnormal (this repeat is not considered rescreening). If the cervical smear is repeated at Visit 2 (screening), it should be performed before the endometrial biopsy. The cervical smear at screening may be waived if a normal result has been documented in the subject's medical records within the previous 6 months. Subjects with ASCUS can be included in the study if they have an HPV deoxyribonucleic acid test that is negative for high-risk HPV. As a guidance, a cervical smear should only be repeated once in case of insufficient material.

9.6.3.4 Physical and gynecological examinations

Complete physical examinations and gynecological examinations, including breast palpation, will be performed at the time points shown in Table 9—1. In case of any suspicious finding, further diagnostic investigations will be performed at the discretion of the investigator.

Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

9.6.3.5 Vital signs, weight, and height

Blood pressure and heart rate will be determined after 5 minutes of rest in a sitting position. Body weight, height, and BMI will be determined at the time points shown in Table 9—1.

9.6.3.6 Ultrasound (safety)

If possible, the same examiner should conduct all ultrasound examinations of a subject throughout the study and the same ultrasound machine (per site) should be used throughout the study. Preferably the safety evaluation should be performed by transvaginal ultrasound (TVU). However, if deemed appropriate, transabdominal or transrectal ultrasound examinations can be performed instead. The chosen method should be used consistently throughout the study.

The following safety parameters will be documented at all the time points when ultrasound is performed (see Table 9—1): endometrial thickness (double layer), evaluation of ovaries, and any pathology detected during the examination. Endometrial thickness will be measured in the medio-sagittal section as double-layer in millimeters.

If endometrial thickness (double layer) >18 mm is detected after start of treatment, the subject should undergo immediate evaluation by endometrial biopsy as described in Section 9.7.4.

If cyst like structures >30 mm without suspicious appearance (ie, functional cysts) are visualized in the ovaries, unscheduled ultrasound examinations to document regression/outcome of these findings should be performed as described in Section 9.7.6.

In case of any suspicious finding, further diagnostic investigations will be performed at the discretion of the investigator.

The minimum documentation at the site will include printouts from the ultrasound machine

showing the endometrium in sagittal section and both ovaries. The printouts have to be labeled unambiguously, containing at least the study number, SID number, time point, endometrial thickness, and side (left/right) for ovaries.

For efficacy ultrasound procedures, see Section 9.4.4.

9.6.3.7 Contraception and pregnancy test

An acceptable nonhormonal method of contraception (ie, either male condom, cap, diaphragm or sponge, each in combination with spermicide) has to be used starting at Visit 1 and continued until the end of the study. This is not required if contraception is achieved by a permanent method such as bilateral fallopian tube blockage (including Essure) of the subject or vasectomy of her partner(s). Barrier contraception (eg, condoms with spermicide) will be dispensed as required by the subject.

At the time points shown in Table 9—1, urine pregnancy tests will be performed at the study site. A pregnancy test must be performed before the start of study drug treatment in each treatment period (by the subject at home), and always before the endometrial biopsy.

Additional tests should be performed at home if the subject is concerned about being pregnant. All home pregnancy tests will be documented in the eDiary.

If any of the pregnancy tests performed at Visits 1 or 2 (screening) or Visit 3 (randomization) is positive, the subject will not be included in the treatment period. If a pregnancy test shows a positive result during treatment, the subject must stop study drug treatment and contact the study site immediately. If pregnancy is confirmed, the subject will be discontinued from the study.

Any pregnancies during the study must be reported as detailed in Section 9.6.2.

9.7 Other procedures and variables

9.7.1 Iron supplementation

This section was changed in Amendment 2, see Section 15.1.1

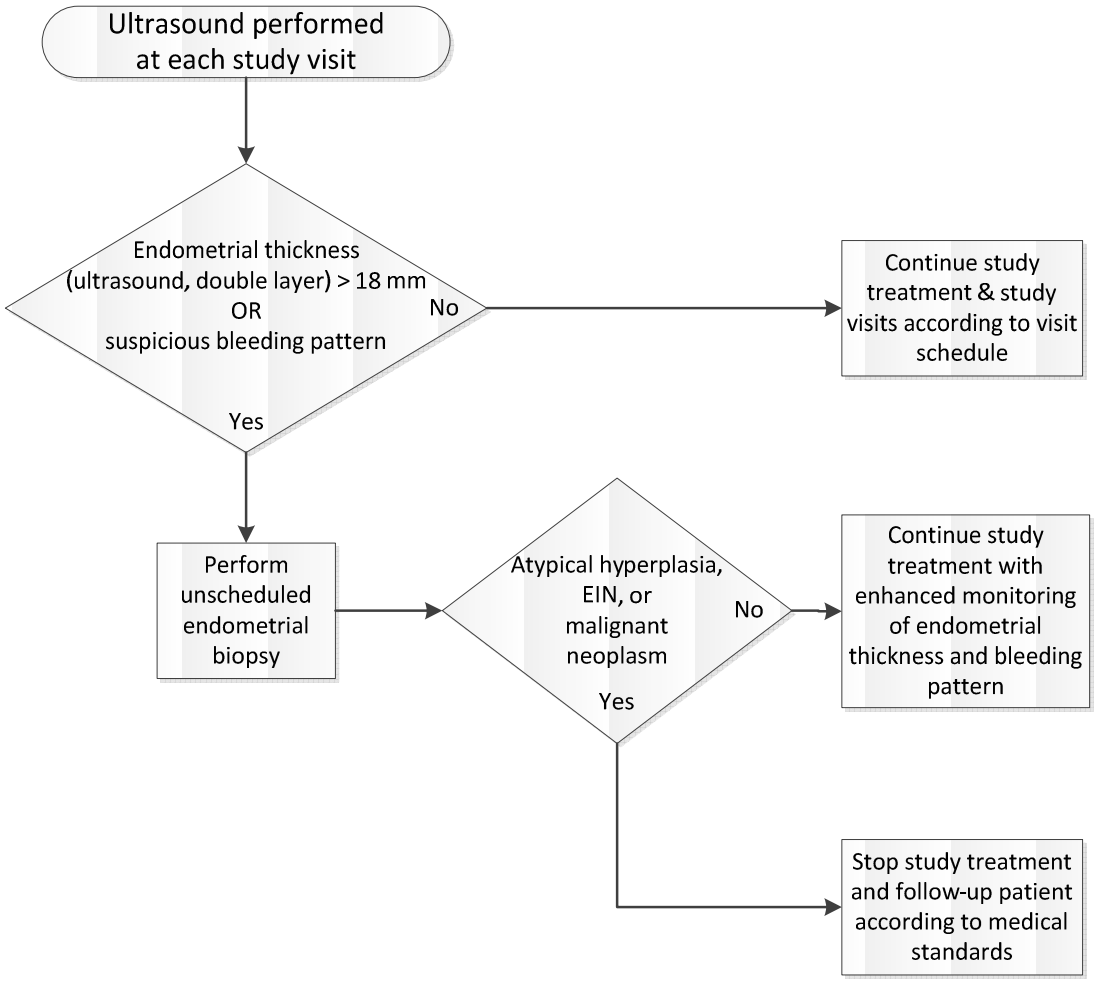
If causes for anemia unrelated to HMB are suspected these subjects should not be enrolled.

Moderate anemia is defined as hemoglobin ≤10.9 g/dL (12). Iron supplementation should be offered to subjects with hemoglobin ≤10.9 g/dL consistent with local standards of practice and at the investigator's discretion. Iron supplementation will not be considered as study drug and should be documented as concomitant medication.

9.7.2 Algorithm for monitoring of endometrial safety

Histological changes in the endometrium like PAEC are known findings during treatment with PRMs. Therefore, a careful endometrial safety monitoring will be applied in this study including regular ultrasound investigations during the active treatment period, observation of bleeding patterns, and endometrial biopsies (see Figure 9–1).

Figure 9–1 Endometrial monitoring



EIN = Endometrioid Intraepithelial Neoplasia

9.7.3 Heavy menstrual bleeding / suspicious bleeding pattern

This section was changed in Amendment 2, see Section 15.1.1

The site is asked to actively contact subjects who upon review of the eDiary entries have entered more than 10 consecutive days of bleeding (intensity of "mild" or more) during study drug intake (ie, during a treatment period).

In case of suspicious bleeding pattern (eg, continuous spotting, unusually heavy bleeding) after the start of treatment, which does **not** resemble the subject's natural cycle or bleeding pattern, detected from the AH, MP or UF-DBD, the subject should undergo immediate evaluation by the investigator.

Especially if during intake of the study drug and after the initial reduction of bleeding and/or onset of amenorrhea, any recording in the MP, worsened bleeding detected from the AH

analysis, or bleeding of an intensity of "mild" or worse occurs continuously for 10 days or more the subject should be instructed to contact the site for immediate evaluation.

The investigator should evaluate the presence of possible contributing factors (eg, new concomitant medication, abnormal findings in the ultrasound examination). Further diagnostic or therapeutic measures may be performed as needed at the discretion of the investigator. It is recommended that in such cases the subject should stop the intake of study drug. The evaluations performed should be documented to the EoT visit in RAVE.

HMB should be recorded as an AE only as specified in Section 9.6.1.6. If HMB fulfills the criteria of an SAE (see Section 9.6.1.1), the study drug is to be stopped immediately and an appropriate treatment (eg, curettage) is to be performed after an endometrial biopsy has been taken.

9.7.4 Unscheduled endometrial biopsy

In case of increased endometrial thickness (>18 mm) or suspicious bleeding pattern (eg, continuous spotting, unusually heavy bleeding) after start of treatment, which does **not** resemble the subject's natural cycle or bleeding pattern, the subject should undergo immediate evaluation by endometrial biopsy. Heavy menstrual bleeding is expected to occur in the FUP phase after cessation of treatment and should not automatically trigger the performance of an endometrial biopsy.

Depending on the result of the endometrial biopsy the following procedure applies:

- Normal result of the endometrial biopsy (absence of hyperplasia as result of the endometrial biopsy will be reported to the investigator): unscheduled ultrasound examination after about 4 weeks and close observation of bleeding pattern. If endometrial thickness remains above 18 mm and/or unusually heavy bleeding occurs further procedure should be done according to local medical practice and as defined in Section 9.7.3.
- Atypical hyperplasia, EIN or malignant neoplasm: immediate stop of study drug, further procedures should be performed according to local medical practice.

9.7.5 Induction of bleeding

Subjects will be given an appropriate progestin therapy that in the experience and practice of the investigator will induce withdrawal bleeding in this particular subject. Progestin therapy will not be considered as study medication and will be documented as concomitant medication (see Section 8.1.2).

For details and pre-requisites for the endometrial biopsy sampling, see Section 9.6.3.2.2.

During treatment break: If, for any of the treatment groups, no bleeding occurs within 7 weeks after the end of a treatment period, an ultrasound will be performed after which bleeding will be induced..

After EoT visit: If spontaneous menstrual bleeding does not occur within 7 weeks after the EoT, an ultrasound will be performed after which the bleeding will be induced. The planned

endometrial biopsy (ie, FUP visit) will be performed at Day 7 to 15 (inclusive) of the first menstrual cycle after the induced bleeding episode (first bleeding episode after induction of bleeding).

9.7.6 Monitoring of ovarian cysts

If cyst like structures >30 mm without suspicious appearance (ie, functional ovarian cysts) are visualized in the ovaries, unscheduled ultrasound examinations should be performed every 4 weeks or more frequently, if required due to symptoms, to document the regression/ outcome.

If the subject demonstrates menstrual cyclicity, the ultrasound should be performed after menstruation as soon as possible, preferably in the early follicular phase. The monitoring will be continued until resolution, ie, until cyst can no longer be distinguished from functional follicles. If the cysts persist after 3 months or grow, decision on further treatment should be made according to local medical practice.

In the event of cyst like structures with suspicious appearance, further procedures should be performed according to local medical practice.

9.8 Appropriateness of procedures / measurements

All efficacy and safety parameters, as well as the methods to measure them, are standard variables/methods in clinical studies and/or clinical/gynecological practice. They are widely used and generally recognized as reliable, accurate, and relevant.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analyses will be conducted by or under the supervision of the sponsor's study statistician, except for the analysis of PK/PD data, which will be performed and reported under the supervision of the sponsor´s pharmacometrics group.

Statistical analyses will be performed using Statistical Analysis Software (SAS Institute Inc., Cary, North Carolina, US). The SAS version and further details on the statistical analyses will be provided in the SAP that will be approved before database release.

All target variables will be described according to their type using descriptive statistics frequencies or mean, standard deviation (SD), minimum, maximum, median, first and third quartiles. Where appropriate, the individual change from baseline to end of treatment will also be analyzed.

10.2 Analysis sets

The documentation of important deviations from the protocol and validity findings and the assignment of subjects to analysis sets will be performed according to the sponsor's applicable Standard Operating Procedures and/or Instruction Manuals. The definition for important deviations and validity findings will be provided in the Specification of assessment criteria and identification requirements before unblinding the data.

The following statistical analysis sets will be defined:

Full analysis set (FAS): All randomized subjects. Subjects will be analyzed as randomized.

Per protocol set (PPS): All subjects in the FAS without any validity findings impacting the primary efficacy variable.

Safety analysis set (SAF): All subjects who took at least 1 dose of study drug. Subjects will be analyzed as treated.

The primary efficacy variable will be analyzed on the FAS and PPS, where the analysis on the FAS is considered to be the primary one. Safety analyses will be performed on the SAF. The FAS will be used for the display of all other variables.

10.3 Variables and planned statistical analyses

10.3.1 Variables

This section was changed in Amendment 2, see Section 15.1.1

The primary efficacy variable and secondary efficacy variables will be calculated based on the alkaline hematin method (unless otherwise specified). Other efficacy variables related to menstrual blood loss will be calculated based on the two methods, the alkaline hematin method and the menstrual pictogram.

10.3.1.1 Primary efficacy variable

This section was changed in Amendment 2, see Section 15.1.1

The primary efficacy variable is amenorrhea (yes/no), defined as MBL <2 mL during the last 28 days of treatment.

If an endometrial biopsy was conducted during this time period, bleeding on the day of biopsy and the 3 days thereafter will not be considered in this evaluation.

For the primary analysis, the amenorrhea rates at the end of Treatment Period 1 of Treatment Groups A1, B1, and B2 and at the end of Treatment Period 2 of Treatment Groups A1, A2, and B2 will be used.

Subjects who discontinue treatment prior to completion of treatment Week 8 of the respective treatment period will be considered not having amenorrhea.

10.3.1.2 Secondary efficacy variables

This section was changed in Amendment 2, see Section 15.1.1

The secondary efficacy variables are:

- HMB response defined as blood loss <80.00 mL during the last 28 days of treatment and >50% reduction compared to baseline

- Time to onset of amenorrhea. Onset of amenorrhea is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <2 mL.
- Time to onset of controlled bleeding. Onset of controlled bleeding is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <80.00 mL.
- Absence of bleeding (spotting allowed) during the last 28 days of the treatment; based on the UF-DBD

10.3.1.3 Other efficacy variables

This section was changed in Amendment 2, see Section 15.1.1

Other efficacy variables are:

- Treatment success rate defined as percentage of subjects who fulfill the criteria of HMB response (<80.00 mL, >50% reduction in menstrual blood loss as compared to baseline) and who have not been withdrawn from the study due to AEs, due to non-fulfillment of selection criteria (related to fibroid size or HMB at baseline) or due to fibroid surgery having been performed during the study.
- Amenorrhea (yes/no), defined as MBL < 2 mL per 28 days of treatment (for treatment time/method not considered as primary variable)
- HMB response defined as blood loss <80.00 mL and >50% reduction compared to baseline per 28 days of treatment (for treatment time/method not considered as secondary variable)
- Time to onset of amenorrhea. Onset of amenorrhea is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <2 mL (for treatment time/method not considered as secondary variable)
- Time to onset of controlled bleeding. Onset of controlled bleeding is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <80.00 mL (for treatment time/method not considered as secondary variable)
- Volume of menstrual blood loss per 28 days
- Volume of menstrual blood loss per bleeding episode for the first, second, and if applicable third bleeding episode after the EoT
- Volume of menstrual blood loss per bleeding episode within the treatment break (not applicable for Treatment Groups A2). All days of the bleeding episodes will be used even if some days of the episode lie outside the treatment break.
- Percentage of subjects with 50% reduction in menstrual bleeding per 28 days compared to baseline

- Time to start of bleeding after last study drug intake (assessed by the UF-DBD in addition to the other two measurement methods). If bleeding has to be induced, the subject´s data will be censored at that time point for the induction.
- Percent change in volume of 3 largest fibroids compared to baseline (measured by ultrasound)
- Percent change in volume of uterus compared to baseline (measured by ultrasound)
- Percentage of subjects with a volume reduction of ≥25% of the 3 largest fibroids (measured by ultrasound)
- Percentage of subjects with a reduction of ≥25% of uterine volume (measured by ultrasound)
- Percentage of subjects undergoing surgical treatment for uterine fibroids
- Change in UF-DSD individual items compared to baseline
- Change in UFS-QoL scores compared to baseline
- Change in SF-36v2 scores compared to baseline
- PGI-C assessments
- Change in CGI-I/PGI-S scores compared to baseline
- Patient satisfaction assessed by the TSQM-9 at the 12 week and at end of treatment visit
- Change from baseline in hemoglobin, hematocrit, and ferritin
- Percentage of subjects with normal hemoglobin >12 g/dL and normal hematocrit >36%

10.3.1.4 Pharmacokinetics (PK)

For details, see Section 9.5.2 and 9.5.3 and the separate M&S Analysis plan.

10.3.1.5 Secondary safety variables

- Endometrial histology (eg, benign endometrium, presence or absence of hyperplasia or malignancy)
- Endometrial thickness (13)

10.3.1.6 Other safety variables

This section was changed in Amendment 2, see Section 15.1.1

- Endometrial histology (diagnosis of PAEC, individual features of PAEC)
- Ovarian cysts (number, size)
- Laboratory parameters
- AEs

- Cervical smear
- Vital signs
- Percentage of subjects with moderate to severe anemia (ie, hemoglobin ≤10.9 g/dL)

10.3.2 Statistical and analytical plans

10.3.2.1 Demographic and other baseline characteristics

Demographic variables and baseline characteristics will be summarized overall by means of descriptive statistics and/or frequency tables as appropriate.

Medical history findings and AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes and medications by Anatomical Therapeutic Chemical (ATC) codes (World Health Organization Drug Dictionary [WHO-DD]).

10.3.2.2 Efficacy analysis

This section was changed in Amendment 2, see Section 15.1.1

For the confirmatory efficacy analysis, a hierarchical testing approach will be applied, involving the primary efficacy variable amenorrhea (yes/no) and the first three secondary efficacy variables HMB response, time to onset of amenorrhea and time to onset of controlled bleeding. These tests always include a comparison of vilaprisan 2 mg versus placebo and can be applied in three different situations:

1 After 12 weeks of treatment in Treatment Period 1:
Comparison of vilaprisan 2 mg in pooled Treatment Groups A1 and B2 (as the treatments are the same and pooling increases the power) vs. placebo in Treatment Group B1

2 After 12 weeks of treatment in Treatment Period 2:
Comparison of vilaprisan 2 mg in Treatment Group A1 vs. placebo in Treatment Group B2

3 After 24 weeks of treatment:
Comparison of vilaprisan 2 mg in Treatment Group A2 vs. placebo in Treatment Period 2 of Treatment Group B2

In total, ten tests will be carried out each to an alpha level of 0.05: First, the tests for the primary efficacy variable amenorrhea (yes/no) will be carried out in scenarios 1, 2 and 3 in this order, followed by the tests for HMB response (yes/no) in scenarios 1, 2 and 3, the tests for time to onset of amenorrhea in scenarios 1 and 2, and finally, the tests for onset of controlled bleeding in scenarios 1 and 2. As the hierarchical testing procedure follows a fixed sequence, it stops as soon as any of these tests cannot be rejected to an alpha level of 0.05 and all further tests after failing to reject one null hypothesis in the testing sequence will be considered exploratory. This fixed sequence procedure accounts for the multiplicity created by carrying out multiple tests.

Amenorrhea (yes/no), defined as MBL <2 mL during the last 28 days of treatment

The primary efficacy variable amenorrhea (yes/no) will be analyzed by means of a two-sided Cochran-Mantel-Haenszel test stratified by region/country at a local 0.05 significance level.

The number of subjects with amenorrhea (yes/no) is assumed to be binomial distributed. Thus, the Cochran-Mantel-Haenszel test is applied to test the null hypothesis $H_{0,i}$ that the amenorrhea rates in the vilaprisan 2 mg group ($p_{v,i}$) and in the placebo group ($p_{p,i}$) in the respective situations i =1, 2 or 3 are equal versus the alternative hypothesis $H_{1,i}$ that they are not:

$$H_{0,i}: p_{v,i} = p_{p,i} \quad \text{vs.} \quad H_{1,i}: p_{v,i} \neq p_{p,i}.$$

HMB response defined as blood loss <80.00 mL during the last 28 days and >50% reduction compared to baseline

The first secondary efficacy variable HMB response (yes/no) will be analyzed analogously to the primary efficacy variable amenorrhea.

Time to onset of amenorrhea

Onset of amenorrhea is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <2 mL. Subjects are treated as censored if they did not experience an onset of amenorrhea during the respective treatment period. Censoring rules will be described in more detail in the SAP.

In order to investigate the null hypothesis that there is no difference in time to onset of amenorrhea between vilaprisan 2mg and placebo versus the alternative hypothesis that there is a difference, a logrank test stratified by region/country is conducted at a local 0.05 significance level.

Time to onset of controlled bleeding

Onset of controlled bleeding is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <80.00 mL. Subjects are treated as censored if they did not experience an onset of controlled bleeding during the respective treatment period. Censoring rules will be described in more detail in the SAP.

Time to onset of controlled bleeding will be analyzed analogously to the secondary efficacy variable time to onset of amenorrhea.

The study will be considered successful if at least superiority of vilaprisan 2 mg vs. placebo after Treatment Period 1 based on the primary variable could be demonstrated.

Sensitivity analyses will be conducted for the primary efficacy variable and the first three secondary efficacy variables as applicable. These will be described in the SAP.

All primary and secondary efficacy variables will also be analyzed descriptively in frequency tables by treatment period within each treatment group, except for time to event variables which will be analyzed by treatment group using the Kaplan-Meier estimates.

Other efficacy variables will be evaluated and presented by means of descriptive statistics.

10.3.2.3 Pharmacokinetic analysis

For details, see Sections 9.5.1 and 9.5.3 and the separate M&S Analysis Plan. Results will be reported in a separate M&S Report, if applicable.

10.3.2.4 Safety analysis

Safety analyses will be performed on the SAF. AEs and other safety variables will be summarized descriptively by treatment group.

The incidence of treatment-emergent AEs and drug-related AEs will be summarized using MedDRA preferred term and the primary system organ class.

10.3.2.5 Subgroup analysis

This section was changed in Amendment 2, see Section 15.1.1

Subgroup analyses are planned using descriptive statistics for the primary and secondary efficacy variables separately for each country (China and the US), race and ethnicity. Further subgroup analyses will be described in the SAP.

10.3.3 Missing data/drop outs

This section was changed in Amendment 2, see Section 15.1.1

For the primary efficacy variable and secondary efficacy variables included in the testing strategy described in section 10.3.2.2 it is assumed that data measured with the AH method will be only available on days when vaginal bleeding occurred. To differentiate missing AH data and days without vaginal bleeding the bleeding intensity collected in the UF-DBD will be used.

Missing bleeding data in the subject diaries will be imputed. For the UF-DBD, the worst case approach will be used for missing bleeding intensity for the single or two consecutive missing days (ie, the maximum of the bleeding intensities of the day before and the day after the missing day[s] will be assumed).

If an endometrial biopsy was conducted during the time period under treatment, bleeding on the day of biopsy and the 3 days thereafter will not be considered as day(s) with bleeding/spotting and the AH value will be set to 0 mL. For the primary efficacy variable amenorrhea and the secondary efficacy variable HMB response, subjects will be defined as not having amenorrhea/ not being a HMB responder if they did not complete at least 8 weeks of treatment. Generally, in case a daily bleeding intensity is recorded with the UF-DBD as “no vaginal bleeding” or “spotting”, the missing AH value for this day will be set to 0 mL.

For days with bleeding intensity of light bleeding or higher in the UF-DBD, missing AH values will be replaced by the mean value of AH values of the days with the same bleeding intensity. In case there are no AH values with the same bleeding intensity, the mean of the AH values of next higher intensity will be used. In case there is no intensity higher than the bleeding intensity of the missing AH values available, either, no replacement for the missing AH values will be done for such days; but if there at least one such day occurs within the respective 28 days of treatment for a subject, the subject will be considered as not having

amenorrhea/ not being a HMB responder.

Furthermore, the last days under treatment with at least 28 days with non-missing bleeding intensity/AH values under treatment until the initial bleeding episode when the treatment started (after the imputations above) (without missing information: Days 57 to 84 under treatment) will be used to calculate the primary efficacy variable and the secondary efficacy variable HMB response. After these imputations a subject will be considered as not having amenorrhea in the presence of missing AH values if the sum of all non-missing AH values is not lower than 2 mL or if for missing AH values the bleeding intensity in the UF-DBD is light or higher, otherwise the subject will be considered as having amenorrhea. An equivalent approach as described for the amenorrhea rate will be applied for the secondary variable HMB response, ie, after the imputations as described above a subject will be considered as not being a HMB responder in the presence of missing AH values if the sum of all non-missing AH values is ≥80.00 mL or the reduction of blood loss is ≤50% as compared to baseline or if for missing AH values the bleeding intensity in the UF-DBD is light or higher, otherwise the subject will be considered as a HMB responder.

For the secondary variables onset of amenorrhea and onset of controlled bleeding the first 28 days with non-missing bleeding/AH values until the last 28 days with non-missing bleeding/AH values under treatment will be considered. An analogous approach as described above for the primary efficacy variable and the secondary efficacy variable HMB response will be applied to assess the bleeding status for each of these 28-day windows in terms of amenorrhea and controlled bleeding. If a subject does not achieve amenorrhea or controlled bleeding until end of treatment the subject will be considered as censored for the respective endpoint.

Sensitivity analyses will be conducted to evaluate the impact of missing data. These will be described in the SAP.

10.4 Determination of sample size

This section was changed in Amendment 2, see Section 15.1.1

Assumptions for sample size calculations are based on the ASTEROID 1 study (Study 15788) and the ASTEROID 2 study (Study 17541) with treatment durations of 12 and 24 weeks.

In ASTEROID 1, amenorrhea rates (defined as MBL <2 mL during last 28 days of treatment) of about 0.7, 0.9, and 0.9 for vilaprisan 2 mg and of about 0.2, 0.0, and 0.1 for placebo for the regions US/Japan/European Union and Canada, respectively, were observed with differences between vilaprisan 2 mg and placebo of about 0.5 to 0.9. In ASTEROID 2, similar amenorrhea rates were observed with numerical variation between the treatment periods. HMB response rates in the last 28 days amounted to percentages above 90% for vilaprisan 2 mg and 33% or lower for placebo. Median onset of amenorrhea was reached on day 6 after start of treatment for vilaprisan 2 mg. Due to the low number of subjects achieving amenorrhea until the end of placebo treatment, no median onset of amenorrhea could be calculated for placebo. Onset of controlled bleeding was reached on day 2 after start of treatment for vilaprisan 2 mg. Again, as for onset of amenorrhea, no median onset of controlled bleeding could be calculated for placebo due to the low number of subjects

achieving controlled bleeding until the end of placebo treatment. At the end of treatment controlled bleeding was reported for about 97% of subjects for vilaprisan 2 mg and for 49% of subjects for placebo, respectively.

Taking these aspects into account, a difference in amenorrhea rates of at least 0.4 between vilaprisan 2 mg and placebo is assumed after 12 weeks and 24 weeks. Sample size calculation is further based on a balanced randomization scheme of 1:1:1:1 (A1:A2:B1:B2), an overall power of 0.9 for the study (ie, higher for each individual test), and the application of the two-sided Cochran-Mantel-Haenszel test for the primary variable and the secondary variable HMB response as well as the logrank test for the secondary variables onset of amenorrhea and onset of controlled bleeding (stratified by region/country), each to a local 0.05 significance level.

Assuming a dropout rate of about 20%, the number of subjects to be randomized into the study is planned to be 260; 65 subjects in each treatment group.

Approximately 50% of subjects are planned to be enrolled from the US (based on feedback from the FDA).

Based upon the anticipated screen failures rates (60% in the US and 50% in China and in the other countries), about 585 subjects will be enrolled to achieve the planned number of randomized subjects.

PASS version 13.0.11 was used for sample size calculation.

10.5 Planned interim analyses

No interim analysis is planned.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be a validated, internet-based, electronic data capture (EDC) software system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (Clinical Information Environment).

RAVE, which Bayer has licensed from Medidata Solutions Worldwide, has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

Access to RAVE is through a password-protected security system that is part of the RAVE software. All Bayer and investigator site personnel must be trained before they are granted access. Training records will be maintained.

All personnel with access to RAVE are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained so data entry can proceed in a timely manner.

RAVE contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made, and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

Source documentation

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data have source documentation available at the site except for the data entered directly into the eCRF (eg, HMB questions, ClinRO) and ePRO data; these data will be the source and no additional source documentation will be available. The data entered directly into the eCRF/ePRO are not needed for the subject's routine medical care.

Data recorded from screening failures (screening failure confirmed at Visit 1)

At a minimum, the following data should be recorded in the eCRF, which will be transferred to the respective database:

- Demographic information (SID number, year of birth, age, race, ethnicity)
- Date of informed consent
- Date of Visit 1
- Relevant inclusion/exclusion criteria
- Reason for screening failure
- Date of last visit.

For all subjects continuing after Visit 1, all data have to be reported until screen failure was declared or randomization occurred. Additionally to the above mentioned data these will include**:**

- All available data from Visit 1, Visit 2, and Visit 3 including visit independent folder data, if applicable (AE, concomitant medication, and medical history data)
- Endometrial biopsy results (if done before screen failure was declared)
- Reason for premature discontinuation

For screening failures with an SAE or a pregnancy all information related to the SAE/pregnancy should be recorded in the eCRF (eg, the SAE, concomitant medication,

medical history, other information needed for SAE/pregnancy complementary page).

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data management will be performed consistent with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (eg, IVRS/IWRS, laboratory, ePRO).

For data coding (eg, AEs, medication), internationally recognized and accepted dictionaries will be used. MedDRA will be used for AEs and medical history and WHO Drug Dictionary for prior and concomitant medication.

The results of endometrial biopsies taken after the FUP visit will be entered into the clinical database at a pre-planned database re-opening, if needed. These results will not be part of the clinical study report, but will be reported in a separate addendum to the report after all the relevant data are available if applicable. Also, a re-opening of the database may become necessary in order to include the results of the PK measurements.

11.4 Missing data

Most important is to avoid missing data (eg, by monitoring in time for completeness; see Section 11.2) and by training the investigators, especially instructing them to motivate subjects to be compliant with the study protocol. Study site personnel will be trained to monitor the completeness of the eDiary data using the web portal, and the importance of the regular checks throughout the study for all subjects will be emphasized in the training and by the Clinical Research Associate during the study. The subjects will be informed on all aspects of the collection, storing and return of the used sanitary products, and the reasons for adhering to these practices will be emphasized at the beginning of the study and reviewed with them during the site visits.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (eg, relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [eg, treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study (eg, SAEs)
    - Results of parallel clinical studies
    - Results of parallel animal studies (on eg, toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (eg, recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (eg, IECs/IRBs; competent authority[ies]; study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 6.4.1.

13. Ethical and legal aspects

13.1 Investigators and other study personnel

Study Medical Expert is identified on the Title Page of this protocol (see Section 1). From among the participating investigators, the Global Clinical Leader will select the coordinating investigator, who will be responsible for signing the clinical study report. All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (eg, health authority, ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IECs/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (eg, IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent provided by the sponsor or the study center. A sample subject information and informed consent is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant

aspects of the study to each subject, prior to her entry into the study (ie, before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit description described in Section 9.2.4 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the SAP
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (eg, image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the SAP. The subject has the right to object to the generation and processing of this post-withdrawal data. The subject's oral objection may be documented in the subject's source data.

Each subject will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject voluntarily agrees to sign the informed consent and has done so, may she enter the study. Additionally, the investigator will personally sign and date the form. The subject will receive a copy of the signed and dated form.

The signed informed consent is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution. A paper copy of the signed eConsent can be provided.

If the informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written informed consent. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm her participation in the study by signing the revised informed consent. Any revised informed consent text and other information must receive the IEC/IRB's approval/favorable opinion in advance of use.

13.5 Publication policy and use of data

All relevant aspects regarding publication will be part of the contract between the sponsor and

the investigator/institution.

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the SID number will be recorded in the eCRF, and if the subject name appears on any other document (eg, pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

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15. Protocol amendments

15.1 Amendment 2 – Dated 15 NOV 2017

Amendment 2 is the first global amendment. The following is an overview of the changes made to the original protocol Version 1.0.

15.1.1 Overview of the changes to the study

The protocol was amended to maintain consistency across Vilaprisan Phase 3 studies and to modify the collection period of the sanitary products.

15.1.1.1 Change 1: Modification of the collection periods of sanitary products

The collection period for sanitary products was extended to cover the entire study.

Rationale

Currently, the alkaline hematin method is the only validated method to collect information on menstrual blood loss volume accepted by the FDA. In order not to jeopardize the data collection in the two pivotal studies, Asteroid 3 and 4, by using a non-validated method, ie, the menstrual pictogram, the decision was made to use both, AH and MP, throughout the entire study.

Affected sections:

- Section 9.2.3 Scheduled visits
- Section 9.2.3.1 Visit 1 Screening
- Section 9.2.3.2 Visit 2 Screening
- Section 9.2.3.3 Visit 3 Randomization
- Section 9.2.3.4 Visits 4, 5, and 6

- Section 9.2.3.5 EoT visit
- Section 9.4.3 Alkaline hematin method to assess HMB

15.1.1.2 Change 2: Changes in the statistical analysis

Statistical sections of the protocol were updated.

Rationale:

In order to consider feedback from Authorities and to support label claims on the endpoints HMB response, time to onset of amenorrhea and time to onset of controlled bleeding, time to onset of amenorrhea was elevated to a secondary endpoint and all of these above-mentioned endpoints were included in the hierarchical testing strategy. Description of analyses and missing data considerations were added for these endpoints and the rationale for the study sample size was modified with respect to these changes in the testing strategy. Furthermore, the calculation of the primary efficacy variable was adapted and further efficacy variables were added to 'other' efficacy variables.

Affected sections:

- Section 9.6.3.1 Laboratory evaluations
- Section 10.3.1 Variables
- Section 10.3.1.1 Primary efficacy variable
- Section 10.3.1.2 Secondary efficacy variables
- Section 10.3.1.3 Other efficacy variables
- Section 10.3.1.6 Other safety variables
- Section 10.3.2.2 Efficacy analysis, Section 10.3.2.3 Secondary efficacy analysis and Section 10.3.2.4 other efficacy
- Section 10.3.2.5 Subgroup analysis
- Section 10.3.3 Missing data/drop-outs
- Section 10.4 Determination of sample size

15.1.1.3 Change 3: Modifications of the tabular schedule of evaluations

Footnotes were modified.

Rationale:

Footnotes were revised to reflect the actual requirements correctly.

Affected sections:

- Section 9.1 Tabular schedule of evaluations

15.1.1.4 Change 4: Minor clarifications for consistency

Clarifications were made throughout the document to ensure readability, logic and consistency of the protocol and across studies.

Affected sections:

- Section 2 Synopsis
- Section 5 Study design
- Section 6.2 Exclusion criteria
- Section 9.1 Tabular schedule of evaluations
- Section 9.2.2 Optional pre-screening phone contact
- Section 9.4.4 Ultrasound (efficacy) to assess uterine fibroids
- Section 9.6.1.1 Definitions
- Section 9.6.3.3 Cervical smear
- Section 9.7.1 Iron supplementation
- Section 9.7.3 Heavy menstrual bleeding / suspicious bleeding pattern

15.1.2 Changes to the protocol text

In this section, all changes are detailed by presenting the "old text" and the "new text", and the sequence of the sections follows the structure of the protocol. Deletions are crossed out and additions are underlined. Corrections of typos or omissions, as well as automatic update of referenced numbers and changes in the list of abbreviations, are not highlighted.

15.1.2.1 Section 2 Synopsis

Old text:

[…]	
Methodology	Subjects will document the intensity of their daily menstrual bleeding in the Uterine Fibroid Daily Bleeding Diary (UF-DBD) and assess the intensity of their menstrual blood loss daily using a visual scoring system (MP) in an electronic diary (eDiary). Subjects will collect the sanitary products used during ~~specified periods of~~ the study to analyze the volume of blood loss using the AH method. **[…]**
[…]	

Plan for statistical analysis	The primary efficacy will be assessed by testing the amenorrhea rates of vilaprisan after 12 weeks of treatment in Treatment Period 1 and after 24 weeks of treatment in Treatment Period 2 (with and without a break) versus placebo after 12 weeks of treatment using two-sided Cochran-Mantel-Haenszel test at a 0.05 significance level. A hierarchical (fixed sequence) testing procedure will be used. In addition, efficacy and safety variables will be summarized by descriptive statistics.

New text:

[…]

	[…]
Methodology	Subjects will document the intensity of their daily menstrual bleeding in the Uterine Fibroid Daily Bleeding Diary (UF-DBD) and assess the intensity of their menstrual blood loss daily using a visual scoring system (MP) in an electronic diary (eDiary). Subjects will collect the sanitary products used during the study to analyze the volume of blood loss using the AH method. **[…]**
	[…]
Plan for statistical analysis	The primary efficacy will be assessed by testing the amenorrhea rates of vilaprisan after 12 weeks of treatment in Treatment Period 1 and after 24 weeks of treatment in Treatment Period 2 (with and without a break) versus placebo after 12 weeks of treatment using two-sided Cochran-Mantel-Haenszel test at a 0.05 significance level. A hierarchical (fixed sequence) testing procedure will be used<u>, involving the primary efficacy variable amenorrhea and key secondary efficacy variables HMB response, time to onset of amenorrhea and time to onset of controlled bleeding</u>. In addition, efficacy and safety variables will be summarized by descriptive statistics.

15.1.2.2 Section 5 Study design

Old text:

[…]

Overview of the study design is shown in Figure 5–1.

Figure 5–1 Design overview

Treatment Group A1	Screening ~~about~~ 120 days	RND	Vilaprisan 2 mg 12 week	*B*	Vilaprisan 2 mg 12 week	~~12-week~~ ~~follow~~-up
Treatment Group A2	Screening ~~about~~ 120 days	RND	Vilaprisan 2 mg 12 week		Vilaprisan 2 mg 12 week	~~12-week~~ ~~follow~~-up
Treatment Group B1	Screening ~~about~~ 120 days	RND	Placebo 12 week	*B*	Vilaprisan 2 mg 12 week	~~12-week~~ ~~follow~~-up
Treatment Group B2	Screening ~~about~~ 120 days	RND	Vilaprisan 2 mg 12 week	*B*	Placebo 12 week	~~12-week~~ ~~follow~~-up

B = bleeding episode; RND = randomization.

During the screening period, subjects will have to demonstrate eligibility including the presence of at least 1 uterine fibroid ≥30 mm and <120 mm in largest diameter based on ultrasound, HMB in at least 2 bleeding periods, each with menstrual blood loss (MBL) >80.00 mL, documented by the alkaline hematin (AH) method, and endometrial biopsy results without significant histological disorder. The duration of the screening period should be kept to a minimum (~~about~~ 120 days). In the event that the screening endometrial biopsy yielded an inadequate sample and needs to be repeated before randomization, the screening period interval is allowed to be extended in order to accommodate the endometrial sample analysis. In this case, the randomization visit (Visit 3) should take place: 1) after the biopsy results are available, 2) when all the eligibility criteria are confirmed, and 3) as close to the screening period interval as possible.

[…]

After the end of the final treatment period, subjects will be followed up ~~for 12 weeks~~.

[…]

Dose and regimen:

~~Nine~~ Phase 1 studies with vilaprisan have been completed. Vilaprisan has been tested at a maximum oral dose of 30 mg for up to 28 days (Study 14721, Report A52153) in postmenopausal women and at oral doses of 0.1, 0.5, 1.0, 2.0 and 5.0 mg for up to 12 weeks (Study 14723, Report A56310) in healthy young women.

[…]

New text:

[…]

Overview of the study design is shown in Figure 5–1.

Figure 5–1 Design overview

Treatment Group A1	Screening up to 120 days	RND	Vilaprisan 2 mg 12 week	*B*	Vilaprisan 2 mg 12 week	Follow-up Day 7 to 15 of the 2nd menstrual cycle after EoT
Treatment Group A2	Screening up to 120 days	RND	Vilaprisan 2 mg 12 week		Vilaprisan 2 mg 12 week	Follow-up Day 7 to 15 of the 2nd menstrual cycle after EoT
Treatment Group B1	Screening up to 120 days	RND	Placebo 12 week	*B*	Vilaprisan 2 mg 12 week	Follow-up Day 7 to 15 of the 2nd menstrual cycle after EoT
Treatment Group B2	Screening up to 120 days	RND	Vilaprisan 2 mg 12 week	*B*	Placebo 12 week	Follow-up Day 7 to 15 of the 2nd menstrual cycle after EoT

B = bleeding episode; RND = randomization.

During the screening period, subjects will have to demonstrate eligibility including the presence of at least 1 uterine fibroid ≥30 mm and <120 mm in largest diameter based on ultrasound, HMB in at least 2 bleeding periods, each with menstrual blood loss (MBL) >80.00 mL, documented by the alkaline hematin (AH) method, and endometrial biopsy results without significant histological disorder. The duration of the screening period should be kept to a minimum (maximum up to 120 days). In the event that the screening endometrial biopsy yielded an inadequate sample and needs to be repeated before randomization, the screening period interval is allowed to be extended in order to accommodate the endometrial sample analysis. In this case, the randomization visit (Visit 3) should take place: 1) after the biopsy results are available, 2) when all the eligibility criteria are confirmed, and 3) as close to the screening period interval as possible.

[…]

After the end of the final treatment period, subjects will be followed up until day 7 to 15 of the 2nd menstrual cycle after end of treatment visit.

[…]

Dose and regimen:

Ten Phase 1 studies with vilaprisan have been completed. Vilaprisan has been tested at a maximum oral dose of 30 mg for up to 28 days (Study 14721, Report A52153) in postmenopausal women and at oral doses of 0.1, 0.5, 1.0, 2.0 and 5.0 mg for up to 12 weeks (Study 14723, Report A56310) in healthy young women.

[…]

15.1.2.3 Section 6.2 Exclusion criteria

Old text:

[…]

8. Use of other treatments that might interfere with the conduct of the study or the interpretation of the results including

[…]

- Contraceptive devices with or without hormone release (implant, intra-uterine device), if not removed at Visit

[…]

New text:

[…]

8. Use of other treatments that might interfere with the conduct of the study or the interpretation of the results including

[…]

- Contraceptive devices with or without hormone release (implant, intra-uterine device), if not removed at Visit 1 (not applicable in cases of bilateral fallopian tube blockage of the subject (including Essure®))

[…]

15.1.2.4 Section 9.1 Tabular schedule of evaluations

Old text:

[…]

Table 9—1: Schedule of procedures

Study Phase	**Screening**			**TP 1** [a]		**TP 2** [b]		**FUP**
Visit	**1**	**2**	**3**	**4** [c]	**5**	**6** [d]	**EoT Visit** [e]	**FUP Visit** [f]
Timing		Day 7-15 (inclusive) of the 1st or 2nd menstrual cycle after Visit 1	RND	Day 22-42/ Wk 4-6 after start of TP1	Day 78-84/ Wk 12 after start of TP1	Day 22-42/ Wk 4-6 after start of TP2	Day 78-84/ Wk 12 after start of TP2	Day 7-15 (inclusive) of the 2nd menstrual cycle after EoT
Informed consent	X							
In-/exclusion criteria	X	X	X					
Demographics/smoking/alcohol consumption	X							
Medical/reproductive/menstrual/fibroids histories	X							
HMB questions	X							
Prior/ concomitant medications	X	X	X	X	X	X	X	X
AE assessments	X	X	X	X	X	X	X	X
Physical examination	X						X	X
Vital signs [g]/body weight/BMI/height at Visit 1 only	X		X				X	X
Gynecological/breast exam	X							X
Urine pregnancy test [h]	X	X	X	X	X	X	X	X
Cervical smear	X [i]							X

Table 9—1: Schedule of procedures

Study Phase	**Screening**			**TP 1** [a]		**TP 2** [b]		**FUP**
Visit	**1**	**2**	**3**	**4** [c]	**5**	**6** [d]	**EoT Visit** [e]	**FUP Visit** [f]
Timing		Day 7-15 (inclusive) of the 1st or 2nd menstrual cycle after Visit 1	RND	Day 22-42/ Wk 4-6 after start of TP1	Day 78-84/ Wk 12 after start of TP1	Day 22-42/ Wk 4-6 after start of TP2	Day 78-84/ Wk 12 after start of TP2	Day 7-15 (inclusive) of the 2nd menstrual cycle after EoT
Ultrasound examination [j]	X	X [k]	X	X	X	X	X	X [b]
Instruct subject to ~~call~~ site at start of next menstrual bleed	X				~~X~~		X at the 2nd bleed	
Endometrial biopsy [l]		X [m]					X [n]	X [b]
Laboratory (blood) [o]	X				X		X	X
PK sampling [p]					X	X		
Supervised study drug intake at site					X	X		
Urinalysis	X							
Barrier contraception/sanitary protection/home pregnancy test dispensed	X	X	X	X	X	X	X	
Alkaline hematin kit dispensed (as needed)	X	X		X	X	X	X	
Collect pads and tampons (as needed)		→		→	→	→	→	→
Randomization			X					
Study drug dispensed			X	X	X	X		
Unused study drug and empty drug packs collected/drug accountability				X	X	X	X	X if applicable
Return unused study drug to subject				X	X [q]	X	X [q]	
Assess subject's study drug compliance				→	→	→	→	→ if applicable
eDiary dispensed/collected	X							X
eDiary checked via web-report	→	→	→	→	→	→	→	→
PRO (eDiary/hand held device) [r]**:**								
UF-DSD	→	→	→	→	→	→	→	→
UF-DBD [s]	→	→	→	→	→	→	→	→
Menstrual pictogram	→	→	→	→	→	→	→	→
PRO (tablet computer) – completed at the site [t]**:**								
UFS-QoL			X		X		X	X
PGI-S			X		X		X	
PGI-C					X		X	
SF-36v2			X		X		X	X
TSQM-9					X		X	
ClinRO (RAVE): CGI_I			X				X	X

Treatment Day 1 is defined as the first day of study drug intake (ie, start of treatment).

a If no bleeding episode occurs within 7 weeks after the end of the TP, an ultrasound will be performed after which bleeding will be induced (Treatment Groups A1, B1, and B2).

b If spontaneous menstrual bleeding does not occur within 7 weeks after the EoT, the scheduled ultrasound will be performed as planned after which bleeding will be induced. The scheduled endometrial biopsy (ie, at FUP visit) will be performed thereafter at Day 7-15 (inclusive) of the first menstrual cycle after the induced bleeding episode. Ultrasound and pregnancy test will be performed before the endometrial biopsy as described in Section 9.6.3.2.

~~c Remind subjects randomized to Treatment Groups A1, B1 and B2 to start collecting sanitary items on Day 50 of the TP1.~~

~~d Remind all subjects to start collecting sanitary items on Day 50 of the TP2; for subjects randomized to Treatment Group A2; this is Day 134 of treatment.~~

~~e~~ EoT visit is also to be performed if a subject is prematurely withdrawn from the study during treatment phase.

~~f~~ FUP visit is also to be performed, if a subject is prematurely withdrawn from the study during FUP phase.

~~g~~ Vital signs after 5 minutes of rest in a sitting position.
~~h~~ Instruct the subject to perform a home pregnancy test before the start of study drug treatment (all groups at TP 1, and all but Group A2 at TP 2), document it in the eDiary and only start study drug if the test is negative.
~~i~~ The cervical smear may be waived if a normal result has been documented in the subject's medical records within the previous 6 months.
~~j~~ If endometrial thickness (double layer) >18 mm is detected after the start of treatment, the subject should undergo immediate evaluation by endometrial biopsy as described in Section 9.6.3.2. If cyst like structures >30 mm without suspicious appearance (ie, functional cysts) are visualized in the ovaries, unscheduled ultrasound examinations to document regression/outcome of these finding should be performed every 4 weeks or more frequently, if required due to symptoms.
~~k~~ Ultrasound for safety only.
~~l~~ For scheduling the visits, consider for subjects with menstrual cycles that biopsies should be taken between Day 7-15 (inclusive) of a menstrual cycle, which may require scheduling an additional visit. The EoT biopsy should be taken while under treatment; this biopsy may require to be scheduled before the EoT visit. A pregnancy test and ultrasound have to be performed before an endometrial biopsy is taken. See Section 9.6.3.2 for details.
~~m~~ Check laboratory results prior to the biopsy at Visit 2 to ensure subject is still eligible for the study.
~~n~~ For subjects with amenorrhea, biopsies are to be taken without considering any day in a cycle.
~~o~~ Coagulation parameters will be determined at Visit 1 only.
~~p~~ PK sampling. At Visit 5, one sample is to be taken pre-dose. At Visit 6, 1 sample is to be taken pre-dose, and 2 samples are to be taken after supervised study drug intake at the site (one between 0.5-1 hour after, and one between 2-4 hours after study drug intake). Document the following in the eCRF: the date and time of the last 2 study drug doses prior to the first PK sample at each visit, the time of the supervised drug intake at the study site (Visits 5 and 6), and the time of all blood samples. For China, a minimum of 30 subjects with ~~two~~ PK samples is required from some centers. See Section 9.5.1.
~~q~~ For subjects who have completed the TP, collect unused study drug and empty packaging. For subjects who have not completed TP, collect empty packaging and provide unused study drug back to the subject. Instruct the subject to complete the treatment period.
~~r~~ PROs on the eDiary/electronic hand-held device will be responded by the subjects until the next visit at home as required.
~~s~~ Check for any suspicious bleeding pattern and/or HMB at each visit except Visit 1.
~~t~~ PROs on the tablet computer will be responded by the subjects at scheduled visits under standardized conditions in the same visit-relevant sequence and prior to other activities and evaluations.

→ = continuous collection of data (eg, daily or weekly questionnaire) or collection of data in a schedule different to the visit time point; AE = adverse event; BMI = body mass index; CGI_I = Clinical Global Impression - Investigator; ClinRO= Clinician-reported outcome; EoT = end of treatment; FUP = follow-up; HMB = heavy menstrual bleeding; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; PRO = patient-reported outcome; RND = randomization; SF-36v2 = Short Form 36 Health Survey Version 2; TP = Treatment Period; TSQM-9 = Treatment Satisfaction Questionnaire for Medication (9 items); UF-DBD = Uterine Fibroid Daily Bleeding Diary; UF-DSD = Uterine Fibroid Daily Symptom Diary; UFS-QoL = Uterine Fibroid Symptom and Quality of Life questionnaire; Wk = week.

New text:

[…]

Table 9—1: Schedule of procedures

Study Phase	**Screening**			**TP 1 [a]**		**TP 2 [b]**		**FUP**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**EoT Visit [c]**	**FUP Visit [d]**
Timing		Day 7-15 (inclusive) of the 1st or 2nd menstrual cycle after Visit 1	RND	Day 22-42/ Wk 4-6 after start of TP1	Day 78-84/ Wk 12 after start of TP1	Day 22-42/ Wk 4-6 after start of TP2	Day 78-84/ Wk 12 after start of TP2	Day 7-15 (inclusive) of the 2nd menstrual cycle after EoT
Informed consent	X							
In-/exclusion criteria	X	X	X					
Demographics/smoking/alcohol consumption	X							
Medical/reproductive/menstrual/fibroids histories	X							

Table 9—1: Schedule of procedures

Study Phase	**Screening**			**TP 1** [a]		**TP 2** [b]		**FUP**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**EoT Visit** [c]	**FUP Visit** [d]
Timing		Day 7-15 (inclusive) of the 1st or 2nd menstrual cycle after Visit 1	RND	Day 22-42/ Wk 4-6 after start of TP1	Day 78-84/ Wk 12 after start of TP1	Day 22-42/ Wk 4-6 after start of TP2	Day 78-84/ Wk 12 after start of TP2	Day 7-15 (inclusive) of the 2nd menstrual cycle after EoT
HMB questions	X							
Prior/ concomitant medications	X	X	X	X	X	X	X	X
AE assessments	X	X	X	X	X	X	X	X
Physical examination	X						X	X
Vital signs [e]/body weight/BMI/height at Visit 1 only	X		X				X	X
Gynecological/breast exam	X							X
Urine pregnancy test [f]	X	X	X	X	X	X	X	X
Cervical smear	X [g]							X
Ultrasound examination [h]	X	X [i]	X	X	X	X	X	X [b]
Instruct subject to contact site at start of next menstrual bleed	X						X at the 2nd bleed	
Endometrial biopsy [j]		X [k]					X [l]	X [b]
Laboratory (blood) [m]	X				X		X	X
PK sampling [n]					X	X		
Supervised study drug intake at site					X	X		
Urinalysis	X							
Barrier contraception/sanitary protection/home pregnancy test dispensed	X	X	X	X	X	X	X	
Alkaline hematin kit dispensed (as needed)	X	X	X	X	X	X	X	
Collect pads and tampons (as needed)		→	→	→	→	→	→	→
Randomization			X					
Study drug dispensed			X	X	X	X		
Unused study drug and empty drug packs collected/drug accountability				X	X	X	X	X if applicable
Return unused study drug to subject				X	X [o]	X	X [o]	
Assess subject's study drug compliance				→	→	→	→	→ if applicable
eDiary dispensed/collected	X							X
eDiary checked via web-report	→	→	→	→	→	→	→	→
PRO (eDiary/hand held device) [p]**:**								
UF-DSD	→	→	→	→	→	→	→	→
UF-DBD [q]	→	→	→	→	→	→	→	→
Menstrual pictogram	→	→	→	→	→	→	→	→
PRO (tablet computer) – completed at the site [r]**:**								
UFS-QoL			X		X		X	X
PGI-S			X		X		X	
PGI-C					X		X	
SF-36v2			X		X		X	X
TSQM-9					X		X	
ClinRO (RAVE): CGI_I			X				X	X

Treatment Day 1 is defined as the first day of study drug intake (ie, start of treatment).

a If no bleeding episode occurs within 7 weeks after the end of the TP, an ultrasound will be performed after which bleeding will be induced (Treatment Groups A1, B1, and B2).

b If spontaneous menstrual bleeding does not occur within 7 weeks after the EoT, the scheduled ultrasound will be performed as planned after which bleeding will be induced. The scheduled endometrial biopsy (ie, at FUP visit) will be performed thereafter at Day 7-15 (inclusive) of the first menstrual cycle after the induced bleeding episode. Ultrasound and pregnancy test will be performed before the endometrial biopsy as described in Section 9.6.3.2.
c EoT visit is also to be performed if a subject is prematurely withdrawn from the study during treatment phase.
d FUP visit is also to be performed, if a subject is prematurely withdrawn from the study during FUP phase.
e Vital signs after 5 minutes of rest in a sitting position.
f Instruct the subject to perform a home pregnancy test before the start of study drug treatment (all groups at TP 1, and all but Group A2 at TP 2), document it in the eDiary and only start study drug if the test is negative.
g The cervical smear may be waived if a normal result has been documented in the subject's medical records within the previous 6 months.
h 1. Ultrasound measurements do not have to be done on the same day as other assessment on that visit, but have to be performed as close to the specified visit as possible. On visits where a biopsy will be taken, the ultrasound must be done before the biopsy.
2. If endometrial thickness (double layer) >18 mm is detected after the start of treatment, the subject should undergo immediate evaluation by endometrial biopsy as described in Section 9.6.3.2. If cyst like structures >30 mm without suspicious appearance (ie, functional cysts) are visualized in the ovaries, unscheduled ultrasound examinations to document regression/outcome of these finding should be performed every 4 weeks or more frequently, if required due to symptoms.
i Ultrasound for safety only.
j For scheduling the visits, consider for subjects with menstrual cycles that biopsies should be taken between Day 7-15 (inclusive) of a menstrual cycle, which may require scheduling an additional visit. The EoT biopsy should be taken while under treatment; this biopsy may require to be scheduled before the EoT visit. A pregnancy test and ultrasound have to be performed before an endometrial biopsy is taken. See Section 9.6.3.2 for details.
k Check laboratory results prior to the biopsy at Visit 2 to ensure subject is still eligible for the study.
l For subjects with amenorrhea, biopsies are to be taken without considering any day in a cycle.
m Coagulation parameters will be determined at Visit 1 only.
n PK sampling. At Visit 5, one sample is to be taken pre-dose. At Visit 6, 1 sample is to be taken pre-dose, and 2 samples are to be taken after supervised study drug intake at the site (one between 0.5-1 hour after, and one between 2-4 hours after study drug intake). Document the following in the eCRF: the date and time of the last 2 study drug doses prior to the first PK sample at each visit, the time of the supervised drug intake at the study site (Visits 5 and 6), and the time of all blood samples. For China, a minimum of 30 subjects with PK samples from V5 and V6 are required from some centers. See Section 9.5.1.
o For subjects who have completed the TP, collect unused study drug and empty packaging. For subjects who have not completed TP, collect empty packaging and provide unused study drug back to the subject. Instruct the subject to complete the treatment period.
p PROs on the eDiary/electronic hand-held device will be responded by the subjects until the next visit at home as required.
q Check for any suspicious bleeding pattern and/or HMB at each visit except Visit 1.
r PROs on the tablet computer will be responded by the subjects at scheduled visits under standardized conditions in the same visit-relevant sequence and prior to other activities and evaluations.

→ = continuous collection of used sanitary products (pads or tampons), data (eg, daily or weekly questionnaire) or collection of data and used sanitary products in a schedule different to the visit time point;

AE = adverse event; BMI = body mass index; CGI_I = Clinical Global Impression - Investigator; ClinRO= Clinician-reported outcome; EoT = end of treatment; FUP = follow-up; HMB = heavy menstrual bleeding; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PK = pharmacokinetics; PRO = patient-reported outcome; RND = randomization; SF-36v2 = Short Form 36 Health Survey Version 2; TP = Treatment Period; TSQM-9 = Treatment Satisfaction Questionnaire for Medication (9 items); UF-DBD = Uterine Fibroid Daily Bleeding Diary; UF-DSD = Uterine Fibroid Daily Symptom Diary; UFS-QoL = Uterine Fibroid Symptom and Quality of Life questionnaire; Wk = week.

15.1.2.5 Section 9.2.2 Optional pre-screening phone contact

Old text:

[…]

After the telephone discussion, the patient information and informed consent form may be sent to the subject for further information. Regardless of whether the patient information and

informed consent form is sent to the subject, it must be thoroughly discussed and reviewed with her ~~at the Screening Visit 1~~ before obtaining the signed informed consent form.

[…]

New text:

[…]

After the telephone discussion, the patient information and informed consent form may be sent to the subject for further information. Regardless of whether the patient information and informed consent form is sent to the subject, it must be thoroughly discussed and reviewed with her <u>in person</u> before obtaining the signed informed consent form.

[…]

15.1.2.6 Section 9.2.3 Scheduled visits

Old text:

For timing of the visits see Table 9—1. Site personnel will determine the start of each treatment period from the eDiary provider web portal. Subjects must be contacted (eg, via phone call) after the first dose is taken in each treatment period to schedule the subsequent visits.

New text:

For timing of the visits see Table 9—1. Site personnel will determine the start of each treatment period from the eDiary provider web portal. <u>For Scheduling Visit 6 and the EoT visit in Treatment Group A2, the Day 1 of the TP2 is the next day after Day 84 of TP1.</u> Subjects must be contacted (eg, via phone call) after the first dose is taken in each treatment period to schedule the subsequent visits.

15.1.2.7 Section 9.2.3.1 Visit 1 Screening

Old text:

[…]

- ~~Dispense AH kit~~
- Dispense sanitary protection. Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss.
- Remind the subject to return all used sanitary protection items as soon as the bleeding episode has been completed.

[…]

New text:

[…]

[…]

- Dispense AH kit and sanitary protection. Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss
- Remind the subject to return all used sanitary protection items as soon as the bleeding episode has been completed (but no later than 12 days from the start of the collection of the first item)

[…]

15.1.2.8 Section 9.2.3.2 Visit 2 Screening

Old text:

[…]

- Dispense AH kit
- ~~Dispense sanitary protection~~

[…]

- Remind the subject to return all used sanitary protection items as soon as a bleeding episode has been completed

[...]

New text:

[…]

- Dispense AH kit and sanitary protection. Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss.

[…]

- Remind the subject to return all used sanitary protection items as soon as a bleeding episode has been completed, (but no later than 12 days from the start of the collection of the first item).

[…]

15.1.2.9 Section 9.2.3.3 Visit 3 Randomization

Old text:

[…]

- Dispense sanitary protection

[…]

- Complete ClinRO (RAVE): CGI_I (see Section 9.4.2)

New text:

[…]

- Dispense AH kit and sanitary protection. Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss

[…]

- Remind the subject to return all used sanitary protection items as soon as a bleeding episode has been completed (but no later than 12 days from the start of the collection of the first item).
- Complete ClinRO (RAVE): CGI_I (see Section 9.4.2)

15.1.2.10 Section 9.2.3.4 Visits 4, 5, and 6

Old text:

[…]

- Dispense AH kit
- ~~Dispense sanitary protection~~
- ~~Visit 4: Remind subjects randomized to Treatment Groups A1, B1, and B2 to start collecting sanitary items on day 50 of the TP1; collection to be continued until the end of this TP.~~
  ~~Remind the subject to return all used sanitary protection items as soon as the bleeding episode has been completed.~~
- ~~Visit 5: Collect used sanitary protection items, if they have not yet been provided to the site. If a subject is continuing her treatment after the visit, remind her to continue collecting the used sanitary items until the end of their treatment and advise the subject to return them to the site as soon as bleeding episode has been completed.~~
- ~~Visit 6: Remind all subjects to start collecting sanitary items on Day 50 of the TP2; for subjects randomized to Treatment Group A2; this is Day 134 of their treatment. ;~~
  ~~Collection is to be continued until the end of this TP.~~
  ~~Remind the subject to return all used sanitary protection items as soon as the bleeding episode has been completed.~~

[…]

- Remind the subject to complete eDiary-based questionnaires until the next visit as required (UF-DSD, UF-DBD, and MP) (see Sections 9.4.1.1 and 9.4.1.2.2)
- Check of eDiary entries via web; check for suspicious bleeding pattern and HMB (see Section 9.7.3)

[…]

New text:

[…]

- Dispense AH kit and sanitary protection. Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss
- Collect used sanitary protection items, if they have not yet been provided to the site.

[…]

- Remind the subject to complete eDiary-based questionnaires until the next visit as required (UF-DSD, UF-DBD, and MP) (see Sections 9.4.1.1 and 9.4.1.2.2)
- Remind the subject to return all used sanitary protection items as soon as a bleeding episode has been completed, (but no later than 12 days from the start of the collection of the first item).
- Check of eDiary entries via web; check for suspicious bleeding pattern and HMB (see Section 9.7.3)

[…]

15.1.2.11 Section 9.2.3.5 EoT visit

Old text:

[…]

- Collect used sanitary protection items, if they have not yet been provided to the site. ~~If a subject is continuing her treatment after the visit, remind her to continue collecting the used sanitary items until the end of her treatment and remind the subject to return them to the site as soon as bleeding episode has been completed.~~
- Remind the subject to return all used sanitary protection items as soon as a bleeding episode has been completed
- Endometrial biopsy (see Section 9.6.3.2)
- Laboratory evaluations excluding coagulation parameters and urinalysis (see Section 9.6.3.1)
- Dispense barrier contraception (eg, condoms with spermicide) (see Section 9.6.3.7)
- Dispense AH kit
- ~~Dispense sanitary protection~~

[…]

New text:

[…]

- Collect used sanitary protection items, if they have not yet been provided to the site.
- Remind the subject to continue collecting the used sanitary products during the follow-up.
- Remind the subject to return all used sanitary protection items as soon as a bleeding episode has been completed, (but no later than 12 days from the start of the collection of the first item).
- Endometrial biopsy (see Section 9.6.3.2)
- Laboratory evaluations excluding coagulation parameters and urinalysis (see Section 9.6.3.1)
- Dispense barrier contraception (eg, condoms with spermicide) (see Section 9.6.3.7)
- Dispense AH kit and sanitary protection. Explain procedure for collection of sanitary protection items for measurement of menstrual blood loss.

[…]

15.1.2.12 Section 9.4.3 Alkaline hematin method to assess HMB

Old text:

During the duration of the study, subjects will be required to use selected types of sanitary products provided (pads and/or tampons). During ~~specified periods~~ of the study, subjects need to collect their used sanitary products and return them to the study site as soon as the episode is completed to be sent to the central laboratory for analysis.

The AH method will be applied to measure MBL ~~during~~ Screening ~~and~~ during ~~the last 35 days of each treatment period~~. ~~Collection for 35 days at the end of each treatment period is chosen to avoid missing data for calculation of the primary endpoint (last 28 days of treatment) in cases where subjects stop treatment prematurely.~~

[…]

New text:

During the duration of the study, subjects will be required to use selected types of sanitary products provided (pads and/or tampons). During the entire duration of the study, subjects need to collect their used sanitary products and return them to the study site as soon as the bleeding episode is completed to be sent to the central laboratory for analysis.

The AH method will be applied to measure MBL from Screening onwards during the entire study.

[…]

15.1.2.13 Section 9.4.4 Ultrasound (efficacy) to assess uterine fibroids

Old text:

[…]

The minimum source documentation will include printouts from the ultrasound machine showing the 3 largest fibroids. The printouts have to be labeled unambiguously, containing at least the study number, SID number, time point, and longest diameter of 3 largest fibroids.

For safety ultrasound procedures, see Section 9.6.3.6.

New text:

[…]

The minimum source documentation will include printouts from the ultrasound machine showing the 3 largest fibroids. The printouts have to be labeled unambiguously, containing at least the study number, SID number, time point, and longest diameter of 3 largest fibroids. It is also possible that the site has a CD with the ultrasound images available, when in the source the evaluation of the US images from the CD is available as well. The CRA should be able to review the data on the CD and compare the images with the evaluations in the source during the onsite monitoring visits.

Furthermore, if the US machine is SESAC (Site Electronic Source Assessment Checklist) conform, ie, GCP conform electronic data storage is possible, then no print out is needed

For safety ultrasound procedures, see Section 9.6.3.6.

15.1.2.14 Section 9.6.1.1 Definitions

Old text:

In a clinical study, an AE is any untoward medical occurrence (ie, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

[…]

New text:

In a clinical study, an AE is any untoward medical occurrence (ie, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Treatment emergent adverse event (TEAE) is defined as any event that occurred after the first study drug intake until the end of FUP.

[…]

15.1.2.15 Section 9.6.3.1 Laboratory evaluations

A footnote was added to Laboratory evaluations of hematocrit, hemoglobin, and ferritin stating that hemoglobin, hematocrit and ferritin are also efficacy variables.

15.1.2.16 Section 9.6.3.3 Cervical smear

Old text:

The cervical smear should be obtained with the gynecological examination at the visits shown in Table 9—1. It may be repeated once during the screening period if the results are abnormal (this repeat is not considered rescreening). If the cervical smear is repeated at Visit 2 (screening), it should be performed before the endometrial biopsy. The cervical smear at screening may be waived if a normal result has been documented in the subject's medical records within the previous 6 months. Subjects with ASCUS can be included in the study if they have an HPV deoxyribonucleic acid test that is negative for high-risk HPV.

New text:

The cervical smear should be obtained with the gynecological examination at the visits shown in Table 9—1. It may be repeated once during the screening period if the results are abnormal (this repeat is not considered rescreening). If the cervical smear is repeated at Visit 2 (screening), it should be performed before the endometrial biopsy. The cervical smear at screening may be waived if a normal result has been documented in the subject's medical records within the previous 6 months. Subjects with ASCUS can be included in the study if they have an HPV deoxyribonucleic acid test that is negative for high-risk HPV. As a guidance, a cervical smear should only be repeated once in case of insufficient material.

15.1.2.17 Section 9.7.1 Iron supplementation

Old text:

If causes for anemia unrelated to HMB are suspected these subjects should not be enrolled.

Moderate anemia is defined as hemoglobin ≤10.9 g/dL (12). Iron supplementation should be offered to subjects with hemoglobin ≤10.9 g/dL consistent with local standards of practice and ~~the Centers for Disease Control and Prevention recommendation, ie, 50 to 60 mg of oral elemental iron (the approximate amount of elemental iron in one 325 mg tablet of ferrous sulfate) twice daily for 3 months for the treatment of iron deficiency anemia.~~ Iron supplementation will not be considered as study drug and should be documented as concomitant medication.

New text:

If causes for anemia unrelated to HMB are suspected these subjects should not be enrolled.

Moderate anemia is defined as hemoglobin ≤10.9 g/dL (12). Iron supplementation should be offered to subjects with hemoglobin ≤10.9 g/dL consistent with local standards of practice and at the investigator's discretion. Iron supplementation will not be considered as study drug and should be documented as concomitant medication.

15.1.2.18 Section 9.7.3 Heavy menstrual bleeding / suspicious bleeding pattern

Old text:

[…]

In case of suspicious bleeding pattern (eg, continuous spotting, unusually heavy bleeding) after the start of treatment, which does **not** resemble the subject's natural cycle or bleeding pattern, detected from the MP or UF-DBD, the subject should undergo immediate evaluation by the investigator.

Especially if during intake of the study drug and after the initial reduction of bleeding and/or onset of amenorrhea, any recording in the MP, or bleeding of an intensity of "mild" or worse occurs continuously for 10 days or more the subject should be instructed to contact the site for immediate evaluation.

[…]

New text:

[…]

In case of suspicious bleeding pattern (eg, continuous spotting, unusually heavy bleeding) after the start of treatment, which does **not** resemble the subject's natural cycle or bleeding pattern, detected from the AH, MP or UF-DBD, the subject should undergo immediate evaluation by the investigator.

Especially if during intake of the study drug and after the initial reduction of bleeding and/or onset of amenorrhea, any recording in the MP, worsened bleeding detected from the AH analysis, or bleeding of an intensity of "mild" or worse occurs continuously for 10 days or more the subject should be instructed to contact the site for immediate evaluation.

[…]

15.1.2.19 Section 10.3.1 Variables

Old text:

The primary efficacy variable will be calculated based on the alkaline hematin method. ~~Secondary and o~~ther variables related to menstrual blood loss will be calculated based on the two methods, the alkaline hematin method and the menstrual pictogram~~, depending on the planned application of the methods~~.

New text:

The primary efficacy variable and secondary efficacy variables will be calculated based on the alkaline hematin method (unless otherwise specified). Other efficacy variables related to menstrual blood loss will be calculated based on the two methods, the alkaline hematin method and the menstrual pictogram.

15.1.2.20 Section 10.3.1.1 Primary efficacy variable

Old text:

[…]

Subjects who discontinue treatment ~~due to lack of efficacy, AEs, or~~ prior to completion of treatment Week 8 of the respective treatment period will be considered not having amenorrhea.

~~Further, based on scientific advice by FDA, subjects who did not adequately fulfill selection criteria or require fibroid surgery during study participation will be considered not having amenorrhea.~~

New text:

[…]

Subjects who discontinue treatment prior to completion of treatment Week 8 of the respective treatment period will be considered not having amenorrhea.

15.1.2.21 Section 10.3.1.2 Secondary efficacy variables

Old text:

The secondary efficacy variables are:

- ~~Absence of bleeding (spotting allowed) during the last 28 days of the treatment; based on the UF-DBD~~
- ~~Time to onset of controlled bleeding. Onset of controlled bleeding is defined by the first day, for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <80.00 mL~~
- HMB respon~~der rate (percentage of subjects with~~ blood loss <80.00 mL ~~per~~ 28 days and 50% reduction compared to baseline~~)~~

[…]

New text:

The secondary efficacy variables are:

- HMB respon<u>se defined as</u> blood loss <80.00 mL <u>during the last</u> 28 days <u>of treatment</u> and <u>≥</u>50% reduction compared to baseline
- <u>Time to onset of amenorrhea. Onset of amenorrhea is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <2 mL.</u>
- <u>Time to onset of controlled bleeding. Onset of controlled bleeding is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <80.00 mL.</u>

- Absence of bleeding (spotting allowed) during the last 28 days of the treatment; based on the UF-DBD

15.1.2.22 Section 10.3.1.3 Other efficacy variables

Old text:

Other efficacy variables are:

- Amenorrhea (yes/no), defined as MBL < 2 mL ~~during the last~~ 28 days of treatment (for treatment time/method not considered as primary variable)
- Volume of menstrual blood loss per 28 days
- Volume of menstrual blood loss per bleeding episode for the first, second, and if applicable third bleeding episode after the EoT
- Percentage of subjects with 50% reduction in menstrual bleeding per 28 days compared to baseline
- ~~Time to onset of amenorrhea. Onset of amenorrhea is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <2 mL.~~
- Time to start of bleeding after last study drug intake (assessed by the UF-DBD). If bleeding has to be induced, the subject´s data will be censored at that time point for the induction.

[…]

- Patient satisfaction

New text:

Other efficacy variables are:

- Treatment success rate defined as percentage of subjects who fulfill the criteria of HMB response (<80.00 mL, >50% reduction in menstrual blood loss as compared to baseline) and who have not been withdrawn from the study due to AEs, due to non-fulfillment of selection criteria (related to fibroid size or HMB at baseline) or due to fibroid surgery having been performed during the study.
- Amenorrhea (yes/no), defined as MBL < 2 mL per 28 days of treatment (for treatment time/method not considered as primary variable)
- HMB response defined as blood loss <80.00 mL and >50% reduction compared to baseline per 28 days of treatment (for treatment time/method not considered as secondary variable)

- Time to onset of amenorrhea. Onset of amenorrhea is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <2 mL (for treatment time/method not considered as secondary variable)
- Time to onset of controlled bleeding. Onset of controlled bleeding is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <80.00 mL (for treatment time/method not considered as secondary variable)
- Volume of menstrual blood loss per 28 days
- Volume of menstrual blood loss per bleeding episode for the first, second, and if applicable third bleeding episode after the EoT
- Volume of menstrual blood loss per bleeding episode within the treatment break (not applicable for Treatment Groups A2). All days of the bleeding episodes will be used even if some days of the episode lie outside the treatment break.
- Percentage of subjects with 50% reduction in menstrual bleeding per 28 days compared to baseline
- Time to start of bleeding after last study drug intake (assessed by the UF-DBD in addition to the other two measurement methods). If bleeding has to be induced, the subject´s data will be censored at that time point for the induction.

[…]

- Patient satisfaction assessed by the TSQM-9 at the 12 week and at end of treatment visit
- Change from baseline in hemoglobin, hematocrit, and ferritin
- Percentage of subjects with normal hemoglobin >12 g/dL and normal hematocrit >36%

15.1.2.23 Section 10.3.1.6 Other safety variables

Old text:

[…]

- Vital signs
- ~~Change from baseline in hemoglobin, hematocrit, and ferritin~~
- ~~Percentage of subjects with normal hemoglobin >12 g/dL and normal hematocrit >36%~~
- Percentage of subjects with moderate to severe anemia (ie, hemoglobin ≤10.9 g/dL)

New text:

[…]

- Vital signs
- Percentage of subjects with moderate to severe anemia (ie, hemoglobin ≤10.9 g/dL)

15.1.2.24 Section 10.3.2.2 Efficacy analysis, Section 10.3.2.3 Secondary efficacy analysis and Section 10.3.2.4 other efficacy

Old text:

10.3.2.2 ~~Primary~~ efficacy analysis

The primary efficacy will be ~~assessed by testing the amenorrhea (yes/no) for superiority of vilaprisan 2 mg after 12 weeks of treatment in Treatment Period 1 and after 24 weeks of treatment in Treatment Period 2 (with and without a break) versus placebo after 12 weeks of treatment using~~ two-sided Cochran-Mantel-Haenszel test stratified by region/country at a 0.05 significance level.

The number of subjects with amenorrhea (yes/no) is assumed to be binomial distributed.

~~In order to adjust for the multiplicity created by the testing of 3 hypotheses a fixed sequence procedure is applied:~~

~~1. $H_{0,1x12}: p_{1x12,V} = p_{1x12,P}$ vs. $H_{1,1x12}: p_{1x12,V} \neq p_{1x12,P}$~~

~~2. $H_{0,2x12}: p_{2x12,V} = p_{2x12,P}$ vs. $H_{1,2x12}: p_{2x12,V} \neq p_{2x12,P}$~~

~~3. $H_{0,1x24}: p_{1x24,V} = p_{2x12,P}$ vs. $H_{1,1x24}: p_{1x24,V} \neq p_{2x12,P}$~~

~~where $p_{1x12,V}$ and $p_{1x12,P}$ are the amenorrhea rate during the last 28 days of vilaprisan treatment after 12 weeks of treatment (in pooled Treatment Groups A1 and B2, as the treatments are the same and pooling increases the power) and the amenorrhea rate during the last 28 days of placebo treatment after 12 weeks of treatment (in Treatment Group B1), respectively. Similarly, $p_{2x12,V}$ and $p_{2x12,P}$ represent the amenorrhea rate during the last 28 days of vilaprisan treatment after 2x12 weeks of treatment (in Treatment Group A1) and the amenorrhea rate during the last 28 days of placebo treatment after 2x12 weeks of treatment (in Treatment Group B2). The term $p_{1x24,V}$ stands for the amenorrhea rate during the last 28 days of vilaprisan treatment after 24 weeks of treatment (in Treatment Group A2).~~

~~First $H_{0,1x12}$ is tested to the significance level of 0.05. If $H_{0,1x12}$ is rejected, the procedure moves on to test the second hypothesis $H_{0,2x12}$ to the same alpha level, otherwise the procedure stops at $H_{0,1x12}$. If $H_{0,2x12}$ is rejected, the procedure moves on to test the third hypothesis $H_{0,1x24}$ to the same alpha level, otherwise the procedure stops at $H_{0,2x12}$.~~

~~10.3.2.3 Secondary efficacy analysis~~

~~The~~ secondary efficacy variables will be analyzed descriptively in frequency tables by treatment period within each treatment group, except for time to event variables which will be

analyzed by treatment group using the Kaplan-Meier estimates.

~~**10.3.2.4 Other efficacy**~~

Other variables will be evaluated and presented by means of descriptive statistics.

New text:

10.3.2.2 Efficacy analysis

For the confirmatory efficacy analysis, a hierarchical testing approach will be applied, involving the primary efficacy variable amenorrhea (yes/no) and the first three secondary efficacy variables HMB response, time to onset of amenorrhea and time to onset of controlled bleeding. These tests always include a comparison of vilaprisan 2 mg versus placebo and can be applied in three different situations:

1 After 12 weeks of treatment in Treatment Period 1:
Comparison of vilaprisan 2 mg in pooled Treatment Groups A1 and B2 (as the treatments are the same and pooling increases the power) vs. placebo in Treatment Group B1

2 After 12 weeks of treatment in Treatment Period 2:
Comparison of vilaprisan 2 mg in Treatment Group A1 vs. placebo in Treatment Group B2

3 After 24 weeks of treatment:
Comparison of vilaprisan 2 mg in Treatment Group A2 vs. placebo in Treatment Period 2 of Treatment Group B2

In total, ten tests will be carried out each to an alpha level of 0.05: First, the tests for the primary efficacy variable amenorrhea (yes/no) will be carried out in scenarios 1, 2 and 3 in this order, followed by the tests for HMB response (yes/no) in scenarios 1, 2 and 3, the tests for time to onset of amenorrhea in scenarios 1 and 2, and finally, the tests for onset of controlled bleeding in scenarios 1 and 2. As the hierarchical testing procedure follows a fixed sequence, it stops as soon as any of these tests cannot be rejected to an alpha level of 0.05 and all further tests after failing to reject one null hypothesis in the testing sequence will be considered exploratory. This fixed sequence procedure accounts for the multiplicity created by carrying out multiple tests.

Amenorrhea (yes/no), defined as MBL <2 mL during the last 28 days of treatment

The primary efficacy variable amenorrhea (yes/no) will be analyzed by means of a two-sided Cochran-Mantel-Haenszel test stratified by region/country at a local 0.05 significance level.

The number of subjects with amenorrhea (yes/no) is assumed to be binomial distributed. Thus, the Cochran-Mantel-Haenszel test is applied to test the null hypothesis $H_{0,i}$ that the amenorrhea rates in the vilaprisan 2 mg group ($p_{v,i}$) and in the placebo group ($p_{p,i}$) in the respective situations i =1, 2 or 3 are equal versus the alternative hypothesis $H_{1,i}$ that they are not:

$$H_{0,i}: p_{v,i} = p_{p,i} \quad \text{vs.} \quad H_{1,i}: p_{v,i} \neq p_{p,i}.$$

HMB response defined as blood loss <80.00 mL during the last 28 days and >50% reduction compared to baseline

The first secondary efficacy variable HMB response (yes/no) will be analyzed analogously to the primary efficacy variable amenorrhea.

Time to onset of amenorrhea

Onset of amenorrhea is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <2 mL. Subjects are treated as censored if they did not experience an onset of amenorrhea during the respective treatment period. Censoring rules will be described in more detail in the SAP.

In order to investigate the null hypothesis that there is no difference in time to onset of amenorrhea between vilaprisan 2mg and placebo versus the alternative hypothesis that there is a difference, a logrank test stratified by region/country is conducted at a local 0.05 significance level.

Time to onset of controlled bleeding

Onset of controlled bleeding is defined by the first day for which the menstrual blood loss for all subsequent 28-day periods up to the end of the treatment period is <80.00 mL. Subjects are treated as censored if they did not experience an onset of controlled bleeding during the respective treatment period. Censoring rules will be described in more detail in the SAP.

Time to onset of controlled bleeding will be analyzed analogously to the secondary efficacy variable time to onset of amenorrhea.

The study will be considered successful if at least superiority of vilaprisan 2 mg vs. placebo after Treatment Period 1 based on the primary variable could be demonstrated.

Sensitivity analyses will be conducted for the primary efficacy variable and the first three secondary efficacy variables as applicable. These will be described in the SAP.

All primary and secondary efficacy variables will also be analyzed descriptively in frequency tables by treatment period within each treatment group, except for time to event variables which will be analyzed by treatment group using the Kaplan-Meier estimates.

Other efficacy variables will be evaluated and presented by means of descriptive statistics.

Sections 10.3.2.3 (Secondary efficacy analysis) and 10.3.2.4 (Other efficacy) have been incorporated into Section 10.3.2.2 Efficacy analysis. Due to this section numbering of sections 10.3.2.3 Pharmacokinetic analysis, 10.3.2.4 Safety analysis and 10.3.2.5 Subgroup analysis have changed.

15.1.2.25 Section 10.3.2.5 Subgroup analysis

Old text:

Subgroup analyses are planned using descriptive statistics for the primary and secondary efficacy variables separately for each country (China and the US), race and ethnicity.

New text:

Subgroup analyses are planned using descriptive statistics for the primary and secondary efficacy variables separately for each country (China and the US), race and ethnicity. Further subgroup analyses will be described in the SAP.

15.1.2.26 Section 10.3.3 Missing data/drop-outs

Old text:

For the primary efficacy variable it is ~~planned to collect~~ the AH ~~data~~ only on days when vaginal bleeding occurred. To differentiate missing AH data and days without vaginal bleeding the bleeding intensity collected in the UF-DBD will be used.

Missing bleeding data in the subject diaries will be imputed. For the UF-DBD, the worst case approach will be used for missing bleeding intensity for the single or two consecutive missing days (ie, the maximum of the bleeding intensities of the day before and the day after the missing day[s] will be assumed).

If an endometrial biopsy was conducted during the time period under treatment, bleeding on the day of biopsy and the 3 days thereafter will not be considered as day(s) with bleeding/spotting and AH value will be set to 0 mL. For the primary efficacy ~~analysis~~, subjects will be defined as not having amenorrhea if they did not complete at least 8 weeks of treatment. Generally, in case a daily bleeding intensity is recorded as “no vaginal bleeding” or “spotting”, the missing AH value for this day will be set to 0 mL.

For days with bleeding intensity of light bleeding or higher in the UF-DBD, missing AH values will be replaced by the mean value of AH values of the days with the same bleeding intensity. In case there are no AH values with the same bleeding intensity, the mean of the AH values of next higher intensity will be used. In case there is no intensity higher than bleeding intensity of the missing AH values available, either, no replacement for the missing AH values will be done for such days; but if there at least one such day occurs within the respective 28 days of treatment for a subject, the subject will be considered as not having amenorrhea.

Furthermore, the last days under treatment with at least 28 days with non-missing bleeding intensity/AH values under treatment until the initial bleeding episode when the treatment started (after the imputations above) (without missing information: Days 57 to 84 under treatment) will be used to calculate the primary variable. After these imputations a subject will be considered as not having amenorrhea in the presence of missing AH values if the sum of all non-missing AH values is not lower than 2 mL or if for missing AH values the bleeding intensity in the UF-DBD is light or higher, otherwise the subject will be considered as having amenorrhea. Sensitivity analyses will be conducted to evaluate the impact of missing data. These will be described in the SAP.

New text:

For the primary efficacy variable and secondary efficacy variables included in the testing strategy described in section 10.3.2.2 it is assumed that data measured with the AH method will be only available on days when vaginal bleeding occurred. To differentiate missing AH data and days without vaginal bleeding the bleeding intensity collected in the UF-DBD will be used.

Missing bleeding data in the subject diaries will be imputed. For the UF-DBD, the worst case approach will be used for missing bleeding intensity for the single or two consecutive missing days (ie, the maximum of the bleeding intensities of the day before and the day after the missing day[s] will be assumed).

If an endometrial biopsy was conducted during the time period under treatment, bleeding on the day of biopsy and the 3 days thereafter will not be considered as day(s) with bleeding/spotting and the AH value will be set to 0 mL. For the primary efficacy variable amenorrhea and the secondary efficacy variable HMB response, subjects will be defined as not having amenorrhea/ not being a HMB responder if they did not complete at least 8 weeks of treatment. Generally, in case a daily bleeding intensity is recorded with the UF-DBD as "no vaginal bleeding" or "spotting", the missing AH value for this day will be set to 0 mL.

For days with bleeding intensity of light bleeding or higher in the UF-DBD, missing AH values will be replaced by the mean value of AH values of the days with the same bleeding intensity. In case there are no AH values with the same bleeding intensity, the mean of the AH values of next higher intensity will be used. In case there is no intensity higher than the bleeding intensity of the missing AH values available, either, no replacement for the missing AH values will be done for such days; but if there at least one such day occurs within the respective 28 days of treatment for a subject, the subject will be considered as not having amenorrhea/ not being a HMB responder.

Furthermore, the last days under treatment with at least 28 days with non-missing bleeding intensity/AH values under treatment until the initial bleeding episode when the treatment started (after the imputations above) (without missing information: Days 57 to 84 under treatment) will be used to calculate the primary efficacy variable and the secondary efficacy variable HMB response. After these imputations a subject will be considered as not having amenorrhea in the presence of missing AH values if the sum of all non-missing AH values is not lower than 2 mL or if for missing AH values the bleeding intensity in the UF-DBD is light or higher, otherwise the subject will be considered as having amenorrhea. An equivalent approach as described for the amenorrhea rate will be applied for the secondary variable HMB response, ie, after the imputations as described above a subject will be considered as not being a HMB responder in the presence of missing AH values if the sum of all non-missing AH values is ≥80.00 mL or the reduction of blood loss is ≤50% as compared to baseline or if for missing AH values the bleeding intensity in the UF-DBD is light or higher, otherwise the subject will be considered as a HMB responder.

For the secondary variables onset of amenorrhea and onset of controlled bleeding the first 28 days with non-missing bleeding/AH values until the last 28 days with non-missing bleeding/AH values under treatment will be considered. An analogous approach as described

above for the primary efficacy variable and the secondary efficacy variable HMB response will be applied to assess the bleeding status for each of these 28-day windows in terms of amenorrhea and controlled bleeding. If a subject does not achieve amenorrhea or controlled bleeding until end of treatment the subject will be considered as censored for the respective endpoint.

Sensitivity analyses will be conducted to evaluate the impact of missing data. These will be described in the SAP.

15.1.2.27 Section 10.4 Determination of sample size

Old text:

Assumptions for sample size calculations are based on the ASTEROID 1 study (Study 15788) with treatment duration of 12 weeks ~~and take into account scientific advice from Health Authorities~~.

In ASTEROID 1, amenorrhea rates (defined as MBL <2 mL during last 28 days of treatment) of about 0.7, 0.9, and 0.9 for vilaprisan 2 mg and of about 0.2, 0.0, and 0.1 for placebo for the regions US/Japan/European Union and Canada were observed with differences between vilaprisan 2 mg and placebo of about 0.5 to 0.9.

~~Based on scientific advice by FDA an analysis will be required in which certain groups of patients are counted as treatment failures (patients who did not adequately fulfill selection criteria; patients who require fibroid surgery during study participation).~~

Taking these aspects into account, a difference of at least 0.4 between vilaprisan and placebo is assumed after 12 weeks and 24 weeks. Sample size calculation is further based on a balanced randomization scheme of 1:1:1:1 (A1:A2:B1:B2), a power of 0.9 for the study (ie, higher for each individual test), and the application of the two-sided Cochran-Mantel-Haenszel test (stratified by region/country) to a 0.05 significance level.

Assuming a dropout rate of about 20%, the number of subjects to be randomized into the study is planned to be 260; 65 subjects in each treatment group.

Approximately 50% of subjects are planned to be enrolled from the US.

Based upon the anticipated screen failures rates (60% in the US and 50% in China and in the other countries), about 585 subjects will be enrolled to achieve the planned number of randomized subjects.

PASS version 13.0.11 was used for sample size calculation.

New text:

Assumptions for sample size calculations are based on the ASTEROID 1 study (Study 15788) and the ASTEROID 2 study (Study 17541) with treatment durations of 12 and 24 weeks.

In ASTEROID 1, amenorrhea rates (defined as MBL <2 mL during last 28 days of treatment) of about 0.7, 0.9, and 0.9 for vilaprisan 2 mg and of about 0.2, 0.0, and 0.1 for placebo for the regions US/Japan/European Union and Canada, respectively, were observed with differences

between vilaprisan 2 mg and placebo of about 0.5 to 0.9. In ASTEROID 2, similar amenorrhea rates were observed with numerical variation between the treatment periods. HMB response rates in the last 28 days amounted to percentages above 90% for vilaprisan 2 mg and 33% or lower for placebo. Median onset of amenorrhea was reached on day 6 after start of treatment for vilaprisan 2 mg. Due to the low number of subjects achieving amenorrhea until the end of placebo treatment, no median onset of amenorrhea could be calculated for placebo. Onset of controlled bleeding was reached on day 2 after start of treatment for vilaprisan 2 mg. Again, as for onset of amenorrhea, no median onset of controlled bleeding could be calculated for placebo due to the low number of subjects achieving controlled bleeding until the end of placebo treatment. At the end of treatment controlled bleeding was reported for about 97% of subjects for vilaprisan 2 mg and for 49% of subjects for placebo, respectively.

Taking these aspects into account, a difference in amenorrhea rates of at least 0.4 between vilaprisan 2 mg and placebo is assumed after 12 weeks and 24 weeks. Sample size calculation is further based on a balanced randomization scheme of 1:1:1:1 (A1:A2:B1:B2), an overall power of 0.9 for the study (ie, higher for each individual test), and the application of the two-sided Cochran-Mantel-Haenszel test for the primary variable and the secondary variable HMB response as well as the logrank test for the secondary variables onset of amenorrhea and onset of controlled bleeding (stratified by region/country), each to a local 0.05 significance level.

Assuming a dropout rate of about 20%, the number of subjects to be randomized into the study is planned to be 260; 65 subjects in each treatment group.

Approximately 50% of subjects are planned to be enrolled from the US (based on feedback from the FDA).

Based upon the anticipated screen failures rates (60% in the US and 50% in China and in the other countries), about 585 subjects will be enrolled to achieve the planned number of randomized subjects.

PASS version 13.0.11 was used for sample size calculation.

16. Appendices

16.1 Strong CYP3A4 inhibitors

Table 16—1: Strong CYP3A4 inhibitors

Substance name	Inhibitor strength
Boceprevir	Strong
Clarithromycin	Strong
Grapefruit juice	Depend on dose: Moderate or strong
Cobicistat	Strong
Conivaptan	Strong
Idelalisib	Strong
Indinavir	Strong
Itraconazole	Strong
Ketoconazole	Strong
Lopinavir	Strong
Mibefradil	Strong
Miconazole	Strong
Nefazodone	Strong
Nelfinavir	Strong
Posaconazole	Strong
Ritonavir	Strong
Saquinavir	Strong
Telaprevir	Strong
Telithromycin	Strong
Tipranavir	Strong
Voriconazole	Strong

16.2 Strong CYP3A4 inducers

Table 16—2: Strong CYP3A4 inducers

Substance name	Inducer strength
Phenobarbital	Strong
Avasimibe	Strong
Carbamazepine	Strong
Enzalutamide	Strong
St. John’s Wort (Hypericum)	Strong
Lumacaftor	Strong
Methylphenobarbital	Strong
Mitotane	Strong
Phenytoin	Strong
Rifampicin	Strong
Rifamycin	Strong