Document Type:	Study Protocol
Official 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
NCT Number:	NCT03400943
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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
- **Amendment 03** (global amendment described in Section 15.2)
  forming integrated protocol Version 3.0, dated 04 JUL 2018
- **Amendment 04 (**global stand-alone amendment described in Section 15.3)
  forming global protocol Version 4.0, dated 11 DEC 2018
- **Amendment 05** (global amendment described in Section 15.4)
  forming integrated protocol Version 5.0, dated 21 NOV 2019
- **Amendment 06** (global amendment described in Section 15.5)
  forming integrated protocol Version 6.0, dated 17 FEB 2020

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:	17 FEB 2020
Registration:	EudraCT: 2017-002997-38	Version no.:	6.0
Sponsor's study no.:	15787		
Sponsor:	Non-US territory: Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer HealthCare Pharmaceuticals, Inc. 100 Bayer Boulevard, PO Box 915, Whippany, NJ 07981-0915, US		
Sponsor's medical expert:	PPD Bayer U.S. LLC Pharmaceuticals Study Medical Experts Women's Health 11 Waterview Blvd Parsippany, NJ 07054, USA Tel: PPD Email: PPD		

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: PPD Role: Global Clinical Leader

Date: 17 Feb 2020 Signature: PPD

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. With the implementation of protocol amendment 5 (version 5.0), additional focus will be put on safety evaluations of the endometrium, adrenal glands and skin. 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	**Not any longer applicable due to the closing of the clinical study. With the implementation of protocol amendment 5 (version 5.0) and aligned with the previous temporary pause measures, no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study. Originally, the information and instructions related to the test drug were the following:** 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	**Not any longer applicable due to the closing of the clinical study. With the implementation of protocol amendment 5 (version 5.0) and aligned with the previous temporary pause measures, no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study. Originally, the information and instructions related to the reference drug were the following:** 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	**With the implementation of protocol amendment 5 (version 5.0) and aligned with the previous temporary pause measures, no new subjects will be enrolled in the study.** **Originally, the study population had to fulfill the following criteria:** 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	**With the implementation of protocol amendment 5 (version 5.0) no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study.** **Subjects are not any longer required to document anything in the electronic diary (eDiary).** **Any subjects who have taken at least one dose of study medication (including the subjects who completed the study or were prematurely terminated) will be asked to undergo the safety evaluation procedures described in this document.** Prior to the temporary pause subjects were asked to 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 (Menstrual Pictogram [MP]) in an electronic diary (eDiary). Subjects were to collect the sanitary products used during the study to analyze the volume of blood loss using the AH method. Uterine fibroids were assessed during the study through ultrasound. Patient-reported outcome (PRO) data were 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 were collected using the Clinical Global Impression Investigator (CGI_I). Safety is assessed by the evaluation of adverse events (AEs), laboratory parameters, endometrial biopsies, cervical smears, physical and gynecological examinations including ultrasound, and vital signs. In addition, liver parameters were monitored on a monthly basis during treatment. The (population) pharmacokinetics (PK) and the effect of intrinsic and extrinsic factors on the variability in exposure were assessed by population PK analysis using sparse vilaprisan concentration samples.
Type of control	**Not any longer applicable as with the implementation of protocol amendment 5 (version 5.0) no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study.** Placebo
Number of subjects	**With the implementation of protocol amendment 5 (version 5.0) no new subjects will be enrolled in the study and no subjects will be treated. Any subjects who have taken at least one dose of study medication (including the subjects who completed the study or were prematurely terminated) will be asked to undergo the safety monitoring procedures described in this document.** Based upon the anticipated screen failures rates (60% in the US and 50% in China and the other countries), about 585 subjects were planned to be enrolled to achieve the planned number of randomized subjects. A total of 260 subjects were 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
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 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.

Protocol Amendment Summary of Changes Table

Amendment 6 (17 FEB 2020)

Overall Rationale for the Amendment:

Bayer has decided to close all clinical studies with vilaprisan, which were put on temporary pause in December 2018 (protocol amendment 4, version 4.0) while pre-clinical toxicology findings and their relevance to humans were being further investigated. Although the outcome of Bayer's investigation revealed that the observed pre-clinical findings are regarded to be of limited relevance to the human situation (refer to vilaprisan Investigator's Brochure [IB] version 11.0 including associated amendment and Introduction section), a comprehensive safety follow up will be conducted to provide additional confirmatory evidence. The amendment (protocol amendment 5, version 5.0) introduced measures and processes to prepare this study for an orderly closure, including safety follow up measures in all study participants who received at least one dose of study drug vilaprisan.

Recently Bayer received comments from FDA regarding details of the safety follow-up measures introduced in the protocol amendment 5 (version 5.0). The current amendment (protocol amendment 6, version 6.0) implements these FDA recommendations.

Section # and Name	Description of Major Changes	Brief Rationale
Short summary for sites	Described how subjects will be counseled when test results (e.g., hormone, liver, physical examination) are abnormal but still below the thresholds to trigger outside evaluation in the context of the study.	To address FDA requests
9 Procedures and variables; 9.6.3.4 Physical and gyn. examination	Added text and deleted footnote to Physical examination as this needs to be performed in all subjects.	To address FDA requests
9.6.3.1 Laboratory evaluations	Revised the interval for blood sampling after intake of high doses of biotin from 8 to 72 hours.	To address FDA requests
	Added glycosylated hemoglobin (HbA1c) to the parameters measured for adrenal monitoring also in subjects who have completed or discontinued the study before or during the temporary pause.	To address FDA requests
9.6.3.2.7 Heavy menstrual bleeding / suspicious bleeding pattern	Described that, for comparison of subject's subjective report with documented bleeding pattern and amount of blood loss, bleeding data of UF-DBD, MP, and/or AH method, if available, from the months preceding the safety closeout visit will be used.	To address FDA requests
10.2 Analysis sets	Added clarification that all randomized subjects belong to the FAS, excluding randomized subjects who did not start Treatment Period 1 **due to the study being temporarily on hold.**	To address FDA requests

Short summary for sites:

With the implementation of protocol amendment 5 (version 5.0) no new subjects will be enrolled in the study and no subjects will re-start treatment. All subjects who were randomized and started treatment before the temporary pause will be asked to have the comprehensive safety evaluation (with particular focus on endometrial, adrenal and skin safety) performed. This also applies to subjects who have completed or discontinued the study before or during the temporary pause, provided they have taken at least one dose of study medication.[1]
All these subjects are asked to come to the site for the "Safety closeout visit" which is implemented with amendment 5 (version 5.0). In most cases the procedures scheduled for this safety closeout visit will not take place on the same day. The second scheduled visit, the "Safety result reporting visit" can be done as a telephone visit.

The following procedures are to be performed in the context of the Safety closeout visit; for details please refer to Sections 9.1 and 0:

- Reconsenting the subject
- Documentation of concomitant medication and AEs
- Check for adrenal disorder signs and symptoms, incl. vital signs and body weight
- MRI of adrenal glands
- Dispensation and collection of saliva test tubes
- Referral to dermatology expert
- Physical examination
- Gynecological/breast exam
- Cervical smear
- Urine pregnancy test
- Ultrasound examination
- Endometrial biopsy
- Laboratory (blood sampling)
- Collection of unused study drug and empty drug packs/drug accountability, if applicable
- Collection of eDiary devices and review of bleeding data for unusual bleeding pattern (see Section 9.6.3.2.7)
- Deactivation of the subject on the tablet computer without selecting a particular visit

At the second scheduled visit ("Safety result reporting visit"), the investigator is asked to communicate the results from the safety evaluations to the subject. This can be done as a telephone visit.

Details regarding the safety evaluation procedures and algorithms for identified abnormalities can be found in the respective chapters of this amendment. Test results (e.g., hormone, liver, physical examination) may be abnormal but still below the thresholds to trigger outside

[1] In subjects with exceptional circumstances, e.g., pregnancy, timing of the safety evaluations should be decided case by case.

evaluation in the context of the study. In these cases subjects should at least be counselled about medical follow up according to local practice.

Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.

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List of abbreviations

ACTH	adrenocorticotropic hormone
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
CRF	case report form
CRO	contract research organization
CYP3A4	cytochrome P450 isoenzyme 3A4
DHEA-S	Dehydroepiandrosterone sulfate
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
MRI	magnetic resonance imaging
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
PRAC	Pharmacovigilance Risk Assessment Committee
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
tT	total testosterone
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

With the implementation of protocol amendment 5 (version 5.0) no new subjects will be enrolled in the study and no subjects will receive any further study drug treatment. Any subjects who have taken at least one dose of study medication (including the subjects who completed the study or were prematurely terminated) will be asked to undergo the safety monitoring procedures described in this document.

Based on findings in preclinical carcinogenicity studies in rats and mice all vilaprisan clinical studies were temporarily paused since December 2018. In those carcinogenicity studies, adenocarcinomas of the endometrium and tumors of the adrenal cortex (benign and malignant) were seen in female rats and mice. Furthermore, skin sarcomas were found in female mice at a high exposure, representing 100 times the human therapeutic dose of 2 mg.

Bayer has decided to close all clinical studies with vilaprisan, which were put on temporary pause in December 2018 (protocol amendment 4, version 4.0) while pre-clinical toxicology findings and their relevance to humans were being further investigated. Although the outcome of this investigation revealed that the observed pre-clinical findings are regarded to be of limited relevance to the human situation (IB version 11.0 including the associated amendment and Introduction section), Bayer will conduct a comprehensive safety follow up to confirm this. Amendment 5 (version 5.0) introduced measures and processes to prepare this study for an orderly closure, including safety follow up measures in all study subjects who received at least one dose of study drug.

Amendment 5 (version 5.0) introduced endometrial, adrenal, and skin safety evaluations with the aim to confirm that the carcinogenicity study findings do not translate into an increased risk for subjects when treated with the regimens and doses tested in the current studies.

In conclusion, all ongoing clinical studies with vilaprisan will be closed after implementation of a structured safety follow-up in all exposed subjects which aims to:

- provide certainty to subjects that they leave the study without any concerning finding,
- generate clinical data that will support a thorough analysis of human safety data to confirm the hypothesis that the animal findings are of limited relevance to humans.

While closing the current clinical studies for the reasons explained above, the newly collected safety data will be thoroughly evaluated in addition to the already collected efficacy data.

Further detailed information and assessment of the carcinogenicity study findings are described below and also in the current version (V 11.0 including the associated amendment) of the vilaprisan Investigator's Brochure.

Results from chronic carcinogenicity studies with vilaprisan in rodents (rat and mice)

In preclinical chronic carcinogenicity studies in rats and mice, adenocarcinomas of the endometrium were found. Furthermore, in female rats, benign and malignant tumors of the adrenal cortex were seen. Such tumors were not seen in male rats or in mice. In addition, skin sarcoma (not otherwise specified) were found with increased incidence of statistical significance at the high dose of 60 mg/kg in female mice only. This corresponds to about 100 fold of the daily dose of 2 mg administered in this study. The tumors were derived from various cell lineages and were seen at various anatomical locations. The cause and the relevance of these skin tumors in mice is unclear but based on the high margin of exposure at which these tumors were found, the relevance for humans treated at the intended therapeutic

dose is regarded as limited.

Bayer assessment of human relevance of the observed rodent tumors:

The etiology of the observed endometrial and adrenal tumors is regarded as related to vilaprisan's mode-of-action with species-specific consequences. There was no indication of any direct carcinogenic or direct tumor-promoting effect of vilaprisan, which is non-genotoxic. Male animals did not show any findings and in female animals, effects were limited to reproductive and endocrine organs, with the exemption of the skin sarcomas, where the high margin of exposure suggested limited human relevance. Reasons why the endometrial and adrenal tumors are regarded as of limited relevance in the human setting are described in more detail below:

In the course of these carcinogenicity studies, rats and mice were treated with life-long and uninterrupted doses of vilaprisan leading to much higher unbound exposures compared to the human dose of 2 mg/day. As a consequence, progesterone action was blocked in these animals during their whole life-span. Compatible with this are signs of estrogen dominance that were observed in the aging female rats and mice. Such signs have not been found in clinical trials of vilaprisan in humans. In the carcinogenicity study rodents entered into reproductive senescence during the treatment phase leading to rodent specific endocrine changes resulting under continuous blockade of the progesterone receptor in the formation of tumors in the endometrium and adrenal cortex. The rodent specific endocrinology does not resemble the situation in humans.

Relevant differences between the treatment of humans with vilaprisan and the setting of the carcinogenicity studies in rodents are:

- Female rodents undergo specific endocrine changes during reproductive senescence that do not resemble human menopause, human premenopausal endocrine status or the endocrine situation during vilaprisan treatment.
- Prolonged estrous periods with high estradiol levels occur in rodent reproductive senescence, or a pseudopregnancy state with moderately high estradiol levels. This process takes place due to neurodegeneration on the hypothalamus-pituitary gland and in the presence of follicles in the ovaries which are capable of producing hormones. In the presence of vilaprisan with its strong antagonistic effect on the progesterone receptor this leads to a prolonged, fully unopposed estradiol exposure in the animals. Specifically, in rats, life-long vilaprisan treatment seems to promote prolonged estrous periods with follicular cysts and reduce states of pseudopregnancy, thus further enhancing estrogen dominance.
- Prolonged phases of unopposed estrogen are a recognized risk factor for development of endometrial adenocarcinoma in rodents as well as in humans. However, in contrast to the rodents in the pre-clinical carcinogenicity studies, available clinical data for vilaprisan do not indicate the occurrence of an unopposed estrogen effect on human endometrium. This is supported by the estrogen-lowering effect of vilaprisan shown in the Phase 1 and Phase 2 studies as well as by the morphological features of endometrial histology in humans under vilaprisan treatment which do not seem to indicate a relevant proliferative effect. There was no increased incidence of relevant endometrial pathology (hyperplasias, neoplasms) seen in biopsies taken after up to 12 months of treatment with vilaprisan.

- Furthermore, vilaprisan is administered in treatment regimens with regular breaks for one or two menstrual bleeds, to allow for ovulation, endogenous progesterone production, menstruation, and endometrial shedding (versus life-long continuous treatment in the rodent carcinogenicity study).

With regards to the development of adrenal tumors, a role of estrogen dominance in adrenal stimulation (e.g. hormonal imbalance) is recognized in rodents, whereas in humans adrenal functional disorders and adrenal tumors have a different etiology and are not known to be influenced in a relevant way by unopposed estrogen. In addition, adrenal tumors under vilaprisan treatment occurred only in female rats, but not in mice. Vilaprisan treatment in the chronic monkey study also did not result in any hypertrophic or hyperplastic adrenal changes. In rats there were likely further species-specific contributing factors like pituitary dysregulation and activation of the hypothalamic-pituitary-adrenal (HPA) axis, which was not found in the other tested species.

In conclusion, the combination of a hyperestrogenic background status in reproductive senescence of female rodents (unopposed estrogen effect) with a continuous blockade of progesterone action by vilaprisan is a conclusive mechanistic hypothesis to explain the endometrial and adrenal tumors observed in the rodent carcinogenicity studies. Based on these major differences between rats and humans, the observed findings are most likely to be rodent specific with limited relevance to the human situation.

However, in order to demonstrate endometrial and adrenal safety of repeated intermittent treatment with vilaprisan, study subjects will be carefully monitored.

- A thorough endometrial monitoring program has been part of the vilaprisan studies from the start.
- With the protocol amendment 5 (version 5.0, a robust adrenal safety monitoring program is being implemented in this study as well as in all ongoing vilaprisan studies, to adequately address this new topic in the clinical program.

The cause and the relevance of the skin sarcomas observed in the mouse carcinogenicity study is unclear but based on the high exposure at which these tumors were found, the relevance for humans treated at the intended therapeutic dose is regarded as limited.

Nevertheless, all study subjects who took at least one dose of vilaprisan in any of the currently paused clinical studies will be asked to undergo careful evaluation in order to demonstrate skin safety of repeated intermittent treatment with vilaprisan via a thorough skin examination by a dermatology expert.

Benefit risk assessment

The parameters measured in the context of the endometrial, adrenal and skin monitoring have been aligned with clinical experts and represent a positive benefit risk balance between their ability to detect relevant pathologies and the low procedure related risks associated with them.

These safety measures for subjects participating in the vilaprisan studies intend to ensure that potential tumors or diseases of the uterus, the skin or the adrenal glands are detected. If detected, it is important to understand that these tumors or diseases are not automatically related to the study drug as they can occur in a certain number of women independently of participation in a clinical study and independently of whether vilaprisan was taken as a study drug or not (“background incidence”). These measures can help to detect such findings, probably even at an earlier stage than it would have become apparent otherwise. Furthermore,

the safety measures will generate important data allowing to examine whether vilaprisan has a role in the development of such tumors and diseases.

The safety of short-term treatment with vilaprisan is supported by the available pre-clinical and clinical data. Therefore, it is Bayer's assessment that no acute or long-term risk is expected for the subjects who have been treated in any of the clinical studies performed with vilaprisan.

With regards to efficacy vilaprisan has demonstrated in Phase 1 a dose-dependent ovulation inhibition and induction of amenorrhea in healthy women. Two Phase 2 studies (15788 – ASTEROID 1 and 17541 – ASTEROID 2) 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 subjects' health-related quality of life (HRQoL) and a reduction of fibroid size.

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. With the implementation of protocol amendment 5 (version 5.0), additional focus will be put on safety evaluations of the endometrium, adrenal glands and skin.

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 was applied to Treatment Groups A1, B1, and B2; Treatment Group A2 was open-label.

The study is conducted in the US, Bulgaria, Czechia, China, Israel, Malaysia, New Zealand, Singapore and South Africa.

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

With the implementation of protocol amendment 5 (version 5.0), this study design is no longer valid. No subjects will receive further study drug.

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;., EoT = end of treatment

During the screening period, subjects had 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.

Eligible subjects were 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).Treatment was started as described in Section 7.1.

After the end of the final treatment period, subjects were planned to 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) was 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 were planned to receive active treatment during a part of the study. Treatment Group A2 was open-label because the subjects and the investigators knew the treatment regimen since there was no break between the treatment periods.

Study design valid with the implementation of protocol amendment 5 (version 5.0):

The study was temporarily paused since December 2018. No further subjects will be recruited and none of the enrolled subjects will receive further study drug treatment. All subjects who were randomized and started treatment before the temporary pause will be asked to have a comprehensive safety evaluation (with particular focus on endometrial, adrenal and skin safety) performed. This also applies to subjects who have completed or discontinued the study before or during the temporary pause, provided they have taken at least one dose of study medication.

Efficacy / pharmacodynamic assessments:

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

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

Safety monitoring:

Safety parameters are regularly and closely monitored throughout the study (eg, questioning for adverse events (AEs), measurement of laboratory values, close observation of subjects in case of increased liver parameters, a separate liver symptom questionnaire, i.e. the liver symptom inquiry, vital signs, endometrial thickness, abnormal menstrual bleeding, and size of follicle like structures comprising follicles and functional ovarian cysts). A comprehensive screening program for adrenal tumors and a skin examination by a dermatology expert are implemented with protocol amendment 5 (version 5.0).

Endometrial monitoring

A careful endometrial safety monitoring assessment was applied in this study from the beginning, 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 for the clinical management of endometrial thickening/HMB/abnormal menstrual bleeding pattern (see Section 9.7.2). Highly reliable diagnosis of any findings in the endometrial biopsies is ensured through the involvement of a panel of highly experienced and well renowned expert pathologists who will assess every biopsy sample taken from study subjects.

With protocol amendment 5 (version 5.0), additional requirements for endometrial safety screening are outlined for subjects who took at least one dose of study medication, see Section 9.6.3.2.

Liver monitoring

A liver-related safety signal was observed with some selective progesterone receptor modulator (PRM) compounds which display differences in molecular structure compared to vilaprisan.

Monthly monitoring of liver parameters under treatment was introduced with an earlier version of this protocol (protocol amendment 3, version 3.0). With this protocol amendment (protocol amendment 5, version 5.0), subjects who remained in the study during the temporary pause will receive one further laboratory assessment, including liver parameters.

Adrenal monitoring

A comprehensive adrenal screening program is implemented with amendment 5 (version 5.0). This program is described in more detail in Section 9.6.3.8. It encompasses adrenal imaging, as well as laboratory tests aimed at identifying overproduction of adrenal hormones in the context of tumors of the adrenal cortex. Tumors of the adrenal glands (cortical or medullary in origin, benign as well as malignant) are known to occur in a certain frequency (1) in the general population, independent of an exposure to the study drug vilaprisan. In case adrenal tumors are detected by the screening program in this study, a causal relationship to vilaprisan can therefore not be automatically assumed. However, it is expected that all subjects, irrespective of their exposure to vilaprisan, will benefit from detection of potential adrenal gland disorders through the study monitoring program. All study subjects who took at least one dose of study medication in any of the currently paused clinical studies will be asked to undergo adrenal monitoring in order to demonstrate adrenal safety of repeated intermittent treatment with vilaprisan.

Skin monitoring

In the above-mentioned carcinogenicity studies performed in mice and rats, skin sarcomas were found at a dose representing about 100 times the human therapeutic dose of 2 mg. The tumors were derived from various cell lineages and were seen at various anatomical locations. The cause and the relevance of the skin tumors in mice is unclear but based on the high exposure at which these tumors were found, the relevance for humans treated at the intended therapeutic dose is regarded as limited.

Nevertheless, all study subjects who took at least one dose of study medication in any of the currently paused clinical studies will be asked to undergo a thorough skin examination by a dermatology expert in order to demonstrate skin safety of repeated intermittent treatment with vilaprisan.

Effects related to study conduct

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.

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

No longer valid, since no new subjects will be enrolled in this study with the implementation of protocol amendment 5 (version 5.0). Originally the study population had to fulfill the following criteria:

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 source documents 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 [2] 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)
    - Abnormal liver parameters (presence of at least one of the following criteria, please see also section 9.6.3.1Laboratory evaluations)[3]:
        - 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)
        - Total bilirubin outside the upper limit of normal range[4]
        - International normalized ratio (INR) outside the upper limit of the normal[5]
    - Diagnosis of hepatitis B infection, i.e., Hbs-antigen positive at Visit 1 [6]
    - Diagnosis of hepatitis C infection, i.e., hepatitis C-antibodies and HCV-RNA positive at Visit 1 [7]
    - Chronic bowel diseases, eg, M. Crohn and Colitis ulcerosa

2 As specified in the laboratory manual and in the reports from the central laboratory

3 For the liver-related laboratory parameters ALT, AST, and AP the laboratory test also needs to be repeated if results of the first test at visit 1 are raised above the ULN, but still < 2x ULN (i.e. still within inclusion range). The patient is eligible only if the second test shows a stabilization or decline in those values (see Section 9.6.3.1).

4 As specified in the laboratory manual and in the reports from the central laboratory.

5 As specified in the laboratory manual and in the reports from the central laboratory.

6 This will be applied only to subjects newly enrolled into the study after protocol version 3.0 has become valid

7 This will be applied only to subjects newly enrolled into the study after protocol version 3.0 has become valid

- 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). Ketoconazole and other triazole antifungal drugs are allowed for topical/local use (including vaginal application). 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 [Hypericum], 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 (except endometrioma)
   - 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). For progesterone receptor modulators see next bullet point
   - Previous use of ulipristal acetate, if there were not at least two menstruations after the last intake before Visit 1

- 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 were 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

No longer valid, since with the implementation of protocol amendment 5 (version 5.0) no subjects will start or continue treatment in this study. Originally, the criteria for withdrawal from the study or from the study treatment were the following:

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 (>5%)
- 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

With the implementation of protocol amendment 5 (version 5.0), subjects who do not consent to the updated study design and the additional safety measures will be regarded as “dropouts”.

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”.

Dropout

A subject who discontinues study participation prematurely for any reason (including subjects who do not consent to this protocol amendment which defines safety measures before study closure) is defined as a “dropout” if the subject has already been randomized.
Those subjects who were randomized but never started the study medication will not need to consent to the safety follow up, but will be handled as drop outs after having been informed about the study closure.

Contacting of treated subjects who already left the study

The investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s source document.

General procedures

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

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 was assigned a unique multi-digit SID number by the site for unambiguous identification. The SID number was 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 identified the subject throughout the study.

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

7. Treatments

Instructions in Sections 7.1 to 7.4 are no longer valid, since with the implementation of protocol amendment 5 (version 5.0) no subjects will start or continue treatment in this study.

Originally, the instructions in Sections 7.1 to 7.4 were the following:

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.

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

Forward looking instructions regarding blinding are no longer valid, since with the implementation of protocol amendment 5 (version 5.0) no subjects will start or continue treatment in this study. However, for the subjects randomized in this study before the temporary pause, the blinding will be maintained until database lock.

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

No longer valid, since with the implementation of protocol amendment 5 (version 5.0) no subjects will start or continue treatment in this study and therefore no study medication will be newly distributed. All unused study drug should have been returned during the temporary pause and this should have been documented in the drug accountability section of the eCRF and on the appropriate drug dispensing form by the investigator or designee.

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 were required to complete an electronic Diary (eDiary) daily throughout the study. The date of each study drug intake was tracked via the eDiary. The eDiary was dispensed at Visit 1 and the completeness of the eDiary data 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

All concomitant medications administered after signing of informed consent until the completion of study participation[8], including topical (eg, vaginal) preparations and over the counter drugs are to be recorded in the eCRF (trade name, dose, unit, frequency, route, start and stop dates, and indication). This applies with specific focus for medications that could interfere with the testing of adrenal parameters.

Restrictions regarding forbidden concomitant medications were valid before and during the treatment phase of this study, but were lifted during the treatment-free safety FUP phase that started during the temporary pause and continues with amendment 5 (version 5.0). Please see also Section 6.2.

Subjects who withdrew from study drug and subjects who withdrew during FUP were asked to not take hormonal treatments before the first menstruation after end of treatment (EoT) was 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).

Reasonable efforts should be undertaken to capture such interventions also in subjects who had already left the study and are now returning.

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) consistent with local standards of practice and at the investigator's discretion. Iron supplementation will not be considered a study medication and will be documented as concomitant medication.

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[8] In subjects who have completed or discontinued the study before or during the temporary pause, who are asked to participate in the safety evaluation, the concomitant medication used during the off study period until re-consenting to this protocol amendment should also be recorded in the eCRF.

8.1.2 Progestin therapy for induction of bleeding

If required, subjects were 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.

8.2 Post-study therapy

Before the temporary pause, it was foreseen that subjects completing the treatment periods will participate in the post treatment FUP without drug treatment. According to the rules of the temporary pause, subjects were required to not start any new treatment period and thereby those subjects entered a study drug free FUP phase if they agreed to remain in the study.

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.

9. Procedures and variables

9.1 Tabular schedule of evaluations

No longer valid, since with the implementation of protocol amendment 5 (version 5.0) no subjects will be recruited and none of the enrolled subjects will receive further study drug treatment. All subjects who were randomized and started treatment before the temporary pause will be asked to have the comprehensive safety evaluation (with particular focus on endometrial, adrenal and skin safety) performed. This also applies to subjects who have completed or discontinued the study before or during the temporary pause, provided they have taken at least one dose of study medication. All these subjects are asked to come to the site for the "Safety closeout visit" which is implemented with amendment 5 (version 5.0). The second scheduled visit, the "Safety result reporting visit" can be done as a telephone visit.

This "Safety closeout visit" should be performed in all subjects as soon as possible after implementation of amendment 5 (version 5.0). The following procedures are to be done:

Table 9–1: Schedule of procedures

Visit	Safety closeout visit [a]	Safety result reporting visit (can be a telephone visit)
Timing	After implementation of protocol amendment 5 (version 5.0)	Once all safety results are available
Informed consent	**X**	
Concomitant medications	→	→
AE assessments	→	→
Adrenal disorder signs and symptoms incl. vital signs [b]	**X**	
MRI of adrenal glands [c]	**X**	
Dispense saliva test tubes [d]	**X**	
Collect saliva test tubes	**X**	
Referral to dermatology expert	**X**	
Physical examination	**X**	
Body weight	**X**	
Gynecological/breast exam [e]	**X**	
Urine pregnancy test	**X**	
Cervical smear [f]	**X**	
Ultrasound examination [g]	**X**	
Endometrial biopsy [h]	**X**	
Laboratory (blood) [i]	**X**	
Collection of unused study drug and empty drug packs/drug accountability	**X** if applicable	
Collection of eDiary device and review of bleeding data for unusual bleeding pattern	**X** if applicable	
Deactivation of the subject on the tablet computer without selecting a particular visit	**X**	
Communication of results from safety evaluations to the subject		**X**

a. In most cases the procedures scheduled for this visit will not take place on the same day
b. Blood pressure in triplicates and heart rate after 5 minutes of rest in a sitting position
c. Negative pregnancy test is a prerequisite
d. Saliva tests should be performed as soon as possible after dispense, to allow for a repeat in case of unevaluable results or for review by one of the adrenal experts in case of abnormal results. Saliva test tubes should be returned to site on the next day after samples have been taken on two consecutive days.
e. Only to be performed if subject did not have these performed with normal result after end of treatment
f. Only to be performed if subject did not have this performed with normal or clinically insignificant result after end of treatment
g. The ultrasound must be done before the biopsy
h. Negative pregnancy test is a prerequisite. Only to be performed in subjects who did not have a post-treatment endometrial biopsy (defined as biopsy taken at the earliest 7 days before last study drug intake) with a normal result. This is defined as diagnosis of safety read and of all 3 individual components of the multiread to be “benign endometrium” in Part II of the evaluation form. In addition, the majority diagnosis needs to be “PAEC no” in Part IV of the evaluation form. Furthermore, an endometrial biopsy may also be triggered by results of ultrasound examination or bleeding data (see Section 9.6.3.2.8). The biopsy CRF page needs to be completed for all subjects, including cases where according to protocol no biopsy is required. For subjects with menstrual cycles the endometrial biopsy should be taken between Day 7 to 15 (inclusive) of a menstrual cycle.
i. In subjects who take biotin, the last dose of biotin should be at least 72 hours prior to hormone testing.

AE = adverse event, MRI = magnetic resonance imaging, PAEC = progesterone receptor modulator-associated endometrial changes

9.2 Visit description

No longer valid, since with the implementation of protocol amendment 5 (version 5.0) all subjects will need to come to the site for the safety closeout visit. In most cases the procedures scheduled for this visit will not take place on the same day.

The second scheduled visit, the "Safety result reporting visit" can be done as a telephone visit. During this visit the subject will be informed about the results of the safety investigations. In case follow-up assessments are required, these should be documented as unscheduled assessments.

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. A possible reason for unscheduled visits would be the requirement for follow up investigations.

9.2.2 Optional pre-screening phone contact

No longer valid, since with the implementation of protocol amendment 5 (version 5.0) no new subjects will be recruited.

9.2.3 Scheduled visits

With the implementation of protocol amendment 5 (version 5.0) all subjects who took at least one dose of study medication will need to come to the site for the safety closeout visit. For details regarding this safety closeout visit please see Section 9.1. The second scheduled visit, the "Safety result reporting visit" can be done as a telephone visit.

9.3 Population characteristics

With implementation of protocol amendment 5 (version 5.0) no new subjects will be recruited. This section describes the data collection performed in subjects enrolled before the temporary pause.

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 were collected consistent with the original schedule of procedures in protocol amendment 3 (version 3.0).

9.3.2 Medical history

Medical history findings (ie, previous diagnoses, diseases or surgeries) meeting all criteria listed below were 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 was stabilized by medication at the time of signing the informed consent should also be documented in the eCRF. The medication being used had to be recorded in the prior and concomitant medication eCRF.

All new or worsened findings after signing the informed consent had to 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 could have been used at Visit 1 and the responses could have been entered directly into electronic data capturing system RAVE, which is considered as primary source data. The questionnaire could also have been used as a pre-screening tool. Print outs of the questionnaire were provided to the sites as needed.

9.4 Efficacy

This section details the procedures for collecting efficacy variables. A concise listing of efficacy variables as collected before the temporary pause 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 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 were required to use selected types of sanitary products provided (pads and/or tampons). During the entire duration of the study, subjects were to collect their used sanitary products and return them to the study site as soon as the bleeding episode was completed to be sent to the central laboratory for analysis.

The AH method is 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 (2). 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 was to be reported by day and bleeding episode. This test was performed at the central laboratory. For details refer to the laboratory manual.

9.4.2 Ultrasound (efficacy) to assess uterine fibroids

This section was changed in Amendment 2, see Section 15.1.1

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

Ultrasound examinations were to be performed consistent with the original schedule of

procedures. The 3 largest fibroids were to be identified during the screening period. The largest transverse, longitudinal, and antero-posterior diameters of these 3 fibroids were to be documented at each efficacy ultrasound examination for volume calculation.

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

The minimum source documentation included electronic or paper documentation from the ultrasound machine showing the 3 largest fibroids. The printouts had 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 has to 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

With the implementation of protocol amendment 5 (version 5.0) no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study. This section describes processes performed in subjects enrolled before the temporary pause.

9.5.1 Drug measurements

Blood samples for measurement of vilaprisan in plasma for PK were to be collected at the time points given in the original schedule of procedures. At Visit 5, the PK sample was to be taken predose. At Visit 6, 3 PK samples were to be taken. The first sample was to be taken before intake of study drug. After the predose sample was taken at Visits 5 and 6, the subject should have taken her study drug under supervision at the site. The second sample at Visit 6 was to be taken 0.5 to 1 hour after drug intake and the third sample was to 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 had to be documented in the eCRF.

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

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

If a subject discontinued study treatment permanently, no blood sampling for PK was required. Pharmacokinetic analyses are based on a population modeling approach (see Section 9.5.2). Blood samples are 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 were to 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 are determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS). Quality control (QC) and calibration samples are 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 the initial 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 the initial 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).
- In subjects who completed or discontinued before or during the temporary pause and now get reconsented conditions that newly occurred or worsened during the off-study period should be documented as AEs.

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 and/or as defined below

All instances of liver parameter testing which meet the criteria for withdrawal defined in the original study protocol (see section 6.4.1) of a subject from the study should be reported as SAEs.

Endometrial biopsies with a safety read diagnosis of "simple or complex atypical hyperplasia" (according to WHO 1994 criteria) or "EIN" (according to WHO 2014 criteria) (3) or with a diagnosis of "malignant neoplasm" ("endometrial" or "other") should be reported as a serious adverse event. The subsequent multi-reader assessment should trigger a follow-up report and an update of the diagnosis should be considered, if the majority assessment is different from the initial safety read diagnosis.

Endometrial biopsies with a majority diagnosis based on the multi-reader assessment of "simple or complex atypical hyperplasia" (according to WHO 1994 criteria) or "EIN" (according to WHO 2014 criteria) or in a diagnosis of "malignant neoplasm" ("endometrial" or "other") should be reported as a serious adverse event or trigger an update of the respective initial SAE report.

An adrenal tumor needs to be reported as an SAE.

Any dermatology expert´s diagnosis of a malignant skin lesion, including cutaneous sarcoma confirmed by biopsy diagnosis, needs to be reported as an SAE.

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 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 of the informed consent, and will end with the last visit. After the Safety result reporting visit there is no requirement to actively collect new AEs.

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. For adverse events of special safety interest efforts should be made to follow them up until resolution or stabilization (even after the Safety result reporting visit, if applicable).

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 9.7.2.

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. Adverse events from the following areas should be considered for reporting as AESI according to the following guidance:

- HMB (especially 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 Section 9.7.3).
- Liver disorders:
  - For all cases which qualified for "close observation" before implementation of amendment amendment 5 (version 5.0) and/or qualify for "ruling out of alternative cause" after approval of amendment 5 (version 5.0) (see Section 9.6.3.9), the underlying event should be recorded as AESI in the AE eCRF.
- Endometrial disorders:
  - Endometrial hyperplasia (all subcategories according to WHO 2014 [and WHO 1994] classification), for monitoring and FUP see Section 9.6.3.2
  - 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.
- Skin disorders:
  - Any dermatology expert´s diagnosis of a pre-cancerous or malignant skin lesion, including cutaneous sarcoma confirmed by biopsy diagnosis, qualify as an AESI. Malignant skin lesions should be reported as an SAE to ensure timely reporting to regulatory agencies.
- Adrenal disorders
  - A robust adrenal safety monitoring program has been implemented in all ongoing vilaprisan studies, including MRI of the adrenal glands, laboratory parameters, and evaluation of signs and symptoms indicative of adrenal disorder. A systematic approach of assessment and evaluation of adrenal gland findings will be applied as described in Section 9.6.3.8. Any adrenal abnormality assessed as relevant by either the adrenal gland expert or the local specialist will need to be documented as an AESI and to be reported to the sponsor's pharmacovigilance department following the same standard process (reporting timelines, AE CRF and AE complementary pages) as serious AE. Tumors of the adrenal glands (diagnosed by the MRI central read, the adrenal gland expert or the local specialist) should in addition be reported as SAEs to ensure timely reporting to regulatory agencies.

Progesterone receptor modulator-associated endometrial changes (PAEC) will be assessed and documented in a systematic way (see Section 9.6.3.2.5). 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 Section 9.7.3), endometrial hyperplasia and endometrial thickening (see Sections 9.7.2 and 9.7.4), and liver parameters.

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

Any planned pregnancy should be postponed until the end of the study. This was to be discussed with the subject at screening. If an investigator became aware that a subject wished to conceive or planned an insemination directly after EoT (thereby deviating from study protocol), subject should have been made aware that she is participating in a clinical study with a new drug in early clinical development. Therefore she should preferably have completed 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.

In subjects who are currently pregnant or lactating, timing of the safety evaluations required in the context of the safety closeout visit should be decided case by case.

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 was detected before initiation of study drug, the subject was not to 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 was 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 following parameters will be assessed at the safety closeout visit in subjects who remained in the study during the temporary pause:

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

Hemoglobin (Hb concentration)

Serum chemistry: creatinine, chloride, potassium, sodium, calcium, total protein, albumin, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, ALT, AST, AP, gamma-glutamyl transpeptidase (γ GT), and total bilirubin (in case the result is > 2xULN, conjugated and unconjugated bilirubin will be determined).

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

Biochemistry: glycosylated hemoglobin (HbA1c) and ferritin.

Additional parameters[9]**:** hormones (follicle-stimulating hormone [FSH], luteinizing hormone [LH], estradiol [E2], progesterone [P], prolactin, and thyroid-stimulating hormone [TSH]), and vitamin D (serum 25-hydroxyvitamin D).

In case of elevated liver enzymes requiring investigation of alternative cause the following parameters will have to be determined (in earlier CSP versions this was summarized in a particular section "close observation"): Serum chemistry panel (see above), A1AT level, conjugated bilirubin, ceruloplasmin, cholinesterase, CK, ferritin, full blood count (incl. eosinophilia), hemoglobin, INR, iron, LDH, platelets, PT, total iron binding capacity (TIBC), testing to rule out Hepatitis A-, Hepatitis B-, Hepatitis C, Hepatitis E-, Cytomegalo-, Epstein-Barr-, and Herpes simplex virus infection, brucellosis, leptospirosis, and toxoplasmosis, ANA/ANCA screening with further tests depending on result and IgA, IgG, and IgM, potentially also testing to rule out Hepatitis D.

Parameters measured for adrenal monitoring:

- serum cortisol (to be measured between 6 am and 10 am)
  - ACTH will be assessed from the same sampling if the cortisol measurement yields an abnormal value.
- late night salivary cortisol (to be obtained between 11 PM and midnight)
- Serum dehydroepiandrosterone sulfate (DHEA-S)
  - the age-specific DHEA-S ratio (derived by dividing the subject's DHEA-S value by the lower limit of the age-specific reference range) will be calculated. In case of an abnormal DHEA-S ratio ACTH will be assessed from the sample taken for serum cortisol measurement.
- serum total testosterone (tT)
- serum glucose measurement under fasting conditions
- serum potassium.

The following parameters will be assessed at the safety closeout visit in subjects who have completed or discontinued the study before or during the temporary pause:

- estradiol
- vitamin D (serum 25-hydroxyvitamin D)
- **Parameters measured for adrenal monitoring:**
  - serum cortisol (to be measured between 6 am and 10 am)
    - ACTH will be assessed from the same sample if the cortisol measurement yields an abnormal value.
  - late night salivary cortisol (to be obtained between 11 PM and midnight)

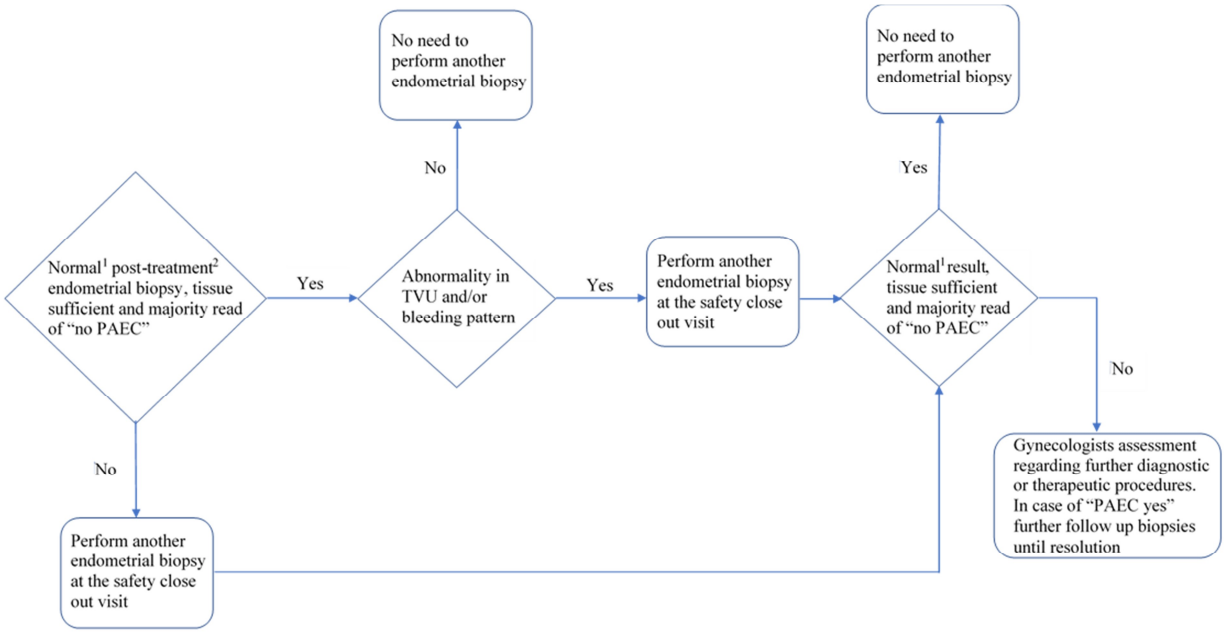
[9] Blood samples should be taken at least 72 hours after the intake of high doses of biotin, since the laboratory results of ferritin, TSH, FSH, LH, estradiol, prolactin, progesterone, cortisol, ACTH and β-CTx may be affected, if the subject had a biotin intake at a concentration higher than 5 mg per day which occurred less than 72 hours before the sample is taken

- serum dehydroepiandrosterone sulfate (DHEA-S)
  - the age-specific DHEA-S ratio (derived by dividing the patient's DHEA-S value by the lower limit of the age-specific reference range) will be calculated. In case of an abnormal DHEA-S ratio ACTH will be assessed from the sample taken for serum cortisol measurement.
- serum total testosterone (tT)
- serum glucose measurement under fasting conditions
- serum potassium
- glycosylated hemoglobin (HbA1c).

9.6.3.2 Endometrial biopsies

9.6.3.2.1 Algorithm for endometrial biopsy evaluations

Figure 9–1: Overview of the endometrial safety monitoring algorithm



1 Normal is defined as: Diagnosis of safety read of all 3 individual components of the multiread needs to be "benign endometrium" in Part II of the evaluation form. In addition, the majority diagnosis needs to be "PAEC no" in Part IV of the evaluation form.
2 Post-treatment is defined as biopsy taken at the earliest 7 days before last study drug intake. For subjects with menstrual cycles the endometrial biopsy should be taken between Day 7 to 15 (inclusive) of a menstrual cycle.
PAEC = progesterone receptor modulator-associated endometrial changes, TVU = transvaginal ultrasound

9.6.3.2.2 Timing of last endometrial biopsies

Each subject should have an endometrial biopsy with a normal[10] result documented from a timepoint taken at the earliest 7 days before last study drug intake. For subjects with menstrual cycles the endometrial biopsy should be taken between Day 7 to 15 (inclusive) of a menstrual cycle.Subject who did not have such a biopsy before or during the temporary pause or those who have an abnormality in TVU and/or bleeding pattern are required to undergo an endometrial biopsy at the safety closeout visit.

This also applies to subjects who started treatment and have completed or discontinued the study before or during the temporary pause. The investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.

The biopsy CRF page should be filled out for every subject at the safety closeout visit. This also applies to subjects who do not require a new biopsy according to the guidance above. The CRF page allows to capture the reason why a biopsy was not done.

Depending on the result of this last biopsy repeat unscheduled endometrial biopsies should be performed in addition. See Sections 9.6.3.2.1 and 9.6.3.2.8 for details.

9.6.3.2.3 Sampling of endometrial biopsies

All endometrial biopsies must be collected by a gynecologically well experienced physician.

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.

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).

9.6.3.2.4 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, i.e. safety assessment

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[10] Normal is defined as: Diagnosis of safety read of all 3 individual components of the multiread needs to be "benign endometrium" in Part II of the evaluation form. In addition, the majority diagnosis needs to be "PAEC no" in Part IV of the evaluation form.

and multi-reader assessment. In cases where an abnormality, e.g. atypia or malignancy, cannot be ruled out, readers will select the most severe diagnosis:

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:

- 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
- A repeat endometrial biopsy will be requested, if sample is inadequate for evaluation in the safety assessment.
- For follow-up of biopsies with abnormalities see Section 9.6.3.2.5.

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.

A majority consensus diagnosis of the multi-reader assessment is derived from the individual diagnoses of the pathologist panel (single-reader diagnoses), according to pre-specified rules. In the absence of a majority consensus, the most severe diagnosis is used. The derived diagnosis resulting from these rules will be used for primary analysis of endometrial biopsy data. The individual diagnoses of each reader will be captured in addition.

Starting with Protocol Amendment 5 (version 5.0), the majority diagnosis of the multi-reader assessment including the single reader assessments (part II of the evaluation form, i.e. the diagnosis of either benign endometrium, endometrial hyperplasia or malignant neoplasm) will be communicated to the study sites once the majority consensus diagnosis is available.

A repeat endometrial biopsy will be requested, if sample is inadequate for evaluation in the majority multi-reader assessment.

For follow-up of biopsies with abnormalities see Section 9.6.3.2.5.

Besides standard safety criteria (e.g., proliferative/secretory/atrophic endometrium, endometrial hyperplasia, malignant neoplasm) the pathologists will document the presence of PAEC (see Section 9.6.3.2.6). The results of the PAEC assessment are not reported back to the investigators except if in the last biopsy within the study, PAEC is still present and further biopsy sampling is needed.

The main study analysis will be based on the majority diagnosis of the multi-reader assessment. An analysis of single-reader diagnoses that is more severe than the majority diagnosis will be provided in the Study Report.

While the relevant diagnosis for study purposes is the majority result of the multi-reader assessment, any single reader diagnosis that is more severe than the majority diagnosis, should be evaluated by the investigator (or by a gynecologist in case the investigator or sub-investigator is not specifically trained in gynecology) for the necessity of therapeutic interventions. The minimal diagnostic requirement for those cases is a follow up biopsy. For all follow-up examinations and/or therapeutic interventions all efforts should be taken that

these examinations are conducted according to the standards of this protocol (e.g. biopsies should undergo multi-reader assessment) and are documented within the study framework.

9.6.3.2.5 Follow-up of endometrial biopsies with abnormalities

Endometrial biopsies with a safety-reader diagnosis (Part II of the evaluation form) other than "benign endometrium" (i.e. "Malignant neoplasm", "Endometrial Hyperplasia" with or without atypia) should undergo an expedited multi-reader assessment. If an expedited multi-reader assessment is not possible (e.g. due to sample export regulations), follow-up procedures will be decided based on the safety-reader diagnosis.

Endometrial biopsies with a multi-reader majority diagnosis (Part II of the evaluation form) other than "benign endometrium" (i.e. "Malignant neoplasm", "Endometrial Hyperplasia" with or without atypia) should be followed-up according to investigator[11] assessment, i.e., either by performing endometrial biopsies until resolution (i.e. until a follow-up biopsy shows a majority diagnosis of "Benign endometrium") and/or by performing a therapeutic intervention as per local standard of care.

The timing of follow-up biopsies and/or possible therapeutic interventions according to local standard of care will be determined by the investigator (or by a gynecologist in case the investigator or sub-investigator is not specifically trained in gynecology) according to the observed abnormality. Typically, at least one endometrial shedding should have occurred before a follow-up biopsy is performed.

The follow-up biopsies should be performed within the study framework and analyzed by blinded multi-reader assessment. In case follow-up biopsies and/or other interventions are conducted at non-study sites, all efforts should be taken that results are obtained and documented appropriately.

For FUP of a majority diagnosis of "Benign endometrium – PAEC yes" please see Section 9.6.3.2.6.

For reporting of abnormal biopsy results as adverse event of special interest or SAE, please see Sections 9.6.1.1 and 9.6.1.6.

9.6.3.2.6 Follow-up of PAEC

Besides standard diagnostic criteria (i.e., proliferative/secretory/atrophic endometrium, endometrial hyperplasia) presence of PAEC will be analyzed in all endometrial biopsy samples as part of the multi-reader assessment. 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 subjects 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.

If PAECs have been detected in the biopsy at the last visit before leaving the study according to the majority diagnosis resulting from the multi-reader assessment, the site will be informed and an additional 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, with the timepoint of this additional biopsy to be determined case-by-case. If needed, more than

[11] or by a gynecologist in case the investigator or sub-investigator is not specifically trained in gynecology.

one repeated biopsy may be taken and analyzed, except for cases with PAEC already present in the pre-treatment biopsy.

9.6.3.2.7 Heavy menstrual bleeding / suspicious bleeding pattern

The study drug was administered in a study population with symptomatic heavy menstrual bleeding. The study drug itself leads to changes in bleeding pattern, mostly amenorrhea during treatment, but can also be associated with intermittent spotting or mild intermittent bleeding of short duration. Heavy menstrual bleeding is expected to return in the FUP phase after cessation of treatment.

Because unusual bleeding patterns or unusually heavy menstrual bleeding can also be a sign of endometrial pathology, the subject should be instructed to report changes in bleeding pattern or bleeding volume that seem unusual to her (and does not resemble the subject´s natural cycle or bleeding pattern). In case such unusual bleeding events are reported or are detected from the AH, MP or UF-DBD the subject should undergo immediate evaluation by the investigator.

Standard criteria for subjects with unusual HMB or bleeding pattern identified from review of bleeding data or reports by the subject during the temporary pause

As guidance the following occurrences should be considered for further evaluation in the context of unusual bleeding:

- Prolonged bleeding:
  Evaluation should be initiated if
  - Prolonged bleeding is reported by the subject and/or
  - the subject entered more than 10 consecutive days of bleeding in the e-diary (intensity of "mild" or more) with a maximum of 2 non-bleeding days in between.
- Continuous spotting:
  Evaluation should be initiated if
  - Continuous spotting is reported by the subject and/or
  - the subject entered more than 10 consecutive days of spotting in the e-diary with a maximum of 2 non-spotting days in between.
- Unusual heavy bleeding:
  Evaluation should be initiated if
  - Unusually heavy bleeding is reported by the subject and/or
  - If blood loss per bleeding episode is more than 50% higher than the subject´s baseline blood loss (when observed via the menstrual pictogram or alkaline hematin method).

Evaluation plan for subjects with unusual HMB or new onset bleeding pattern

The evaluation should include the following assessments:

- Comparison of subject's subjective report with documented bleeding pattern and amount of blood loss (UF-DBD, MP, and/or AH method, if available from the months preceding the safety closeout visit).
- Unscheduled ultrasound

- In case of HMB or prolonged bleeding, unscheduled blood sample to assess for anemia
- Possible contributing factors (eg, new concomitant medication, variability of disease, perception of increased HMB after period of amenorrhea)

An unscheduled endometrial biopsy should be conducted in case of

- Endometrial thickness (double layer) > 18 mm and/or
- Clinical suspicion of relevant endometrial pathology

Further follow-up measures will be determined by the outcome of the endometrial biopsy (see Section 9.6.3.2.5).

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), if needed, an appropriate treatment as per local standard of care (eg, curettage) is to be performed.

9.6.3.2.8 Unscheduled endometrial biopsy

Unscheduled endometrial biopsies can result from the requirement to follow-up on abnormal results of a previous biopsy, see Section 9.6.3.2.5. In addition, also the following two findings trigger unscheduled biopsies:

- In case of increased endometrial thickness (>18 mm)
- Work up of suspicious bleeding pattern as described.

For unscheduled biopsies triggered by increased endometrial thickness or unusual bleeding events, the following procedure applies, depending on the result of the unscheduled endometrial biopsy:

- Normal result of the endometrial biopsy: unscheduled ultrasound examination after about 4 weeks and close follow up of bleeding pattern. If endometrial thickness remains above 18 mm and/or unusually heavy bleeding occurs further procedures should be performed according to local medical practice and as defined in Section 9.6.3.2.7.
- For procedures in case of an abnormal result of the unscheduled biopsy, please see Section 9.6.3.2.5.

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 safety closeout visit in subjects who did not have this performed with normal result after end of treatment. 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 will be done in all subjects. Gynecological examinations, including breast palpation, will be performed in subjects who did not have this performed with normal result after end of treatment. 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

Vital signs (blood pressure in triplicates and heart rate) should be documented at the safety closeout visit. Blood pressure should be measured in triplicates after 5 minutes of rest, while the subject is sitting. Measurements should be made at least 1 minute apart using the same arm at each visit and should be recorded on the eCRF. Body weight will be determined once again at the safety closeout visit.

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 the safety closeout visit: 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 9.7.5.

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 9.4.2.

9.6.3.7 Contraception and pregnancy test

With the implementation of protocol amendment 5 (version 5.0) no further restrictions apply to the use of contraception. New placement of intrauterine devices should only happen once it is clear that no further biopsies are needed. At safety closeout visit a urine pregnancy test will be performed at the study site. A pregnancy test must also be performed in case of any further repeat of an endometrial biopsy.

Any pregnancies during the study and during the off study period in subjects who return for the safety closeout visit must be reported as detailed in Section 9.6.2.

9.6.3.8 Adrenal monitoring

A robust adrenal safety monitoring program is implemented in all ongoing vilaprisan studies with this protocol amendment.

A plan for subjects showing adrenal neoplasms or hormonal abnormalities has been developed with the input of external endocrinology experts, see Adrenal monitoring algorithm below.
A panel of three external clinical adrenal gland experts has been set up, that will support and guide further evaluations and/or referral to local specialists in case an abnormality is detected in a study subject. The assessment by the experts will be performed in 2 steps:

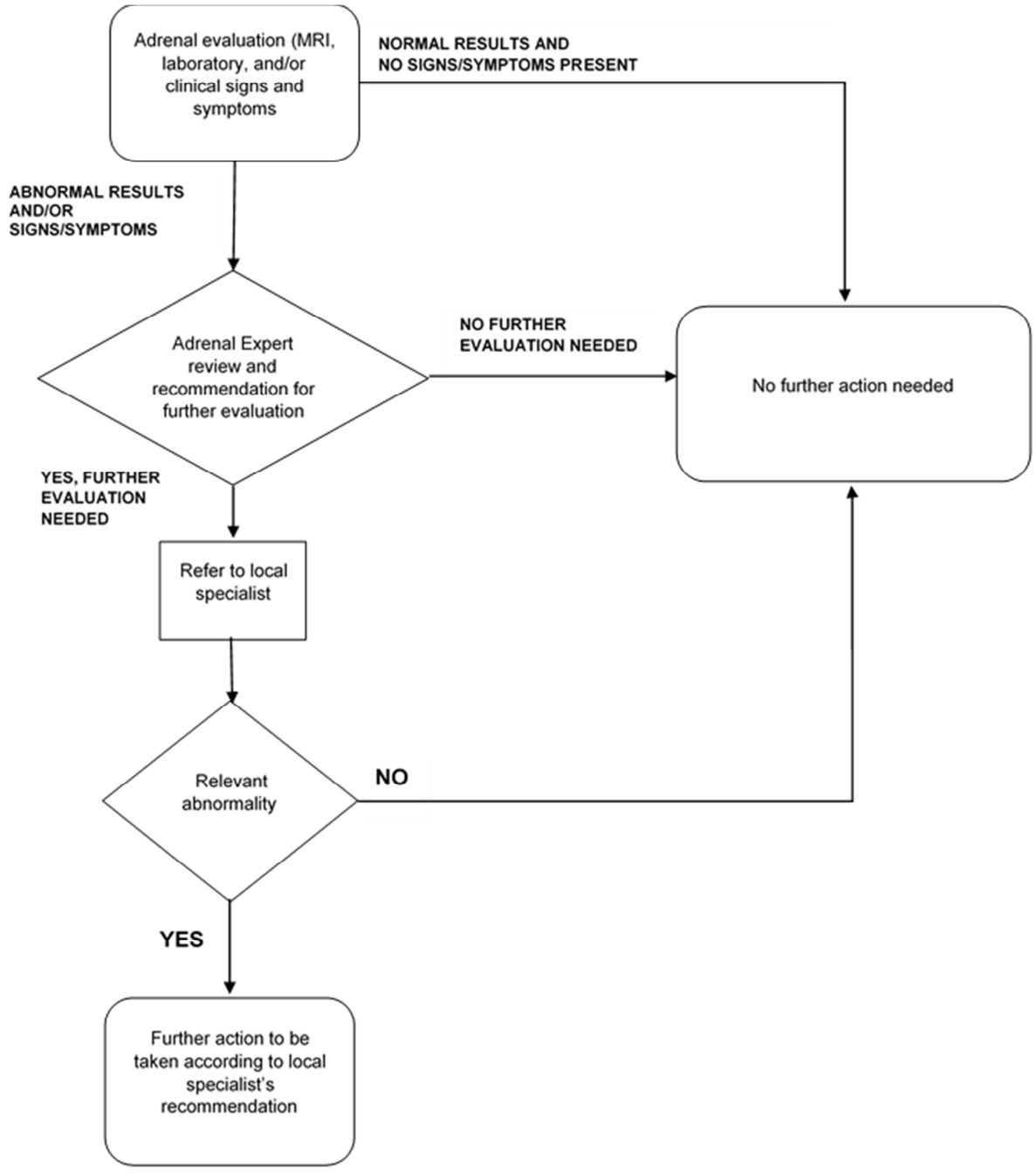
- A safety assessment of cases showing abnormalities will be performed by one of these experts. The results of this assessment will be available in time to document
    - Any relevant finding that requires further diagnostic or therapeutic measures according to local medical practice
    - Absence of clinically relevant adrenal findings before the subject discontinues from the study.

In case of a local specialist consult, the work-up and results will be captured in a dedicated CRF page.

- In addition, the expert panel will perform a central evaluation of all cases after the outcome of the local specialist referral or other evaluations is available. The panel will meet once a sufficient number of cases is available to perform a comprehensive data analysis by using uniform diagnostic standards and classifications (see also Adrenal Monitoring Manual).

The further details of adrenal monitoring are described in the Adrenal Monitoring Manual.

Figure 9–2: Adrenal monitoring algorithm



MRI = magnetic resonance imaging

9.6.3.8.1 Timing of adrenal monitoring

Subjects will undergo scheduled adrenal monitoring at the safety closeout visit.

Signs and symptoms possibly related to hypercortisolism (such as Cushing's syndrome, and hirsutism/virilization) or hyperaldosteronism will be documented on a dedicated CRF page (see Section 9.6.3.8.4).

Adrenal monitoring also needs to be performed in subjects who started treatment and have completed or discontinued the study before or during the temporary pause. After re-consenting, data related to adrenal monitoring and their results are to be documented in the CRFs, and if applicable, same applies to any related AEs and respective concomitant medications. The investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.

9.6.3.8.2 Adrenal MRI

Non-contrast-enhanced (native) MRI will be implemented as the standard adrenal imaging modality. Due to the associated radiation exposure, non-contrast-enhanced (native) CT scan is permitted as an alternative option only if an MRI is not feasible, e.g., due to a subject having a contraindication to MRI or a site has no access to MRI. Further details on the procedures of the image acquisition and reading process will be provided in a separate Imaging Manual.

The images will be evaluated by two central readers with an established adjudication process in case of discrepant results. Abnormalities indicative of an adrenal tumor or of any other relevant adrenal disorder need to be further evaluated (for details see Section 9.6.3.8 and Adrenal monitoring algorithm above). During the central review process, the independent reader may detect clinically significant pathological imaging findings that are not part of the primary review purpose, i.e., evaluating the adrenal glands. If deemed relevant, these incidental findings will be reported to GCIS at the discretion of the readers. GCIS will forward the incidental finding report to the study team, who will then inform the principal investigator.

Any procedure-related complaints will be documented as AEs.

9.6.3.8.3 Laboratory testing

Adrenal monitoring:

- Serum cortisol, to be measured between 6 am and 10 am
  - ACTH will be assessed from the same sample if the cortisol measurement yields an abnormal value.
- Late night salivary cortisol (to be obtained between 11 PM and midnight)
  Subjects will be instructed to use the specifically provided saliva test tubes on two consecutive evenings for separate sampling. The time of sampling needs to be documented on the test tube / requisition form. Subjects will be asked to return samples to the site to ensure standardized transport and processing at the central laboratory (please see algorithm above).
- Serum glucose measurements under fasting conditions

- Serum DHEA-s (Dehydroepiandrosterone sulfate) and total testosterone (tT) Furthermore, the age-specific DHEA-s ratio (derived by dividing the subject's DHEA-s value by the lower limit of the age-specific reference range) will be calculated[12].

9.6.3.8.4 Adrenal signs and symptom inquiry

Vital signs (blood pressure in triplicates and heart rate) will be documented at the safety closeout visit. Blood pressure should be measured in triplicates after 5 minutes of rest, while the subject is sitting. Measurements should be made at least 1 minute apart using the same arm at each visit and should be recorded on the eCRF[13].

During the visit the subject should also be evaluated for clinical signs and symptoms of adrenal disorders, such as Cushing's syndrome, and hirsutism/virilization. A dedicated CRF page has been implemented to document those, if applicable.

9.6.3.9 Liver symptom inquiry

Investigators, subjects and their family members should be alert for non-specific symptoms which may be associated with liver dysfunction including anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, malaise, jaundice, fever, and rash.
Before the implementation of protocol amendment 5 (version 5.0), investigators were asked to regularly inquire about symptoms that according to their medical judgement may indicate liver disturbance and document the result of this inquiry in the respective eCRF page. This structured inquiry was used to determine withdrawal criteria and is therefore not needed at the safety closeout visit.

9.6.3.10 Liver monitoring

In the past, investigators, subjects and their family members were instructed to be alert for non-specific symptoms which may be associated with liver dysfunction. In addition, the liver inquiry had to be completed at regular intervals. Based on the long interval between implementation of protocol amendment 5 (version 5.0) and last intake of study drug this is no longer needed on a routine basis.

Investigation of potential causes (which replaces the close observation procedures applied before this protocol amendment) has to be initiated and recorded in the dedicated liver case report form if at least one of the options below applies:

- GPT/ALT or GOT/AST value increases to >3 x ULN
  or

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[12] High levels of tT and/or DHEA-s may be indicators of an androgen-producing adrenal cortical tumor and are measured in this study in conjunction with adrenal imaging to support their early detection. Therefore, despite the fact that many confounders are present in the female study population (e.g., PCOS, influence of Vilaprisan or other concomitant medications on hormone levels), tT and DHEA-s concentrations will be measured to screen for androgen-producing tumors. Highly abnormal values of one or both parameters, i.e., tT >240 ng/dL and/or DHEA-s > 600 µg/dL, will trigger an assessment by one of the external adrenal panel experts.

[13] 2018 Draft Guidance for Industry: Assessment of Pressor Effects of Drugs (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinforma tion/guidances/ucm609185.pdf

- GPT/ALT or GOT/AST value 2-fold increases above the lowest baseline value for subjects with elevated values before drug exposure
  or
- AP (alkaline phosphatase) value increases to > 2x ULN and irrespective of the level of transaminase (GPT/ALT or GOT/AST) values
    - in cases with baseline showing normal AP
    - in cases of at least 2 times the baseline values if slightly above the upper limit of normal at baseline

In those cases, a search for underlying causes should be performed including:

- Repeating a serum chemistry panel (including liver parameters and bilirubin).
- Obtaining a more detailed history of the symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease. This may require performing additional procedures, e.g. ultrasound examinations.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function as appropriate, (eg, international normalized ratio [INR], total bilirubin measurements).
- Referral for a liver ultrasound.

Any of these additional findings is to be recorded on the corresponding eCRF pages in RAVE.

9.6.3.11 Skin monitoring

All subjects who have taken at least one dose of the study medication will undergo a thorough skin examination by a dermatology expert.

The outcome of the dermatology expert's examinations will be reported in the CRF. Any dermatology expert´s diagnosis of a pre-cancerous or malignant skin lesion, including cutaneous sarcoma confirmed by biopsy diagnosis, qualify as an AESI. Any dermatology expert´s diagnosis of a malignant skin lesion, including cutaneous sarcoma confirmed by biopsy diagnosis, needs to be reported as an SAE to ensure timely reporting to regulatory agencies (see Section 9.6.1.6).

Subjects who were randomized, started treatment, and have completed or discontinued the study before or during the temporary pause should be contacted by the site and asked to have the skin monitoring performed. After re-consenting, data related to the skin exam by a dermatology expert and the results are to be captured and if applicable any related AEs and respective concomitant medications.

The investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.

9.7 Other procedures and variables

9.7.1 Iron supplementation

This section was changed in Amendment 2, see Section 15.1.1

Subjects in whom causes for anemia unrelated to HMB are suspected should not have been enrolled.

Moderate anemia is defined as hemoglobin ≤10.9 g/dL (4). 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

See Section 9.6.3.2.1.

9.7.3 Heavy menstrual bleeding / suspicious bleeding pattern

See Section 9.6.3.2.7.

9.7.4 Unscheduled endometrial biopsy

See Section 9.6.3.2.8.

9.7.5 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, excluding randomized subjects who did not start Treatment Period 1 due to the study being temporarily on hold. Subjects will be analyzed as randomized.

Per protocol set (PPS): All subjects in the FAS without any validity findings impacting the primary efficacy variable in Treatment Period 1.

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 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
- Subject 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

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)
- Findings resulting from liver monitoring
- Findings resulting from adrenal monitoring
- Findings resulting from skin monitoring

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:

> 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

In total, four tests will be carried out each to an alpha level of 0.05: First, the test for the primary efficacy variable amenorrhea (yes/no) will be carried out, followed by the test for HMB response (yes/no), the test for time to onset of amenorrhea, and finally, the test for onset of controlled bleeding. 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 that the amenorrhea rates in the vilaprisan 2 mg group (p_v) and in the placebo group (p_p) in Treatment Period 1 are equal versus the alternative hypothesis H_1 that they are not:

$$H_0: p_v = p_p \quad \text{vs.} \quad H_1: p_v \neq p_p.$$

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 1 is <2 mL. Subjects are treated as censored if they did not experience an onset of amenorrhea during Treatment Period 1. 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 2 mg 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 Treatment Period 1 is <80.00 mL. Subjects are treated as censored if they did not experience an onset of controlled bleeding during Treatment Period 1. 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 "mild" 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 "mild" 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 "mild" 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

No longer applicable as with the implementation of protocol amendment 5 (version 5.0) no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study. This section describes the original sample size planning prior to the decision to temporarily pause the study. The originally planned sample size has not been reached.

Assumptions for sample size calculations were 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 was 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 was planned to be 260; 65 subjects in each treatment group.

Approximately 50% of subjects were 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 were planned to 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

With the implementation of protocol amendment 5 (version 5.0) a safety and efficacy analysis is planned after all subjects have completed their treatment period. Data of the follow-up period available at that time point will also be included in the analysis. Remaining data of the follow-up phase will be analyzed after all subjects have completed the follow-up period. For all other data this safety and efficacy analysis is considered the final analysis.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study is 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 have been 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 had to be reported until screen failure was declared or randomization occurred. Additionally, to the above mentioned data these 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, if applicable

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 contacted 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 also included identification and documentation of source data items.

The sponsor/designee is monitoring 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 is 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 are used. MedDRA is 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 has been 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 were emphasized in the training and by the Clinical Research Associate during the study. The subjects were informed on use of the dispensed sanitary products, and the reasons for adhering to these practices were 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.

Subject (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 protocol amendment 3 (version 3.0) 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 subject's note/file of the medical institution.

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 source documents 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.

14. Reference list

1. Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B. Incidentally discovered adrenal masses. Endocr Rev. 1995;16(4):460-84.
2. Hallberg L, Nilsson L. Determination of Menstrual Blood Loss. Scand J Clin Lab Invest. 1964;16:244-8.
3. Emons G, Beckmann MW, Schmidt D, Mallmann P, for the Uterus commission of the Gynecological Oncology Working G. New WHO Classification of Endometrial Hyperplasias. GebFra - DGGG-Gesellschaftsausgaben. 2015(01):135-6.
4. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity (WHO/NMH/NHD/MNM/11.1). Available from: http://who.int/vmnis/indicators/haemoglobin.pdf, accessed 26 Jan 2016. 2011.

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, 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.

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~~ ~~f~~follow-up
Treatment Group A2	Screening ~~about~~ 120 days	RND	Vilaprisan 2 mg 12 week		Vilaprisan 2 mg 12 week	~~12 week~~ ~~f~~follow-up
Treatment Group B1	Screening ~~about~~ 120 days	RND	Placebo 12 week	*B*	Vilaprisan 2 mg 12 week	~~12 week~~ ~~f~~follow-up
Treatment Group B2	Screening ~~about~~ 120 days	RND	Vilaprisan 2 mg 12 week	*B*	Placebo 12 week	~~12 week~~ ~~f~~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
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 source documents 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							
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 source documents 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 in person 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. 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.

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 source documents 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 source documents 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>
- <u>Absence of bleeding (spotting allowed) during the last 28 days of the treatment; based on the UF-DBD</u>

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.

15.2 Amendment 3

Amendment 3 (04 JUL 2018)

Overall Rationale for the Amendment:

This amendment is based on recommendations provided for ulipristal acetate on 18 May 2018 from the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) and guidance from Health Authorities regarding hepatic monitoring to provide a robust data base for evaluation of hepatic safety of vilaprisan. In addition to health authority triggered changes additional updates had to be performed, which are listed below, together with the respective reasons for the updates.

Section # and Name	Description of Major Changes	Brief Rationale
3 Introduction	1) Text added describing hepatic safety signal with Esmya® (ulipristal acetate), a compound that belongs to the compound group of selective PRMs, and the result of the respective PRAC review procedure including risk minimization measures. 2) Provided rationale that vilaprisan is structurally different from other selective PRMs.	1) EMA Pharmacovigilance Risk Assessment Committee (PRAC) review procedure concluded in May 2018 2) For clarification
5. Study design	1) Description of increased frequency of liver monitoring and its background in subsection	1) FDA feedback in January and May 2018; FDA

Section # and Name	Description of Major Changes	Brief Rationale
	"safety monitoring" 2) Creation of a separate section on Benefit Risk Assessment	Guidance for Industry Drug-Induced Liver Injury (July 2009) 2) Feedback received from health authorities in the initial submission of Asteroid protocols
6.2 Exclusion criteria	1) The criterion about abnormal liver parameters was revised. 2) The diagnosis of chronic hepatitis B / C infection was added to exclusion criteria. 3) The criterion about intake of strong CYP inducer was updated; correcting information about metronidazole. 4) A clarification that endometrioma are exempt was added to the criterion regarding ovarian cysts.	1) + 2) To address FDA' requirement on more robust liver safety data and to closely align with specific feedback received in Jan and May 2018 and the 2009 FDA DILI guideline. 3) correction 4) clarification
9.1 Tabular schedule of evaluations 9.2.3 Scheduled visits	Added additional visits (e. Visits 4.1, 5.1 and 6.1); added liver symptom inquiry for all visits	To address FDA requirement on more robust liver safety data, and to closely align with specific feedback received in Jan and May, 2018 and the 2009 FDA DILI guideline
9.6.1.1 Definition	Newly included sentences "Any fibroid surgery should always be reported as serious adverse event (SAE), irrespective of associated hospitalization" and "All instances of liver parameter testing which meet criteria for withdrawal of a subject from the study treatment should be reported as SAE."	To address FDA recommendation in response to SPA for Asteroid 3 received in Jul 2017 and to align with FDA 2009 DILI guidance
9.6.1.3 Assessments and documentation of adverse events	Added details about follow up of AEs of special safety interest.	For clarity
9.6.1.6 AEs of special interest	Added more detailed instructions for the monitoring of liver parameters and liver disorders and for close observation in cases with increased liver parameters and liver disorders; added a flow chart aiding the understanding of the intended processes for	FDA feedback in Jan and May 2018 regarding improved liver monitoring

Section # and Name	Description of Major Changes	Brief Rationale
	liver function monitoring	
9.6.3.1 Laboratory evaluations	Added more details on laboratory parameters including liver related parameters, screening tests for hepatitis A, B, and C, hemoglobin, and additional parameters. Added parameters measured under close observation in cases of increased liver parameters after start of treatment	To address FDA' requirement on more robust liver safety data received in Jan and May 2018
9.6.3.2 Further safety	Added description for liver symptom inquiry.	To address FDA requirement on more robust liver safety data received in Jan and May 2018
9.7.4 Unscheduled endometrial biopsy	Following procedures regarding the case of a diagnosis that does not fall into the categories that require immediate stop of study drug (e.g. simple hyperplasia) were added.	For clarity
8.1.1 Iron supplementation	Addition of "consistent with local standards of practice and at the investigator's discretion"	Clarification needed because of regional differences in medical practice
9.1 Tabular schedule of evaluations, 9.2.3 Scheduled visits, 9.3.4 HMB questions	Addition of "not mandatory" for HMB- related pre-screening questions	For clarity, to avoid unnecessary burden to investigators and subjects
10.3.1.6 Other safety variables	Details for laboratory parameters were added	To address FDA requirement on more robust liver safety data received in Jan and May 2018
16.1 Strong CYP3A4 inhibitors	Added delavirdine and troleandomycin to the listing of strong CYP3A4 inhibitors	New compounds which need to be added to the list of excluded concomitant medications

15.3 Amendment 4

Stand-alone global amendment 4 was not integrated into the integrated version of the protocol as it explained why Bayer decided to temporarily pause enrollment and randomization, and to temporarily withdraw study treatment in already randomized patients after completion of the ongoing treatment period. This global amendment provided background, justification, as well as a detailed description of the transient temporary measures to be taken.

15.4 Amendment 5

The rationale for changes in this amendment 5 and all affected sections are provided in the below'Protocol Amendment Summary of Changes Table'

Section # and Name	Description of Major Changes	Brief Rationale
3 Introduction	Information on carcinogenicity studies with vilaprisan in rodents as well as details regarding the additional safety measures were added to the section, included adrenal skin, and endometrial evaluation, added the new benefit-risk assessment	Provision of comprehensive information about recent events To re-assess benefits/risks, including the findings from the carcinogenicity studies into consideration and address the newly introduced monitoring
4. Study objectives	Added additional focus on safety evaluations of the endometrium, adrenal glands and skin	To address FDA requests
5. Study design	Updated study design; information deleted that is no longer relevant	To address FDA requests With the implementation of protocol amendment 5 (version 5.0) no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study
6 Study population 7. Treatments 8. Non-study therapy 9.3 Population characteristics 9.4 Efficacy 9.5	Updated based on new study design; information deleted that is no longer relevant	To address FDA requests

Section # and Name	Description of Major Changes	Brief Rationale
Pharmacokinetics/pharmacodynamics 11. Data handling and quality assurance		
9.1 Tabular schedule of evaluations 9.2 Visit description	Information deleted that is no longer relevant; added "Safety closeout visit" and "Safety result reporting visit"	To depict the procedures of the "Safety closeout visit"and the "Safety result reporting visit".
9.6.1.1 Definition	New criteria for SAE reporting for endometrial biopsies, adrenal tumors, and malignant skin tumors	To address FDA requests
9.6.1.6 AEs of special interest	New AESIs added for adrenal and skin disorders.	To address FDA requests
9.6.3.1 Laboratory evaluations	Added more details on laboratory parameters associated with adrenal disorders. Added requirement for Vit D measurement	To address FDA requests on adrenal monitoring; Vit D measurement for harmonization of data across all studies
9.6.3 Further safety	Deleted "In addition, the subjects should be reminded regularly to contact the study site immediately, if they are concerned about such symptoms and testing for unscheduled liver parameters should be considered."	No longer required as no further treatment will be administered
9.6.3.3 Endometrial biopsies	Added more details on endometrial biopsies	To address FDA requests
9.6.3.4 Cervical smear 9.6.3.5 Physical and gynecological examinations 9.6.3.6 Vital signs, weight, and height 9.6.3.7	Revised to reflect the collection of the parameters at the safety closeout visit.	Update necessary due to new visit structure

Section # and Name	Description of Major Changes	Brief Rationale
Ultrasound (safety) 9.6.3.8 Contraception and pregnancy test		
9.6.3.9 Adrenal monitoring	Added description for adrenal monitoring (MRI, laboratory investigations and inquiry)	To address FDA requests
9.6.3.10 Liver monitoring	Content shifted from previous Section 9.6.1.6 and added alkaline phosphatase (AP) value increasing to > 2x ULN in cases with normal baseline AP as a close observation criterion	To address FDA requests
9.6.3.11 Skin monitoring	New section added on skin monitoring	To address FDA requests
9.7.2 Algorithm for monitoring of endometrial safety 9.7.3 Heavy menstrual bleeding / suspicious bleeding pattern 9.7.4 Unscheduled endometrial biopsy	Content shifted to Sections 9.6.3.3.1, 9.6.3.3.7, and 9.6.3.3.8	To address FDA requests
10.2 Analysis sets	Adapted FAS and PPS definitions	FAS needed to be newly defined to take the handling of subjects into account who were not allowed to start TP1 due to the clinical hold. PPS needed to be newly defined in order to account for the changed analysis (only evaluation of Treatment Period 1).
10.3.1.1 Primary	Changed text since primary efficacy analysis	Data for Treatment Period 2 is not sufficient to draw

Section # and Name	Description of Major Changes	Brief Rationale
efficacy variable	will only be performed for Treatment Period 1	valid conclusions.
10.3.1.6 Other safety variables	Added adrenal monitoring and skin safety	To address FDA requests
10.3.2.2 Efficacy analysis	Changed text and hypothesis since primary efficacy analysis will only be performed for Treatment Period 1. Comparison of vilaprisan 2 mg against placebo after 24 weeks dropped (treatment arm A2).	Data for Treatment Period 2 is not sufficient to draw valid conclusions. Due to dropping A2 arm, analysis after 24 weeks of treatment is not valid anymore
10.4 Determination of sample size	Added text to clarify that the sample size calculation described is not valid anymore.	No new subjects will be included in the study.
10.5 Planned interim analyses	Added text on additional analysis planned before the end of the study.	Added to reflect new analysis strategy

15.5 Amendment 6

The rationale for the HA requested changes in this amendment and all affected sections are provided in the ‘Protocol Amendment Summary of Changes Table’ directly before the Table of Contents in this document. A separate file with tracked changes as against the last integrated protocol version is available upon request.

16. Appendices

16.1 Strong CYP3A4 inhibitors

Table 16—1: Strong CYP3A4 inhibitors

Substance name	Inhibitor strength
Boceprevir	Strong
Clarithromycin	Strong
Cobicistat	Strong
Conivaptan	Strong
Delavirdine	Strong
Grapefruit juice	Depending on dose: Moderate or 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
Troleandomycin	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