Document Type:	Study Protocol
Official Title:	An open-label, parallel-group, randomized, multicenter study to assess the safety and efficacy of vilaprisan in subjects with uterine fibroids versus standard of care
NCT Number:	NCT03194646
Document Date:	17 FEB 2020

Cover page of the integrated protocol

An open-label, parallel-group, randomized, multicenter study to assess the safety and efficacy of vilaprisan in subjects with uterine fibroids versus standard of care

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

- **Original protocol**, Version 1.0, dated 17 MAR 2017
- **Amendment 03** (global amendment described in Section 15.1) forming integrated protocol Version 2.0, dated 13 JUN 2017
- **Amendment 04** (global amendment described in Section 15.2) forming integrated protocol Version 3.0, dated 13 SEP 2017
- **Amendment 06** (global amendment described in Section 15.3) forming integrated protocol Version 4.0, dated 04 JUL 2018
- **Amendment 07** (global amendment described in Section 15.4) forming integrated protocol Version 5.0, dated 20 AUG 2018
- **Amendment 09** (global amendment described in Section 15.5) forming global protocol Version 6.0, dated 11 DEC 2018
- **Amendment 10** (global amendment described in Section 15.6) forming integrated protocol Version 7.0, dated 21 NOV 2019
- **Amendment 11** (global amendment described in Section 15.7) forming integrated protocol Version 8.0, dated 17 FEB 2020

Local amendments not forming part of this integrated global protocol:

- **Amendment 01** (dated 18 APR 2017) (local amendment, valid for Japan only)
- **Amendment 02** (dated 16 MAY 2017) (local amendment, valid for the United States only)
- **Amendment 05** (dated 13 SEP 2017) (local amendment, valid for the South Africa only)
- **Amendment 08** (dated 30 AUG 2018) (local amendment, valid for Japan only)

1. Title page

An open-label, parallel-group, randomized, multicenter study to assess the safety and efficacy of vilaprisan in subjects with uterine fibroids versus standard of care

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

Acronym: ASTEROID 6

Test drug:	Vilaprisan (BAY 1002670)		
Clinical study phase:	3	Date:	17 FEB 2020
Registration:	EudraCT: 2016-004822-41	Version no.:	8.0
Sponsor's study no.:	16953		

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, United States

Sponsor's medical expert: PPD
Bayer U.S. LLC
100 Bayer Boulevard
Whippany NJ 07981-0915
United States
Phone no. 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 integrated 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 integrated 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 4, see Section 15.2.1

Title	An open-label, parallel-group, randomized, multicenter study to assess the safety and efficacy of vilaprisan in subjects with uterine fibroids versus standard of care
Short title	**A**ssess **S**afety and Efficacy of Vilaprisan in Subjects with U**ter**ine Fibr**oid**s
Acronym	ASTEROID 6
Clinical study phase	3
Study objectives	The primary objective of this study is to evaluate the safety of vilaprisan in subjects with uterine fibroids in comparison to nonhormonal medical treatment in accordance with local standard of care. The secondary objective of this study is to evaluate the efficacy of vilaprisan in subjects with uterine fibroids in comparison to nonhormonal medical treatment in accordance with local standard of care. 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 10 (version 7.0) and aligned with the previous temporary pause measures, no new subjects will be recruited and no study medication or standard of care symptomatic nonhormonal 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 Subgroup 1	About 1 year of treatment: Treatment Group A1: 4 treatment periods of 12 weeks, each separated by 1 bleeding episode (3/1 regimen) Treatment Group A2: 2 treatment periods of 24 weeks, separated by 2 bleeding episodes (6/2 regimen) Treatment Group A3: 3 treatment periods of 12 weeks, each separated by 2 bleeding episodes (3/2 regimen)
Duration of treatment Subgroup 2	About 2 years of treatment: Treatment Group A1: 8 treatment periods of 12 weeks, each separated by 1 bleeding episode (3/1 regimen) Treatment Group A2: 4 treatment periods of 24 weeks, each separated by 2 bleeding episodes (6/2 regimen) Treatment Group A3: 6 treatment periods of 12 weeks, each separated by 2 bleeding episodes (3/2 regimen)

Reference treatment	**Not any longer applicable due to the closing of the clinical study. With the implementation of Protocol Amendment 10 (version 7.0) and aligned with the previous temporary pause measures, no new subjects will be recruited and no study medication or standard of care symptomatic nonhormonal 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:** Standard of care symptomatic nonhormonal medical treatment as determined by the investigators and/or watch and wait (Subgroup 1: 52 weeks, Subgroup 2: 104 weeks)
Name of active ingredient	Not applicable
Doses	Not applicable
Route of administration	Not applicable
Duration of treatment	Not applicable
Indication	Uterine fibroids
Diagnosis and main criteria for inclusion/exclusion	**With the implementation of Protocol Amendment 10 (version 7.0) 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 symptomatic uterine fibroids or at high risk for recurrence after surgery 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 an open-label, parallel-group, randomized, multicenter study.
Methodology	**With the implementation of Protocol Amendment 10 (version 7.0) 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 any data 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) and SoC subjects who are still in the study will be asked to undergo a DEXA scan and the safety evaluation procedures described in this document.** Prior to the temporary pause, approximately 60% of eligible subjects were randomized to one of three vilaprisan treatment groups (Groups A1, A2, or A3) or to the standard of care group (Group B) for about one year of treatment (Subgroup 1). The remaining eligible subjects (about 40%) were randomized to one of three vilaprisan treatment groups (Groups A1, A2, or A3) or to the standard of care group (Group B) for about 2 years of treatment (Subgroup 2). After the end of treatment (EoT), subjects were followed up for 24 weeks (Subgroup 1) or for 12 weeks (Subgroup 2). Bone mineral density (BMD) of the lumbar spine, hip, and femoral neck are assessed by DEXA

	• at baseline, after about 1 year of treatment, and follow-up 2 (FUP2) (Subgroup 1) • at baseline, after about 1 year of treatment, and at the EoT visit (Subgroup 2) Subjects documented the intensity of their menstrual bleeding in the Uterine Fibroid Daily Bleeding Diary (UF-DBD) and assessed the intensity of their menstrual blood loss daily using a visual scoring system (Menstrual Pictogram [MP]) in an electronic diary (eDiary). Uterine fibroids were assessed during the study by ultrasound. Patient-reported outcome (PRO) data were also collected using the Uterine Fibroid Daily Symptom Diary (UF-DSD) and the Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QoL). Clinician-reported outcome (ClinRO) data were collected using the Clinical Global Impression - Investigator (CGI_I). Safety is also assessed by the evaluation of adverse events (AEs), laboratory parameters, endometrial biopsies, cervical smears, physical and gynecological examinations, and vital signs. In addition, liver parameters were monitored on a monthly basis during treatment. The (population) 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. Leftover material from the endometrial biopsies scheduled for histological examinations were used to investigate biomarkers from subjects who have consented to this research.
Type of control	**Not any longer applicable as with the implementation of Protocol Amendment 10 (version 7.0), no new subjects will be recruited and no study medication or standard of care symptomatic nonhormonal will be given to the subjects who have been enrolled in the study** Standard of care symptomatic nonhormonal medical treatment as determined by the investigator and/or watch and wait
Number of subjects	**With the implementation of Protocol Amendment 10 (version 7.0) 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) and SoC subjects who are still in the study will be asked to undergo a DEXA scan and the safety evaluation procedures described in this document.** About 2170 subjects were planned to be enrolled in order to achieve the planned number of randomized subjects. A total of 1302 subjects were planned to be randomized as follows: 372 subjects each in Treatment Groups A1, A2, and B; 186 subjects in Treatment Group A3 The sample size was chosen to fulfill the regulatory requirements for safety data.
Primary variable	Percentage change in BMD of lumbar spine from baseline to about one year after start of treatment (SoT)

Time point/frame of measurement for primary variable	About one year after SoT
Plan for statistical analysis	The primary analysis comprises the display of the percentage change in BMD of lumbar spine from baseline to about one year after SoT in all randomized and treated subjects with measurements at those 2 time points in each treatment group. The mean and the two-sided 95% confidence interval (CI) for the mean difference of the percentage change in BMD of lumbar spine from baseline to about one year after SoT will be calculated for each vilaprisan treatment group as compared to standard of care. No statistical hypothesis is planned to be tested.

Protocol amendment summary of changes table

Amendment 11 (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 (refer to Protocol Amendment 9 [version 6.0]) 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 the associated amendment and Introduction Section 3), a comprehensive safety follow up will be conducted to provide additional confirmatory evidence. The protocol amendment 10 (version 7.0) 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. Also subjects randomized to SoC who are still in the study will be asked to undergo these procedures.

Recently Bayer received comments from FDA regarding details of the safety follow-up measures introduced in the protocol amendment 10 (version 7.0). The current amendment (protocol amendment 11, version 8.0) 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. In such cases subjects should at least be counseled about medical follow up according to local practice.	To address FDA requests
9.1 and 9.6.3.4 Procedures and variables	Text adjusted and footnote "Physical examination" deleted, as physical examination needs to be performed to 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
9.6.3.9.3 Laboratory testing	Footnote was adjusted to trigger an assessment by one of the external adrenal panel experts in case tT level >150 ng/dL.	To address FDA request

Short summary for sites:

With the implementation of Protocol Amendment 10 (version 7.0) 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 which is implemented. 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. Likewise, subjects randomized to SoC who are still in the study will be asked to undergo these procedures.
All these subjects are asked to come to the site for the "Safety closeout visit" which is implemented with the protocol amendment 10 (Version 7.0). 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 9.2 and Table 9–1:

- 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)

- Bone mineral density
- 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 sections of the protocol amendment 10 (Version 7.0). Test results (e.g., hormone, liver, physical examination) may be abnormal but still below the thresholds to trigger outside 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's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.

Table of contents

Table of tables

Table of figures

List of abbreviations

ACTH	adrenocorticotropic hormone
AE(s)	adverse event(s)
AESI	adverse event of special safety interest
AG	*Aktiengesellschaft*, incorporated company
ALT	alanine aminotransferase (also known as GPT)
ANA/ANCA	antinuclear antibody/antineutrophil cytoplasmic antibody
AP	alkaline phosphatase
aPTT	activated partial thromboplastin time
ASCUS	atypical squamous cells of undetermined significance
AST	aspartate aminotransferase (also known as GOT)
ATC	Anatomical Therapeutic Chemical
B	bleeding episode
β-HCG	beta human chorionic gonadotropin
BMD	bone mineral density
CD	compact disc
CGI_I	Clinical Global Impression - Investigator
CI	confidence interval
ClinRO	clinician-reported outcome
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSP	clinical study protocol
CTX	collagen type 1 cross-linked C-telopeptide
CYP3A4	cytochrome P450 isoenzyme 3A4
DEXA	dual-energy X-ray absorptiometry
DHEA-s	dehydroepiandrosterone sulfate
dL	deciliter

EA	endometrial ablation
eConsent	electronic informed consent
eCRF	electronic Case Report Form
EDC	electronic data capture
eDiary	electronic diary
eg	*exempli gratia*, for example
EIN	endometrial intraepithelial neoplasia
EMA	European Medicines Agency
EoT	end of treatment
ePRO	electronic patient-reported outcome
ESP	European Spine Phantoms
EU	European Union
EudraCT	European Union data repository for clinical trials
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FUP	follow-up
g	gram
GCIS	general clinical imaging services
GCP	Good Clinical Practice
γ GT	gamma-glutamyl transpeptidase
GMP	Good Manufacturing Practice
GnRH	gonadotropin-releasing hormone
GnRHa	gonadotropin-releasing hormone agonist
GOT	glutamic oxaloacetic transaminase (also known as AST)
GPT	glutamic pyruvic transaminase (also known as ALT)
HA	health authority
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 for Harmonisation
ie	*id est*, that is
IEC	Independent Ethics Committee
INN	international nonproprietary name
INR	international normalized ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
IVRS/IWRS	interactive voice/web response system
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDL	low density lipoprotein
LH	luteinizing hormone
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MD	doctor of medicine
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mo	month
MP	menstrual pictogram
MRI	magnetic resonance imaging

mRNA	messenger ribonucleic acid
M&S	Modeling and Simulation
mSV	milisievert
NA	not applicable
P	progesterone
PAEC	progesterone receptor modulator-associated endometrial changes
PD	pharmacodynamic(s)
pH	negative logarithm of proton concentration
PK	pharmacokinetic(s)
PM	post meridiem
PRM	progesterone receptor modulator
PRO	patient-reported outcome
QC	quality control
RAVE	electronic data capturing system
RND	randomization
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCR	screening
SD	standard deviation
SERM	selective estrogen receptor modulators
SESAC	site electronic source assessment checklist
SID	subject identification
SoC	standard of care
SoT	start of treatment
SUSAR	suspected, unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
THIN	The Health Improvement Network
TOSCA	Tools for Statistical Analysis
TP	Treatment Period
trt	treatment
TSH	thyroid-stimulating hormone
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	uterine preserving procedure
US	United States
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
3/2 regimen	3 months(ie, 3 x 28 days) of treatment with 2 bleeding episodes between treatment periods

6/2 regimen	6 months (ie, 6 x 28 days) of treatment with 2 bleeding episodes between treatment periods
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 10 (version 7.0) 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) and SoC subjects who are still in the study will be asked to undergo a DEXA scan and 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 (refer to Protocol Amendment 9 [version 6.0]) 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 (refer to IB version 11.0 including the associated amendment and Introduction Section 3) Bayer will conduct a comprehensive safety follow up to confirm this. The protocol amendment 10 (Version 7.0) 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.

The protocol amendment 10 (Version 7.0) introduced endometrial, adrenal, and skin safety evaluations with the aim to confirm that the carcinogenicity study findings did 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.

Further detailed information and assessment of the carcinogenicity study findings are described below and also in the current version (V 11.0) 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.
- Regarding the development of endometrial adenocarcinomas, 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 current protocol amendment, 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 safety 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 measures newly introduced with the protocol amendment 10 (Version 7.0) were applicable also to subjects in the SoC group since a background incidence of adrenal and skin abnormalities renders such safety investigations also beneficial for subjects not exposed to vilaprisan.

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 patients' health-related quality of life (HRQoL) and a reduction of fibroid size.

4. Study objectives

The primary objective of this study is to evaluate the safety of vilaprisan in subjects with uterine fibroids in comparison to nonhormonal medical treatment in accordance with local standard of care.

The secondary objective of this study is to evaluate the efficacy of vilaprisan in subjects with uterine fibroids in comparison to nonhormonal medical treatment in accordance with local standard of care. With the implementation of Protocol Amendment 10 (version 7.0), additional focus will be put on safety evaluations of the endometrium, adrenal glands and skin.

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 4, see Section 15.2.1.

Design overview

This is an open-label, parallel-group, randomized, multi-center study.

The study is conducted in Europe, North America, South America, South Africa, and Asia Pacific.

An overview of the study design before the temporary pause is shown in Figure 5–1.

With the implementation of Protocol Amendment 10 (version 7.0), this study design is no longer valid. No subjects will receive further study drug treatment.

Figure 5–1: Design overview

Subgroup 1 (about 1 year of treatment)

A1	SCR up to 90 days	RND	12 wk trt	*B*	12 wk trt	*B*	12 wk trt	B	12 wk trt	24 wk FUP

A2	SCR up to 90 days	RND	24 wk trt	*B*	*B*	24 wk trt	24 wk FUP

A3	SCR up to 90 days	RND	12 wk trt	*B*	*B*	12 wk trt	*B*	*B*	12 wk trt	24 wk FUP

B	SCR up to 90 days	RND	Symptomatic nonhormonal medical treatment as determined by the investigators and/or watch and wait	24 wk FUP

Subgroup 2 (about 2 years of treatment)

A1	SCR up to 90 days	RND	12 wk trt	*B*	12 wk trt	*B*	12 wk trt	B	12 wk trt	*B*	12 wk trt	*B*	12 wk trt	*B*	12 wk trt	*B*	12 wk trt	12 wk FUP

A2	SCR up to 90 days	RND	24 wk trt	*B*	*B*	24 wk trt	*B*	*B*	24 wk trt	*B*	*B*	24 wk trt	12 wk FUP

A3	SCR up to 90 days	RND	12 wk trt	*B*	*B*	12 wk trt	*B*	*B*	12 wk trt	*B*	*B*	12 wk trt	*B*	*B*	12 wk trt	*B*	*B*	12 wk trt	12 wk FUP

B	SCR up to 90 days	RND	Symptomatic nonhormonal medical treatment as determined by the investigators and/or watch and wait	12 wk FUP

Groups A1, A2, and A3 treated daily with vilaprisan 2 mg during treatment periods; Group B treated with standard of care symptomatic nonhormonal medical treatment as determined by the investigators and/or watch and wait.
B = bleeding episode; FUP = follow-up; RND = randomization; SCR = screening; trt = treatment; wk = week.

During the screening period, subjects had to demonstrate eligibility including presence of at least 1 uterine fibroid documented by ultrasound at screening and / or during a uterine preserving procedure within 3 months prior to screening, at least one symptom of uterine fibroid(s), and an endometrial biopsy result without significant histological disorder. If possible, fibroid-related symptom(s) should be confirmed before the endometrial biopsy is performed at Visit 2.

Eligible subjects were randomized to one of three vilaprisan treatment groups (Groups A1, A2, or A3) or the standard of care group (Group B) and started treatment as described in

Section 7.1. After the end of the treatment, subjects were planned to be followed up for 12 weeks (Subgroup 2) or 24 weeks (Subgroup 1).

The **primary safety variable** is the percentage change in BMD of lumbar spine from baseline to about one year after SoT. With Protocol Amendment 10 (version 7.0) becoming valid, all subjects who received vilaprisan treatment will be asked to undergo a BMD at least 6 months after the last intake of vilaprisan, to document absence of bone loss or adequate recovery after the end of treatment.

For secondary variables, see Sections 10.3.1.2 and 10.3.1.4.

Justification of the design

Comparators:

Standard of care symptomatic nonhormonal medical treatment and watch and wait were considered appropriate to examine comparative safety and efficacy of vilaprisan versus available treatment option(s). Hormonal medical treatments and surgical interventions were not permitted as comparators. The fact that in all study treatment arms active treatment was provided, translated into a comparable level of benefit for all enrolled subjects.

Blinding:

Due to the character of the treatments in the control group, blinding of subjects and investigators is not possible in this study. However, the primary endpoint will be assessed by central readers who are blinded with regard to treatment of the subject.

Study design valid with the implementation of Protocol Amendment 10 (version 7.0):

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. Any subjects who have taken at least one dose of study medication (including the subjects who completed the study or were prematurely terminated) and SoC subjects who are still in the study will be asked to have comprehensive safety evaluation(s) (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 / PD assessments:

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

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

Safety monitoring:

Safety parameters are regularly and closely monitored throughout the study (eg, questioning for AEs, measurement of laboratory values, 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 were implemented with the protocol amendment 10 (Version 7.0).

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 unscheduled endometrial biopsy in case of endometrial thickening and/or on the clinical management of endometrial thickening/HMB/abnormal menstrual bleeding pattern (see Section9.6.3.2.1). 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 10 (version 7.0), 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 6 [version 4.0]). With this protocol amendment (Protocol Amendment 10 [version 7.0]), 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 was implemented with the protocol amendment 10 (Version 7.0) (Protocol Amendment 10 [version 7.0]). This program is described in more detail in Section 9.6.3.9. 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.

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.

Assessment of effects on bone mineral density

Selective PRMs such as vilaprisan induce a degree of ovulation suppression, accompanied by a moderate decrease in endogenous estradiol levels. To supplement data on estradiol levels under vilaprisan therapy this study examines bone mineral density (BMD) and any potential impact that changes in estradiol levels under treatment may have. BMD is assessed using dual-energy X-ray absorptiometry (DEXA). To increase the accuracy of the assessment, 2 measurements are performed at each time point and location and the mean value will be used for evaluation. After the first measurement the subject should get up and should be re-positioned for the second measurement to reduce influence of positioning on the results.

BMD measurement of the spine (lumbar anterior posterior, L1-L4) and hip/femoral neck is performed using the same type of device for all measurements of any subject in this study.

DEXA is associated with radiation exposure but the total exposure per examination is only approximately 0.005 mSV corresponding to 3 to 4 hours of natural background radiation. No contrast agent is needed for this examination.

All subjects who received vilaprisan treatment should have an off-treatment DEXA scan[1] performed at the Safety closeout visit to document absence of bone loss or adequate recovery.

Subjects randomized to Treatment group B who were still in the study when the protocol amendment 10 (Version 7.0) became valid should also have undergone a DEXA scan at the safety closeout visit, unless they had a DEXA scan performed within the last 3 months prior to the safety closeout visit.

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).

[1] DEXA scans performed 5.5 to 6 months after last study drug intake are acceptable off-treatment DEXA scans

6. Study population

Eligibility

No longer valid, since no new subjects will be enrolled in this study with the implementation of Protocol Amendment 10 (version 7.0). Originally the study population had to fulfill the following criteria:

Women with symptomatic uterine fibroids or at high risk for recurrence after surgery meeting all inclusion and presenting none of the exclusion criteria will be eligible for enrollment in the study.

Subjects who were screen failures from another ASTEROID study do not have to repeat the screening laboratory evaluations, cervical smear, and endometrial biopsy provided that the criteria for inclusion were met in the previous study and are within an acceptable time frame, ie, within 4 weeks for laboratory parameters and within 6 months for the cervical smear and endometrial biopsy). In case endometrial thickness (double layer) >18 mm is detected during the ultrasound measurements at screening (ie, Visit 1 or 2), the subject should undergo an evaluation by endometrial biopsy.

6.1 Inclusion criteria

This section was changed in Amendment 4, see Section 15.2.1.

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 AND/OR during a uterine preserving procedure within 3 months prior to screening in subjects with high risk for recurrence[2]
4. Symptoms of uterine fibroids documented by one or more of the following symptoms:
    - Heavy menstrual bleeding (HMB) > 80.00 mL documented by menstrual pictogram (MP) in a bleeding period[3] during the screening period
    - HMB during 3 bleeding episodes within 6 months prior to screening as reported by the subject

[2] High risk for recurrence is defined as satisfying at least one of the following criteria:
- Subject had 2 or more uterine preserving procedures in the past
- Subject has a positive family history for recurrent uterine fibroids
- Subject is below age 35 at screening

[3] To facilitate the assessment of the inclusion criterion 4 at the site during the screening period, a modified definition of bleeding episode ("bleeding period") will be implemented in the programming of reports for the sites, based solely on data from the Menstrual Pictogram (MP). Thus, a bleeding period is defined as a period of time when use of sanitary products is reported in the MP, preceded and followed by 2 days when no sanitary products were reported. In cases where the screening period starts with a day or with several days in which sanitary products have been reported (ie, if a bleeding episode is ongoing at the start of the screening period and the very first eDiary entry is a day with use of sanitary protection), this will also be recognized as a bleeding period. This simplification will only be used in the programming of reports supporting the sites in assessing inclusion criterion 4. Information from the Uterine Fibroid Daily Bleeding Diary (UF-DBD), used in the standard definition of a bleeding episode (see Section 7.1), is not used for this definition of a "bleeding period".

- Pelvic pressure/pain likely to be associated with uterine fibroids during 3 months prior to screening as reported by the subject
- Any of the symptoms above documented in the subject's file before an uterine preserving procedure that was conducted within 3 months prior to screening in a subject with high risk for recurrence [2]

5. Good general health (except for findings related to uterine fibroids) as proven by medical history, physical and gynecological examinations, and laboratory test results
6. Normal or clinically insignificant cervical smear not requiring further follow-up. The cervical smear may be waived if a normal result has been documented in the subject's medical records within the previous 6 months.

   Human papilloma virus (HPV) testing in subjects with atypical squamous cells of undetermined significance (ASCUS) can be used as an adjunctive test. Subjects with ASCUS can be included if they are negative for high-risk HPV strains.
7. 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.
8. Use of an acceptable nonhormonal 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 3, see Section 15.1.1., and in Amendment 4, see Section 15.2.1.

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[4] 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[4])

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

- Abnormal liver parameters (presence of at least one of the following criteria, please see also Section 9.6.3.1 Laboratory evaluations)[5]:
  - 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 outside the upper limit of normal [6]
  - International normalized ratio (INR) outside the upper limit of the normal range [7]
- Diagnosis of hepatitis B infection, i.e., Hbs-antigen positive at Visit 1[8]
- Diagnosis of hepatitis C infection, i.e., hepatitis C-antibodies and HCV-RNA positive at Visit 1 [9]
- Chronic bowel diseases, eg, M. Crohn and Colitis ulcerosa
- Intake of strong cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors within the last 2 weeks before the randomization visit and during the treatment period including: antivirals (eg, viekira pak, telaprevir, boceprevir), protease inhibitors (eg, ritonavir, lopinavir, indinavir, nelfinavir, saquinavir), antifungals (eg, itraconazole, voriconazole, posaconazole), antibiotics (eg, clarithromycin, telithromycin), grapefruit and any grapefruit containing food products (eg, grapefruit juice). 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, phenytoin, phenobarbital, St John´s wort [Hypericum]) within the last 2 weeks before the randomization visit and during the treatment period, unless randomized to treatment group B. 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

---

5 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 subject is eligible only if the second test shows a stabilization or decline in those values (see Section 9.6.3.1).

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

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

8 This will be applied only to subjects newly enrolled into the study after protocol version 4.0 has become valid

9 This will be applied only to subjects newly enrolled into the study after protocol version 4.0 has become valid

- History of or current uterine, cervical, ovarian, or breast cancer, except cervical cancers 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
- Current bone and musculoskeletal disease (eg, osteoporosis, Morbus Scheuermann, osteogenesis imperfecta, hypo- or hyperparathyroidism, Paget's disease, osteomalacia or other metabolic disease of bone, hypo- or hypercalcemia, uncontrolled vitamin D deficiencies[10])
- Screening DEXA results of the lumbar spine (L1-L4), femoral neck, or total hip BMD corresponding to 2.0 or more standard deviations below normal (Z score ≤ -2.0 SD) as per central read.[11]

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 the 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
        - Subjects randomized to Treatment Group B will be allowed to take tranexamic acid as symptomatic nonhormonal treatment

[10] According to local guidance
[11] This will be applied only to subjects newly enrolled into the study after protocol version 4.0 has become valid.

- Anticoagulants, if not stopped at Visit 1
- Raloxifene (or similar SERMs), fluoride, calcitonin, if not stopped 3 months before the start of the screening period
- Current intake (ie, at Visit 1) of bisphosphonates, parathyroid hormone, GnRH antagonists, vitamin D analogues, systemic corticosteroids or other agents known or suspected to affect bone metabolism

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 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)
14. Any other contraindication listed in the local labeling for medication used in Treatment Group B

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 10 (version 7.0) 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:

This section was changed in Amendment 4, see Section 15.2.1.

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
- In the event excessive loss of BMD >6% at the lumbar spine is accompanied by a Z-score reading of <-2 standard deviations (SD) (determined either by the central reading imaging laboratory or by assessment at the site and confirmed by the central reading imaging laboratory at the 12 month visit or later). For additional details and follow-up procedures for these subjects see Section 9.6.3.8
- In case induction of bleeding becomes necessary more than once per subject during the study treatment

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 subject prematurely withdrawing from study treatment or during FUP

With the implementation of Protocol Amendment 10 (version 7.0), 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 study medication or SoC 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 medical records.

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

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

6.4.2 Replacement

Dropouts will not be replaced.

6.5 Subject identification

At screening upon signing the informed consent and registering the subject in the interactive voice/web response system (IVRS/IWRS), each subject was assigned a unique multi-digit subject identification (SID) number by the site for unambiguous identification. The SID 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); the 6th digit will be "6" for this ASTEROID 6 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 Section 7.1 to 7.4 are no longer valid, since with the implementation of Protocol Amendment 10 (version 7.0) no subjects will start or continue treatment in this study.

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

7.1 Treatments to be administered

This section was changed in Amendment 4, see Section 15.2.1.

Approximately 60% of eligible subjects will be assigned to Subgroup 1 and the remaining eligible subjects will be assigned to Subgroup 2 with the following treatment groups:

Subgroup 1

- A1: 4 treatment periods of 12 weeks, each separated by 1 bleeding episode
- A2: 2 treatment periods of 24 weeks, separated by 2 bleeding episodes
- A3: 3 treatment periods of 12 weeks, each separated by 2 bleeding episodes
- B: Standard of care as determined by the investigators

Subgroup 2

- A1: 8 treatment periods of 12 weeks, each separated by 1 bleeding episode
- A2: 4 treatment periods of 24 weeks, each separated by 2 bleeding episodes
- A3: 6 treatment periods of 12 weeks, each separated by 2 bleeding episodes
- B: Standard of care as determined by the investigators

The assignment to the 2 subgroups will be done in a sequential manner, with 60% being recruited into Subgroup 1 and the remainder into Subgroup 2. Subjects will be randomized to treatment groups A1:A2:A3:B in a 2:2:1:2 manner. Some of the local regulatory agencies requested a minimum number of subjects included into the study and well balanced with respect to treatment received. Therefore randomization to treatment will be stratified by region/country (US, Japan, China and all other countries).

In Groups A1 and A3, each treatment period will consist of 12 weeks (84 days). In Group A2, each treatment period will be 24 weeks (168 days). One tablet is 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 study drug (applies to all treatment periods).

The start of each treatment period following Treatment Period 1 will be as follows (see Figure 5–1):

- For Treatment Group A1, Treatment Period 2 and subsequent treatment periods will start within Days 3 to 7 of the first bleeding episode following the end of the previous treatment period. If no bleeding episode occurs within 7 weeks after end of the previous treatment period, sites were to proceed with the induction of bleeding.
- For Treatment Groups A2 and A3, Treatment Period 2 and subsequent treatment periods will start within Days 3 to 7 of the second bleeding episode following the end of the previous treatment period. If no bleeding episode occurs within 7 weeks after the end of the previous treatment period or if the 2nd bleeding episode does not occur within 7 weeks after the end of the first bleeding episode, sites were to 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 electronic diary (eDiary):

- 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).

Subjects randomized to Treatment Group B will discuss with the investigators whether they

need any treatment to get relief from fibroid related symptoms or whether watch and wait is the appropriate option. During the study, a subject can switch from "watch and wait" to symptomatic nonhormonal treatment or vice versa. If treatment is needed, the investigator will prescribe the most appropriate symptomatic nonhormonal treatment to the subject, which will be documented in the eCRF.

Missed intake of study drug

If a subject in Treatment Groups A1, A2, or A3 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 and 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 diets of subjects in Treatment Groups A1, A2, and A3 during treatment because these foods contain constituents that inhibit cytochrome P450 3A4.

7.2 Identity of study treatment

The investigational medicinal product vilaprisan is a round immediate-release tablet, 6 mm in diameter and coated with a dark red coat (see Table 7–1). Standard of care symptomatic nonhormonal medical treatment for uterine fibroids is not considered investigational medicinal product.

Table 7–1: Identity of test drug/vilaprisan tablets

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

INN = International nonproprietary name.

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

For all study drugs, a system of numbering consistent 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 ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance 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 study file.

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

7.3 Treatment assignment

At the 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 subjects' 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

Subjects and investigators are not blinded.

Central readers for BMD and endometrial biopsies will be blinded with regard to treatment group and time point of assessment.

7.6 Drug logistics and accountability

No longer valid, since with the implementation of Protocol Amendment 10 (version 7.0) 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 consistent with 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, 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 between the visits regularly, and together with the subject at every subsequent 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[12], 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 continued with the protocol amendment 10 (Version 7.0). Please see 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 EoT was completed and an endometrial biopsy was performed.

Calcium and vitamin D were not excluded for subjects in the study, but for assessment of possible influence on BMD measurements, the intake should be documented on the concomitant medication eCRF throughout the study.

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 consistent with local standards of practice and at the investigator's discretion (see Section 9.7.1). Iron supplementation will not be considered a study medication and will be documented as concomitant medication.

8.1.2 Progestin therapy for induction of bleeding

If required, subjects 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

This section was changed in Amendment 4, see Section 15.2.1.

Before the temporary pause, it was foreseen that subjects completing the treatment periods will participate in the post treatment FUP without drug treatment. Subjects randomized to Treatment Group B continued with symptomatic nonhormonal medical treatment as

[12] 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.

determined by the investigators and/or watch and wait method. During the temporary pause, subjects randomized to Treatment Group B were not affected by the requirements of the temporary pause (as reflected in standalone Protocol Amendment 9 [version 6.0]) and were scheduled to continue with their originally planned visits and investigations. 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. Integrated Protocol Amendment 10 (version 7.0) now applies to all study subjects irrespective of the Treatment Group that they were assigned to.

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 the study, 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 10 (version 7.0) 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 which is implemented with the protocol amendment 10 (Version 7.0). 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. Likewise, subjects randomized to SoC who are still in the study will be asked to undergo these procedures.

Those subjects randomized to Treatment group B who are still in the study when Protocol Amendment 10 (version 7.0) becomes valid are also asked to undergo a DEXA scan and the comprehensive safety evaluation.

All these subjects are asked to come to the site for the "Safety closeout visit" which is implemented with the protocol amendment 10 (Version 7.0). A second scheduled visit, the "Safety result reporting visit" can be done as a telephone visit.

The "Safety closeout visit" should be performed in all subjects as soon as possible after implementation of Protocol Amendment 10 (version 7.0). 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 the amendment	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, i]	X	
Laboratory (blood) [j]	X	
Bone mineral density [k]	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. Negative pregnancy test is a prerequisite.
g. The ultrasound must be done before the biopsy
h. 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).
i. The biopsy CRF page needs to be completed for all subjects, including cases where according to protocol no biopsy is required
j. In subjects who take biotin, the last dose of biotin should be at least 72 hours prior to hormone testing.

k. This DEXA scan can be waived, if the requirements described in Section 9.6.3.8 (BMD) are fulfilled. Negative pregnancy test is a prerequisite.

CRF = case report form, BMD = bone mineral density, DEXA = dual-energy X-ray absorptiometry, incl. = including, 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 10 (version 7.0) 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 required, these should be documented as unscheduled assessments.

9.2.1 Optional pre-screening phone contact

No longer valid, since with the implementation of Protocol Amendment 10 (version 7.0) no new subjects will be recruited.

9.2.2 Scheduled visits

With the implementation of Protocol Amendment 10 (version 7.0) all subjects 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.

9.2.3 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 visit would be the requirement for follow up investigations.

9.3 Population characteristics

With implementation of Protocol Amendment 10 (version 7.0), 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.

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 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 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 section was changed in Amendment 4, see Section 15.2.1.

This set of questions has been developed as a tool to identify women with HMB. It could have been used at Visit 1 only and the responses could have been entered directly into the electronic data capturing system (RAVE), which is considered as primary source data. The questionnaire could also have been used as a pre-screening tool. A printed version 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 Ultrasound (efficacy) to assess uterine fibroids

This section was changed in Amendment 4, see Section 15.2.1.

Ultrasound examinations were performed by a well experienced examiner. If possible, the same examiner should have conducted all 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 schedule of procedures in Protocol Amendment 7 (version 5.0). 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, subject 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 10 (version 7.0), no new subjects will be recruited and no study medication or standard of care symptomatic nonhormonal will be given to the subjects who have been enrolled in the study. This Section 9.5 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 schedule of procedures in Protocol Amendment 7 (version 5.0) from subjects in Treatment Groups A1, A2, and A3 only. At the EoT Visit (Subgroup 1) and Visit 6 (Subgroup 2, Treatment Group A3) and Visit 7 (Subgroup 2, Treatment Groups A1 and A2), 3 PK samples were to be taken. The first sample was to be taken before intake of study drug. Afterwards the subject should have taken her study drug under supervision at the site. The second sample 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 vilaprisan doses prior to the first PK sample at each visit, 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.

For Subgroup 2 (Treatment Groups A1, A2, and A3), one PK sample was to be taken predose at the EoT visit. The date and time of the last 2 vilaprisan doses prior to the PK sample, the time of the supervised drug intake at the study site, and the time of the blood sample 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 should have been recorded and not the time of the time window.

If a subject discontinued study treatment permanently, no blood sampling for PK was required.

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

Pharmacokinetic analyses are based on a population modeling approach (see Section 9.5.2) using valid PK samples. 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 the calibration samples and QC 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.

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

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. 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, population PK/PD modeling could be applied 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 used to describe the PK of vilaprisan as outlined in Section 9.5.1 will be linked to relevant PD parameters (ie, fibroid size, uterus size, endocrine hormone levels, and bleeding) to investigate the (PK/PD) 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

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 signed and dated 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 on or after the first study drug intake (for Treatment Groups A1, A2, and A3) / randomization (for SoC group) until the end of FUP.

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

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

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

A serious AE (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 (ie, elective or scheduled surgery arranged before 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 medically important serious event as judged by the investigator and/or 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) (2) or in 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.

A diagnosis of 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 adverse event 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 consistent with 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 clear alternative explanation, eg, mechanical bleeding at surgical site.

or

2. Non-plausibility, eg, the subject is struck by an automobile when no indication exists 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 a reasonable suspicion exists that the AE is 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 subjects response after re-challenge should be considered in the 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 be suspected to cause 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 drug treatment, coupled with the individual subject's PD 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.

- Drug withdrawn
- Drug interrupted
- Dose not changed
- Not applicable (only option for Treatment Group B)
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- 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 adverse events

Attention is to be paid to the occurrence of AEs at all stages of the examination. Thus, all subjects 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 reporting visit, there is no requirement to actively collect new AEs including deaths.

The outcome of recorded non-serious AEs should be followed up between the signing of the informed consent and the end of the FUP phase. For adverse events of special safety interest, efforts should be made to follow them up until resolution or stabilization (even after the telephone 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 perform a separate assessment for expectedness, seriousness, and causal relationship to study drug.

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

For details on monitoring algorithms see Section 9.7.

9.6.1.4 Reporting of serious adverse events

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 11.1) 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 consistent with all applicable regulations.

Notification of the IECs/IRBs

Notification of the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) about all relevant events (eg, SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator consistent with 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 consistent with all applicable regulations.

Sponsor's notification of the investigational site

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

9.6.1.5 Expected adverse events

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 consistent with the applicable reference document and consistent with all local regulations.

9.6.1.6 Adverse events of special safety interest

This section was changed in Amendment 4, see Section 15.2.1.

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 during treatment breaks or after EoT) should be recorded as an AE (and then it automatically qualifies as an AESI) only if one or more of the following applies:
  - Leads to study discontinuation
  - Leads to diagnostic procedures
  - Requires any treatment
  - Shows a clinically significant worsening during the study that, in the judgment of the investigator, is not consistent with the expected clinical course
  - Meets any seriousness criterion and is to be recorded as an SAE

  HMB will be documented in detail throughout the study (see Section 9.7.3).
- Liver disorders:
  - For all cases which qualified for "close observation" before implementation of Protocol Amendment 10 (version 7.0) and/or qualify for "ruling out of alternative cause" after implementation of the protocol amendment 10 (Version 7.0) (see Section 9.6.3.10), 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 9.6.3.9. 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 9.6.3.2.4). The results of the PAEC assessment will only be reported back to the investigators if they trigger the request for a repeat biopsy. Apart from cases where such a repeat biopsy is necessary, no clinical action for an individual subject is required based on the PAEC assessment results. PAEC assessment results are systematically collected for all samples and will be reported in aggregated form at the end of the study. They should therefore not be reported as AE for an individual subject.

- Relevant loss of BMD during treatment:
  - BMD loss of >6% of the lumbar spine that is accompanied by a Z-score reading of <-2 SD (determined either by central reading or by assessment at the site and confirmed by the central reading at the 12 months visit or later).
  - "Lack of adequate bone recovery in subjects treated with vilaprisan or significant bone loss in subjects randomized to Treatment group B" defined as BMD loss ≥ 3% bone loss at any site and/or Z-score of ≤ -2 at any site compared to baseline, irrespective of the absolute bone loss in an off-treatment DEXA scan (determined either by central reading or by assessment at the site and confirmed by central reading).

A same systematic approach of assessment and evaluation will 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

This section was changed in Amendment 4, see Section 15.2.1.

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

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

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

In subjects who were currently pregnant or lactating when the protocol amendment 10 (Version 7.0) was implemented, timing of the safety evaluations required in the context of the safety closeout visit should have been 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 is detected before initiation of study drug, the subject will not be enrolled into the study (see Section 6.2).

The investigator must report to the sponsor any pregnancy occurring in a study subject during the subject's participation in this study. The report should be submitted within the same timelines as an SAE (ie, no later than 24 hours of having gained knowledge of the event; see Section 9.6.1.4), although a pregnancy per se is not considered an AE or SAE. The subject 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 beta 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 FUP 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 dates 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 FUP periods will be followed for the outcome for both the mother and fetus/child (in case of a live birth) until first birthday of the child. The outcome will be documented on a pregnancy outcome form and a FUP report is requested at 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 4, see Section 15.2.1.

Only blood and urine samples analyzed at the central laboratory will be considered for analysis. The name and address for the central laboratory 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 enzymes.

Biochemistry:
Glycosylated hemoglobin (HbA1c) and ferritin

Additional parameters[13]:
Hormones (follicle-stimulating hormone [FSH], luteinizing hormone [LH], estradiol [E2], progesterone [P], prolactin, and thyroid-stimulating hormone [TSH]), bone markers (bone-specific alkaline phosphatase, osteocalcin, and collagen type 1 cross-linked C-telopeptide [CTX]), 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.

---

[13] 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

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 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.

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:

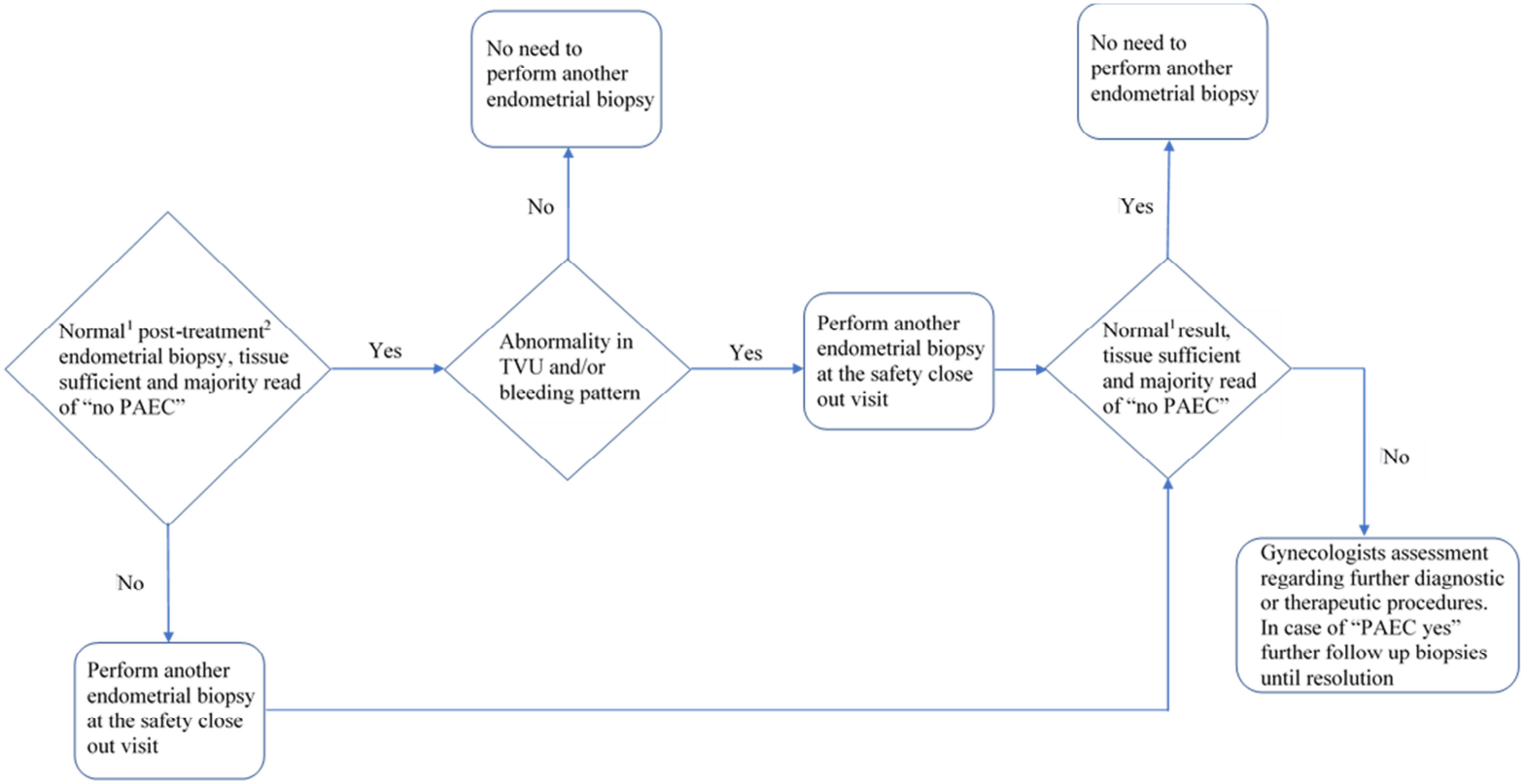
- estradiol
- vitamin D (serum 25-hydroxyvitamin D)
- **Parameters measured for adrenal monitoring:**
    - serum cortisol (to be measured between 6 am and 10 am)
        - ACTH will be assessed from the same sample if the cortisol measurement yields an abnormal value.
    - late night salivary cortisol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

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

9.6.3.2 Endometrial biopsies

9.6.3.2.1 Algorithm for evaluation of endometrial safety

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 biopsy 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 biopsy

Each subject should have an endometrial biopsy with a normal[14] 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.

Subjects 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. At least three attempts and a certified letter should be made by the site to get in contact with such subjects. The attempts should be documented in the patient file.

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 the last scheduled biopsy repeat unscheduled endometrial biopsies should be performed in addition. See Sections 9.6.3.2.5 and 9.6.3.2.7 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).

---

[14] Normal defined as: Diagnosis of safety read and 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.

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 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 this Protocol Amendment 10 (version 7.0), the majority diagnosis of the multi-reader assessment including the single reader assessment (Part II of the evaluation form, i.e. the diagnoses 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 will not be 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 evaluation 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 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[15] assessment, i.e., either by performing endometrial biopsies, until resolution (i.e. until a follow-up biopsy shows a majority diagnosis of "Benign endometrium") 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 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

---

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

features that, taken together, are characteristic. None of the features is unique, and to some extent any may be seen in patients who have not been treated with PRMs. The common histologic features are endometrial glands showing cystic dilatation and an irregular architecture lined by inactive gland cells and compact, nondecidualized stroma.

If PAECs have been detected in the biopsy at the last visit before leaving the study (i.e. at the scheduled FUP visit or at a premature discontinuation visit) according to the majority diagnosis resulting from the multi-reader assessment, the site will be informed and an additional FUP biopsy should be scheduled. In case PAEC findings are still present, the study site will be informed and an additional biopsy is to be taken to evaluate resolution, with the timepoint of this additional biopsy to be determined case-by-case. If needed, more than 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 MP or UF-DBD the subject should undergo immediate evaluation by the investigator. With the safety closeout visit a review of the bleeding data entered during the temporary pause should rule out any suspicious bleeding that would need immediate evaluation.

Standard criteria for evaluation of 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) during study drug intake (ie, during a treatment period).
- Continuous spotting:
  Evaluation should be initiated if
    - Continuous spotting is reported by the subject and/or

- if the subject entered “spotting” into the bleeding diary component of the e-diary consecutively for 10 days or more, with a maximum of 2 spotting-free 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 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 and MP, if available from the months preceding the safety closeout visit).
- Unscheduled ultrasound (if bleeding abnormality is reported outside of visit with scheduled 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 after an endometrial biopsy has been taken.

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 4, see Section 15.2.1.

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

This section was changed in Amendment 4, see Section 15.2.1.

Complete physical examination will be done for all subjects. Gynecological examination, 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)

This section was changed in Amendment 4, see Section 15.2.1.

Ultrasound examinations will be performed by a well experienced examiner. If possible, the same examiner should conduct all 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 (see Table 9–1): endometrial thickness (double layer), evaluation of ovaries, and any pathology detected during the examination. Endometrial thickness will be measured in the medio-sagittal section as double-layer in millimeters.

If endometrial thickness (double layer) >18 mm is detected after the start of treatment, the subject should undergo immediate evaluation by endometrial biopsy as described in Section 9.6.3.2.8.

If cyst like structures >30 mm without suspicious appearance (ie, functional cysts) are visualized in the ovaries after randomization, 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 electronic or paper documentation 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, subject number, time point, endometrial thickness, and side (left/right) for ovaries.

It is also possible that the site has a CD with the ultrasound images available, when in the source the evaluation of the ultrasound images from the CD is available as well. The CRA should be able to review the data on the CD and compare the images with the evaluations in the source during the onsite monitoring visits.

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

For efficacy ultrasound procedures, see Section 9.4.1.

9.6.3.7 Contraception and pregnancy test

With the implementation of Protocol Amendment 10 (version 7.0) 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 the 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 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 Bone mineral density

This section was changed in Amendment 4, see Section 15.2.1.

To document bone safety in all subjects leaving the study, a DEXA scan of the lumbar spine (lumbar anterior-posterior, L1-L4) and the hip/femoral neck will be performed as follows:

Every subject who received vilaprisan treatment should have a DEXA scan performed at the “safety closeout visit”, which in most subjects from active treatment arms corresponds to a timepoint of ≥ 12 months after last study drug intake.

This DEXA scan may be waived if the following requirement is fulfilled:

- an off-treatment DEXA scan was already performed at a timepoint with an interval of ≥ 5.5 months (22 weeks) after last study drug intake, which is of sufficient quality

(evaluable) and shows either no BMD loss[16] or adequate recovery, compared to baseline.

- Adequate recovery is defined as ≤ 1.5% bone loss in the spine and ≤ 2.5% bone loss in the total hip compared with baseline and a Z-score >-2 at any site

Subjects randomized to Treatment group B who are still in the study when Protocol Amendment 10 (version 7.0) becomes valid should also undergo a DEXA scan at the safety closeout visit, unless they had a DEXA scan performed within the last 3 months prior to the safety closeout visit.

The results of the DEXA scan performed at the safety closeout visit should be reviewed according to the following principles:

- If the safety closeout DEXA shows a BMD loss of ≥ 3% bone loss at any site and/or an abnormal Z-score (defined as ≤ -2 at any site irrespective of the absolute bone loss) compared to baseline, the subject should be referred to a local bone specialist. The results of the assessment should be captured in RAVE via update of the AE report.

If referral to a bone specialist is not required based on the criteria above the subject does not require further FUP, but should be counseled adequately for supplementation with Vit D and calcium, taking into account the Vit D measurements performed in the study context.

Technical requirements for DEXA scans:

Bone mineral density measurements will be then taken for the lumbar spine, hip, and femoral neck. To increase accuracy of the assessment, 2 measurements per location will be performed at each time point and the mean value will be used for evaluation. After the first measurement, the subject should get up and should be re-positioned for the second measurement to reduce influence of positioning on the results.

The same type of device/manufacturer for all measurements of any subject in this study should be used. Switching machine device/manufacturer during the study should be avoided.

Preferably, the same technician should conduct the examination throughout the study course of given subject. In addition to the measurement performed at the site, measurements will also be performed in a central reading by independent imaging technicians at the central reading imaging laboratory. Assessment of the screening DEXA results for subject's study eligibility and subsequent study related BMD assessments and associated decisions will be based on the central reading. The final data evaluation will be performed on results that include the correction factor from cross-calibration.

Bone mineral density measurements do not have to be done on the same day as other assessments of that visit, but have to be performed within the time window of the time points shown in Table 9–1. The BMD measurements are to be performed only after the subject has been tested negative for pregnancy using a urine pregnancy test.

More details on the calibration and procedure of central reading will be provided in a separate manual.

Cross calibration

[16] Defined as a percentage change from baseline of ≥ 0%

Phantom image acquisition will be standardized across DEXA imaging facilities participating in the 16953 Asteroid 6 study. The responsibility to schedule, ship, and monitor the rotation of cross-calibration phantoms and to collect the cross-calibration imaging rests with the cross-calibration central imaging provider. European Spine Phantoms (ESP) and a shipping container will be supplied by this provider. Instructions on cross-calibration will be specified in a manual that will be provided to all study sites. The ESP will be scanned according to the manual and the data will be sent to the cross-calibration central imaging provider for analysis. The cross-calibration central imaging provider will track the receipt of these scans and follow-up on missing data. Statistical results will summarize the relative calibration and linearity of each system participating in the study. Correction factors will be provided by the cross-calibration central imaging provider and applied by the DEXA central imaging provider.

The final data evaluation will be performed on results that include the correction factor from cross-calibration.

9.6.3.9 Adrenal monitoring

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

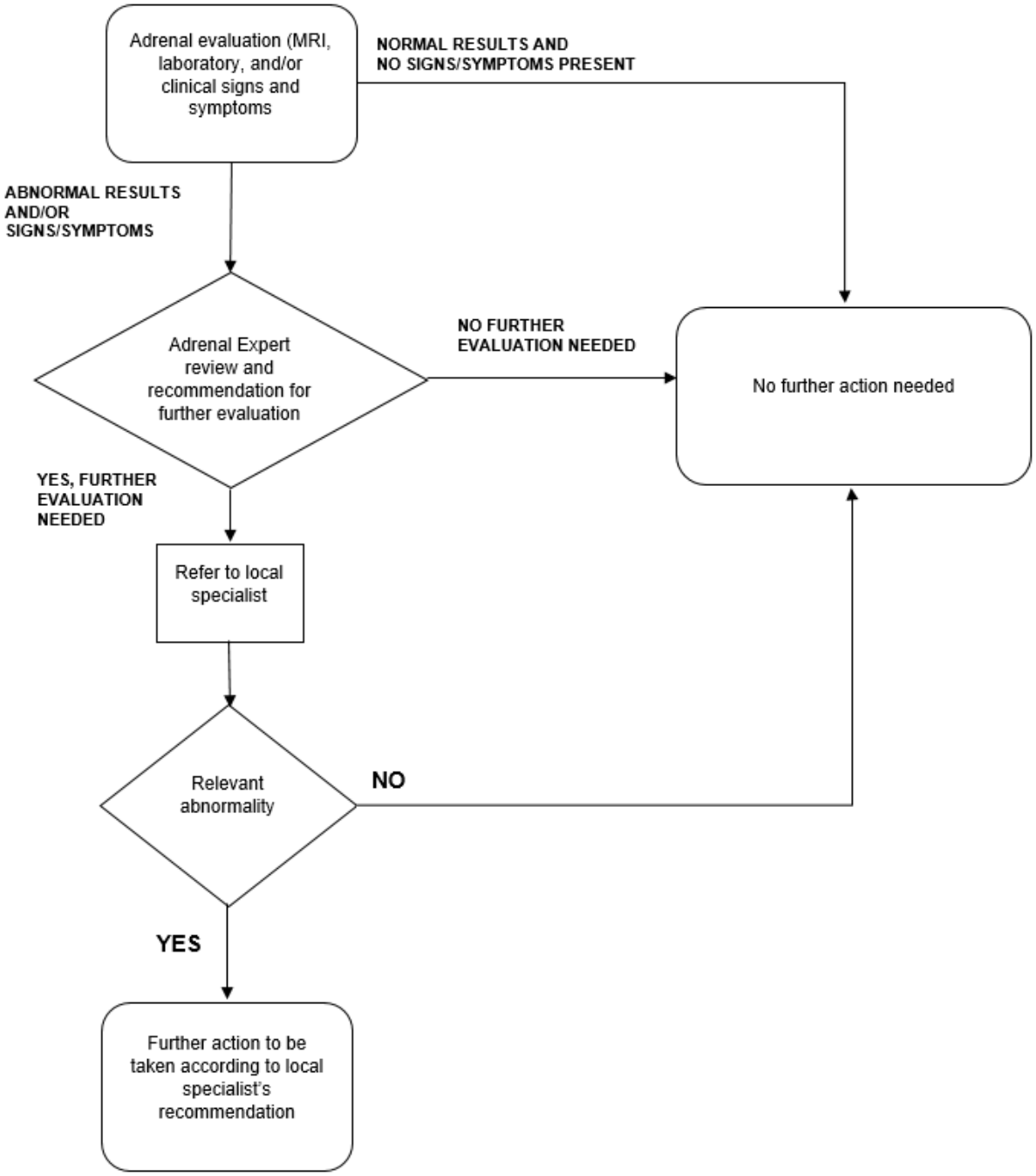
A plan for subjects showing adrenal neoplasms or hormonal abnormalities has been developed with the input of external endocrinology experts, see Adrenal monitoring algorithm below. A panel of three external clinical adrenal gland experts has been set up, that will support and guide further evaluations 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).

Figure 9–2: Adrenal monitoring algorithm



Note: 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.

Clinical signs and symptoms are to be evaluated in each subject. In case of relevant abnormalities, i.e. symptoms accompanied by laboratory abnormalities, the process described in this algorithm has to be followed.

MRI = magnetic resonance imaging

9.6.3.9.1 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 9.6.3.9.4).

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 reported and if applicable any related AEs and respective concomitant medications. At least three attempts should be made by the site to get in contact with such subjects. The attempts should be documented in the patient file.

9.6.3.9.2 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 9.6.3.9 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.

9.6.3.9.3 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 patient's

DHEA-s value by the lower limit of the age-specific reference range) will be calculated [17].

9.6.3.9.4 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[18].

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.

9.6.3.10 Liver monitoring

In the past, investigators, subjects and their family members were instructed to be alert for nonspecific symptoms which may be associated with liver dysfunction, see Section 9.6.3.11. In addition, the liver inquiry had to be completed at regular intervals. Based on the long interval between implementation of Protocol Amendment 10 (version 7.0) and last intake of study drug this is no longer needed on a routine basis.

Investigation of potential alternative 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
- 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:

---

[17] 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 >150 ng/dL and/or DHEA-s > 600 µg/dL, will trigger an assessment by one of the external adrenal panel experts.

[18] 2018 Draft Guidance for Industry: Assessment of Pressor Effects of Drugs (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinforma tion/guidances/ucm609185.pdf

- 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 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 10 (version 7.0), 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.

9.6.3.12 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. Malignant skin lesions should 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.

At least three attempts should be made by the site to get in contact with such subjects. The attempts should be documented in the patient file.

9.6.3.13 Reporting of medical device failures (Japan only)

The investigator must report immediately all non-approved medical device failures that could cause health damage, as well as any health damage that may be causally associated with a non-approved medical device failure. For this reporting, the forms provided are to be used and sent to the designated recipient.

9.6.4 Hemoglobin

This section was moved in Amendment 4, see Section 15.2.1.

Hemoglobin concentrations in blood will be measured within the safety laboratory in blood samples taken at safety closeout visit.

9.7 Other procedures and variables

9.7.1 Iron supplementation

This section was changed in Amendment 4, see Section 15.2.1.

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.(3) 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 after randomization, 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 of 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.

9.7.6 Exploratory biomarker analysis

This section was changed in Amendment 4, see Section 15.2.1.

Biomarker investigations in this study will be whole genome expression profiling from endometrial biopsy samples. Each subject, except for women included in China, has the option to choose whether her biopsy tissue samples can be used for this biomarker research or not unless precluded by local guidelines. From the subjects who have agreed by providing their particular consent, leftover material from the endometrial biopsies scheduled for histological examinations that were scheduled to be taken at the time points according to (see Table 9–1 and Section 9.6.3.2.1) will be used.

There will be no additional sampling for this part.

The explorative mRNA analysis is not part of the efficacy or safety assessment and may be performed at a later time point to characterize specific effects of vilaprisan on the endometrium. Results of this analysis will be detailed in a separate report.

Intra-individual and inter-individual analyses of the mRNA changes in the different treatment arms/regimen will be performed. This will reflect the pharmacodynamic effects of the treatment on the endometrium.

In addition to the whole genome expression profiling listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (ie, mode of action related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing studies and/or literature data.

Details on the collection, processing, storage, and shipment of samples for biomarker research will be provided in separate documents (eg, sample handling sheets or laboratory manual).

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.

The measurement of BMD by DEXA is the gold standard method for investigation of bone mass. The type, number and frequency of the BMD measurements were determined to provide valid data while limiting the exposure of radiation to the required minimum.

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 variables will be described according to their type using descriptive statistics frequencies or mean, SD, minimum, maximum, median, first and third quartiles. Where appropriate, the individual change from baseline to EoT will also be analyzed.

10.2 Analysis sets

This section was changed in Amendment 4, see Section 15.2.1.

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 of important deviations and validity findings will be provided in the Specification of assessment criteria and identification requirements.

The following statistical analysis sets will be defined:

Full analysis set (FAS): All subjects randomized to vilaprisan treatment groups, excluding randomized subjects who did not start treatment Period 1 due to the study being temporarily on hold and all subjects randomized to Treatment Group B will be included in the FAS. Subjects will be analyzed as randomized.

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

Modified SAF: will include all subjects in the SAF without any validity findings which may potentially affect the primary safety endpoint. Validity findings leading to exclusion from the modified SAF will be specified in the 'Specification of assessment criteria and identification requirements', which will be finalized before database lock. Subjects will be analyzed as treated.

All subjects randomized to Treatment Group B will be analyzed as treated, regardless whether they actually took any medication (ie, symptomatic, nonhormonal medical treatment).

All safety analyses will be performed on the SAF population. The FAS will be used for the display of all other variables. The analysis for the primary safety endpoint and all BMD related endpoints will be performed on the modified SAF as well.

10.3 Variables and planned statistical analyses

10.3.1 Variables

10.3.1.1 Primary safety variable

The primary safety variable is the percentage change in BMD of lumbar spine from baseline to about one year after SoT.

10.3.1.2 Secondary efficacy variable

This section was changed in Amendment 4, see Section 15.2.1.

- Number of bleeding days from Day 1 of the first treatment period until the day before a new treatment period would start again following the last treatment period for that respective treatment group. Number to be normalized by 28 days

10.3.1.3 Other efficacy variables

This section was changed in Amendment 4, see Section 15.2.1.

- Volume of menstrual blood loss per 28 days (assessed by MP)

- Volume of menstrual blood loss per bleeding episode (assessed by MP) for first, second, and third bleeding episode after the EoT
- Amenorrhea (yes/no), defined as menstrual blood loss <2 mL during last 28 days, based on the MP
- Absence of bleeding (spotting allowed) during the last 28 days of the treatment; based on the UF-DBD
- Time to onset of amenorrhea
  Onset of amenorrhea is defined by the first day for which the menstrual blood loss (assessed by MP) for all subsequent 28-day periods up to the end of the treatment period is <2 mL.
- Time to onset of controlled bleeding for each treatment period
  Onset of controlled bleeding is defined by the first day for which the menstrual blood loss (assessed by MP) for all subsequent 28-day periods up to the end of the treatment period is <80.00 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.
- Percent change in volume of largest fibroid compared to baseline (baseline = last value obtained before randomization; measured by ultrasound examination)
- 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
- Change in UF-DSD individual items compared to baseline
- Change in UFS-QoL scores compared to baseline
- CGI_I

10.3.1.4 Secondary safety variables

- Endometrial histology (eg, benign endometrium, presence or absence of hyperplasia or malignancy)
- Endometrial thickness
- Percentage change from baseline in BMD measured at lumbar spine (other time points not mentioned as primary safety variable), hip, and femoral neck by DEXA

10.3.1.5 Other safety variables

- Endometrial histology (diagnosis of PAEC, individual features of PAEC)

- Percentage of subjects with BMD decrease >6% and Z-score <-2 measured at the lumbar spine
- Change in Z-score over time
- Ovarian cysts (number, size)
- Laboratory parameters
- AEs
- Cervical smear
- Vital signs
- UF-DBD bleeding pattern per 28 days and 84 days
- 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)
- 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 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 Primary safety analysis

In this open-label study to assess the safety of vilaprisan as compared to standard of care. The primary analysis comprises the display of the percentage change in BMD of lumbar spine (using the central reading results corrected by the cross-calibration factor) from baseline to about one year after SoT separately in all randomized and treated subjects with measurements at baseline and about one year after SoT in each treatment group using descriptive statistical methods. Two-sided 95% confidence interval (CI) for the mean difference for the percentage change in BMD of lumbar spine from baseline to about one year after SoT will be calculated for each vilaprisan treatment group as compared to standard of care.

The primary variable is assumed to be at least approximately normal distributed.

10.3.2.3 Secondary efficacy analysis

The secondary efficacy variables will be analyzed descriptively.

10.3.2.4 Other efficacy

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

10.3.2.5 Secondary safety analysis

Percentage change in BMD of lumbar spine (other time points not mentioned as primary safety analysis), hip, and femoral neck from baseline will be analyzed using the same statistical methods as used for the primary variable. All secondary safety variables will be summarized using descriptive statistics.

10.3.2.6 Other safety analysis

Adverse events will be summarized using MedDRA. Other safety variables will be summarized using descriptive statistics.

10.3.2.7 Subgroup analysis

Subgroup analyses will be performed for Chinese women.

10.3.3 Missing data/drop outs

In this study, no statistical hypothesis is planned to be tested. The observed study data including the occurrence of missing data will be displayed using descriptive statistical methods.

10.4 Determination of sample size

No longer valid, since with implementation of Protocol Amendment 10 (version 7.0) no new subjects will be recruited and no study medication or standard of care symptomatic nonhormonal 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 original planned sample size has not been reached.

As an integral part of the development program, the sample size of this study was chosen to fulfill the regulatory requirement for safety data and is increased with this protocol version 4.0. The increased sample size will contribute to the database in which safety events of interest can be evaluated, with the main area of interest being the generation of a robust database for the evaluation of the safety of vilaprisan with regards to adverse liver events. This regulatory requirement for safety data encompasses further areas of interest, amongst them the need for adequate characterization of the effects of vilaprisan on bone mineral density and the need for sufficient data on the occurrence of relevant endometrial pathology.

These safety parameters will be evaluated based not only on the data from this study alone, but also in the context of an integrated analysis across several studies in the vilaprisan development program.

A total of 1302 subjects are planned to be randomized as follows: 372 subjects each in Treatment Groups A1, A2, and B; 186 subjects in Treatment Group A3. It is assumed that about 20% and 10% of the randomized subjects will drop out during the first and second year, respectively. It is also assumed that about 10% of the BMD measurement will not be evaluable in the first and the second year, respectively. Moreover, 60% of subjects will be assigned to Subgroup 1 and about 50% of subjects will be enrolled from the US. In addition, it is described how the primary safety variable can be precisely estimated based on the chosen sample size. For the sample size consideration, a decrease of 0.5% and a SD of ~3% for the percentage change in BMD of lumbar spine per ~1 year in Treatment Group B, at least approximately normal distribution, one-sided t-test situation and alpha=0.025 are predicted. In order to evaluate what decrease would be viewed as indicative for a medically relevant

change in BMD of lumbar spine in the active treatment arms, a publication by Carr et al was consulted. (4) This publication refers to a consultation with FDA and assumes that in a population for which no physiological decline of BMD is anticipated, a mean BMD percentage change from baseline of -1.2% and -0.5% for the spine and femur, respectively, at Weeks 24 and 48 with the lower bound of the 2-sided 95% CI around the treatment group mean percentage change from baseline in BMD not lower than -2.2% would not constitute a relevant BMD decrease. Juxtaposing this assumption to a population with a higher mean age, as it is anticipated for this study, which projects a physiological decline of BMD of about 0.5% per year, we assume that no relevant decrease of BMD is concluded from the data of this study if the lower bound of the 2-sided 95% CI around the treatment group mean percentage change from baseline in BMD is not lower than -2.7% or not lower than -2.2% relative to Treatment Group B (comparison to the untreated Treatment Group B is expected to allow for differentiation between physiological BMD decline in the target population and effect induced by study drug).

Table 10–1: Percentage change in BMD of lumbar spine from baseline to about one year after SoT relative to Treatment Group B can be ruled out with planned sample size and corresponding power

	Sample size	Percentage change from baseline in BMD can be ruled out (relative to Treatment Group B)	Power
Overall population: Treatment Group A1 or A2 versus Treatment Group B	268 versus 268	-0.84% or more	90%
US population: Treatment Group A1 or A2 versus Treatment Group B	134 versus 134	-1.19% or more	90%
Overall population: Treatment Group A3 versus Treatment Group B	134 versus 268	-1.03 or more	90%
US population: Treatment Group A3 versus Treatment Group B	67 versus 134	-1.46% or more	90%

BMD = bone mineral density; SoT = start of treatment

Table 10–2: Power to rule out -2.2% (the clinical meaningful percent change in BMD of lumbar spine from baseline to about one year after SoT relative to Treatment Group B) with planned sample size

	Sample size	Power
Overall population: Treatment Group A1 or A2 versus Treatment Group B	268 versus 268	100%
US population: Treatment Group A1 or A2 versus Treatment Group B	134 versus 134	100%
Overall population: Treatment Group A3 versus Treatment Group B	134 versus 268	100%
US population: Treatment Group A3 versus Treatment Group B	67 versus 134	99.8%

BMD = bone mineral density; SoT = start of treatment

10.5 Planned interim analyses

With the implementation of Protocol Amendment 10 (version 7.0) 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) 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 (subject 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 the data from Visit 1, Visit 2, and/or Visit 3 including visit independent folder data, if applicable (AE, concomitant medication, and medical history data)
- Endometrial biopsies results and/or ultrasound/BMD (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

Consistent with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors contacted the site before 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 consistent with the currently approved protocol (including study treatment being used consistent 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 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 and BMD measurements and the biomarker analysis.

11.4 Missing data

The main source of missing data in clinical trials is due to subjects who discontinue the assigned treatment due to AEs or lack of efficacy.

It should be underlined that the discontinuation of study treatment is not equivalent to withdrawal of informed consent. In case where a subject indicates she does not want to continue the study, the investigator must determine whether this refers to discontinuation of study treatment or unwillingness to attend the EoT visit.

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 IECs/IRBs are possible. The investigator should notify the sponsor immediately of any such inspection.

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

11.6 Archiving

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

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

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

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

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

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [eg, treatment groups, 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 any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies (eg, toxicity, teratogenicity, carcinogenicity or reproduction toxicity)
- If the study conduct (eg, recruitment rate, dropout rate, data quality, protocol compliance) does not suggest a proper completion of the study within a reasonable period.

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 consistent with 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 given by the sponsor for destruction.
- In case of a partial study closure, ongoing subjects, including those in post-study FUP, 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

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, about the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines

and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations.

Documented approval from appropriate IECs/IRBs will be obtained for all participating centers/countries before start of the study, consistent with GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and forwarded to the sponsor. The responsible unit (eg, IEC/IRB, head of the study center/medical institution) must supply to the sponsor, on 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 consistent with 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 change or alter the procedures described in this protocol.

Modifications to the study protocol will not be performed 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

This section was changed in Amendment 4, see Section 15.2.1.

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol. Additional consent will be required for participation in the biomarker research. Electronic informed consent (eConsent) is planned to be used at sites in the US.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject, before her entry into the study (ie, before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

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

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

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit description described in the Protocol Amendment 7 (version 5.0) premature discontinuation visit section 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.

If a subject who has signed the informed consent for Subgroup 1 is in screening while the Subgroup 1 reaches the required number of subjects, this subject can be assigned to Subgroup 2 if eligible by signing the informed consent for Subgroup 2 without repeating any of the screening procedures.

Only if the subject voluntarily agrees to sign the informed consent and has done so, may she enter the study. Additionally, the investigator or designee 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. A paper copy of the signed eConsent can be provided.

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

The informed consent and any other 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 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 before 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 subjects 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 subject 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 that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

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

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

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. 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.
3. 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.
4. Carr B, Dmowski WP, O'Brien C, Jiang P, Burke J, Jimenez R, et al. Elagolix, an oral GnRH antagonist, versus subcutaneous depot medroxyprogesterone acetate for the treatment of endometriosis: effects on bone mineral density. Reprod Sci. 2014;21(11):1341-51.

15. Protocol amendments

15.1 Amendment 3 – dated 13 JUN 2017

Amendment 3 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 reflect conclusions from data which was received from a drug-drug-interaction study.

The protocol was amended to exclude the use of strong CYP3A4 inducers.

Protocol sections affected include:

- Section 6.2 Exclusion criteria
- Section 8.1 Prior and concomitant therapy
- Section 16.2 Strong CYP3A4 inducers

15.1.2 Changes to the protocol text

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version. As applicable, changes to the protocol text are highlighted as follows:

1. **Addition of a whole new portion**	Brief identification of the new portion
2. **Removal of a whole portion**	Complete display of the removed portion, formatted as ~~crossed out~~

3. **Editing of an existing portion**	Comparative presentation of "old text" versus "new text", with "old text" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "old text". Additions are <u>underlined</u> in the "new text".
• **Tables / figures**	The term "amended" is added to the caption.
• **Terminological changes**	Brief specification of the terminological change Thus, in this section, a terminological change (e.g. "period" versus "epoch") is defined only once, without displaying "old text" versus "new text" for each appearance.

Corrections of typos are not highlighted in this section.

15.1.2.1 Section 6.2 Exclusion criteria

Exclusion criterion 5

Old text:

[…]

- Intake of strong cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors within the last 2 weeks before ~~first study drug intake~~ and during the treatment period including: antivirals (eg, viekira pak, telaprevir, boceprevir), protease inhibitors (eg, ritonavir, lopinavir, indinavir, nelfinavir, saquinavir), antifungals (eg, itraconazole, voriconazole, posaconazole), antibiotics (eg, clarithromycin, telithromycin), grapefruit and any grapefruit containing food products (eg, grapefruit juice). Metronidazole, ketoconazole and other triazole antifungal drugs are allowed for topical/local use (including vaginal application) within the last 2 weeks before ~~first study drug intake~~ and during the treatment period.

New text:

[…]

- Intake of strong cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors within the last 2 weeks before <u>the randomization visit</u> and during the treatment period including: antivirals (eg, viekira pak, telaprevir, boceprevir), protease inhibitors (eg, ritonavir, lopinavir, indinavir, nelfinavir, saquinavir), antifungals (eg, itraconazole, voriconazole, posaconazole), antibiotics (eg, clarithromycin, telithromycin), grapefruit and any grapefruit containing food products (eg, grapefruit juice). Metronidazole, ketoconazole and other triazole antifungal drugs are allowed for topical/local use (including vaginal application) within the last 2 weeks before <u>the randomization visit</u> and during the treatment period. <u>A detailed list is provided in Section 16.1.</u>
- <u>Intake of strong CYP3A4 inducers (eg, rifampicin, rifabutin, carbamazepine, phenytoin, phenobarbital, St John´s wort [hypericum]) within the last 2 weeks</u>

before the randomization visit and during the treatment period. A detailed list is provided in Section 16.2.

15.1.2.2 Section 8.1 Prior and concomitant therapy

Old text:

[…]
For prohibited prior and concomitant medication, see Section 6.2. Prohibited strong CYP3A4 inhibitors are listed in Table 16-1.

New text:

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

15.1.2.3 Section 16.2 Strong CYP3A4 inducers

New section, no old text

Table 16-2: Strong CYP3A4 inducers

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

15.2 Amendment 4 – dated 13 SEP 2017

15.2.1 Overview of the changes to the study

Amendment 4 is the second global amendment. The following is an overview of the changes made to the integrated protocol Version 2.0.

15.2.1.1 Change 1: Changes requested by health authorities

Changes requested by health authorities (HA) and updated wording based on discussions with other Health Authorities and Ethic Committees deemed to provide further helpful clarification.

Rationale:

These changes were implemented as requested by the Norwegian HA and also the wording was updated based on discussions with other Health Authorities and Ethic Committees to provide further helpful clarification.

Sections affected by exact request of the Norwegian HA: Section 3 Introduction, Section 5 Study design

Other affected sections: Section 6.4.1 Withdrawal, Sections 9.2.2.1-9.2.2.12 Visit descriptions, Section 9.6.2 Pregnancies, Section 9.6.3.7 Contraception and pregnancy test, Section 9.7.5 Induction of bleeding

15.2.1.2 Change 2: Removal of Rifabutin from the examples of strong CYP3A4 inducers

Rifabutin was removed from the list of strong CYP3A4 inducers in exclusion criteria 4

Rationale:

Rifabutin is a moderate CYP3A4 inducer and was therefore removed from the examples of strong CYP3A4 inducers.

Affected section: Section 6.2 Exclusion criteria

15.2.1.3 Change 3: Revision of prior and concomitant therapy

Section 8.1 Prior and concomitant therapy was revised

Rationale:

This section was revised to minimize the risk that hormonal treatment is started before the endometrial biopsy is taken.

Affected section: Section 8.1 Prior and concomitant therapy

15.2.1.4 Change 4: Modifications on the tabular schedule of evaluations

Footnotes were modified.

Rationale:

Footnotes were revised to reflect the actual requirements correctly.

Affected section: Section 9.1 Tabular schedule of evaluations

15.2.1.5 Change 5: Gynecological examination was added to the premature discontinuation visit

Gynecological examination was added to the visit description of the premature discontinuation visit.

Rationale:

The visit description was revised to ensure that subjects who prematurely discontinue during the treatment phase get those gynecological examinations, including the cervical smear

performed in order to make sure that they did not develop any abnormalities during the treatment.

Affected section: Section 9.2.4 Premature discontinuation visit

15.2.1.6 Change 6: Ultrasound personnel

Ultrasound can be performed by an experienced examiner.

Rationale:

Revised to clarify that the ultrasound does not necessarily have to be performed by a physician as this is not common practice in all participating countries.

Affected sections: Section 9.4.2 Ultrasound (efficacy) to assess uterine fibroids, Section 9.6.3.6 Ultrasound (safety)

15.2.1.7 Change 7: Section on Hemoglobin was moved

Section on hemoglobin was moved from efficacy to safety.

Rationale:

Changes in hemoglobin are regarded as safety parameter and therefore the section on hemoglobin was added to the safety section.

Affected sections: Section 9.4.3 Hemoglobin, Section 9.6.4 Hemoglobin

15.2.1.8 Change 8: Rewording sampling of endometrial biopsies

Rationale:

Description of sampling of endometrial biopsies was revised to make sure that the biopsy sampling via a disposable device Pipelle de Cornier does not require a hysteroscopy.

Affected section: Section 9.6.3.2.2 Sampling of endometrial biopsies

15.2.1.9 Change 9: Correction of the number of enrolled subjects

Rationale:

The originally wrongly displayed number was corrected in order to be consistent with the planned number.

Affected section: Section 2 Synopsis

15.2.1.10 Change 10: 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 3 Introduction, Section 6.1 Inclusion criteria, Section 6.4.1 Withdrawal, Section 7.1 Treatments to be administered, Section 8.2 Post-study therapy,

Section 9.3.4 Heavy menstrual bleeding questions, Section 9.6.1.6 Adverse events of special interest, Section 9.6.3.1 Laboratory evaluations, Section 9.6.3.2.3 Assessment of endometrial biopsies, Section 9.6.3.3 Cervical smear, Section 9.6.3.4 Physical and gynecological evaluations, Section 9.7.1 Iron Supplementation, Section 10.3.1.2 Secondary efficacy variable, Section 10.3.1.3 Other efficacy variables, Section 13.4 Subject information and consent

15.2.2 Changes to the protocol text

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version. As applicable, changes to the protocol text are highlighted as follows:

4. **Addition of a whole new portion**	Brief identification of the new portion
5. **Removal of a whole portion**	Complete display of the removed portion, formatted as ~~crossed out~~
6. **Editing of an existing portion**	Comparative presentation of "old text" versus "new text", with "old text" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "old text". Additions are underlined in the "new text".
• **Tables / figures**	The term "amended" is added to the caption.
• **Terminological changes**	Brief specification of the terminological change Thus, in this section, a terminological change (e.g. "period" versus "epoch") is defined only once, without displaying "old text" versus "new text" for each appearance.

Corrections of typos are not highlighted in this section.

15.2.2.1 Section 2 Synopsis

Old text:

[…]

Number of subjects	About ~~2100~~ subjects will be enrolled in order to achieve the planned number of randomized subjects. A total of 1050 subjects are planned to be randomized as follows: 300 subjects each in Treatment Groups A1, A2, and B; 150 subjects in Treatment Group A3 The sample size was chosen to fulfill the regulatory requirements for safety data.

[…]

New text:

[…]

Number of subjects	About 1750 subjects will be enrolled in order to achieve the planned number of randomized subjects. A total of 1050 subjects are planned to be randomized as follows: 300 subjects each in Treatment Groups A1, A2, and B; 150 subjects in Treatment Group A3 The sample size was chosen to fulfill the regulatory requirements for safety data.

[…]

15.2.2.2 Section 3 Introduction

Old text:

[…]

Not surprisingly, many women would prefer not to have surgery at all. A US based national survey revealed that 84% of women under the age of 40 with symptoms related to their uterine fibroids thought that it was important to have a leiomyoma treatment option that did not involve invasive surgery (7). Therefore, there is a great medical need for effective pharmacological treatment suitable for long-term treatment of uterine fibroids. Unfortunately, there is no approved medical therapy in the US that addresses this need for a prolonged treatment strategy that can serve as an acceptable alternative to surgery.

[…]

Safety data also showed a favorable safety profile with no relevant safety concerns.

The investigator's brochure (IB) contains further comprehensive information on the study drug.

New text:

[…]

Not surprisingly, many women would prefer not to have surgery at all. A US based national survey revealed that 84% of women under the age of 40 with symptoms related to their uterine fibroids thought that it was important to have a leiomyoma treatment option that did not involve invasive surgery (7). Therefore, there is a great medical need for effective pharmacological treatment suitable for long-term treatment of uterine fibroids. Unfortunately, there is no approved medical therapy in the US and Japan that addresses this need for a prolonged treatment strategy that can serve as an acceptable alternative to surgery.

[…]

Safety data also showed a favorable safety profile with no relevant safety concerns. Based on the results of these studies it is expected that the significant benefits of vilaprisan shown over up to 2 treatment courses will translate to similarly significant benefits in patients randomized to vilaprisan treatment in the phase 3 studies, which will have a duration of up to 8 treatment courses.

The investigator's brochure (IB) contains further comprehensive information on the study drug.

15.2.2.3 Section 5 Study design

Old text:

[…]

During the screening period, subjects will have to demonstrate eligibility including presence of at least 1 uterine fibroid, at least one symptom of uterine fibroid(s), and an endometrial biopsy result without significant histological disorder.

[…]

Justification of the design

Comparators:

Standard of care symptomatic nonhormonal medical treatment and watch and wait are considered appropriate to examine comparative safety and efficacy of vilaprisan versus available treatment option(s). Hormonal medical treatments and surgical interventions are not permitted as comparators.

[…]

It is anticipated that the number of days with HMB per time interval (eg, 12 months) will be reduced in the 6/2 and 3/1 regimens as compared to the 3/2 regimen, which is considered a clinically relevant benefit for patients.

[…]

Safety monitoring:

Safety parameters will be regularly and closely monitored throughout the study (eg, questioning for AEs, measurement of laboratory values, vital signs, endometrial thickness, abnormal menstrual bleeding, and size of follicle-like structures comprising follicles and functional ovarian cysts). Normal or clinically insignificant results of these parameters as well as from an endometrial biopsy are prerequisites for randomization to treatment. Criteria for withdrawal of individual subjects or termination of the entire study are described in Sections 6.4 and 12, respectively.

[…]

Clear decision trees are outlined as to when to perform an unscheduled endometrial biopsy in case of endometrial thickening and/or on the clinical management of endometrial thickening/HMB/abnormal menstrual bleeding pattern (see Section 9.7.2).

PRMs such as vilaprisan induce a degree of ovulation suppression, accompanied by a moderate decrease in endogenous estradiol levels.

[…]

However, possible risks are regarded as acceptable because the planned methods are used routinely in clinical studies, clinical and/or gynecological practice. Adverse effects will be monitored throughout the study, with systematic monitoring of parameters of special interest (eg, endometrial thickness and volume of menstrual bleeding).

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

[…]

New text:

[…]

During the screening period, subjects will have to demonstrate eligibility including presence of at least 1 uterine fibroid documented by ultrasound at screening and / or during a uterine preserving procedure within 3 months prior to screening, at least one symptom of uterine fibroid(s), and an endometrial biopsy result without significant histological disorder.

[…]

Justification of the design

Comparators:

Standard of care symptomatic nonhormonal medical treatment and watch and wait are considered appropriate to examine comparative safety and efficacy of vilaprisan versus available treatment option(s). Hormonal medical treatments and surgical interventions are not permitted as comparators. The fact that in all study treatment arms active treatment is provided, translates into a comparable level of benefit for all enrolled patients.

[…]

It is anticipated that the number of days with HMB per time interval (eg, 12 months) will be reduced in the 6/2 and 3/1 regimens as compared to the 3/2 regimen, which is considered a clinically relevant benefit for patients. The safety of all tested regimens is continuously monitored throughout the study, via scheduled assessment at pre-defined intervals and via pre-defined criteria for unscheduled assessments (eg, unscheduled biopsies or temporary discontinuation in case of defined break-through bleeding as well as regular laboratory and ultrasound examinations).

[…]

Safety monitoring:

Safety parameters will be regularly and closely monitored throughout the study (eg, questioning for AEs, measurement of laboratory values, vital signs, endometrial thickness, abnormal menstrual bleeding, and size of follicle-like structures comprising follicles and functional ovarian cysts). Normal or clinically insignificant results of these parameters as well as from an endometrial biopsy are prerequisites for randomization to treatment. Criteria for withdrawal of individual subjects or termination of the entire study are described in Sections 6.4 and 12, respectively. Section 9.7 contains instructions for assessment and/or follow-up of specific findings such as eg, ovarian cysts or endometrial thickness over 18 mm.

[…]

Clear decision trees are outlined as to when to perform an unscheduled endometrial biopsy in case of endometrial thickening and/or on the clinical management of endometrial thickening/HMB/abnormal menstrual bleeding pattern (see Section 9.7.2). 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 participants.

PRMs such as vilaprisan induce a degree of ovulation suppression, accompanied by a moderate decrease in endogenous estradiol levels.

[…]

However, possible risks are regarded as acceptable because the planned methods are used routinely in clinical studies, clinical and/or gynecological practice. Adverse effects, both related to study drug and related to study procedures, will be monitored throughout the study, with systematic monitoring of parameters of special interest (eg, endometrial thickness and volume of menstrual bleeding).

The overall benefit-risk assessment for the present study is considered favorable based on the available data. Vilaprisan is expected to provide efficacious long-term management of symptoms associated with uterine fibroids. Potential safety risks have been identified and will be closely monitored during the further clinical program. It is expected that the information gained from the study will help in the development of better treatment for women with uterine fibroids in the future. For further information on the data available from previous studies with vilaprisan, please refer to the Investigator's brochure (IB).

[…]

15.2.2.4 Section 6.1 Inclusion criteria

Old text:

[…]

4. Symptoms of uterine fibroids documented by one or more of the following symptoms:
   - Heavy menstrual bleeding (HMB) >80.0 mL documented by menstrual pictogram (MP) in a bleeding period[2] during the screening period

[…]

New text:

[…]

4. Symptoms of uterine fibroids documented by one or more of the following symptoms:
   - Heavy menstrual bleeding (HMB) >80.00 mL documented by menstrual pictogram (MP) in a bleeding period[2] during the screening period

[…]

15.2.2.5 Section 6.2 Exclusion criteria

Old text:

[…]

- Intake of strong CYP3A4 inducers (eg, rifampicin, ~~rifabutin,~~ carbamazepine, phenytoin, phenobarbital, St John´s wort [hypericum]) within the last 2 weeks before the randomization visit and during the treatment period. A detailed list is provided in Section 16.2.

[…]

- Anticoagulants, if not stopped at Visit 1
- Raloxifene, fluoride, calcitonin, if not stopped 3 months before the start of the screening period
- Current intake (ie, at Visit 1) of bisphosphonates, parathyroid hormone, ~~GnRH agonists,~~ GnRH antagonists, vitamin D analogues, systemic corticosteroids or other agents known or suspected to affect bone metabolism

[…]

New text:

[…]

- Intake of strong CYP3A4 inducers (eg, rifampicin, carbamazepine, phenytoin, phenobarbital, St John´s wort [hypericum]) within the last 2 weeks before the randomization visit and during the treatment period. A detailed list is provided in Section 16.2.

[…]

- Anticoagulants, if not stopped at Visit 1
- Raloxifene (or similar SERMs), fluoride, calcitonin, if not stopped 3 months before the start of the screening period
- Current intake (ie, at Visit 1) of bisphosphonates, parathyroid hormone, GnRH antagonists, vitamin D analogues, systemic corticosteroids or other agents known or suspected to affect bone metabolism

[…]

15.2.2.6 Section 6.4.1 Withdrawal

Old text:

[…]

- At the specific request of the sponsor and in liaison with the investigator (eg, obvious non-compliance, safety concerns).
- ~~In case induction of bleeding becomes necessary more than once per subject during the study~~
- Pregnancy

[…]

- GPT/ALT or GOT/AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia
- Atypical hyperplasia, endometrial intraepithelial neoplasia (EIN) or malignant neoplasm
- In the event excessive loss of BMD >6% at the lumbar spine is accompanied by a Z-score reading of <-2 standard deviations (SD) (determined either by the central reading imaging laboratory or by assessment at the site and confirmed by the central reading imaging laboratory at the 12 month visit or later). For additional details and follow-up procedures for these subjects see Section 9.6.3.8.

[…]

New text:

[…]

- At the specific request of the sponsor and in liaison with the investigator (eg, obvious non-compliance, safety concerns).
- Pregnancy

[…]

- GPT/ALT or GOT/AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper <u>abdominal</u> quadrant pain or tenderness, fever, rash, and/or eosinophilia
- Atypical hyperplasia, endometrial intraepithelial neoplasia (EIN) or malignant neoplasm
- In the event excessive loss of BMD >6% at the lumbar spine is accompanied by a Z-score reading of <-2 standard deviations (SD) (determined either by the central reading imaging laboratory or by assessment at the site and confirmed by the central reading imaging laboratory at the 12 month visit or later). For additional details and follow-up procedures for these subjects see Section 9.6.3.8.
- <u>In case induction of bleeding becomes necessary more than once per subject during the study</u>

[…]

15.2.2.7 Section 7.1 Treatments to be administered

Old text:

[…]

The assignment to the 2 subgroups will be done in a sequential manner, with the first 50% being recruited into Subgroup 1 and the remainder into Subgroup 2. Subjects will be randomized to treatment groups A1:A2:A3:B in a 2:2:1:2 manner. ~~Randomization to treatment will be stratified by region/country.~~

In Groups A1 and A3, each treatment period will consist of 12 weeks (84 days). In Group A2, each treatment period will be 24 weeks (1~~8~~8 days). One tablet is 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 ~~in Groups A1, A2, and A3~~ will start within Days 3 to 7 of the first bleeding episode following randomization ~~or which~~ is ongoing at randomization. A negative pregnancy test is a prerequisite for starting study drug (applies to all treatment periods).

[…]

New text:

[…]

The assignment to the 2 subgroups will be done in a sequential manner, with the first 50% being recruited into Subgroup 1 and the remainder into Subgroup 2. Subjects will be randomized to treatment groups A1:A2:A3:B in a 2:2:1:2 manner. Some of the local regulatory agencies requested a minimum number of subjects included into the study and well balanced with respect to treatment received. Therefore randomization to treatment will be stratified by region/country (US, Japan, China and all other countries).

In Groups A1 and A3, each treatment period will consist of 12 weeks (84 days). In Group A2, each treatment period will be 24 weeks (168 days). One tablet is 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 study drug (applies to all treatment periods).

[…]

15.2.2.8 Section 8.1 Prior and concomitant therapy

Old text:

[…]

Subjects who withdraw from study drug and subjects who withdraw during FUP should not receive hormonal treatments before the first menstruation after EoT is completed and ~~the EoT~~ biopsy was performed. ~~This is true only for subjects randomized to Treatment Groups A1, A2, and A3.~~

[…]

New text:

[…]

Subjects who withdraw from study drug and subjects who withdraw during FUP should not receive hormonal treatments before the first menstruation after EoT is completed and an endometrial biopsy was performed.

[…]

15.2.2.9 Section 8.2 Post-study therapy

Old text:

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

[…]

New text:

Subjects completing the treatment period will participate in the post-treatment FUP without study drug treatment. Subjects randomized to Treatment Group B may continue with symptomatic nonhormonal medical treatment as determined by the investigators and/or watch and wait method.

[…]

15.2.2.10 Section 9.1 Tabular schedule of evaluations

Old text:

[…]

Table 9–1

[…]	
Ultrasound examination [d]	[…]
[…]	

[…]

a If no bleeding episode occurs within 7 weeks after the end of a treatment period (for Groups A1, A2, and A3), or if the second bleeding episode does not occur within 7 weeks after the end of the first bleeding episode (for Groups A2 and A3 only), the scheduled ultrasound will be performed as planned after which bleeding will be induced. ~~The scheduled endometrial biopsy will be performed thereafter at Day 7 to 15 (inclusive) of the induced bleeding. An ultrasound and pregnancy test will be performed before the endometrial biopsy as described in Section 9.6.3.2.2.~~ See Section 9.7.5 for details. In case induction of bleeding becomes necessary more than once (per subject) no further treatment will be given to this subject.

[…]

d 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. 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 every 4 weeks or more frequently, if required due to symptoms.

[…]

f If no bleeding episode occurs 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, FUP visit) will be performed at Day 7 to 15 (inclusive) of the ~~first menstrual cycle after the induced bleeding~~ episode. An ultrasound and pregnancy test will be performed before the endometrial biopsy as described in Section 9.6.3.2.2. See Section 9.7.5 for details.

g The DEXA scan should be done between Week 50-54 after the start of treatment. At Visit 5 at the latest, determine the exact date for the DEXA measurement and schedule the scan for the BMD visit. ~~Instruct subjects to bring a home pregnancy test to the site to take before the DEXA scan.~~ In the event excessive loss of BMD >6% at the lumbar spine is accompanied by a Z-score reading of <-2 SD (determined either by the central reading imaging laboratory or by assessment at the site and confirmed by the central reading imaging laboratory at the 12 month visit or later), study drug must be discontinued. For additional details and follow-up procedures for these subjects see Section 9.6.3.8.

[…]

Table 9–2

[…]	
Ultrasound examination [d]	[…]
[…]	

[…]

a If no bleeding episode occurs within 7 weeks after the end of a treatment period (for Groups A1, A2, and A3), or if the second bleeding episode does not occur within 7 weeks after the end of the first bleeding episode (for Groups A2 and A3 only), the scheduled ultrasound will be performed as planned after which bleeding will be induced. ~~The scheduled endometrial biopsy will be performed thereafter at Day 7 to 15 (inclusive) of the induced bleeding. An ultrasound and pregnancy test will be performed before the endometrial biopsy as described in Section 9.6.3.2.2.~~ See Section 9.7.5 for details. In case induction of bleeding becomes necessary more than once (per subject) no further treatment will be given to this subject.

[…]

d 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. 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 every 4 weeks or more frequently, if required due to symptoms.

[…]

f If no bleeding episode occurs 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, FUP visit) will be performed at Day 7 to 15 (inclusive) of the first menstrual cycle after the induced bleeding episode. An ultrasound and pregnancy test will be performed before the endometrial biopsy as described in Section 9.6.3.2.2. See Section 9.7.5 for details.

g The DEXA scan should be done between Week 50-54 after the start of treatment. At Visit 5 at the latest, determine the exact date for the DEXA measurement and schedule the scan for the BMD visit. ~~Instruct subjects to bring a home pregnancy test to the site to take before the DEXA scan.~~ In the event excessive loss of BMD >6% at the lumbar spine is accompanied by a Z-score reading of <-2 SD (determined either by the central reading imaging laboratory or by assessment at the site and confirmed by the central reading imaging laboratory at the 12 month visit or later), study drug must be discontinued. For additional details and follow-up procedures for these subjects see Section 9.6.3.8.

[…]

New text:

[…]

Table 9–1

[…]	
Ultrasound examination **d1, d2**	[…]
[…]	

[…]

a If no bleeding episode occurs within 7 weeks after the end of a treatment period (for Groups A1, A2, and A3), or if the second bleeding episode does not occur within 7 weeks after the end of the first bleeding episode (for Groups A2 and A3 only), the scheduled ultrasound will be performed as planned after which bleeding will be induced. See Section 9.7.5 for details. In case induction of bleeding becomes necessary more than once (per subject) no further treatment will be given to this subject.

[…]

d1 Ultrasound measurements do not have to be done on the same day as other assessments of that visit, but have to be performed as close to the specified visit as possible.

d2 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. 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 every 4 weeks or more frequently, if required due to symptoms.

[…]

f If no bleeding episode occurs within 7 weeks after the EoT, the scheduled ultrasound will be performed as planned after which bleeding will be induced. For group A1, the scheduled endometrial biopsy (ie, at endometrial biopsy FUP visit) will be performed at Day 7 to 15 (inclusive) of the induced bleeding episode. For Groups A2, A3 and B, the planned endometrial biopsy will be performed at Day 7 to 15 (inclusive) of the first menstrual cycle after the induced bleeding episode. An ultrasound and pregnancy test will be performed before the endometrial biopsy as described in Section 9.6.3.2.2. See Section 9.7.5 for details.

g The DEXA scan should be done between Week 50-54 after the start of treatment. At Visit 5 at the latest, determine the exact date for the DEXA measurement and schedule the scan for the BMD visit. In the event excessive loss of BMD >6% at the lumbar spine is accompanied by a Z-score reading of <-2 SD (determined either by the central reading imaging laboratory or by assessment at the site and confirmed by the central reading imaging laboratory at the 12 month visit or later), study drug must be discontinued. For additional details and follow-up procedures for these subjects see Section 9.6.3.8.

[…]

Table 9–2

[…]	
Ultrasound examination **d1, d2**	[…]
[…]	

[…]

a If no bleeding episode occurs within 7 weeks after the end of a treatment period (for Groups A1, A2, and A3), or if the second bleeding episode does not occur within 7 weeks after the end of the first bleeding episode (for Groups A2 and A3 only), the scheduled ultrasound will be performed as planned after which bleeding will be induced. See Section 9.7.5 for details. In case induction of bleeding becomes necessary more than once (per subject) no further treatment will be given to this subject.

[…]

d1 Ultrasound measurements do not have to be done on the same day as other assessments of that visit, but have to be performed as close to the specified visit as possible.

d2 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. 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 every 4 weeks or more frequently, if required due to symptoms.

[…]

f If no bleeding episode occurs within 7 weeks after the EoT, the unscheduled ultrasound will be performed after which bleeding will be induced. The scheduled endometrial biopsy (ie, at FUP visit) will be performed at Day 7 to 15 (inclusive) of the induced bleeding episode. An ultrasound and pregnancy test will be performed before the endometrial biopsy as described in Section 9.6.3.2.2. See Section 9.7.5 for details.

g The DEXA scan should be done between Week 50-54 after the start of treatment. At Visit 5 at the latest, determine the exact date for the DEXA measurement and schedule the scan for the BMD visit. In the event excessive loss of BMD >6% at the lumbar spine is accompanied by a Z-score reading of <-2 SD (determined either by the central reading imaging laboratory or by assessment at the site and confirmed by the central reading imaging laboratory at the 12 month visit or later), study drug must be discontinued. For additional details and follow-up procedures for these subjects see Section 9.6.3.8.

[…]

15.2.2.11 Sections 9.2.2.1-9.2.2.12 Visit descriptions for visits 1-10, EoT Visit and FUP 1

Old text:

[…]

- Dispense condoms with spermicide (see Section 9.6.3.7)

[…]

At Visit 5 at the latest, determine the exact date for the DEXA measurement ~~at Visit 6~~ (between Week 50 to 54 after the start of treatment) and schedule the scan for ~~Visit 6. Instruct the subject to bring a home pregnancy test to the site to take before the DEXA scan.~~

New text:

[…]

- Dispense barrier contraception, eg, condoms with spermicide (see Section 9.6.3.7)

[…]

At Visit 5 at the latest, determine the exact date for the DEXA measurement (between Week 50 to 54 after the start of treatment) and schedule the scan for the BMD visit.

15.2.2.12 Section 9.2.2.5 BMD Visit – Subgroups 1 and 2

Old text:

The following procedures will be performed during this visit:

- Urine pregnancy test (see Section 9.6.3.7)

[…]

New text:

The following procedures will be performed during this visit:

- Urine pregnancy test or result of a home pregnancy test done on the same day and as reported by subject (see Section 9.6.3.7)

[…]

15.2.2.13 Section 9.2.4 Premature discontinuation visit

Old text:

Subjects who discontinue the study prematurely during a treatment period should have the EoT visit performed. If no endometrial biopsy is planned at the EoT visit (Subgroup 1), then a biopsy should be taken to document endometrial safety before the subject leaves the study.

[…]

New text:

Subjects who discontinue the study prematurely during a treatment period should have the EoT visit performed. If no endometrial biopsy is planned at the EoT visit (Subgroup 1), then a biopsy should be taken to document endometrial safety before the subject leaves the study. In addition to the assessments scheduled for the EoT visit, a gynecological examination including breast palpation and a cervical smear should be done for the subjects prematurely withdrawing during the treatment phase.

[…]

15.2.2.14 Section 9.3.4 Heavy menstrual bleeding questions

Old text:

[…]

The questionnaire can also be used as a pre-screening tool.

New text:

[…]

The questionnaire can also be used as a pre-screening tool. A printed version of the questionnaire can be provided to the sites as needed.

15.2.2.15 Section 9.4.2 Ultrasound (efficacy) to assess uterine fibroids

Old text:

Ultrasound examinations will be performed by a ~~physician~~ well experienced ~~in gynecology~~. If possible, the same examiner should conduct all examinations of a subject throughout the study and the same ultrasound machine (per site) should be used throughout the study.

[…]

New text:

Ultrasound examinations will be performed by a well experienced examiner. If possible, the same examiner should conduct all examinations of a subject throughout the study and the same ultrasound machine (per site) should be used throughout the study.

[…]

15.2.2.16 Section 9.4.3 Hemoglobin

This was moved from Section 9.4.3 to Section 9.6.4.

15.2.2.17 Section 9.6.1.6 Adverse events of special interest

Old text:

[…]

Progesterone receptor modulator-associated endometrial changes (PAEC) will be assessed and documented in a systematic way (see Section 9.6.3.2.4). The results of the PAEC assessment will ~~normally not~~ be reported back to the investigators ~~and~~ therefore not be reported as AE. The same systematic approach of assessment and evaluation will be applied to HMB (see Sections 9.4.1.1 and 9.7.3), endometrial hyperplasia and endometrial thickening (see Sections 9.7.2 and 9.7.4), and liver function test.

New text:

[…]

Progesterone receptor modulator-associated endometrial changes (PAEC) will be assessed and documented in a systematic way (see Section 9.6.3.2.4). The results of the PAEC assessment will only be reported back to the investigators if they trigger the request for a repeat biopsy. Apart from cases where such 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 individual subject. The same systematic approach of assessment and evaluation will be applied to HMB (see Sections 9.4.1.1 and 9.7.3), endometrial hyperplasia and endometrial thickening (see Sections 9.7.2 and 9.7.4), and liver function test.

15.2.2.18 Section 9.6.2 Pregnancies

Old text:

An acceptable nonhormonal contraceptive method has to be used starting at Screening Visit 1 and continued until the end of the study. ~~C~~ondoms with spermicide will be dispensed as required by the subject.

[…]

New text:

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.

[…]

15.2.2.19 Section 9.6.3.1 Laboratory evaluations

Old text:

Only blood samples analyzed at the central laboratory will be considered for analysis.

[…]

New text:

Only blood and urine samples analyzed at the central laboratory will be considered for analysis.

[…]

15.2.2.20 Section 9.6.3.2.2 Sampling of endometrial biopsies

Old text:

[…]

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, and generally requires no local anesthesia or cervical dilatation.

[…]

New text:

[…]

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.

[…]

15.2.2.21 Section 9.6.3.2.3 Assessment of endometrial biopsies

Old text:

[…]

- Eligibility of the subject before randomization (biopsy at Visit 2)
- Absence of clinically relevant endometrial pathology after about 1 year of treatment and before subjects will leave the study.

[…]

The results of the PAEC assessment will normally not be reported back to the investigators.

New text:

[…]

- Eligibility of the subject before randomization (biopsy at Visit 2)
- Any relevant pathology that requires further diagnostic or therapeutic measures according to local medical practice.
- Absence of clinically relevant endometrial pathology after about 1 year of treatment and before subjects will leave the study.

[…]

The results of the PAEC assessment will normally not be reported back to the investigators.
Further details are included in the Operational Manual.

15.2.2.22 Section 9.6.3.3 Cervical smear

Old Text

[…]

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

[…]

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.

15.2.2.23 Section 9.6.3.4 Physical and gynecological evaluations

Old text:

[…]

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

New text:

[…]

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).

15.2.2.24 Section 9.6.3.6 Ultrasound (safety)

Old text:

Ultrasound examinations will be performed by a ~~physician~~ well experienced ~~in gynecology~~.

[…]

New text:

Ultrasound examinations will be performed by a well experienced examiner.

[…]

15.2.2.25 Section 9.6.3.7 Contraception and pregnancy test

Old text:

[…]

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). ~~C~~condoms with spermicide will be dispensed as required by the subject.

[…]

New text:

[…]

This is not required if contraception is achieved by a permanent method such as bilateral fallopian tube blockage (including Essure) of the subject or vasectomy of her partner(s). Barrier contraception, eg, condoms with spermicide will be dispensed as required by the subject.

[…]

15.2.2.26 Section 9.6.3.8 Bone mineral density

Old text:

[…]

The BMD measurements are to be performed only after the subject has been tested negative for pregnancy using a urine pregnancy test. ~~Subjects will be asked to bring a home pregnancy test to Visit 6 in order to take the test prior to the scan.~~

More details on the calibration and procedure of central reading will be provided in a separate manual.

New text:

[…]

The BMD measurements are to be performed only after the subject has been tested negative for pregnancy using a urine pregnancy test.

More details on the calibration and procedure of central reading will be provided in a separate manual.

[…]

15.2.2.27 Section 9.6.4 Hemoglobin

This was moved from Section 9.4.3 to Section 9.6.4.

15.2.2.28 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.(10) 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.(10) Iron supplementation should be offered to subjects with hemoglobin ≤10.9 g/dL consistent with local standards of practice and <u>at the investigator's discretion.</u> Iron supplementation will not be considered as study drug and should be documented as concomitant medication.

[…]

15.2.2.29 Section 9.7.5 Induction of bleeding

Old text:

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

During treatment breaks: If no bleeding episode occurs within 7 weeks after the end of a treatment period (for Treatment Group A1, A2, and A3) or if the second bleeding episode does not occur within 7 weeks after the end of the first bleeding episode (for Treatment Groups A2 and A3 only), the scheduled ultrasound will be performed as planned after which bleeding will be induced. ~~The scheduled endometrial biopsy will be performed thereafter at Day 7 to 15 (inclusive) of the induced bleeding.~~ For details and prerequisites for the endometrial biopsy sampling, see Section 9.6.3.2.2

After EoT visit: 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. ~~T~~he scheduled endometrial biopsy (ie, FUP visit) will be performed at Day 7 to 15 (inclusive) of the ~~first menstrual cycle after the~~ induced bleeding episode. ~~For details and prerequisites for the endometrial biopsy sampling, see Section 9.6.3.2.2.~~

[…]

New text:

A negative pregnancy test is a prerequisite for induction of bleeding. Subjects will be given an appropriate progestin therapy that in the experience and practice of the investigator will induce withdrawal bleeding in this particular subject. Progestin therapy will not be considered as study medication and will be documented as concomitant medication.

During treatment breaks: If no bleeding episode occurs within 7 weeks after the end of a treatment period (for Treatment Group A1, A2, and A3) or if the second bleeding episode does not occur within 7 weeks after the end of the first bleeding episode (for Treatment Groups A2 and A3 only), the scheduled ultrasound will be performed as planned after which bleeding will be induced. For details and prerequisites for the endometrial biopsy sampling, see Section 9.6.3.2.2

After EoT visit:

- Subgroup 1: 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. For Group A1, the scheduled endometrial biopsy (ie, at endometrial biopsy FUP visit) will be performed at Day 7 to 15 (inclusive) of the induced bleeding. For groups A2, A3 and B, the planned endometrial biopsy will be performed at Day 7 to 15 (inclusive) of the first menstrual cycle after the induced bleeding episode.

- Subgroup 2: Subgroup 2: If spontaneous menstrual bleeding does not occur within 7 weeks after the EoT, an unscheduled ultrasound will be performed after which the bleeding will be induced. The scheduled endometrial biopsy (ie, at FUP visit) will be performed thereafter at Day 7 to 15 (inclusive) of the first menstrual cycle after the induced bleeding episode.

[…]

15.2.2.30 Section 9.7.7 Exploratory biomarker analysis

Old text:

Biomarker investigations in this study will be whole genome expression profiling from endometrial biopsy samples. Each subject has the option to choose whether her biopsy tissue samples can be used for this biomarker research or not unless precluded by local guidelines.

[…]

New text:

Biomarker investigations in this study will be whole genome expression profiling from endometrial biopsy samples. Each subject, except for women included in China, has the option to choose whether her biopsy tissue samples can be used for this biomarker research or not unless precluded by local guidelines.

[…]

15.2.2.31 Section 10.2 Analysis sets

Old text:

[…]

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

All subjects randomized to Treatment Group B will be analyzed as treated, regardless whether they actually took any medication (ie, symptomatic, nonhormonal medical treatment).

All safety analyses will be performed on the SAF population. The FAS will be used for the display of all other variables.

New text:

[…]

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

All subjects randomized to Treatment Group B will be analyzed as treated, regardless whether they actually took any medication (ie, symptomatic, nonhormonal medical treatment).

All safety analyses will be performed on the SAF population. The FAS will be used for the display of all other variables.

Modified SAF: will include all subjects in the SAF without any validity findings which may potentially affect the primary safety endpoint. Validity findings leading to exclusion from the modified SAF will be specified in the 'Specification of assessment criteria and identification requirements', which will be finalized before database lock. Subjects will be analyzed as treated.

All subjects randomized to Treatment Group B will be analyzed as treated, regardless whether they actually took any medication (ie, symptomatic, nonhormonal medical treatment).

All safety analyses will be performed on the SAF population. The FAS will be used for the display of all other variables. The analysis for the primary safety endpoint and all BMD related endpoints will be performed on the modified SAF as well.

15.2.2.32 Section 10.3.1.2 Secondary efficacy variable

Old text:

- Number of bleeding days from Day 1 of the first treatment period until the day before ~~the next~~ treatment period ~~after~~ the last treatment period ~~would start again normalized to~~ 28 days

New text:

- Number of bleeding days from Day 1 of the first treatment period until the day before a new treatment period would start again following the last treatment period for that respective treatment group. Number to be normalized by 28 days

15.2.2.33 Section 10.3.1.3 Other efficacy variables

Old text:

[…]

- Time to onset of controlled bleeding for each treatment period
  Onset of controlled bleeding is defined by the first day for which the menstrual blood loss (assessed by MP) for all subsequent 28-day periods up to the end of the treatment period is <80.0 mL.

[…]

New text:

[…]

- Time to onset of controlled bleeding for each treatment period
  Onset of controlled bleeding is defined by the first day for which the menstrual blood loss (assessed by MP) for all subsequent 28-day periods up to the end of the treatment period is <80.00 mL.

[…]

15.2.2.34 Section 13.4 Subject information and consent

Old text:

[…]

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

[…]

New text:

[…]

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

[…]

15.3 Amendment 6 – dated 04 JUL 2018

Amendment 6 (04 JUL 2018)

Overall Rationale for the Amendment

Overall Rationale: This amendment is based on guidance from Health Authorities' feedback with specific request for monthly liver parameter monitoring, which is to be implemented in all vilaprisan studies including ASTEROID 6 study. 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.	1) EMA Pharmacovigilance Risk Assessment Committee (PRAC) review procedure concluded in in May, 2018
5. Study design	1) Description of increased frequency of liver monitoring and its background in subsection "safety monitoring" 2) Creation of a separate section on Benefit Risk Assessment	1) FDA feedback in January and May 2018; FDA 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 hepatitis B / C infection was added to exclusion criteria. 3) The criterion about intake of strong CYP inducer was updated, correcting information	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

	about metronidazole.	DILI guideline.
		3) correction
	4) A clarification that endometrioma are exempt was added to the criterion regarding ovarian cysts	4) clarification
	5) criterion regarding current bone and musculoskeletal disease were updated (Vit D deficiency was changed to "uncontrolled Vit D deficiency")	5) clarification
	6) A new exclusion criterion was added regarding a z-score of < -2 at baseline	6) Feedback received from FDA in May 2018
	7) The criterion about contraceptive devices was updated	7), 8, 9) clarification
	8) Added "other hormonal treatments for HMB or fibroids, if not stopped before the start of menstrual cycle that follows Visit 1" as an exclusion criterion	
	9) Added "previous use of ulipristal acetate, if there were not at least two menstruations after the last intake before Visit 1" as an exclusion criterion	
8.1.1 Iron supplementation	Addition of "at the investigator's discretion"	Clarification needed because of regional differences in medical practice
9.1 Tabular schedule of evaluations 9.2.2 Scheduled visits	Added additional visits (ie, 3.1, 3.2, 3.3, 4.1, 4.2, 4.3, 5.1, 5.2, 5.3, 6.1, and 6.2) during the study treatment in treatment groups A1, A2, and A3 and also after 4 weeks during the drug-free interval between the treatment periods	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 Definitions	Newly included sentences "Any fibroid surgery should always be reported as 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 serious."	1) To address FDA recommendation in response to SPA for Asteroid 3 received in Jul 2017 and to align with FDA 2009 DILI guidance
	2) Added definition of TEAE	2) For clarity

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 Adverse events 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 enzymes and liver disorders; added a flow chart aiding the understanding of the intended processes for liver function monitoring	FDA feedback in Jan and May 2018 regarding improved liver monitoring
9.6.3.1 Laboratory evaluations	1) Added more details on laboratory parameters including liver related parameters, screening tests for hepatitis A, B, and C, hemoglobin, and additional parameters 2) 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 Further safety	1) Added description for liver symptom inquiry. 2) Added more detailed instructions relating to the operative implementation of the new exclusion criterion regarding z-score, addition of clear instruction not to switch DEXA device during the study	1) To address FDA requirement on more robust liver safety data received in Jan and May 2018 2) clarification
9.6.3.2.2 Sampling of endometrial biopsies	A repeat endometrial biopsy will be requested, if sample is inadequate for evaluation	To address FDA recommendation received in May 2018
9.7.6 Monitoring of ovarian cysts	The monitoring will be continued until resolution, ie, until cyst can no longer be distinguished from functional follicles.	To address FDA recommendation received in May 2018
Section 10.3.1.5 Other safety variables	1) Details for laboratory parameters were added 2) Liver symptom inquiry was added as a safety variable	To address FDA requirement on more robust liver safety data received in Jan and May 2018

		For clarity and consistency
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
10.4 Determination of sample size	The sample size will be increased from 1050 to 1302.	The increased sample size will contribute to this database in which safety events of interest can be evaluated. Explanation added.

15.4 Amendment 7 – dated 20 AUG 2018

Amendment 7 (20 AUG 2018)

Overall Rationale for the Amendment

Update of mismatch between the tables and visit descriptions to avoid site and Health Authority ambiguity.

Section # and Name	Description of Major Changes	Brief Rationale
Table 9-1, Table 9-2, Table 9-3, and Table 9-4: BMD visit at week 50-54 And Section 9.2.2.7	The following inquiries/investigations are NOT to be performed (page 44 ff. of integrated CSP version 4.0): • Laboratory evaluations (Table 9-1) • Concomitant medications • AE assessment • Liver symptom inquiry	The indicated crosses need to be deleted. For consistency with these deletions also in Section 9.2.2.7, those 4 inquiries/ investigations are to be deleted (page 66 of integrated CSP version 4.0)
Table 9-2 Subgroup 2	Blood samples have to be collected at Visit 5 (page 56 of integrated CSP version 4.0)	The indicated cross needs to be added (this is correctly displayed in the visit description sections)
Table 9-3, Subgroup 1	No laboratory investigations are needed at FUP2 (page 56 of integrated CSP version 4.0)	The indicated cross needs to be deleted (this is correctly displayed in the visit description section).

15.5 Amendment 9 – dated 11 DEC 2018

Global amendment 9 to the integrated study protocol version 6.0, dated 11 DEC 2018.

Overall Rationale for the Amendment:

Preliminary findings from 2-year animal carcinogenicity studies (rat/mouse) with vilaprisan that were received very recently showed evidence of an increased incidence in endometrial and adrenal neoplasms. While these unexpected findings and their relevance for humans are being further evaluated, Bayer decided to temporarily pause enrollment and randomization, and to temporarily discontinue study treatment in already randomized subjects after completion of the ongoing treatment periods. This global amendment provides background, justification, as well as a detailed description of the temporary measures to be taken. Subjects in the standard of care arm of the study can continue the study course following the current valid version of the protocol.

15.5.1 Overview of Changes

Section # and Name	Description of Change	Brief Rationale
15.5 Global amendment leading to version 6.0	Added text specifying measures for temporary pause of the study	Temporarily pause enrollment and randomization, and temporarily withdraw study treatment in already randomized subjects after completion of the ongoing treatment periods

15.5.2 Changes to the protocol text

15.5.2.1 Background and justification of changes

Preliminary data from carcinogenicity studies was presented. For the complete (outdated) text, please refer to global amendment 9 to the integrated study protocol, version 5.0.

- **The relevance to human situation** was discussed. For the complete (outdated) text, please refer to global amendment 9 to the integrated study protocol, version 5.0.
- The **clinical data as of to date (end of 2018)** was summarized. For the complete (outdated) text, please refer to global amendment 9 to the integrated study protocol, version 5.0.

Monitoring measures in ongoing studies were presented. For the complete (outdated) text, please refer to global amendment 9 to the integrated study protocol, version 5.0.

15.5.2.2 Description of temporary measures

The temporary measures applied with implementation of amendment 9 (measures for subjects after start of treatment) or were already implemented with the 15-day report on 03 DEC 2018 (temporary suspension of enrolment and randomization) were displayed as well as guidance for subjects awaiting next steps. As they are not of relevance for the restart of the study, they are not displayed here again, but can be found in global amendment 9 to the integrated study protocol, version 5.0. Special attention was drawn to signs and symptoms suggestive of increased levels of adrenal hormones (like hypercortisolism, phaeochromocytoma, and primary hyperaldosteronism).

15.6 Amendment 10 – dated 21 NOV 2019

Global Protocol Amendment 10 to the integrated study protocol version 7.0, dated 21 NOV 2019.

Amendment 10 is presented using a different approach compared with previous amendments to this protocol. The rationale for 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.

The rationale for changes in Amendment 10 and all affected sections are provided as follows.

Overall Rationale for the Amendment

Bayer has decided to close all clinical studies with vilaprisan, which were put on temporary pause in December 2018 (refer to Protocol Amendment 9 [version 6.0]) 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 IB version 11.0 and Introduction Section 3), a comprehensive safety follow up will be conducted to provide additional confirmatory evidence. This amendment introduces 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. Also, subjects randomized to SoC who are still in the study will be asked to undergo these procedures.

15.6.1 Overview of Changes

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; irrelevant	To address FDA requests

Section # and Name	Description of Major Changes	Brief Rationale
	information deleted that is no longer relevant	With the implementation of Protocol Amendment 10 (version 7.0) 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 Pharmacokinetics/pharmacodynamics 11. Data handling and quality assurance	Updated based on new study design; irrelevant information deleted that is no longer relevant	To address FDA requests
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 requirements
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 requirement on adrenal monitoring; Vit D measurement for

Section # and Name	Description of Major Changes	Brief Rationale
		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
9.6.3.2 Endometrial biopsies	Added more details on endometrial biopsies	To address FDA requests
9.6.3.3 Cervical smear 9.6.3.4 Physical and gynecological examinations 9.6.3.5 Vital signs, weight, and height 9.6.3.6 Ultrasound (safety) 9.6.3.7 Contraception and pregnancy test 9.6.3.8 Bone mineral density	Revised to reflect the collection of the parameters at the safety closeout visit.	Update necessary due to new visit structure
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
9.6.3.12 Skin monitoring	New section added on skin monitoring	To address FDA requests

Section # and Name	Description of Major Changes	Brief Rationale
9.6.3.13 Reporting of medical device failures (Japan only)	New section added on reporting medical device failures for Japan	To address country specific requirements
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 9.6.3.2.1, 9.6.3.2.7, and 9.6.3.2.8	To address FDA requests
10.2 Analysis sets	Adapted FAS 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.
10.3.1.5 Other safety variables	Added adrenal monitoring and skin safety	To address FDA request
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

15.7 Amendment 11 - dated 17 FEB 2020

Amendment 11 is presented using the same approach as Amendment 10. The rationale for 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. Changes are made directly in the protocol body without annotations. A separate file with tracked changes 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
Grapefruit juice	Depending on dose: Moderate or strong
Cobicistat	Strong
Conivaptan	Strong
Delavirdine	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

This section was added in Amendment 3, see Section 15.1.1.

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