Document Type:	Study Protocol
Official Title:	A randomized, double-blind, parallel-group, multicenter Phase 2b study to assess the efficacy and safety of two different doses of vilaprisan (BAY1002670) versus placebo in women with symptomatic endometriosis
NCT Number:	NCT03573336
Document Date:	17 FEB 2020

Cover page of the integrated protocol

A randomized, double-blind, parallel-group, multicenter Phase 2b study to assess the efficacy and safety of two different doses of vilaprisan (BAY 1002670) versus placebo in women with symptomatic endometriosis

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

- **Amendment 09** (global amendment described in Section 15.6 and the Protocol Amendment Summary of Changes Table)
  forming integrated protocol Version 7.0, dated 17 FEB 2020
- **Amendment 08** global amendment described in Section 15.5
  forming integrated protocol Version 6.0, dated 28 NOV 2019
- **Amendment 07** (global amendment described in Section 15.4)
  forming integrated protocol Version 5.0, dated 19 NOV 2019
- **Amendment 06** (global amendment described in Section 15.3)
  forming global stand-alone amendment Version 4.0, dated 11 DEC 2018
- **Amendment 03** (global amendment described in Section 15.2)
  forming integrated protocol Version 3.0, dated 26 JUN 2018
- **Amendment 02** (global amendment described in Section 15.1)
  forming integrated protocol Version 2.0, dated 20 MAR 2018
- **Original protocol**, Version 1.0, dated 06 DEC 2017

Local amendments not included in this integrated global protocol:

- **Amendment 05** (dated 06 NOV 2018)
  local amendment, valid for Germany only
- **Amendment 04** (dated 27 AUG 2018)
  local amendment, valid for Japan only
- **Amendment 01** (dated 19 DEC 2017)
  local amendment, valid for South Africa only

1. Title page

A randomized, double-blind, parallel-group, multicenter Phase 2b study to assess the efficacy and safety of two different doses of vilaprisan (BAY 1002670) versus placebo in women with symptomatic endometriosis

Short title: Assess safety and efficacy of vilaprisan in subjects with endometriosis

Acronym: VILLENDO

Test drug:	BAY 1002670 / Vilaprisan		
Study purpose:	Dose finding, safety		
Clinical study phase:	2b	Date:	17 FEB 2020
EudraCT no.:	2013-004768-72	Version	7.0
Study no.:	BAY 1002670 / 15792		
Sponsor:	Non-US territory: **Bayer AG, D-51368 Leverkusen, Germany** US territory: **Bayer HealthCare Pharmaceuticals Inc.** **100 Bayer Boulevard, P.O. Box 915,** **Whippany NJ 07981-0915, United States**		
Geographical scope of amendment:	Global		

Medical Monitor Name and Contact Information will be provided separately

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 protocol amendment as presented.

Name: PPD Role: Global Clinical Leader

Date: 17. Feb 2020 Signature: PPD

Signature of the investigator

The signatory agrees to the content of the final protocol amendment 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

Title	A randomized, double-blind, parallel-group, multicenter Phase 2b study to assess the efficacy and safety of two different doses of vilaprisan (BAY 1002670) versus placebo in women with symptomatic endometriosis
Short title	Assess safety and efficacy of vilaprisan in subjects with endometriosis
Acronym	VILLENDO
Clinical study phase	2b
Study objective(s)	Primary objective: • assess efficacy of two doses of vilaprisan compared to placebo in women with symptomatic endometriosis Secondary objective: • evaluate the safety and tolerability of two different doses of vilaprisan in women with symptomatic endometriosis Exploratory objective: • explore efficacy and safety in sub-populations (e.g. subjects with endometriosis diagnosed by imaging vs subjects with surgically confirmed endometriosis) Other objectives: • evaluate the variability in exposure in relation to the efficacy and safety for vilaprisan in subjects with symptomatic endometriosis • confirm psychometric properties of the newly developed Patient-Reported Outcomes (PRO) instruments: Endometriosis Symptom Diary (ESD v8.0[a]) and Endometriosis Impact Scale (EIS v5.0) (will be analyzed and reported separately) • evaluate biomarkers to investigate the drug (i.e. mode-of-action-related effect and / or safety) and / or the pathomechanism of the disease including assessments of exploratory biomarkers to investigate disease activity **With the implementation of Protocol Amendment 7, no new subjects will be enrolled. The objectives above cannot be reached as only limited data is available from subjects recruited before the temporary pause. Safety evaluations, including the added safety evaluations of the endometrium, adrenal glands, and skin may add to the understanding of the safety of vilaprisan.**
Test drug(s)	**Not any longer applicable due to the closing of the clinical study. With the implementation of Protocol Amendment no. 7 and aligned with the previous temporary pause measures, no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study. Originally, the information and instructions related to the**

a Currently version 8.1 of the ESD is in use

	test drug were the following:
	Vilaprisan
Name of active ingredient	Vilaprisan (BAY 1002670)
Dose(s)	2 mg or 4 mg once daily
Route of administration	Oral
Duration of treatment	Treatment Group 1: 2 mg
	Dose-finding phase: 1 treatment period of 24 weeks
	Safety extension phase: 1 treatment period of 24 weeks
	The two treatment periods will be separated by a drug-free interval encompassing 2 bleeding episodes
	Treatment Group 2: 4 mg
	Dose-finding phase: 1 treatment period of 24 weeks
	Safety extension phase: 1 treatment period of 24 weeks
	The two treatment periods are to be separated by a drug-free interval encompassing 2 bleeding episodes
Reference drug	**Not any longer applicable due to the closing of the clinical study. With the implementation of Protocol Amendment no. 7 no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study. Originally, the information and instructions related to the reference drug were the following:**
	Matching Placebo
Name of active ingredient	Not applicable
Dose(s)	Not applicable, once daily
Route of administration	Oral
Duration of treatment	Treatment Group 3
	Dose-finding phase: 1 treatment period of 24 weeks
	Safety extension phase: 1 treatment period of 24 weeks
	The two treatment periods are to be separated by a drug-free interval encompassing 2 bleeding episodes
Indication	Endometriosis
Diagnosis and main criteria for inclusion /exclusion	**With the implementation of Protocol Amendment no. 7 no new subjects will be enrolled in the study.**
	Originally, the study population had to fulfill the following criteria:
	Premenopausal women 18 years and older with endometriosis confirmed by laparoscopy or laparotomy within 10 years but not less than 8 weeks before Visit 1.
	Expansion cohort: endometriosis diagnosed by imaging (i.e. endometriotic lesion(s) detected by transvaginal ultrasound [TVU] or magnetic resonance

	imaging [MRI]) is acceptable. If the endometriosis was diagnosed by TVU, the lesion needs to be visualized by TVU also at the Visit 1. If the endometriosis was diagnosed by MRI, the diagnosis must have been made within 12 months before Visit 1. Moderate to severe endometriosis-associated pelvic pain (EAPP) of ≥4 in last 28 days before Visit 1 measured on the Numerical Rating Scale (NRS, 4 week recall period). At randomization: subject must demonstrate adherence to the study procedures during the screening period, i.e. at least 24 diary entries of ESD item 1 are required during the first 28 consecutive days after the screening visit (Visit 1), and an average score of the available ESD item 1 ('worst pain' on the daily NRS) entries during this period must be ≥ 3.5 (corresponding to a sum score of at least 84 (by 24 diary entries) or 98 (by 28 diary entries). Otherwise women should be in good general health.
Study design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Study will consist of a screening period, a placebo-controlled dose-finding phase, followed by a drug-free interval encompassing 2 menstrual bleeding episodes, a placebo-controlled extension phase, and a follow-up phase.
Methodology	**With the implementation of Protocol Amendment no. 7 no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study.** **Subjects are not any longer required to document anything in the electronic diary (eDiary).** **Any subjects who have taken at least one dose of study medication vilaprisan (including the subjects who prematurely terminated the study) will be asked to undergo a DEXA scan and the safety evaluation procedures described in this document.** **At their safety closeout visit they are not any more asked to complete the PRO questionnaire(s) on the tablet computer at the site.** **OLD WORDING VALID prior to the temporary pause:** **Efficacy:** - Patient-Reported Outcomes (PROs): • Endometriosis Symptom Diary • Endometriosis Impact Scale • Visual Analogue Scale for EAPP (VAS for EAPP, 4 week recall period) • Patient Global Impression of Severity (PGI-S) • Patient Global Impression of Change (PGI-C) • Short-Form Health Survey with 36 questions, version 2.0 (SF-36v2) • European Quality of Life 5 dimension 5 Level Scale (EQ-5D-5L) - Clinician-Reported Outcomes (ClinROs): • Clinical Global Impression assessed by Investigator (CGI-S and CGI-C) • Modified Biberoglu & Behrman (B&B) severity profile for pelvic symptoms and findings - Treatment compliance

	Safety: • Standard screening examination including medical history, physical and gynecological examination (including breast palpation), vital signs including blood pressure, pulse rate, body weight, height and body mass index (BMI) • Blood/urine laboratory parameters including hematology, clotting status, clinical chemistry, hormones, bone markers. Liver parameters will be monitored monthly during treatment. • Adverse events • Endometrial histology • Cervical cytology • Transvaginal ultrasound for endometrial thickness and endometrial/myometrial/ovarian changes • Bone mineral density **Pharmacokinetics:** • The (population) pharmacokinetics (PK) and the effect of intrinsic and extrinsic factors on the variability in exposure will be assessed by population PK analysis using sparse vilaprisan concentration samples
Type of control	**Not any longer applicable as with the implementation of Protocol Amendment no. 7 no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study** Placebo
Number of subjects	**With the implementation of Protocol Amendment no. 7 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 vilaprisan (including the subjects who prematurely terminated the study) will be asked to undergo a DEXA scan and the safety evaluation procedures described in this document.** Originally, a total of 315 subjects were planned to be randomized, which includes: • At least 210 subjects with surgically diagnosed endometriosis from all countries except for China / Taiwan for primary efficacy analysis • An expansion cohort of up to 105 subjects with endometriosis diagnosed by imaging, Countries / regions: US/Canada, Europe, Japan, China/Taiwan, Subjects were planned to be randomized in ratio 1:1:1 to one of the treatment groups described above.
Primary variable(s)	Change in the subject's 7-day mean 'worst pain' from baseline to Month 3 of the first 24-week treatment period measured on a daily NRS. The subject's 7-day mean 'worst pain' will be calculated for consecutive 28 days intervals using the sum of the subject's 7 'worst' daily assessments of the ESD item 1 ("worst pain" during the last 24 hours) divided by 7. For baseline, the first 28 consecutive days after the screening visit (Visit 1) will be considered and for the Month 3 evaluation, the 3rd 28 days after start of treatment (usually Day 57 to 84).

Time point/frame of measurement for primary variable(s)	Baseline to Month 3, 3rd 28 days after start of treatment
Plan for statistical analysis	All data will be presented in the subject data listing as they are recorded.

Protocol Amendment Summary of Changes Table

Amendment no. 9 (17 FEB 2020)

Overall Rationale for this Protocol Amendment

Recently Bayer received comments from FDA regarding details of the safety follow-up measures introduced in the protocol amendments 7 and 8. The current amendment (protocol amendment 9, version 7.0) implements these FDA recommendations.

Protocol Amendment Summary of Changes Table for the Protocol Amendment no. 9

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 Procedures and variables, 9.6.3.5 Physical and gyneco-logical examinations	Adjusted text and deleted footnote to "Physical examination" as this needs to be performed in all subjects.	To address FDA requests
9.6.3.3 Laboratory evaluations	Revised the interval for blood sampling in after intake of high doses of biotin from 8 to 72 hours.	To address FDA requests
6.3.8.3 Laboratory testing	Text was adjusted to trigger an assessment by one of the external adrenal panel experts in case tT level >150 ng/dL	To address FDA requests

Short summary for sites:

With the implementation of Protocol Amendment no. 7 no new subjects will be enrolled in the study and no subjects will re-start treatment. All subjects who were randomized and started treatment with vilaprisan before the temporary pause will be asked to have the comprehensive safety evaluation (with particular focus on endometrial, adrenal, bone and skin safety) performed, which is implemented with Protocol Amendment no. 7. This applies also to subjects who have discontinued the study before or during the temporary pause, provided they have taken at least one dose of vilaprisan.

All these subjects are asked to come to the site for the "Safety Closeout Visit" which is implemented with Protocol Amendment no. 7. 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:

- Re-consenting 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 cytology
- Urine pregnancy test
- Ultrasound examination
- Endometrial biopsy (in case a valid post-treatment biopsy is not already available)
- Laboratory (blood sampling)
- DEXA scan measurement for bone mineral density
- Collection of unused study drug and empty drug packs/drug accountability, if applicable
- Collection of eDiary device
- 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 Protocol Amendment no. 7. 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 counseled 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 documents.

For subjects who received placebo treatment prior to the temporary pause, no further procedures are required except for the collection of eDiary device and deactivation of the subject on the tablet computer.

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List of abbreviations

25(OH)D	25-hydroxyvitamin D
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AESI	AEs of special interest
ALP/AP	Alkaline phosphatase
ALT	Alanine aminotransferase (also known as GPT)
AMD	Amendment
AP	Alkaline phosphatase
ASCUS	Atypical squamous cells of undetermined significance
AST	Aspartate aminotransferase (also known as GOT)
ASTEROID	**A**ssess **S**afety and Efficacy of Vilaprisan in Subjects with U**ter**ine Fibr**oid**s (studies)
AT	Aminotransferase (ALT or AST)
B&B	Biberoglu & Behrman severity profile for pelvic symptoms and findings
BM	Biomarker
BMD	Bone mineral density
BMI	Body mass index
CD	Compact disk
CDISC	Combined Data Interchange Standard Consortium
CGI-C	Clinical Global Impression (assessed by investigator) of Change
CGI-S	Clinical Global Impression (assessed by investigator) of Severity
ClinRO	Clinician-Reported Outcome
COC	Combined oral contraceptive
CRF	Case report form
CRO	Clinical research organization
CSP	Clinical Study Protocol
CT	Computed tomography
CYP3A4	Cytochrome P450 enzyme 3A4
DHEA-S	Dehydroepiandrosterone sulfate
DEXA	Dual-energy X-ray absorptiometry
DYS	Dysmenorrhea
EAPP	Endometriosis-associated pelvic pain
eCRF	Electronic case report form
EDC	Electronic data capture
e.g.	exempli gratia, for example
EIN	Endometrial intraepithelial neoplasia
EIS	Endometriosis Impact Scale
EMA	European Medicines Agency
EoT	End of treatment
ePRO	Electronic Patient-Reported Outcome (device)
EQ-5D-5L	European Quality of Life 5 dimension 5 Level Scale
ESD	Endometriosis Symptom Diary
EU	European Union

FAS	Full analysis set
FDA	United States Food and Drug Administration
FUP	Follow up
GCP	Good Clinical Practice
γ-GT	Gamma-glutamyl transpeptidase
GMP	Good Manufacturing Practice
GnRH-a	Gonadotropin-releasing hormone agonists
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
HA	Health Authority
HAV	Hepatitis-A-Virus
Hb	Hemoglobin
HBs-Ag	Hepatitis-B-Virus surface antigen
HCV	Hepatitis-C-Virus
HMB	Heavy menstrual bleeding
HPA	Hypothalamic-pituitary-adrenal axis
HPV	Human papilloma virus
HRQoL	Health-related quality of life
IB	Investigator's brochure
ICH-GCP	International Conference on Harmonization- Good Clinical Practice
i.e.	*id est*, that is
IEC	Institutional Ethics Committees
Ig	Immunoglobulin
IME	Important medical event
INN	International nonproprietary name
INR	International normalized ratio
IRB	Institutional Review Boards
IU	International unit
IVRS/IWRS	Interactive Voice Response System / Interactive Web Response System
M&S	Modeling and Simulation
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
µg	Microgram
mRNA	Messenger RNA
MRI	Magnetic resonance imaging
NASH	Nonalcoholic steatohepatitis
NMPP	Non-menstrual pelvis pain
NRS	Numerical Rating Scale
PAEC	Progesterone receptor modulator-associated endometrial changes
PD	Pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PR (A; B)	Progesterone receptor (A; B)
PPS	Per protocol set

PRM	Progesterone receptor modulator
PRO	Patient-Reported Outcome
QA	Quality Assurance
QC	Quality control
RAVE	electronic data capturing system
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
ROW	Rest of world
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SDTM-QS	Study Data Tabulation Model Questionnaire domain
SF-36v2	Short-Form health survey with 36 questions, version 2
SID	Subject identification (number)
SUSAR	Suspected, unexpected serious adverse reaction
TP	Treatment period
TSH	Thyroid-stimulating hormone
tT	Total testosterone
TVU	Transvaginal ultrasound
ULN	Upper limit of normal
UPA	Ulipristal acetate
US	United States (of America)
ULN	Upper limit of normal
VAS	Visual Analogue Scale
VPR	Vilaprisan
WHO	World Health Organization
WHO-DD ATC	WHO Drug Dictionary anatomical-therapeutic-chemical (classification system)

Definitions of terms

6/2 regimen	6 months (i.e., 6 x 28 days) of treatment with 2 bleeding episodes between treatment periods
month	equals 28 days when referring to treatment (i.e., 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 no. 7 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 vilaprisan (including the subjects who prematurely terminated the study) will be asked to undergo a DEXA scan and the safety procedures described in this protocol amendment, as applicable.

Based on findings in preclinical carcinogenicity studies in rats and mice all vilaprisan clinical studies were temporarily paused since December 2018 (refer to Protocol Amendment no. 6). 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 and 50 times the human therapeutic doses of 2 mg and 4 mg, respectively.

Bayer has decided to close all clinical studies with vilaprisan, which were put on temporary pause in December 2018. Bayer performed a thorough evaluation of these preclinical findings and their potential relevance to humans. 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 vilaprisan Investigator's Brochure [IB] version 11.0 including the associated amendment and Introduction section), Bayer decided to not re-start drug treatment. Instead, Bayer will conduct a comprehensive safety follow up to provide additional confirmatory evidence. Subsequently, all clinical studies with vilaprisan will be closed. Protocol Amendment no. 7 introduces measures and processes to prepare this study for an orderly closure, including safety follow up measures in all study participants who received at least one dose of study drug vilaprisan.

Protocol Amendment no. 7 introduces an endometrial, adrenal, and skin safety evaluation with the aim to confirm that the carcinogenicity study findings do not translate into an increased risk for subjects when treated with the regimens and doses tested in the current studies.

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

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

While closing the current clinical studies for the reasons explained above, the collected safety data will be thoroughly evaluated in addition to the already collected efficacy data (applicable for the uterine fibroids indication only).

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

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

In preclinical chronic carcinogenicity studies in rats and mice, adenocarcinomas of the endometrium were found. Furthermore, in female rats, benign and malignant tumors of the adrenal cortex were seen. Such tumors were not seen in male rats or in mice. In addition, skin sarcoma (not otherwise specified) were found with increased incidence of statistical

significance at the high dose of 60 mg/kg in female mice only. This corresponds to 50 fold of the daily dose of 4 mg and 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 within the special setting of the carcinogenicity studies. 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 doses of 2 or 4 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 studies rodents entered into reproductive senescence during the treatment phase leading to rodent specific endocrine changes resulting under continuous blockade of the progesterone receptor in the formation of tumors in the endometrium and adrenal cortex. The rodent specific endocrinology does not resemble the situation in humans.

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

- Female rodents undergo specific endocrine changes during reproductive senescence that do not resemble human menopause, human premenopausal endocrine status or the endocrine situation during vilaprisan treatment.
- Prolonged estrous periods with high estradiol levels occur in rodent reproductive senescence, or a pseudopregnancy state with moderately high estradiol levels. This process takes place due to neurodegeneration on the hypothalamus-pituitary gland and in the presence of follicles in the ovaries which are capable of producing hormones. In the presence of vilaprisan with its strong antagonistic effect on the progesterone receptor this leads to a prolonged, fully unopposed estradiol exposure in the animals. Specifically, in rats, life-long vilaprisan treatment seems to promote prolonged estrous periods with follicular cysts and reduce states of pseudopregnancy, thus further enhancing estrogen dominance.
- Prolonged phases of unopposed estrogen are a recognized risk factor for development of endometrial adenocarcinoma in rodents as well as in humans. However, in contrast to the rodents in the pre-clinical carcinogenicity studies, available clinical data for vilaprisan do not indicate the occurrence of an unopposed estrogen effect on human endometrium. This is supported by the estrogen-lowering effect of vilaprisan shown in

the Phase 1 and Phase 2 studies as well as by the morphological features of endometrial histology in humans under vilaprisan treatment which do not seem to indicate a relevant proliferative effect. There was no increased incidence of relevant endometrial pathology (hyperplasias, neoplasms) seen in biopsies taken after up to 12 months of treatment with vilaprisan.

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

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

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

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

Benefit risk assessment

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

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

With the implementation of Protocol Amendment no. 7 no new subjects will be enrolled in the study. Since only limited data is available from subjects enrolled before the temporary pause (8 out of the planned 315), no statistical analysis will be performed for this study. Data collected so far from subjects who received placebo treatment will not be analyzed. Therefore, further unnecessary invasive procedures of the safety evaluation in these subjects are not justified for ethical reasons.

In conclusion, only subjects who have taken at least one dose of vilaprisan (including the subjects who prematurely terminated the study) will be asked to undergo the safety procedures described in this protocol amendment. The safety data of vilaprisan treated patients including the added safety evaluations of the endometrium, adrenal glands, and skin may add to the understanding of the safety of 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 studies a dose-dependent ovulation inhibition and induction of amenorrhea in healthy women. Based on the Phase 1 data vilaprisan was expected to provide efficacy in reducing endometriosis associated pelvic pain and to improve the negative impact endometriosis has on subjects' daily life.

4. Study objectives

Primary objective:

- assess efficacy of two doses of vilaprisan compared to placebo in women with symptomatic endometriosis.

Secondary objective:

- evaluate the safety and tolerability of two different doses of vilaprisan in women with symptomatic endometriosis.

Exploratory objective:

- explore efficacy and safety in sub-populations (e.g. subjects with endometriosis diagnosed by imaging vs subjects with surgically confirmed endometriosis).

Other objectives:

- evaluate the variability in exposure in relation to the efficacy and safety for vilaprisan in subjects with symptomatic endometriosis.

- confirm psychometric properties of the newly developed Patient-Reported Outcomes (PRO) instruments: Endometriosis Symptom Diary (ESD) and Endometriosis Impact Scale (EIS) (will be analyzed and reported separately).
- evaluate biomarkers to investigate the drug (i.e. mode-of-action-related effect and / or safety) and / or the pathomechanism of the disease including assessments of exploratory biomarkers to investigate disease activity.

With the implementation of Protocol Amendment no. 7 no further recruitment is possible. With the data available from subjects recruited before the temporary pause the objectives above cannot be reached. Safety evaluations including the added safety evaluations of the endometrium, adrenal glands, bone, and skin may add to the understanding of the safety of vilaprisan.

5. Study design

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study.

The study originally includes the following phases: a screening phase, a placebo-controlled dose-finding phase, followed by a drug-free interval encompassing 2 menstrual bleeding episodes[2], a placebo-controlled extension phase, and a follow-up phase.

Endometriosis symptoms and their impact on subjects' daily life was to be documented throughout the study, i.e. from start of the screening until the follow-up phase.

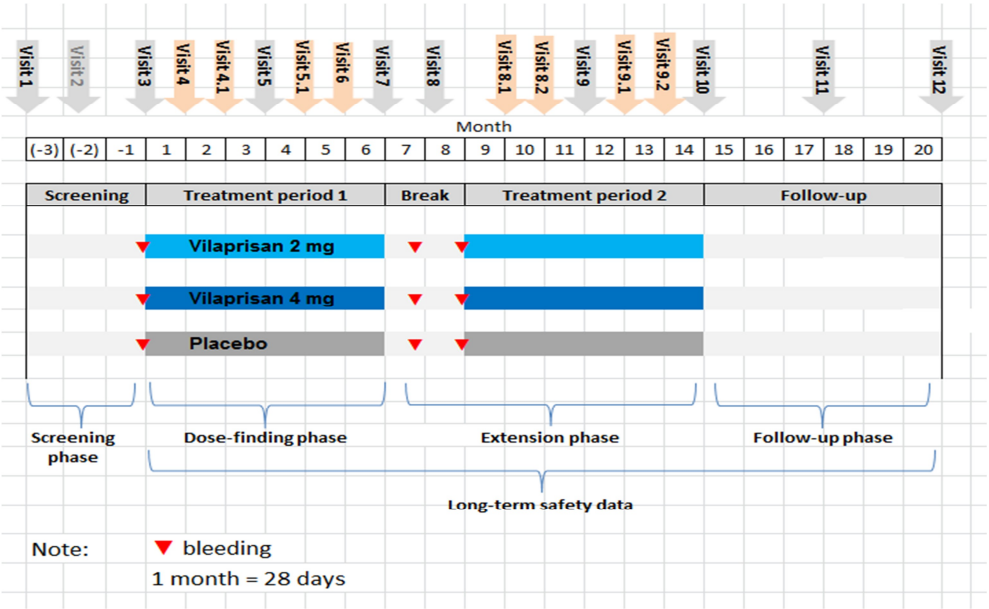
With the implementation of Protocol Amendment no. 7, this study design is no longer valid. No subjects will receive further study drug treatment.

Study design valid with the implementation of Protocol Amendment no. 7:

The study was temporarily paused since December 2018. With the implementation of Protocol Amendment no. 7 no further subjects will be recruited and none of the enrolled subjects will receive further study drug treatment. All subjects who were randomized and started vilaprisan before the temporary pause will be asked to have a comprehensive safety evaluation (with particular focus on endometrial, adrenal, and skin safety) performed, which is implemented with Protocol Amendment no. 7. This also applies to subjects who have discontinued the study before or during the temporary pause, provided they have taken at least one dose of vilaprisan.

Figure 5–1 displays an overview of the original study design.

Figure 5–1: Study Design



[2] i.e, a 6 months treatment period followed by a drug-free interval encompassing 2 menstrual bleeding episodes (6/2 regimen)

Screening phase

Subjects who fulfilled the eligibility criteria entered the screening phase of at least 28 days after the Screening visit (Visit 1) and up to a maximum of 75 days to collect complete results of all screening assessments.

Immediately after Visit 1, subjects started to document their endometriosis symptoms and the impact of the symptoms on their lives in the Endometriosis Symptom Diary (ESD; 24-hour recall period) and the Endometriosis Impact Scale (EIS; 7-day recall period). During the screening period, the subjects stayed on their individual endometriosis treatment; if this was allowed according to the protocol until stopping it for a withdrawal bleeding prior to the randomization visit (see Section 7.1.1). The use of rescue analgesics was standardized (see Section 7.1.3). All other analgesics for the treatment of endometriosis symptoms were stopped at Visit 1. Use of prophylactic analgesics during the screening phase (and throughout the study) was explicitly discouraged.

If subject required a wash out period from prior hormonal treatment with drugs or devices not allowed for the study (e.g. long-acting hormonal contraception, contraceptive device, PRM, GnRH-a, see Section 7.1.1), the occurrence of normal menses before the screening phase was to be documented in the subject's source documents. All subjects who stopped their hormonal contraceptives prior to Visit 3 needed to use a non-hormonal method of contraception starting from the time of discontinuation of their contraceptive.

At the end of the screening phase, subjects' eligibility was confirmed and eligible subjects were randomized to one of the treatment groups.

With respect to pain, subjects should have entered the ESD item 1 "worst pain" measured by the daily Numerical Rating Scale (NRS) in the hand-held device on at least 24 days of the first 28 consecutive days after the screening visit (Visit 1) and the average score of the available ESD item 1 ('worst pain' on the daily NRS) entries during this period were to be ≥ 3.5 (corresponding to a sum score of at least 84 (by 24 diary entries) or 98 (by 28 diary entries).

Dose-finding phase

For all subjects, the treatment period consisted of daily tablet intake for 24 weeks (168 days).

At the randomization visit (Visit 3) eligible subjects were randomized equally to one of the following treatment groups (see Section 9.1) and received study drug as follows:

- Treatment Group 1: 2 mg vilaprisan tablet once daily orally for 168 days or
- Treatment Group 2: 4 mg vilaprisan tablet once daily orally for 168 days or
- Treatment Group 3: matching placebo tablet once daily orally for 168 days.

Extension phase

After the first treatment period, there was a drug-free interval encompassing 2 bleeding episodes to assess the safety, the persistence of treatment effect, and/or recurrence of endometriosis symptoms.

Starting during the 2nd bleeding episode following the drug-free interval, subjects continued their respective study treatment for an additional 168 days.

Follow-up phase

After the end of study treatment in the extension phase, subjects were planned to be followed up for up to 24 weeks. During the follow-up phase, safety and efficacy parameters were planned to be further evaluated, and endometrial biopsies must demonstrate normal or benign findings. If the end of study (EoS) biopsy was abnormal (i.e. hyperplasia or worse), additional biopsy(ies) were planned to be scheduled until a normal result would be obtained or a clear outcome is given. Abnormal findings were to be followed-up according to standard practice.

Subjects who discontinued the study treatment prematurely during a treatment period should have the end of treatment (EoT) visit immediately and should return for follow up (FUP)1 visit; subjects who discontinued the study prematurely during the drug-free interval or the post-treatment FUP period before FUP1 should return for the FUP1 visit.

Primary variable

Primary variable

The primary efficacy variable is the change in the subject's 7-day mean 'worst pain' from baseline to Month 3 measured on a daily NRS (item 1 of the ESD)[3].

Justification of the design

For justification of Protocol Amendment no. 7, see Section 3.

Justification of the original design

Comparators and blinding

A randomized, double-blind, placebo-controlled, parallel-group design was considered standard and appropriate to differentiate drug effects from the natural course of disease and background findings and to derive valid dose-effect information. The efficacy endpoints of this study include pain and other PROs are prone to bias by knowledge of the treatment received. Evaluation of such subjective endpoints requires a double-blind setting. Due to a high and variable placebo response rate in pain trials it is in principle necessary to show superiority to placebo. To minimize subject burden due to randomization to placebo treatment, standardized pain medication will be provided throughout the study. Intake of pain medication will be clearly documented to allow appropriate analysis.

Dose and regimen:

Selection of the doses was based on the data of Phase 1 studies in healthy young women and Phase 2 in subjects with uterine fibroids (ASTEROID 1 and 2). In summary, exposure-response analysis of vilaprisan on induced amenorrhea, ovulation inhibition, and on estradiol (E2) levels supported the used of 2 mg and 4 mg doses for the study because

- doses < 2 mg/day can be excluded because they do not achieve the desired maximum effect on induction of amenorrhea and provide insufficient ovarian suppression.

[3] 3rd 28 days after start of treatment

- a dose > 2 mg/day may provide additional benefit on endometriosis symptoms which could not be detected in the available data generated in healthy women and subjects with uterine fibroids.
- an intermediate dose is not proposed because there is a considerable overlap in exposure with 2 mg/day and 4 mg/day and thus testing is not expected to provide any additional information.

Justification of original regimen:

PRMs are applied either short-term or in an intermittent treatment regimen to minimize or avoid endometrial changes that may result in episodes of heavy menstrual bleeding (HMB) after cessation of treatment.

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

In the absence of data in endometriosis subjects, it is assumed that, like in uterine fibroids, efficacy of long-term (i.e., repeated-intermittent) treatment will be more favorable if treatment phases are longer, because this will result in fewer time with endometriosis-associated pelvic pain (EAPP) and will reduce the slight drops in HRQoL during the treatment-free phases.

Therefore, this study intended to investigate a 6/2 regimen (6 month treatment followed by 2 menstrual bleeding episodes) for long-term, repeated-intermittent treatment with vilaprisan.

Duration of treatment:

Extension of this dose-finding study with a long-term safety study results in a total treatment duration of 12 months was planned. This design was considered justified, because substantial amount of safety data from healthy women and those with uterine fibroids, including repeated treatment courses, was expected to become available. Furthermore, ongoing medical review of study data was conducted to ensure subjects' safety during the study. In subjects with safety findings like suspicious bleeding pattern, increased endometrial thickness or increased liver enzymes treatment was interrupted.

Efficacy / pharmacodynamic assessments:

The endometriosis treatment effect is assessed by investigating the change in the key symptoms of endometriosis (e.g. worst daily pelvic pain, non-menstrual pelvic pain, dysmenorrhea, dyspareunia). In the absence of biomarkers, and considering the inherently subjective nature of the symptoms, this can only be rated appropriately by the subjects themselves, using Patient-Reported Outcomes (PROs) which substantiates the clinical investigation.

Ultrasound assessment of endometriosis lesions, hormone levels, and bleeding will be determined as pharmacodynamic (PD) parameters.

Safety monitoring:

Safety parameters were regularly and closely monitored throughout the study (eg, questioning for adverse events (AEs), measurement of laboratory values, vital signs, endometrial safety monitoring, endometrial thickness, abnormal menstrual bleeding, and size of follicle like structures comprising follicles and functional ovarian cysts). A comprehensive evaluation for adrenal tumors and a skin examination are implemented with Protocol Amendment no. 7.

Endometrial monitoring

A careful endometrial safety monitoring assessment was applied in this study from the beginning including regular ultrasound investigations, observation of bleeding patterns, and endometrial biopsies at defined time points. Clear decision trees are outlined as to when to perform an additional unscheduled endometrial biopsy in case of endometrial thickening and/or on the clinical management of endometrial thickening/HMB/ suspicious bleeding pattern (see Section 9.6.3.1). 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.

With Protocol Amendment no. 7, additional requirements for endometrial safety monitoring are outlined for subjects who took at least one dose of study medication vilaprisan, see section 9.6.3.1.2.

Liver monitoring

A liver-related safety signal was observed with some 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. With this protocol amendment, subjects will receive one further laboratory examinations, including liver parameters.

Adrenal monitoring

A comprehensive adrenal screening program is implemented with Protocol Amendment no. 7. This program is described in more detail in Section 9.6.3.8. It encompasses adrenal imaging, as well as laboratory tests aimed at identifying overproduction of adrenal cortical hormones in the context of tumors of the adrenals. Tumors of the adrenal glands (cortical or medullary in origin, benign as well as malignant) are known to occur in a certain frequency in the general population, independent of an exposure to the study drug vilaprisan (5). For adrenal tumors detected by the screening program in this study, a causal relationship to vilaprisan can therefore not be automatically assumed.

Skin monitoring

In the above-mentioned carcinogenicity study performed in mice, skin sarcomas were found at a dose representing about 100 and 50 times the human therapeutic doses of 2 mg and 4 mg, respectively. 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 participants who took at least one dose of vilaprisan 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. BMD is assessed in this study using dual-energy X-ray absorptiometry (DEXA).

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 performed at a timepoint at least 22 weeks after last intake of vilaprisan, to document absence of bone loss or adequate recovery.

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.

Pregnancy

Due to the mode of action of the tested study drug, information on teratogenic potential of vilaprisan is limited. Therefore clear instructions with regards to contraceptive methods and regular pregnancy testing have been implemented in order to avoid exposure to the study drug during pregnancy.

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 last patient last visit (LPLV).

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

6. Study population

No longer valid, since no new subjects will be enrolled in this study with the implementation of Protocol Amendment no. 7.

Originally the study population had to fulfill the following criteria:

6.1 Eligibility

Women with endometriosis presenting with moderate to severe endometriosis-associated pelvic pain (EAPP) who meet all inclusion criteria and none of the exclusion criteria will be eligible for enrollment to the study.

6.2 Inclusion criteria

The inclusion criteria are as follows:

1. Signed and dated informed consent
2. Age: Pre-menopausal women 18 years (inclusive) and above at the time of Visit 1
3. Women with endometriosis confirmed (via direct visualization with or without biopsy) by laparoscopy or laparotomy within the last ten years but not less than 8 weeks before the Visit 1.

   OR

   Women with endometriosis diagnosed based on imaging (i.e. endometriosis lesion was detected by transvaginal ultrasound [TVU] or magnetic resonance imaging [MRI]). If the subject was diagnosed by TVU, the lesion needs to be visualized by TVU at the screening visit. If the subject was diagnosed by MRI, the diagnosis must have been made within 12 months before the Visit 1.
4. Moderate to severe endometriosis-associated pelvic pain (EAPP) of ≥4 in the last 28 days before the Visit 1 as measured on the NRS (0-10) (4-week recall period) by the subject.
5. At the randomization visit (Visit 3):
   a. Adherence to the study procedures during the screening period, at least 24 diary entries of ESD item 1 during the first 28 consecutive days after the screening visit (Visit 1), and an average score of the available ESD item 1 ('worst pain' on the daily NRS) entries during this period must be ≥ 3.5 (corresponding to a sum score of at least 84 (by 24 diary entries) or 98 (by 28 diary entries).
6. Willingness to use only standardized pain medication if needed, according to investigator's instruction and not use any prophylactic pain medication for EAPP.
7. Good general health (except for findings related to endometriosis) as proven by medical history, physical and gynecological examinations, and laboratory test results.
8. Normal or clinically insignificant cervical cytology not requiring further follow-up (a cervical cytology sample has to be taken at the screening visit (Visit 1) or a normal result has to be documented within the previous six months prior to Visit 1). 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. As a guidance, cervical cytology should only be repeated once in case of insufficient material.

9. An endometrial biopsy performed at the screening phase 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 phase and must be repeated within 6 weeks from the first biopsy in order for the subject to continue. No further repeated biopsies in case of inadequate samples are permitted.
10. Use of an acceptable non-hormonal method of contraception (i.e. either male condom, cap, diaphragm or sponge, each in combination with spermicide) starting at Visit 1 until the end of the study. This is not required if safe contraception is achieved by a permanent method, such as bilateral fallopian tube occlusion (including Essure®) or vasectomy in the partner(s). (Short-acting hormonal contraception [oral, vaginal, or transdermal] for treatment of EAPP are allowed during screening, but need to be stopped and withdrawal bleeding has to be initiated before the randomization visit [Visit 3], see also Section 7.1.1).
11. Willingness / ability to comply with electronic diary entry for the duration of study participation

6.3 Exclusion criteria

The exclusion criteria are as follows:

1. Pregnancy or lactation (less than 3 months since delivery, abortion, or lactation before Visit 1)
2. Hypersensitivity to any ingredient of the study treatments
3. Laboratory values outside the inclusion range[4] before randomization, and considered clinically relevant
4. Any diseases or conditions 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 are not limited to:
    a. Impaired function of the kidneys (laboratory values outside of inclusion range)
    b. Abnormal liver parameters (presence of at least one of the following criteria)[5]:
        i. 2 x upper limit of normal (ULN) for glutamic oxaloacetic transaminase (GOT) / aspartate aminotransferase (AST)
        ii. 2 x ULN for glutamic pyruvic transaminase (GPT) / alanine aminotransferase (ALT)
        iii. 2 x ULN for alkaline phosphatase (AP)

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

[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 patient is eligible only if the second test shows a stabilization or decline in those values .

iv. Total bilirubin outside the upper limit of normal
v. International normalized ratio (INR) outside the upper limit of normal

c. Positive hepatitis B surface antigen (HBs-Ag) indicating chronic hepatitis B infection
d. Positive hepatitis C antibodies (anti-HCV) and HCV-messenger RNA (mRNA) indicating chronic hepatitis C infection.
e. Chronic bowel diseases, eg, Crohn's disease and ulcerative colitis.
f. Intake of strong cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors (see Section 16.1) 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).
g. Intake of strong CYP3A4 inducers (see Section 16.2) (eg, rifampicin, carbamazepine, phenytoin, phenobarbital, St John´s wort) within the last 2 weeks before start of study drug intake and during the treatment periods.

5. Any diseases or conditions that might interfere with the conduct of the study or the interpretation of the results, including
   a. A known severe coagulation or fibrinolytic disorder
   b. Severe hepatic disorders
   c. History of or current anxiety or depression unless stable with or without medical treatment ≥ 6 months
   d. History of or current fibromyalgia
   e. History of or current uterine, cervical, ovarian, or breast cancer, except cervical cancers after curative treatment
   f. History of hysterectomy
   g. One or more ovarian cysts ≥3 cm in diameter as measured by ultrasound (except endometrioma)
   h. Any ovarian tumors or pelvic masses of unclear etiology requiring further diagnostic procedures
   i. Irritable bowel syndrome or other bowel disorders
   j. Current bone and musculoskeletal disease (eg, osteoporosis, Scheuermann's disease, osteogenesis imperfecta, hypo- or hyperparathyroidism, Paget's disease, osteomalacia or other metabolic disease of bone, hypo- or hypercalcemia)
   k. Screening DEXA results of the lumbar spine (L1-L4), femoral neck, or total hip BMD corresponding to 2.0 or more standard deviations (SD) below normal (Z score ⩽ –2.0 SD) as per central read
6. Undiagnosed abnormal genital bleeding
7. Abuse of alcohol, drugs, or medicines (e.g. laxatives) as evaluated by the investigator

8. Use of other treatments that might interfere with the conduct of the study or the interpretation of the results:
    a. Short-acting hormonal contraception (oral, vaginal or transdermal formulations, cyclic or extended regimens) or progestin treatment, if not stopped and if a withdrawal bleeding has not been initiated before randomization visit (Visit 3)
    b. Long-acting hormonal contraception (injectable), if last application was performed less than 1 application interval before Visit 1 and subject has not resumed normal menses before Visit 1.
    c. Contraceptive devices with or without hormone release (subdermal implant, intrauterine device) if not removed before Visit 1 and if subject has not resumed normal menses before Visit 1
    d. Progesterone Receptor modulator, if not stopped at least 28 days before Visit 1 **and if** subject has not resumed normal menses before Visit 1
    e. Gonadotropin-releasing hormone agonist, if not stopped at least one application interval before Visit 1 and if subject has not resumed normal menses before Visit 1
    f. Traditional Chinese medicine or herbal remedies for painful conditions including endometriosis or heavy menstrual bleeding
    g. Raloxifene (or similar selective estrogen receptor modulators [SERMs]), fluoride, calcitonin, if not stopped 3 months before Visit 1
    h. Current intake (ie, at Visit 1) of agents known or suspected to affect bone metabolism, e.g. bisphosphonates, parathyroid hormone, systemic corticosteroids, if not stopped before Visit 1
9. Endometriosis-specific treatments for symptom relief except short-acting contraceptives or progestins (as outlined in exclusion criterion # 8a) used during the screening period and rescue pain medication according to protocol
10. Simultaneous participation in another clinical trial with investigational medicinal product(s). Participation in another trial prior to study entry that might have an impact on the study objectives, at the discretion of the investigator
11. Major surgery scheduled during the study period
12. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of investigational site, or sponsor's staff)
13. 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
14. Previous assignment to treatment (e.g. randomization) during this study (allowing previously randomized subjects to be re-included into the study may lead to bias)
15. Hypersensitivity to any ingredient of standardized pain medication
16. Contraindication for standardized rescue pain medication (according to local label)
17. Wish for pregnancy during the study

18. Regular use of pain medication due to other underlying diseases
19. Any findings that require further diagnostic procedures to avoid harm to the subject (e.g. ovarian tumors of uncertain origin or pelvic masses of unclear etiology, etc.)
20. Non-responsiveness of EAPP to GnRH-a.

6.4 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, which may have an effect on the aims of the study, are excluded.

6.5 Withdrawal of subjects from study

6.5.1 Withdrawal

No longer valid, since with the implementation of Protocol Amendment no. 7 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:

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, for further follow-up, see Section 9.6.2
- Surgical treatment of endometriosis, for further follow-up, see Sections 9.7.2 and 9.6.1.4 (in case of an serious adverse event (SAE))
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being

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

- 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
- Loss of BMD >6% at the lumbar spine compared to baseline accompanied by a Z-score reading of ≤-2 SD (standard deviation) (determined either by the central reading imaging laboratory or by assessment at the site and confirmed by the

central reading imaging laboratory at the end of the 1st 6 months treatment period visit).

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

- Any of the inclusion criteria are no longer fulfilled
- Any of the exclusion criteria apply during treatment.

Screening failure

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

Dropout

A subject who discontinues study participation prematurely for any reason (including subject who does not consent to this protocol amendment which defines safety measures to be performed at the study closeout visit) is defined as a "dropout" if the subject has already been randomized.

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 subjects´ source document.

General procedures

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's source documents. Any medical treatment and interventions are documented.

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 (Premature termination of the study).

6.5.2 Replacement

Dropouts will not be replaced.

6.6 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)

Once allocated, the SID number identifies the subject throughout the study.

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

7. Treatments

Instructions in Sections 7.1 to 7.4 are no longer valid, since with the implementation of Protocol Amendment no. 7 no subjects will start or continue treatment in this study.

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

7.1 Treatments to be administered

Dose-finding phase (treatment period 1):

- Treatment Group 1: One **2 mg vilaprisan** tablet once daily orally for 24 weeks
- Treatment Group 2: One **4 mg vilaprisan** tablet once daily orally for 24 weeks
- Treatment Group 3: One **placebo** tablet matching vilaprisan once daily orally for 24 weeks

Extension phase (treatment period 2):

- Treatment Group 1: One **2 mg vilaprisan** tablet once daily orally for 24 weeks
- Treatment Group 2: One **4 mg vilaprisan** tablet once daily orally for 24 weeks
- Treatment Group 3: One **placebo** tablet matching vilaprisan once daily orally for 24 weeks

7.1.1 Start and end of study treatment

There will be two treatment periods (Treatment period (TP) 1 during the dose-finding phase and TP 2 during the extension phase) separated by a drug-free interval containing 2 bleeding episodes. Each treatment period will consist of 24 weeks (168 days) of once-daily tablet intake.

Study treatment (TP 1) will be started at the clinic during the randomization visit (Visit 3) and according to the following rules depending on subject's endometriosis treatment during the screening period:

1. A subject without any hormonal treatment will start study treatment during the randomization visit (Visit 3). Visit 3 should be scheduled between expected Day 3 and Day 7 of her menstrual cycle.
2. A subject on treatment with a short-acting progestin or with an extended regimen of COC will stop her progestin or COC before scheduling the randomization visit and wait for withdrawal bleeding. Visit 3 should be scheduled between Day 3 and Day 7 of the withdrawal bleeding and study treatment started during the randomization visit (Visit 3)
3. A subject on treatment with cyclic combined hormonal contraception (oral, vaginal, or transdermal) will finish the complete cycle and wait for the withdrawal bleeding. Visit 3 should be scheduled between Day 3 and Day 7 of this withdrawal bleeding and study treatment started during the randomization visit (Visit 3)

TP 2 will start within Day 3 and Day 7 of the second bleeding episode following the end of the TP 1. If no bleeding episode occurs within 7 weeks after end of the TP 1, or if the second bleeding episode does not occur within 7 weeks after the end of the first bleeding episode, proceed with the induction of bleeding according to Section 9.7.1. The subject will call the site on the day of first pill intake for TP2 to schedule the Visits 8.1 – 12.

For the start of TP 2, subjects will determine, based on their own experience, when a bleeding episode has started. In case of unusual patterns (eg, start with some days of spotting) subjects should consult with the investigator.

All subjects who stop their hormonal contraceptives prior to Visit 3 need to use a non-hormonal method of contraception starting from the time of discontinuation of their contraceptive.

A negative pregnancy test is a prerequisite for starting study drug treatment for both treatment periods.

7.1.2 Missed intake of study drug

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

7.1.3 Rescue pain medication

Rescue pain medication for endometriosis-associated pain is prescribed for subjects by the investigator and is limited to ibuprofen tablets (containing ibuprofen 400 mg per tablet [in Japan, ibuprofen 200 mg per tablet]). In addition to ibuprofen, a country-specific narcotic analgesic *may* be prescribed to subjects who do not obtain sufficient relief from study drug and ibuprofen. The narcotic analgesic is defined depending on availability and common use for the indication in the individual country (ie, only one narcotic analgesic is allowed for each country), and is specified in a separate guidance document (i.e. “Rescue Pain Medication Guide”).

The number of tablets and dosing interval of the rescue pain medications can be determined by the investigator and should be in line with the product prescribing information for that particular dosage form in that country.

Investigators prescribed these rescue pain medications for subjects at the time of subject entry into the screening phase, taking into consideration the subject's preference and/or historical use of analgesics. The same rescue pain medication (type and dose preparation) used during the screening phase should be used as needed for rescue during the treatment phase. Subjects are instructed not to increase their total daily dose or frequency of rescue pain medication or to switch the category of analgesic used (e.g., switching from ibuprofen to country specific narcotic analgesic) unless it is necessary for treatment of worsening endometriosis-associated pain that does not respond to their current analgesic medications. Subjects are instructed to contact the site if a change in their analgesic medication is needed, such that appropriate adjustments can be made. All use of analgesic medication should be according to the product prescribing information.

Subjects are instructed to use pain medication only as rescue analgesia; use of prophylactic analgesics at any time during the study is explicitly discouraged.

Daily use of rescue pain medications was recorded by the subject in the hand-held device (ESD item 9a, 9b, 9c, and 9d) during the entire study. This included specific dosing information on the permitted rescue pain medications, including dose and total number of pills/tablets within a 24-hour period and the information whether it was taken for pain in the target area or not.

7.1.4 Other pain medication

Use of all other analgesics beyond the permitted rescue pain medication is discouraged during the study since it will potentially disturb the study outcome.

If, for any reason, analgesics other than the permitted rescue pain medication are taken (ESD item 10a and 10b), this will be documented in the concomitant medication electronic case report form (eCRF) page.

If analgesic medications is used for pain related to other conditions (e.g., headache, joint pain) these conditions should be recorded as adverse events, and analgesics used for their treatment should be documented in the eCRF.

Note that for **any additional pain medication (beyond the permitted rescue pain medication for EAPP)**, it must be specified in eCRF whether it was taken for EAPP or other pain.

7.1.5 Diet

Subjects will be allowed to eat and drink as usual. However, grapefruit and grapefruit juice must be excluded from the subject's diet 2 weeks before start of study treatment and during treatment because these foods contain constituents that inhibit cytochrome P450 3A4.

7.2 Identity of study treatment

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

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

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

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

Sponsor's substance code	BAY 1002670
INN	Vilaprisan
Brand name	Not applicable
Formulation	Film-coated tablet
Tablet strength	2 mg; 4 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)
Marketing Authorization Holder	Not applicable
Sponsor's substance code	Placebo (to BAY 1002670)
INN	Not applicable
Brand name	Not applicable
Formulation	Film-coated tablet
Tablet strength	Not applicable
Composition	Ingredients: Lactose monohydrate, microcrystalline cellulose, magnesium stearate, dark red lacquer (containing hypromellose, macrogol 3350, talc, titanium dioxide, and red ferric oxide)
Marketing Authorization Holder	Not applicable

INN = International nonproprietary name.

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 Interactive Voice Response System / Interactive Web Response System (IVRS/IWRS) to one of the three treatment groups equally.

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

Randomization to treatment will be stratified by countries/regions (eg, US/Canada, Europe, Japan, China/Taiwan) and by the method of endometriosis diagnosed (surgery or imaging). Randomization to time point of the second endometrial biopsy (at the end of TP1 or TP2) will be stratified by treatment.

7.4 Dosage and administration

See Section 7.1 for administration details.

7.5 Blinding

Forward looking instructions regarding blinding are no longer valid, since with the implementation of Protocol Amendment no. 7 subjects will no longer start or continue on treatment. The initial database lock for all subjects in the randomized double-blind parallel group will occur with the database cleaned for safety only, in order to allow for

unblinding of the existing data. Once the database is locked the subjects will be unblinded and subjects treated with vilaprisan will continue into the open label safety follow up. This additional safety data will be cleaned and the open label portion will be locked.

7.5.1 Blinding measures

Vilaprisan tablets containing 2 mg or 4 mg vilaprisan and placebo tablets are identical in appearance (size, shape, color). The packaging and labeling were designed to maintain the blinding of the investigator's team, the Bayer study team, and the subjects.

For control of possible bias in investigators assessments (ClinROs), PROs to be completed at the study site will be completed prior to the investigators assessments. The exact value of the inclusion criteria 4 (at Visit 1) and 5 (at Visit 3 / Randomization) provided by the subject on the PRO device will be hidden (ie, only "eligible yes/no" will be shown to the investigator). At no time is the investigator/site personnel allowed to respond to questions other than the subjects' technical questions for the completion of PROs.

7.5.2 Unblinding

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

7.5.3 Emergency unblinding by the investigator

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

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

7.6 Drug logistics and accountability

No longer valid, since with the implementation of Protocol Amendment no. 7 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.

7.7 Treatment compliance

Any discrepancies between actual and expected amount of returned study medication were discussed with the subject at the time of the visit, and any explanation was documented in the source records. To monitor compliance, subjects were required to complete an electronic diary (on a hand-held device) daily throughout the study. The date of each study drug intake

was tracked via the hand-held device. The hand-held device was dispensed at Visit 1 and the completeness of the electronic diary data was 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[6], 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, see Section 6.3.

Restrictions regarding forbidden concomitant medications were valid before and during the treatment phase of this study, but were lifted during the treatment-free safety FUP phase that started during the temporary pause and continues with Protocol Amendment no. 7. Please see also Section 6.3.

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

Surgical and interventional treatment for endometriosis was to be documented in the eCRF if performed during the study period (ie, until the last visit of the subject) and should be regarded as Adverse Event (AE) if deemed appropriate by the investigator (see Section 9.6.1.1 and 9.7.2). Calcium and vitamin D are not excluded for subjects in the study, but for assessment of possible influence on bone mineral density (BMD) measurements, the intake should be documented on the concomitant medication eCRF throughout the study.

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 Progestin therapy for induction of bleeding

If required, subjects were given an appropriate progestin therapy for induction of bleeding. Progestin therapy is not considered as study medication and is documented as concomitant medication, see Section 9.7.1 for details).

8.2 Post-study therapy

Initially it was planned that subjects completing the treatment periods participate in the post-treatment follow-up without study drug treatment. The standardized rescue pain medication as specified in section 7.1.3 is to be prescribed, if needed and so maintained until end of the study.

With implementation of Protocol Amendment no. 7, all subjects who started vilaprisan treatment before the temporary pause (including those who are in the prolonged break and

[6] In subjects who have discontinued the study 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.

those who discontinued from study prematurely for any reason) will be asked to undergo a "Safety Closeout visit" with a set of safety follow up procedures, followed by a "Safety Result Reporting visit", which will be individual subjects' end of study visit.

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

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

9. Procedures and variables

9.1 Tabular schedule of evaluations

No longer valid, since with the implementation of Protocol Amendment no.7 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 with vilaprisan before the temporary pause will be asked to have the "Safety Closeout visit" with a comprehensive safety evaluation (with particular focus on endometrial, adrenal and skin safety) which is implemented with Protocol Amendment no. 7. This also applies to subjects who have discontinued the study before or during the temporary pause, provided they have taken at least one dose of study medication vilaprisan. The second scheduled visit, the "Safety Result Reporting visit" can be done as a telephone visit.

This "Safety Closeout visit" should be performed in all subjects as soon as possible after implementation of Protocol Amendment no.7. The following procedures are to be done:

Table 9–1: Schedule of procedures

Visit	Safety Closeout Visit [7]	Safety Result Reporting visit (can be Telephone visit)
Timing	After approval of Protocol Amendment no. 7	Once all safety results are available
Informed consent	X	
Concomitant medications	→	→
AE assessments	→	→
Adrenal disorder signs and symptoms incl. vital signs[8]	X	
MRI of adrenal glands[9]	X	
DEXA scan for bone mineral density[10]	X	
Dispense saliva test tubes	X	
Collect saliva test tubes[11]	X	
Referral to dermatology expert	X	
Physical examination	X	
Body weight	X	
Gynecological/breast exam[12]	X	
Urine pregnancy test	X	
Cervical cytology[13]	X	
Ultrasound examination[14]	X	
Endometrial biopsy[15]	X	
Laboratory (blood)[16, 17]	X	
Collection of unused study drug and empty drug packs/drug accountability	X if applicable	
Collection of eDiary device and review of bleeding data and assessment of any abnormal bleeding pattern	X if applicable	
Deactivation of subject on tablet computer without selecting a particular visit	X	
Communication of results from safety evaluations to the subject		X

[7] In most cases the procedures scheduled for this visit will not take place on the same day
8 Blood pressure in triplicates and heart rate after 5 minutes of rest in a sitting position
9 Negative pregnancy test is a prerequisite
[10] Negative pregnancy test is a prerequisite
11 Saliva tests should be performed as soon as possible after this visit to allow for a repeat in case of unevaluable results or for review by one of the adrenal experts in case of abnormal results. The two samples should be returned to the study site preferably on the day after collection of the last sample.
12 Only to be performed if subject did not have these performed with normal result after end of treatment
13 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; for subjects with menstrual cycles the endometrial biopsy should be taken between Day 7 to 15 (inclusive) of a menstrual cycle
14 The ultrasound must be done before the biopsy
15 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 9.6.3.1). The biopsy CRF page needs to be completed for all subjects, including cases where according to protocol no biopsy is required.
16 The blood should be withdrawn under fasting conditions between 6 am and 10 am.
17 In subjects who take biotin, the last dose of biotin should be at least 72 hours prior to hormone testing.

AE = adverse event, DEXA = dual-energy X-ray absorptiometry, MRI = magnetic resonance imaging, PAEC = progesterone receptor modulator-associated endometrial changes

Subjects who received treatment with placebo prior to the temporary pause will be asked to return the eDiary device. Thereafter, subjects will be deactivated on the tablet computer.

9.2 Visit description

No longer valid, since with the implementation of Protocol Amendment no. 7 all subjects treated with vilaprisan will need to come to the site for one scheduled "Safety Closeout visit" only. In most cases the procedures scheduled for this visit will not take place on the same day.

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

9.2.1 Unscheduled visits

If deemed necessary for an individual subject, the investigator or designee, at his/her discretion, may arrange visits in addition to the scheduled study visits. A possible reason for an unscheduled visit would be the requirement for follow up investigations.

9.2.2 Optional pre-screening phone contact

No longer valid, since with the implementation of Protocol Amendment no. 7 no new subjects will be recruited.

9.2.3 Scheduled visits

With the implementation of Protocol Amendment no. 7 all subjects treated with vilaprisan will need to come to the site for one scheduled "Safety closeout visit". A second scheduled visit, the "Safety result reporting visit" can be done as a telephone visit. For details regarding the safety closeout visit and the safety result reporting visit please see section 9.1.

9.3 Population characteristics

With implementation of the amendment no new subjects will be recruited. This section describes the data collection performed in subjects enrolled before the temporary pause.

9.3.1 Demographic

Demographic data (eg, year of birth, age at Visit 1, race, ethnic group, educational level) and other population characteristics including smoking habits, and alcohol consumption were collected consistent with the original schedule of procedures (Protocol Amendment no. 3).

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below were collected as available to the investigator:

- Start before signing of the informed consent
- Considered relevant for the subject's study eligibility.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.3.3 Reproductive, menstrual, and endometriosis history

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

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

9.4 Efficacy

With the implementation of Protocol Amendment no.7 no new efficacy data will be collected.

This section details the procedures for collecting efficacy variables before implementation of Protocol Amendment no. 7.

9.4.1 Patient-reported outcomes

9.4.1.1 Endometriosis Symptom Diary (ESD)

The ESD was filled in daily using the electronic hand-held device consistent with the original schedule of procedures (Protocol Amendment no. 3).

The ESD is a newly developed PRO instrument designed to assess the subject's experience of endometriosis symptoms. Designed as an electronic hand-held device, the ESD was completed by the subject each evening (between 18:00 and 23:59) in the electronic hand-held device, when the subject was to reflect on her experiences in the past 24 hours. Subjects were asked to rate their endometriosis associated pelvic pain (worst EAPP, short term and constant EAPP) in the target area and dyspareunia (painful sexual intercourse) in the past 24 hours. These symptoms were reported using an 11-point (0 to 10) numerical rating scale (NRS): 0 represents no pain while 10 represents unbearable pain. Any use of rescue pain medication (prescribed by the investigator) and the information whether it was taken for pain in the target area or not was recorded. The instrument also consists of a series of dichotomous yes/no questions and others items that are rated based on categorical responses. Bleeding intensity was also be assessed by one of the items, i.e. the subjects were asked to select the response that best describes their vaginal bleeding during the past 24 hours.

9.4.1.2 Endometriosis Impact Scale (EIS)

The EIS was filled in once per week using the same electronic hand-held device consistent with the original schedule of procedures (Protocol Amendment no. 3). The EIS was completed by the subject, when she was to reflect on her experiences during the past 7 days.

The EIS is a newly developed PRO instrument designed to assess the effect of the primary defining symptoms of endometriosis (i.e. pain) on the subjects' lives, describing effects on physical activities, emotional effect, social and leisure activities, paid work or study, household activities, sexual activities, ability to concentrate, and ability to sleep. Subjects were asked to complete the EIS weekly in the evening (between 18:00 and 23:59) of the same day of the week (e.g. always on Mondays) in an electronic hand-held device, when the subjects were to reflect on the effect of endometriosis pain on their daily lives during the "past 7 days".

9.4.1.3 Numeric Rating Scale (NRS) for EAPP

The NRS for EAPP was filled in once at the Screening visit (Visit 1) consistent with the original schedule of procedures (Protocol Amendment no. 3).

Subjects were asked to rate their pelvic pain on a single-item 11 point (0 to 10) NRS, using a recall period of 4 weeks. Zero represents no pain at all while 10 represents the worst imaginable pain.

The NRS is a commonly used and easily understood format for the assessment of pain in various indications.

9.4.1.4 Visual Analogue Scale (VAS) for EAPP

The VAS for EAPP was filled in using the electronic hand-held device consistent with the original schedule of procedures (Protocol Amendment no. 3).

Subjects were asked to rate their EAPP on the VAS, using a recall period of 4 weeks with a single vertical mark on a horizontal line anchored verbally between “no pain” and “unbearable pain” shown on the eDiary screen. The eDiary technology provides the single vertical line with 101 (0-100) individually selectable points on the horizontal line VAS ensuring that the subject’s single vertical mark can be translated into any number/score from 0-100 for the rating of pain. This methodology has been validated (2, 3) and was accepted by the regulatory authorities (FDA, European Medicines Agency [EMA]) in the past.

The VAS (on paper) has been used in the past as a primary endpoint in Phase 3 clinical studies to determine the efficacy of medicinal products indicated for the treatment of endometriosis.

9.4.1.5 Patient Global Impression of Severity (PGI-S)

The PGI-S was filled in using the electronic hand-held device consistent with the original schedule of procedures (Protocol Amendment no. 3).

Subjects were asked to describe their overall endometriosis symptom severity, using a 6-point verbal rating scale (no symptoms, very mild, mild, moderate, severe, and very severe).

9.4.1.6 Patient Global Impression of Change (PGI-C)

The PGI-C was filled in using the electronic hand-held device consistent with the original schedule of procedures (Protocol Amendment no. 3).

The PGI-C is a patient-rated instrument that measures change in the subjects’ overall endometriosis symptom in the past 4 weeks on a 7-point Likert scale ranging from 1 (very much better) to 7 (very much worse). Higher scores indicate a change for the worse.

9.4.1.7 EQ-5D-5L

The EQ-5D-5L was filled in using the tablet computer at the site consistent with the original schedule of procedures (Protocol Amendment no. 3).

The EQ-5D-5L is a widely used measure of health status with well-documented reliability, validity and responsiveness in the general population as well as in various diseases. Use of this instrument enables a comparison of the effects of endometriosis on health-related quality of life with an age-matched normative sample. The instrument comprises five domains and an overall assessment of health status on a visual analogue scale. The five domains include:

mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, where '1' indicates no problem, '2' indicates a moderate problem, and '3' indicates a severe problem. Descriptive assessment was done on the basis of the VAS assessment and on the single-dimension basis. A preference weighted or utility score can be calculated in a further step using statistical algorithms producing values ranging from -0.594 to 0 (dead) to 1.0 (full health).

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

The SF-36v2 was filled using the tablet computer at the site consistent with the original schedule of procedures (Protocol Amendment no. 3).

The SF-36v2 is a widely used measure of health status with well-documented reliability, validity, and responsiveness in the general population as well as in various disease indications. It consists of 36 items. The SF-36v2 comprises 8 domains: physical function, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health.

9.4.2 Clinician-Reported Outcomes (ClinROs)

The following assessments were based on the investigator's clinical evaluation of the subject and entered in the eCRF by the investigator consistent with the original schedule of procedures (Protocol Amendment no. 3).

9.4.2.1 Clinical Global Impression of Change and Severity (CGI-C and CGI-S)

The investigators completed the Clinical Global Impression Investigator (CGI-C and CGI-S). The CGI-C askes the investigator to rate the change of the subject's symptoms since start of study treatment with the following response options: *very much better, much better, a little better, no change, a little worse, much worse,* and *very much worse*. The CGI-S askes the investigator to describe the subject's overall severity of symptoms with the response options: *none, very mild, mild, moderate, severe* and *very severe*.

9.4.2.2 Modified Biberoglu and Behrman severity profile for symptoms and findings

The modified Biberoglu and Behrman (B&B) severity profile for symptoms and findings were filled in.

9.4.3 Ultrasound (efficacy) to assess endometriosis lesions

A qualified expert in performing gynecologic ultrasound exams conducted ultrasound examinations consistent with the original schedule of procedures (Protocol Amendment no. 3). Ultrasound measurements did not have to be done on the same day as other assessments of that visit, but had to be performed as close to the specified visit as possible.

For each subject, the most appropriate ultrasound method(s) (transvaginal, abdominal or transrectal) was to be used depending on location of the possibly visualizable endometriosis lesion(s) (e.g., endometrioma, deep infiltrating endometriosis, adenomyosis) and this method(s) was to be used consistently throughout the study.

The minimum source documentation included printouts and/or compact disk (CD)s with images from the ultrasound machine showing the lesions. The printouts and/or CDs with images were to be labeled unambiguously, containing at least the study number, SID number, time point, and diameter of the lesions.

For safety ultrasound procedures, see Section 9.6.3.6.

9.5 Pharmacokinetics / pharmacodynamics

With the implementation of Protocol Amendment no. 7 no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study. This section describes processes performed in subjects enrolled before the temporary pause.

9.5.1 Drug measurements

Blood samples for measurement of vilaprisan for pharmacokinetics were taken at several time points after start of study treatment unless precluded by local regulatory and/or IEC guidelines consistent with the original schedule of procedures (Protocol Amendment no. 3). The samples were collected and processed as described in detail in the Sample Handling Sheet as a part of a separate Laboratory Manual. At Visit 3, 2 PK samples were to be taken. The first sample was to be taken 0.5 to 1 hour after drug intake; the second sample was to be taken 2 to 4 h after study drug intake under supervision. At Visit 5 and 7, 2 PK samples were to be taken. The first sample was to be taken before intake of study drug. Afterwards the subject was to take her study drug under supervision at the site. The second sample was to be taken 0.5 to 4 hour after drug intake. The date and time of the last 2 doses of study drug prior to the first PK sample at each visit, the exact time of the supervised drug intake at the study site, and the exact time (not the time window) when the blood samples were taken was to be documented in the eCRF.

PK plasma concentrations of vilaprisan were to be determined using a validated liquid chromatography/tandem mass spectrometry method. Quality control (QC) and calibration, samples were to be analyzed concurrently with study samples. The results of calibration samples, QC samples and study samples were to be reported in the bioanalytical report, which was to be included in the clinical study report for this study. Study responsible bioanalytical personnel was to remain unblinded for analysis of study samples. For subjects receiving placebo, no blood samples were to be analyzed to determine the plasma PK.

9.5.2 Population pharmacokinetic analysis of vilaprisan

Blood samples for PK will be taken according to the original schedule of procedures (Protocol Amendment no. 3). Deviations from the specified time points are taken into account when calculating the PK parameters. Those deviations do not qualify as protocol deviations. The times of study drug intake will be documented in the eCRF.

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. As a result, dedicated people (ie, involved in bioanalytics and population PK analysis) may be unblinded. Appropriate measures will be taken to maintain blinding of the study team, which will be described in a Data Operations Plan, which will be provided to the study team.

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 Phase 2 data will be applied to all valid PK samples to evaluate the relationship between variability in PK and covariates (i.e. intrinsic [e.g. body weight, race] and extrinsic factors [e.g. 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

The relationship between vilaprisan exposure and efficacy and safety parameters such as pain response, bleeding intensity and endocrine hormone levels might be evaluated. In such a case, the final population PK model that will be used to describe the PK of vilaprisan as outlined above will be linked to relevant PD parameters (pain, endocrine hormone levels, and bleeding) to investigate the (PK/PD) relationship between vilaprisan exposure and response. Details of the model development and evaluation will be described in a separate M&S Analysis Plan and the results reported in a separate M&S Report, if applicable.

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event (AE)

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

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

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

- 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 (e.g. 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 (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.
- In subjects who discontinued the study 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 serious adverse event (SAE)

A serious adverse event (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
     (e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures)
   - The admission is not associated with an AE
     (e.g. 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. All instances of liver parameter testing which meet criteria for withdrawal of a subject from the study treatment should be reported as SAE.

d. Results in persistent or significant disability / incapacity

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

e. Is a congenital anomaly / birth defect
f. Is another serious or important medical event (IME) as judged by the investigator

All instances of liver parameter testing which meet criteria for withdrawal 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) (13) 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: An 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 adverse events that may be indicative of a serious disease state, the Important Medical Events (IMEs) list published by the EMA, will be periodically reviewed against the non-serious adverse events reported during the study. The investigator may be asked to review and confirm, when deemed necessary, if an event meets the criteria for seriousness, in his/her opinion.

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 according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

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

- Mild
- Moderate
- Severe

9.6.1.2.3 Causal relationship

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

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

Possible answers are “yes” or “no”

An assessment of “no” would include:

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

or

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

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

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

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Subject’s response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject’s pharmacodynamics should be considered.
- The assessment is not possible

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
- 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

The investigator has to record on the respective CRF pages all adverse events occurring in the period between the signing of the informed consent and the end of the follow-up phase; after the end of the follow-up phase there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2

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

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

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 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an

AE page in the CRF as well as the complementary pages provided in the Investigator File must be completed for each SAE.

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

Notification of the Institutional Review Boards (IRBs), Institutional Ethics Committees (IECs)

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

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

Sponsor's notification of the investigational site

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

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the investigator's brochure (IB) / summary of product characteristics (for standardized rescue pain medication).

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

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

9.6.1.6 Adverse events of special safety interest

The investigators will assess all AEs to determine if they are AEs of special interest (AESIs) and document this in the eCRF. Adverse events from the following areas should be considered for reporting as AESI according to the following guidance:

- Liver disorders:
    - For all cases which qualified for "close observation" before implementation of Protocol Amendment no. 7 and/or qualify for "ruling out of alternative cause" after implementation of Protocol Amendment no. 7 (see Section 9.6.3.9), the underlying event should be recorded as AESI in the AE eCRF.
- Endometrial disorders:
    - Endometrial hyperplasia (all subcategories according to WHO 2014 [and WHO 1994] classification), for monitoring and FUP see Section 9.6.3.1

- 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 9.6.3.1.4.

- Skin disorders:
  - Any dermatology expert´s diagnosis of a pre-cancerous or malignant skin lesion, including cutaneous sarcoma confirmed by biopsy diagnosis, qualify as an AESI. Malignant skin lesions should be reported as an SAE to ensure timely reporting to regulatory agencies.
- Adrenal disorders
  - A robust adrenal safety monitoring program has been implemented in all ongoing vilaprisan studies, including MRI of the adrenal glands, laboratory parameters, and evaluation of signs and symptoms indicative of adrenal disorder. A systematic approach of assessment and evaluation of adrenal gland findings will be applied as described in Section 9.6.3.8. Any adrenal abnormality assessed as relevant by either the adrenal gland expert or the local specialist will need to be documented as an AESI and to be reported to the sponsor´s pharmacovigilance department following the same standard process (reporting timelines, AE CRF and AE complementary pages) as serious AE. Tumors of the adrenal glands (diagnosed by the MRI central read, the adrenal gland expert or the local specialist) should in addition be reported as SAEs to ensure timely reporting to regulatory agencies.
- Relevant loss of BMD:
  - During treatment: BMD loss of > 6% of the lumbar spine compared to baseline that 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).
  - Lack of adequate bone recovery in subjects treated with vilaprisan, defined as BMD loss $\geqslant$ 3% compared to baseline at any site and/or Z-score of $\leqslant$ - 2 at any site irrespective of the absolute bone loss in an off-treatment DEXA scan (determined either by the central reading imaging laboratory or by assessment at the site and confirmed by the central reading imaging laboratory).
- HMB (during treatment periods, during the drug-free interval, or after EoT, see also Section 9.6.3.1.7) 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
  - 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 (see also Section 9.6.1.4).

- Worsening of EAPP: EAPP will be documented in detail throughout the study (see Section 9.4.1). EAPP should be recorded as an AE (and then it automatically qualifies as an adverse event of special safety interest) only if one or more of the following applies:
    - Leads to study discontinuation
    - Leads to diagnostic or surgical procedures (the surgery/laparoscopy will not be a study procedure and will lead to exclusion from the study)
    - Requires any treatment other than the standardized pain medication (see Section 7.1.3)
    - 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 (see Section 9.6.1.1, and 9.6.1.4)

Progesterone receptor modulator-associated endometrial changes (PAEC) will be assessed and documented in a systematic way (see Section 9.6.3.1.4). The results of the PAEC assessment will only be reported back to the investigators if they trigger the request for a repeat biopsy. Apart from cases where such a repeat biopsy is necessary, no clinical action for an individual subject is required based on the PAEC assessment results. PAEC assessment results are systematically collected for all samples and will be reported in aggregated form at the end of the study. They should therefore not be reported as AE for an individual subject.

A systematic approach of assessment and evaluation will also be applied to EAPP (see Sections 9.4.1.1 and 9.4.1.3), endometrial hyperplasia, endometrial thickening (see Sections 9.6.3.1 and 9.6.3.4), liver function test (Section 9.6.3.9), adrenal monitoring (Section 9.6.3.8), skin monitoring (9.6.3.10), and BMD (9.6.3.2).

9.6.2 Pregnancies

Contraception and pregnancy test

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

At the time points shown in in the original schedule of procedures (Protocol Amendment no. 3), urine pregnancy tests will be performed at the study site. A pregnancy test must be performed before the start of study drug treatment in each treatment period (by the subject at home), and always before BMD and endometrial biopsy.

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

A positive urine pregnancy test shall be confirmed at the study site, for example, with serum pregnancy test or transvaginal ultrasound.

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

contact the study site immediately. If pregnancy is confirmed, the subject will be discontinued from the study.

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

With the implementation of Protocol Amendment no. 7, 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, an urine pregnancy tests will be performed at the study site. A pregnancy test must also be performed in case of any further repeat endometrial biopsy.

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 6.3).

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

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

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

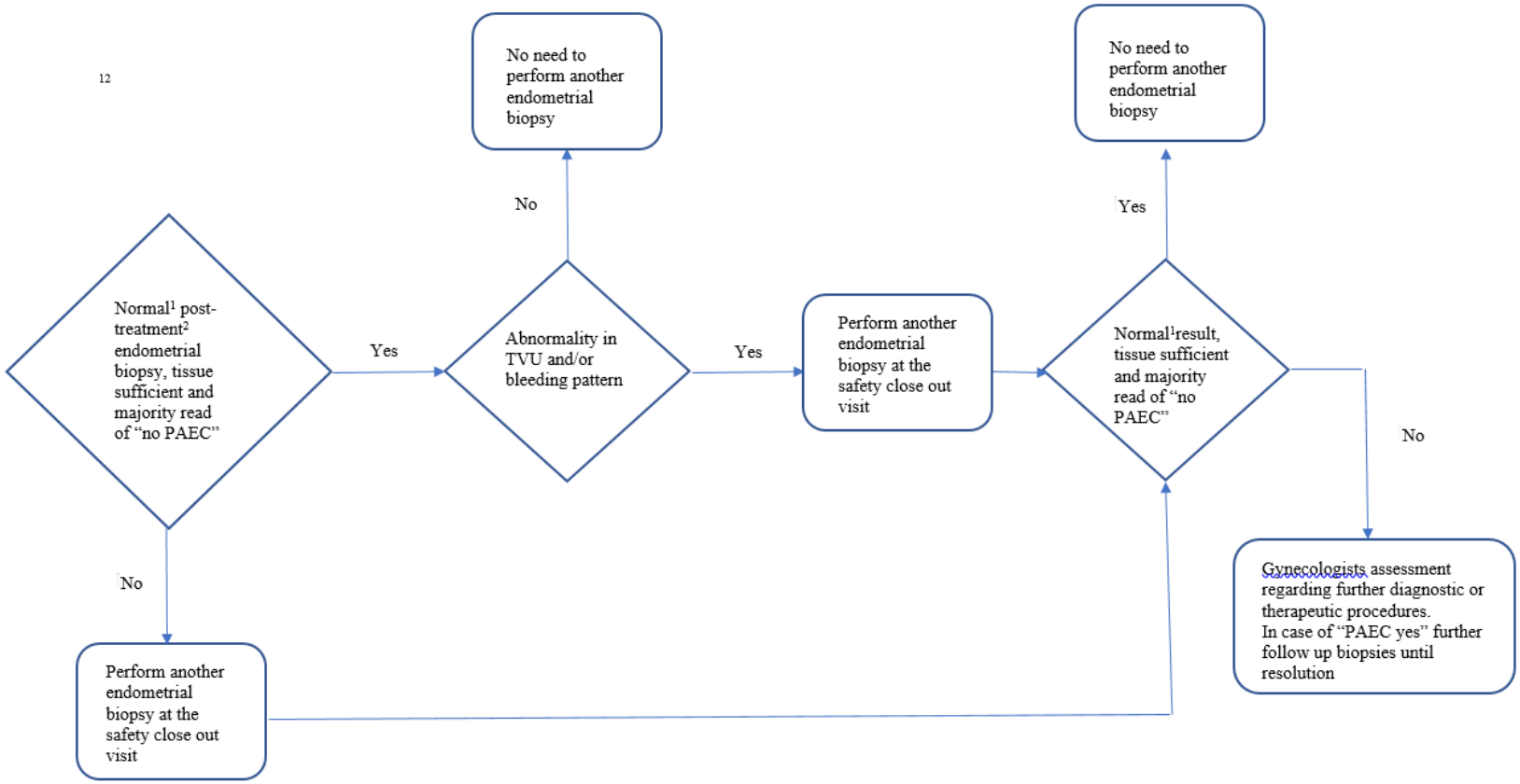
9.6.3 Further safety

9.6.3.1 Endometrial biopsies

9.6.3.1.1 Algorithm for evaluation of endometrial safety

A careful endometrial safety monitoring is applied in this study which included regular ultrasound investigations during the active treatment period (see Section 9.6.3.11 for description of procedure), endometrial biopsies (see Section 9.6.3.1), and observation of bleeding patterns (see Section 9.6.3.1.7). With implementation of Protocol Amendment no. 7 one more examination is planned according to the algorithm below.

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



[1] Normal is 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.

[2] Post-treatment is defined as biopsy taken at the earliest 7 days before last study drug intake.

9.6.3.1.2 Timing of last endometrial biopsy

Each subject should have an endometrial biopsy with a normal[18] result documented from a timepoint after 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 transvaginal ultrasound (TVU) and/or bleeding pattern are required to undergo an endometrial biopsy at the safety closeout visit.

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 captures the reason why a biopsy was not done.

Depending on the result of this last scheduled endometrial biopsy, repeat unscheduled endometrial biopsies should be performed in addition. See Sections 9.6.3.1.5 and Figure 9–1 for details.

9.6.3.1.3 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 cytology sample is collected at the same visit, those procedures have to be performed before performing the biopsy.

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

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

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

9.6.3.1.4 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.

[18] 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.

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 9.6.3.1.5.

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. This assessment will be performed as batch reads when a sufficient number of samples are available.

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

Starting with Protocol Amendment no. 7, the majority diagnosis of the multi-reader assessment (Part II of the evaluation form, i.e. the diagnoses 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 9.6.3.1.5.

Besides standard safety criteria (e.g., proliferative/secretory/atrophic endometrium, endometrial hyperplasia, malignant neoplasm) the pathologists will document the presence of PAEC (see Section 9.6.3.1.6). 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. Investigators will be informed in addition about a single-reader diagnosis (Part II of the evaluation form) that is more severe than the majority diagnosis (Malignant neoplasm > Endometrial Hyperplasia > Benign endometrium).

While the relevant diagnosis for study purposes is the majority result of the multi-reader assessment, any single reader diagnosis that is more severe than the majority diagnosis should be evaluated by the investigator (or by a gynecologist in case the investigator or sub-investigator is not specifically trained in gynecology) for the necessity of therapeutic

interventions. The minimal diagnostic requirement for those cases is a follow up biopsy. For all follow-up examinations and/or therapeutic interventions all efforts should be taken that these examinations are conducted according to the standards of this protocol (e.g. biopsies should undergo multi-reader assessment) and are documented within the study framework.

9.6.3.1.5 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[19] 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 evaluated 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 9.6.3.1.6.

For reporting of abnormal biopsy results as adverse event of special interest or SAE, please see Sections 9.6.1.6 and 9.6.1.4.

9.6.3.1.6 Follow-up of PAEC

Besides standard diagnostic criteria (i.e., proliferative/secretory/atrophic endometrium, endometrial hyperplasia) presence of PAEC will be analyzed in all endometrial biopsy samples as part of the multi-reader assessment. The diagnosis of PAEC is based on a constellation of histologic features that, taken together, are characteristic. None of the features is unique, and to some extent any may be seen in 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 Safety closeout visit or at a premature discontinuation visit) according to the majority diagnosis resulting from the multi-reader assessment, the site will be informed and

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

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.

9.6.3.1.7 Heavy menstrual bleeding / suspicious bleeding pattern

The study drug may lead to changes in bleeding pattern, mostly amenorrhea during treatment, but can also be associated with intermittent spotting or mild intermittent bleeding of short duration.

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). Further the site was asked to actively contact subjects who upon review of the ESD Item 4 have entered more than 10 consecutive days of bleeding (intensity of "mild" or more) during study drug intake (ie, during a treatment period). In case such unusual bleeding events are reported or are detected from the ESD (item 4) 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 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 eDiary (ESD item 4, intensity of "mild" or more) with a maximum of 2 non-bleeding days in between.
- Continuous spotting:
  Evaluation should be initiated if
  - Continuous spotting is reported by the subject and/or
  - if the subject entered more than 10 consecutive days of spotting in the e-diary with a maximum of 2 non-spotting in between.
- Unusual heavy bleeding:
  Evaluation should be initiated if
  - Unusually heavy bleeding is reported by the subject

Evaluation plan for subjects with unusual HMB or bleeding pattern

The evaluation should include the following assessments:

- 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 9.6.3.1.5).

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 9.6.1.2.1), it should be reported as such. An appropriate treatment as per local standard of care (eg, curettage) is to be performed after an endometrial biopsy has been taken.

9.6.3.1.8 Unscheduled endometrial biopsy

Unscheduled endometrial biopsies can result from the requirement to follow-up on abnormal results of a previous biopsy, see Section 9.6.3.1.5. 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 9.6.3.1.7.
- For procedures in case of an abnormal result of the unscheduled biopsy, please see Section 9.6.3.1.5.

9.6.3.2 Bone mineral density

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.

Technical requirements for DEXA scans:

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 be also 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 will be based on the central reading.

In the event excessive loss of BMD >6% at the lumbar spine is accompanied by a Z-score reading of ≤-2 standard deviation (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 end of the TP 1, the subject must have been withdrawn from study drug. Such a decrease constitutes twice the assumed SD in the population included in this study. In addition, the accompanying Z-score measurement of ≤-2 SD can be taken as an indicator that the measured BMD value is below the average BMD for subjects of same age, sex, and ethnicity. Subjects should have had the EoT visit (Visit 10) examinations performed, and should have been asked to come to the FUP 1 and FUP 2 visits. Additional diagnostic procedures, including a further BMD measurement and treatments should have been initiated, as deemed necessary by the investigator.

Cross calibration

Phantom image acquisition will be standardized across DEXA imaging facilities participating in the 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 radiology 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.

DEXA scan performed at the safety closeout visit

Every subject who received vilaprisan treatment should have a DEXA scan performed at the "Safety Closeout visit", which in most subjects corresponds to a timepoint of ⩾ 12 months after EoT.

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% at any site and/or an abnormal Z-score (defined as ⩽ -2 at any site irrespective of the absolute bone loss) compared to the baseline BMD, the subject should be referred to a local bone specialist. The results of the assessment should be captured in the eCRF 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 vitamin D and calcium, taking into account the vitamin D measurements performed in the study context.

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 the original schedule of procedures (Protocol Amendment no. 3). The BMD measurements are to be performed only after the subject has been tested negative for pregnancy. Subjects will be asked to perform a home pregnancy test on the day of the visit prior to the scan. More details on the calibration and procedure of central reading will be provided in a separate manual.

9.6.3.3 Laboratory evaluations

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.

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

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, hemoglobin (Hb), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelets, neutrophils, eosinophils, basophils, lymphocytes, and monocytes.

Blood test for hepatitis A, B, and C (only in case of elevated liver enzymes requiring further follow up): anti-HAV Immunoglobin M (IgM), HBs-Ag, anti-HCV, and HCV-mRNA (assessed only in cases with a positive result for anti-HCV).

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

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

Biochemistry: glycosylated hemoglobin (HbA1c) and ferritin.

Additional parameters[20]: 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-, potentially also Hepatitis D- Hepatitis E-, Cytomegalo-, Epstein-Barr-, and Herpes simplex virus infection, brucellosis, leptospirosis, and toxoplasmosis, ANA/ANCA screening test with further tests depending on result and IgA, IgG, and IgM.

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[20] 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 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.

For **urine pregnancy test**, see Section 9.6.2.

9.6.3.4 Cervical cytology

The cervical cytology 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, cervical cytology should only be repeated once in case of insufficient material.

9.6.3.5 Physical and gynecological examinations

Complete physical examinations will be done for all subjects. Gynecological examinations, including breast palpation, will be performed in subjects who did not have this performed

with normal result after end of treatment. In case of any suspicious finding, further diagnostic investigations will be performed at the discretion of the investigator.

9.6.3.6 Ultrasound

Ultrasound examinations (evaluated for efficacy and safety) will be performed by a qualified expert in performing gynecologic ultrasound exams. 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. 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 within the visit window.

The following safety parameters will be documented: endometrial thickness (double layer), evaluation of ovaries, and any pathology detected during the examination. Endometrial thickness will be measured in the medio-sagittal section as double-layer in millimeters.

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

If cyst like structures >30 mm without suspicious appearance (ie, functional cysts) are visualized in the ovaries, unscheduled ultrasound examinations to document regression/outcome of these findings should be performed as described in Section 9.7.3.

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

The minimum documentation at the site will include printouts and/or CDs with images from the ultrasound machine showing the endometrium in sagittal section and both ovaries. The printouts and/or CD images have to be labeled unambiguously, containing at least the study number, subject number, time point, endometrial thickness, and side (left/right) for ovaries.

For efficacy ultrasound procedures, see Section 9.4.3. (valid only before implementation of Protocol Amendment no. 7).

9.6.3.7 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 and BMI will be determined once again at the safety closeout visit.

9.6.3.8 Adrenal monitoring

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

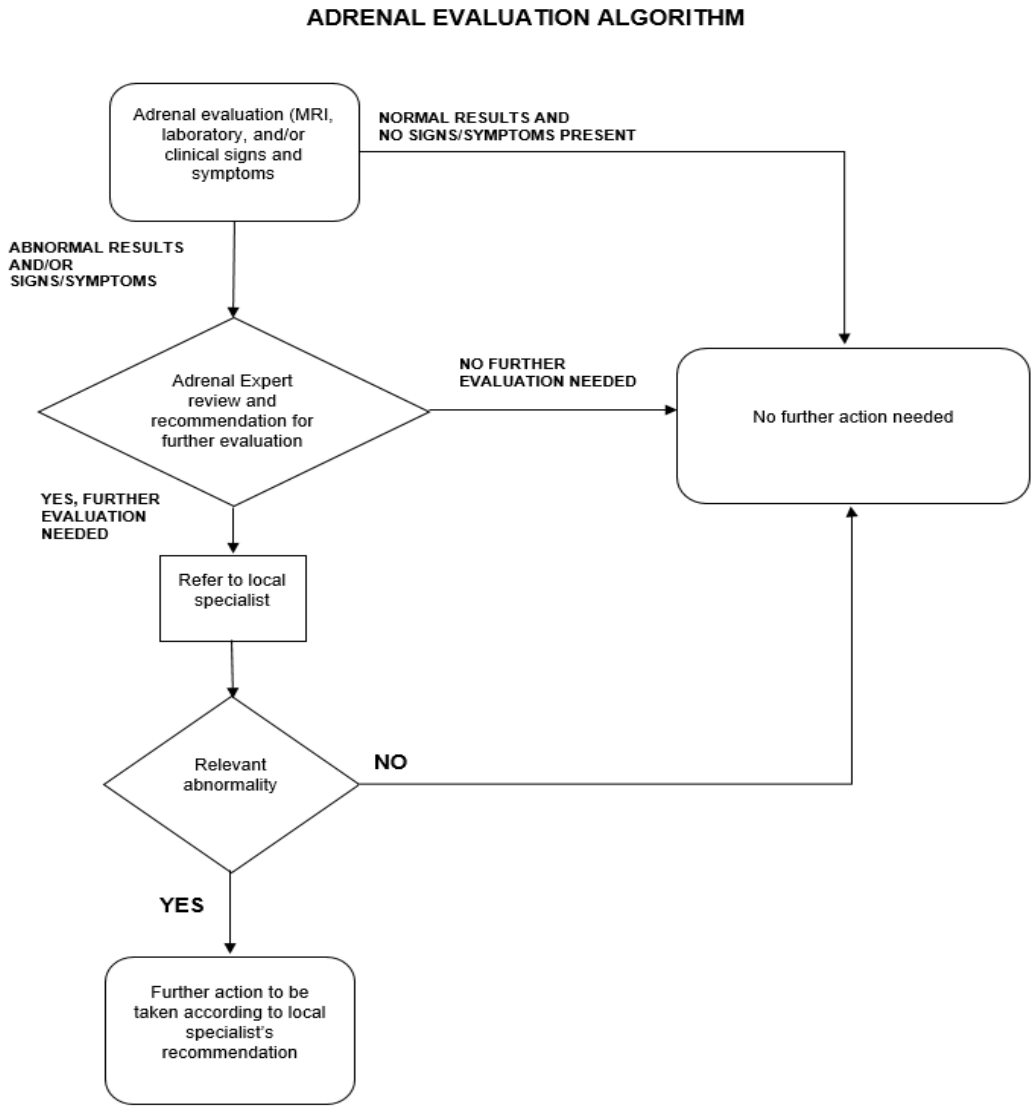
A plan for subjects showing adrenal neoplasms or hormonal abnormalities has been developed with the input of external endocrinology experts, see Adrenal monitoring algorithm below.

A panel of three external clinical adrenal gland experts has been set up, that will support and guide further evaluations and/or referral to local specialists in case an abnormality is detected in a study participant. 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 medical standard
    - 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 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.

EoT = end of treatment, MRI = magnetic resonance imaging

9.6.3.8.1 Timing of adrenal monitoring

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

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

Adrenal monitoring also needs to be performed in subjects who started treatment and have discontinued the study before or during the temporary pause. After re-consenting, data related

to adrenal monitoring and their results will be documented in the CRF 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.

9.6.3.8.2 Adrenal MRI

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

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

Any procedure-related complaints will be documented as AEs.

9.6.3.8.3 Laboratory testing

Adrenal monitoring:

- Serum cortisol, to be measured between 6 am and 10 am
  - ACTH will be assessed from the same sample if the cortisol measurement yields an abnormal value.
- Late night salivary cortisol (to be obtained between 11 PM and midnight)

  Subjects will be instructed to use the specifically provided saliva test tubes on two consecutive evenings for separate sampling. The time of sampling needs to be documented on the test tube / requisition form. Subjects will be asked to return samples to the site to ensure standardized transport and processing at the central laboratory (please see algorithm above).
- Serum glucose measurements under fasting conditions
- Serum DHEA-s (Dehydroepiandrosterone sulfate) and total testosterone (tT) Furthermore, the age-specific DHEA-s ratio (derived by dividing the subject's DHEA-s value by the lower limit of the age-specific reference range) will be calculated.

  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 (see also Figure 9–2).

9.6.3.8.4 Adrenal signs and symptom inquiry

Vital signs (blood pressure in triplicates and heart rate) will be documented at the safety closeout visit. Blood pressure should be measured in triplicates after 5 minutes of rest, while the subject is sitting. Measurements should be made at least 1 minute apart using the same arm at each visit and should be recorded on the eCRF (4).

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

9.6.3.9 Liver 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 9.6.3.9.1. In addition, the liver inquiry had to be completed at regular intervals. Based on the long interval between implementation of Protocol Amendment no. 7 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) however 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 alternative explanations should be performed including:

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

- Obtaining additional tests to evaluate liver function as appropriate, (eg, international normalized ratio [INR], total bilirubin measurements).
- Referral for a liver ultrasound.

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

9.6.3.9.1 Liver symptom inquiry

In the past, 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. Therefore, investigators should ask subjects 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 structures inquiry was used to determine withdrawal criteria and is therefore not needed at the Safety Closeout Visit.**

9.6.3.10 Skin monitoring

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

The outcome of the dermatology expert's examinations will be reported in the eCRF. 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 vilaprisan treatment, and have 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, and if applicable any related AEs and respective concomitant medications are to be captured. 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.

9.6.3.11 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.

9.7 Other procedures and variables

9.7.1 Induction of bleeding

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 (see Section 8.1.1).

During the drug-free interval: If, for any of the treatment groups, no bleeding occurs within 7 weeks after the end of TP1 or if the second bleeding episode does not occur within 7 weeks

after the end of the first bleeding episode, an ultrasound will be performed (in an unscheduled visit) after which bleeding will be induced. TP2 should only start within Day 3 and Day 7 of the second bleeding episode following the end of the TP1, and if one of the two bleeding episodes being spontaneous. If induction of bleeding is required more than once, the investigator should consider any underlying conditions, and assess continued participation of the subject.

After EoT visit: If spontaneous menstrual bleeding does not occur within 7 weeks after the EoT of TP2, an ultrasound will be performed after which the bleeding will be induced. The planned endometrial biopsy (ie, at FUP visit) will be scheduled at Cycle Day 7 to 15 (inclusive) of the first menstrual cycle after the induced bleeding episode (i.e. after the induced and the first spontaneous bleeding).

9.7.2 Histology of endometriotic lesion

If any subject is scheduled to have pelvic surgery during the study, every attempt should be made to obtain histologic data from any visible focus of endometriosis. Surgical excision of any endometriotic lesions during treatment will have to be reported by the sites. A histologic assessment of endometriotic lesions will be performed by expert pathologists as further described in the Operational Manual.

9.7.3 Monitoring of ovarian cysts

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

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

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

9.7.4 Biomarker investigation

The biomarker (BM) investigation will be exploratory. Blood samples and endometrial biopsies (only remaining material from the endometrial biopsies after its safety assessment will be used for exploratory BM investigations) will be collected.

The biomarker investigation is not applicable for China due to regulatory guidance.

Details on the collection, processing, storage and shipment of BM samples will be provided in a separate document (e.g. sample handling sheet or lab manual).

The objective of the BM investigation is to monitor the disease activity and therapeutic efficacy of vilaprisan by molecular BMs (i.e. disease activity BMs). Disease activity BMs will be measured including but not limited to cancer antigen 125, urocortin, annexin V, high sensitivity C-reactive protein and brain derived neurotrophic factor.

Exploratory BM analysis on the expression of endometrial genes/proteins will be performed.

In addition to the BMs listed above, other BMs deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e. mode of action related effect or safety of the drug, disease modifying potential and therapeutic efficacy) may be measured, based on newly emerging data from other ongoing studies and / or literature data.

The monitoring BMs will be investigated by utilizing multiplex immunolabelling approaches (e.g. Luminex technology). BMs not available for multiplexing will be evaluated separately (e.g. by enzyme-linked immunosorbent assay [ELISA] assays).

Details on the description of the methods and the results of the conducted BM analysis will be reported in a separate document (i.e., BM report).

9.8 Appropriateness of procedures / measurements

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

10. Statistical methods and determination of sample size

10.1 General considerations

All data will be presented in the subject data listing as they are recorded. Generation of listings will be conducted by or under the supervision of the sponsor's study statistician.

Listings will be generated using Statistical Analysis System (SAS) software after all **safety data** has been cleaned, locked and released for analysis.

Apart from listing generation no further statistical analysis or summary table generation will be conducted. No interim analysis will be conducted.

10.2 Analysis sets

Safety analysis set (SAF): All subjects who took at least 1 dose of study drug.

10.3 Variables and planned statistical analyses

10.3.1 Variables

10.3.1.1 Efficacy variable

Efficacy data will be listed as they are recorded on the Case Report Form (CRF) and electronic diary (eDiary). Efficacy variables will be not derived.

10.3.1.2 Pharmacokinetics (PK)

Exposure data listings will be generated.

10.3.1.3 Safety variables

Safety variables include the following variables:

- Adverse events
- Vital signs

- Endometrial histology (classical histology, diagnosis of PAEC, individual features of PAEC)
- Endometrial thickness and endometrial/ myometrial/ ovarian changes based on ultrasound
- Laboratory parameters
- Findings resulting from liver monitoring
- Findings resulting from adrenal monitoring
- Findings resulting from skin monitoring Cervical cytology
- Bone mineral density
- Vaginal bleeding pattern

Safety data will be listed as recorded.

10.3.2 Statistical and analytical plans

NA

10.4 Determination of sample size

No longer valid, since with approval of Protocol Amendment no. 7 no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study. This section describes the original sample size planning prior to the decision to temporarily pause the study. The original planned sample size has not been reached.

This Phase 2b dose-finding study was powered for an analysis of the primary efficacy variable in the study population with surgically confirmed endometriosis from North America (US and Canada), Japan, and Europe, i.e. excluding China and Taiwan. Subjects from China and Taiwan and subjects with endometriosis diagnosed based on imaging (MRI and/or transvaginal ultrasound) were planned to be excluded from the primary analysis because these subjects might differ from subjects with surgically confirmed endometriosis in North America, Japan and Europe.

In a Phase 2 study (in the context of another Bayer endometriosis project) in subjects with surgically diagnosed endometriosis, a change of -2.4 units in the subject's 7-day mean 'worst pain' from baseline to end of the 3-month treatment course was observed in placebo treated subjects. For subjects treated with an active comparator (leuprorelin / leuprolide acetate) a change of about -3.7 units and a standard deviation of 2.3 units were observed. The drop-out rate in the placebo arm was 15% and in the active comparator treatment arm the rate was 12.5%.

These estimates were used to determine the sample size for the Dunnett test design of this study using a simulation with the sample size program Pass 13 (Version 13.0.11 Multiple comparisons vs. a control [simulation]).

The simulation of a one-way design with 2 treatment groups and one control group resulted in an average group sample size of 59 subjects for a total sample size of 177 subjects. In the simulation an any-pair power of 0.903 and an all-pair power of 0.696 using the Dunnett's Test procedure for comparing each treatment mean with the control mean were achieved. The target family-wise two-sided error rate was 0.050 and the simulation family-wise error rate

was 0.049. The average within group standard deviation assuming the alternative distribution was 2.3. These results are based on 2000 Monte Carlo samples from the null distributions: the change of all three treatment groups is normal distributed with mean value of -2.4 units and standard deviation of 2.3 units and the alternative distributions: the change of all three treatment groups is normal distributed with standard deviation of 2.3 units and a mean value of -2.4 units for placebo and -3.7 units for 2 mg vilaprisan and 4 mg vilaprisan.

Seventy subjects for a total sample size of 210 subjects were planned to be randomized in each treatment arm to achieve 59 subjects with data after the first 3-month treatment interval assuming a dropout rate of 15% during the first 3-month treatment interval.

It was planned to randomize about 50% of the 210 subjects with surgically diagnosed endometriosis in centers from the US / Canada, 30% in centers from Europe, and 20% in centers from Japan.

To assess the safety of Vilaprisan, approximately 100 actively treated subjects (Vilaprisan 2 mg or Vilaprisan 4 mg) with a treatment duration of one year were planned to be observed. The dropout rate for a one-year treatment was assumed to be 50%. In order to achieve 100 active vilaprisan-treated subjects with a treatment duration of one year, the calculated sample size of 210 subjects was planned to be increased by a further 105 subjects.

These additional 105 subjects could have been either surgical or imaging diagnosed. However, it should have been ensured that the number of imaging diagnosed subjects does not fall significantly below 63.

10.5 Planned interim analyses

With implementation of Protocol Amendment no. 7, the initially planned interim analysis is cancelled.

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 was entered/transmitted into a validated database or data system (Clinical Information Environment).

Data required according to this protocol was recorded by investigational site personnel via data entry into the internet based electronic data capture software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE had 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.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

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

The RAVE System 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 was available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens were 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 electronic Patient-Reported Outcome (device) (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

At a minimum, the following data should be 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 have to be reported until screen failure was declared or randomization occurred. Additionally to the above mentioned data these will 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

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

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

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

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

11.3 Data processing

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

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

The results of endometrial biopsies taken after the FUP/Safety Closeout 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 Audit and inspection

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

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

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

11.5 Missing data

Possible sources of missing data in clinical trials are 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 the equivalent to withdrawal of informed consent. In cases where subjects indicate they do not want to continue the study investigators must determine whether this refers to discontinuation of study treatment or unwillingness to attend the EoT visit. For subjects prematurely discontinuing the study treatment, safety and efficacy data should be further collected until the final visit.

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 (e.g. 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 [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

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

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

For any of the above closures, the following applies:

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

Details for individual subject's withdrawal can be found in Section 6.5.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

All study personnel 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 (e.g. health authority, ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

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

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

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

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

13.3 Ethical and legal conduct of the study

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

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

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

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

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

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent 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.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject), prior to his/her entry into the study (i.e. 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 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 statistical analysis plan.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. 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 statistical analysis plan. 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.

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

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

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

If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative

or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

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

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

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

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

13.6 Compensation for health damage of subjects / insurance

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

13.7 Confidentiality

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

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

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

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

14. Reference list

1. Kennedy, S., Bergqvist, A., Chapron, C., D'Hooghe, T., Dunselman, G., Greb, R., Hummelshoj, L., Prentice, A. & Saridogan, E. 2005. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod,* 20**,** 2698-704.
2. Cook AJ, Roberts DA, Henderson MD, Van Winkle LC, Chastain DC, and Hamill-Ruth RJ 2004 Electronic pain questionnaires: a randomized, crossover comparison with paper questionnaires for chronic pain assessment. *Pain*;110:310-7.
3. Jamison RN, Gracely RH, Raymond SA, Levine JG, Marino B, Herrmann TJ, Daly M, Fram D, and Katz NP 2002 Comparative study of electronic vs. paper VAS ratings: a randomized, crossover trial using healthy volunteers. *Pain*;99:341-7.
4. 2018 Draft Guidance for Industry: Assessment of Pressor Effects of Drugs (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm609185.pdf
5. Kloos RT, Gross MD, Francis, IR, Korobkin, M, Shapiro, B. Incidentally discovered adrenal masses. *Endocr. Rev.* 1995; 16(4):460-84

15. Protocol amendments

Amendment 2 is presented using an updated amendment approach. The rationale for changes in this amendment and all affected sections are provided right before the Table of Contents in this document. A detailed description of changes compared to the last global Clinical Study Protocol (CSP) version is replaced by a track change protocol, separate from this document.

15.1 Overview of changes of AMD 2 triggered by Health Authority feedback

This amendment is based on **FDA's request** on more robust liver safety data because of a possible liver safety signal observed with another drug in the same product group of selective progesterone receptor modulators (PRMs) as vilaprisan**.**

Table 15–1: Proposed update of the design of the Villendo study (Treatment Period 1)

Trial Periods	Screening phase (Maximum 75 days)		Dose-finding phase Treatment-period (TP) 1					Drug-free interval
Visit Number	1	2	3	4	5	6	7	8
Time Window	>28 days before randomi-zation	If biopsy or BMD not taken at Visit 1[u]	Randomi-zation	Week 4-6 Day 22 – 42	Week 12 Day 78 – 84	Week 18 Day 120 – 126	Week 24 Day 162 - 168	6 weeks after last study drug intake
Safety laboratory and urinalysis (including coagulation)	X	X[u]						
Safety laboratory and urinalysis			X[u]	X	X	X	X	X

u For subjects with any elevation of liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase, alkaline phosphatase, and total bilirubin) greater than ULN observed at Visit 1, a repeat blood test for serum chemistry panel will be done and will be considered as baseline values in case the subject is randomized. For those subjects who are randomized, an additional blood test for serum chemistry panel after 2-3 weeks of treatment will be done.

Table 15–2: Proposed update of the design of the Villendo study (Treatment Period 2)

Trial Periods	Extension phase Treatment Period (TP) 2		Follow-up phase	
Visit Number	9	10 End of Treatment	11 Follow-up visit 1	12 Follow-up visit 2
Time Window	Week 12 Day 78 – 84 after start of TP 2	Week 24 Day 162 – 168 after start of TP 2	Weeks 10 – 14 after last study drug	Week 22 – 24 after last study drug
Safety laboratory and urinalysis	X	X	X	

FDA proposed to draw attention to signs and symptoms which may be associated with liver dysfunction.

The section on Adverse Events of Special Interest will be updated with the following new additions (underlined) described below, putting emphasis on patients proactively reporting symptoms that they perceive as unusual or of concern will result in medically meaningful interactions with the investigators. This is because many symptoms associated with liver disorders are also unspecific and may be known to the patients or occur in the context of minor illnesses. Therefore patient judgement with regards to unusualness of symptoms is an important component.

9.6.1.6 Adverse events of special safety interest

[…]

- Liver enzymes and liver disorders:

The study subjects should be made aware of the potential signs and symptoms that could indicate the onset of a relevant liver disorder and should be reminded regularly to contact the study site immediately, if they concerned about such symptoms. Symptoms can include anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, malaise, jaundice, fever, and rash.

- If the GPT/ALT or GOT/AST value increases to >2 x ULN after start of study drug treatment, a close observation has to be initiated. This should include
  - repeating liver enzymes and serum bilirubin measurements 2 to 3 times per week;
  - obtaining a more detailed history of the symptoms, obtaining a history of concomitant drug use, alcohol use, recreational drug use, and special diets, ruling out acute viral hepatitis, additional tests to evaluate liver function as appropriate, (eg, international normalized ratio [INR], direct bilirubin measurements).
  - Any of these additional findings is to be recorded on the corresponding eCRF pages (eg, for concomitant medication, lab assessment) in RAVE. The intense monitoring should be performed until resolution or stabilization of the corresponding lab values.
- Subjects have to be withdrawn from treatment in the following cases:
  - GPT/ALT or GOT/AST value increases to > 8 x ULN
  - GPT/ALT or GOT/AST > 5 x ULN for more than 2 weeks
  - GPT/ALT or GOT/AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia
  - GPT/ALT or GOT/AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** INR > 1.5

- As an additional measure, subjects with mild increases of liver enzyme levels not exceeding the limits for inclusion at Visit 1 (Section6.3, 4b) will undergo two additional serum chemistry panel blood tests, i.e.:

- one within screening phase at Visit 2. A subject will be only eligible if no further increases of liver enzyme levels as compared to those measured at Visit 1, and
- If a subject is randomized, one additional serum chemistry panel blood tests within 3 weeks after start of treatment at an unscheduled visit, prior to Visit 4.

Other changes compared to the last global CSP version are marked in the separate track change protocol.

15.2 Overview of changes of AMD 3 triggered by FDA recommendation

Overall Rationale:. The purpose of this amendment is to address specific recommendations from a Health Authority for liver safety monitoring due the potential risk of liver injury observed with another drug in the same product group of selective progesterone receptor modulators (PRMs) as vilaprisan.

Amendment 3 is presented using a different approach compared with previous amendments to this protocol. The rationale for changes in this amendment and affected sections are provided in the "Protocol Amendment Summary of Changes table " directly before the Table of Contents on this document. A separate document with tracked changes as against the last integrated protocol version is available on request.

Modification 1: Addition / change of exclusion criteria

Exclusion criteria regarding liver symptoms and parameters were updated upon request of the FDA (FDA feedback on 19 January 2018 and 18 May 2018 regarding improved liver monitoring and feedback regarding the inclusion of subjects based on their baseline DEXA Z-score aligned with Asteroid 6 study in the uterine fibroid indication) (see Section6.3):

a. Abnormal liver parameters (presence of at least one of the following criteria):
   i. 2 x upper limit of normal (ULN) for glutamic oxaloacetic transaminase (GOT) / aspartate aminotransferase (AST)
   ii. 2 x ULN for glutamic pyruvic transaminase (GPT) / alanine aminotransferase (ALT)
   iii. 2 x ULN for alkaline phosphatase (AP)
   iv. Total bilirubin outside the upper limit of normal range
   v. International normalized ratio (INR) outside the upper limit of the normal range

21.

Screening DXA Z score ≤ –2.0 SD for lumbar spine (L1-L4), OR femoral neck, OR total hip BMD as per central reading.

Modification 2: Additional blood tests in all patients in the study: monthly during treatment and also after 4 weeks during the drug-free interval between the treatment periods following the FDA request (more robust liver safety data, additional liver parameter tests in all patients with elevated baseline liver parameters).

9.1 Tabular schedule of evaluations and 9.2.3 Scheduled visits displays the modified visit schedule:

Visit 4: Week 4 Day 22-28 (from previous time window Day 22-42);
Visit 4.1: Week 8 Day 50 - 56 (new);
Visit 5: Week 12 Day 78 – 84 (no change);
Visit 5.1: Week 16 Day 106 – 112 (new);
Visit 6 Week 20 Day 134 – 140 (from Day 120-126)
Visit 7: Week 24 Day 162 - 168 (no change);
Visit 8: Week 4-6 after last study drug intake
Day 22-42 (from 6 weeks after last study drug intake)
Visit 8.1: at Week 4 (Day 22-28) after start of TP 2 (new),
Visit 8.2: at Week 8 (Day 50 - 56) after start of TP 2 (new),
Visit 9: at Week 12 (Day 78 - 84) after start of TP 2 (no change),
Visit 9a: at Week 16 (Day 106 – 112) after start of TP 2 (new),
Visit 9b: at Week 20 (Day 134 – 140) after start of TP 2 (new)
Visit 10: Week 24 after start of TP2 Day 162 to 168 (no change)

Section 9.1 Tabular schedule of evaluations was updated accordingly with additional visits 4.1, 6.1, 8.1, 8.2, 9.1, and 9.2 and modification of visit windows.

Table: Update of the design of the Villendo study (Treatment Period 1)

Trial Periods	**Screening phase (Maximum 75 days)**			**Dose-finding phase Treatment-period (TP) 1**						**Drug-free interval**
Visit Number	1	2	3 Rando-mization	4	4.1*	5	5.1*	6*	7	8
Time Window	>28 days before randomi-zation	If biopsy or BMD not taken at Visit 1[u]		Week 4 Day 22 – 28	Week 8 Day 50 - 56	Week 12 Day 78 – 84	Week 16 Day 106 – 112	Week 20 Day 134 – 140	Week 24 Day 162 - 168	Week 4-6 after last study drug intake Day 22-42
Safety laboratory and urinalysis (including hormones, cortisol, coagulation, blood test for hepatitis A, B, and C)[q]	X	X[u]	~~X~~			X			X	X
Safety laboratory for serum chemistry (including at least ALT, AST, AP, total bilirubin, g GT, and albumin)				X	X		X	X		
Liver symptom inquiry	X	X	X	X	X	X	X	X	X	X

q. Coagulation, blood test for hepatitis A, B, and C will be only checked at screening.

u. The safety laboratory tests may be repeated once during the screening period if laboratory values are outside the inclusion range and assessed as clinically relevant (this repeat is not considered rescreening). For the liver-related laboratory parameters ALT, AST, and AP the laboratory test also needs to be repeated if results of the first test at visit 1 are raised above the ULN, but still < 2x ULN (i.e. still within inclusion range). The patient is eligible only if the second test shows a stabilization or decline in those values...

~~X~~ visit deleted from schedule X visit added to schedule

* These visits do not necessarily have to be performed at the study site

Table: Update of the design of the Villendo study (Treatment Period 2)

Trial Periods	**Extension phase Treatment Period (TP) 2**						**Follow-up phase[a]**	
Visit Number	8.1*	8.2*	9	9.1*	9.2*	10 EoT[l]	11 FUP1[l]	12 FUP2
Time Window	Week 4 (Day 22 - 28) after start of TP 2	Week 8 (Day 50 - 56) after start of TP 2	Week 12 (Day 78 - 84) after start of TP 2	Week 16 (Day 106 - 112) after start of TP 2	Week 20 (Day 134 - 140) after start of TP 2	Week 24 (Day 162 to 168) after start of TP 2	Weeks 10 to 14 after last study drug Day 64-98	Week 22 to 24 after last study drug intake Day 148-168
Safety laboratory and urinalysis (including hormones and cortisol)			X			X	X	
Safety laboratory for serum chemistry (including at least ALT, AST, AP, total bilirubin, g GT, and albumin)	X	X		X	X			
Liver symptom inquiry	X	X	X	X	X	X	X	X

* These visits do not necessarily have to be performed at the study site, X visit added to schedule

Modification 3: Need for closer observation of AESIs as described in Section 9.6.1.6 AEs as per Health Authority request (and the 2009 FDA Drug-Induced Liver injury [DILI] guideline) lead to following changes

Liver enzymes and liver disorders:

If the GPT/ALT or GOT/AST value increases to >3 x ULN
OR
2-fold increases above the lowest baseline value after (for subjects with elevated values at baseline) start of study drug treatment, a close observation has to be initiated (see below) and recorded in the dedicated liver case report form.

Study drug can be continued with close observation as long as withdrawal criteria based on liver parameters specified below are not met.

Close observation includes:

- Repeating a serum chemistry panel (including liver enzymes and bilirubin) measurements 2 to 3 times per week. Frequency of retesting can decrease to once a week or less if abnormalities stabilize.
- 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; 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], direct bilirubin measurements).

Any of these additional findings is to be recorded on the corresponding eCRF pages (eg, for concomitant medication, lab assessment) in RAVE. A structured overview on this to-be-collected data can be provided to the site.

Close observation should continue regardless of time point in the study (ie Treatment Periods, drug free intervals, follow up). If liver parameters stabilize to inclusionary range during the drug free interval (no further increase during 3 consecutive measurements) and did not reach withdrawal criteria (as specified below) during the period of close observation, subjects can continue with planned study drug intake in the next treatment period as scheduled, after consultation with the sponsor

Minor changes and typo corrections are not mentioned in this compilation.

15.3 Overview of changes of AMD 6 triggered by FDA recommendation

Preliminary findings from 2-year animal carcinogenicity studies (rat/mouse) with vilaprisan that were received in 2018 showed evidence of an increased incidence in endometrial and adrenal neoplasms. While these unexpected findings and their relevance for humans were being further evaluated, Bayer decided to temporarily pause enrollment and randomization, and to temporarily stop study treatment in already randomized patients after completion of the ongoing treatment period. Global Protocol Amendment 6 (version 4.0) provided background, justification, as well as a detailed description of the temporary measures to be taken.

Section # and Name	Description of Change	Brief Rationale
15.3 Global amendment leading to version 4.0	Added text specifying measures for temporary pause of the study	Temporarily pause enrollment and randomization, and to temporarily stop study treatment in already randomized patients after completion of the ongoing treatment period
	Background and justification of changes with AMD 6 were added, the relevance to the human situation explained, clinical data collected up to the amd summarized, and measures of monitoring in ongoing studies were stated	Rationale and description of temporary measures triggered by preliminary findings in 2-year animal carcinogenicity studies were to be communicated to patients, investigators and HAs
	Enrollment was to be stopped and no patients were to be randomized and/or newly start treatment, procedures for those patients who were randomized and had study drug intake of at least one dose were detailed depending on whether they were in a scheduled treatment break or a treatment period at that time	In addition to the 15-day report on 03 DEC 2018 (temporary suspension of enrolment and randomization) more details were specified with the amd

Section # and Name	Description of Change	Brief Rationale
	Signs and symptoms suggestive of increased levels of adrenal hormones were communicated	

15.4 Overview of changes of AMD 7 to prepare this study for an orderly closure

Amendment no. 7 (19 NOV 2019)

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 no. 6) 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 and introduction section 3), Bayer will conduct a comprehensive safety follow up to provide additional confirmatory evidence. This amendment (Protocol Amendment no.7) introduces measures and processes to prepare this study for an orderly closure, including safety follow up measures in all study participants who received at least one dose of study drug vilaprisan.

Section # and Name	**Description of Major Changes**	**Brief Rationale**
2 Synopsis; 3 Introduction and subsections, and 4 Study objectives	Information on carcinogenicity studies with vilaprisan in rodents as well as details regarding the additional safety measures were added to the section, included adrenal monitoring, endometrial monitoring, 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
5 Study design; Dose and regimen Safety Monitoring 6 Study population 6.5.1	Safety monitoring: adrenal and skin safety section added Information deleted that is no longer relevant Safety monitoring: adrenal, liver and skin safety section added Assessment of effects on bone mineral density	To address FDA request With the implementation of this amendment no new subjects will be recruited and no study medication will be given to the subjects who have been enrolled in the study To address FDA recommendations; to characterize any potential adrenal effects of vilaprisan or effect on skin

Section # and Name	**Description of Major Changes**	**Brief Rationale**
Withdrawal		
7 Treatments	Study medication will not be dispensed again	No study medication will be given to the subjects who have been enrolled in the study
7.5 Blinding	Unblinding will be introduced for all subjects	To avoid invasive procedure in subjects not treated with vilaprisan, since no efficacy data will be analyzed in this study..
8 Non-study therapy, 8.2 Post-study therapy	Specification given for post-temporary pause period	To address the newly introduced Safety Close out visit" and the "Safety Result Reporting visit"
9.1 Tabular schedule of evaluations	Information deleted that is no longer relevant; added "Safety Closeout visit" and "Safety Result Reporting visit"	To depict the procedures of the "Safety Close out visit" and the "Safety Result Reporting visit".
9.2 Tabular schedule of evaluations and 9.2.3 Scheduled visits; 9.2.4 Pre-mature discontinuation visit; 9.2.2 Optional pre-screening phone contact; 9.4 Efficacy	information deleted that is no longer relevant	To address the newly introduced Safety Close out visit" and the "Safety Result Reporting visit"
9.6.1.1 Definitions	New criteria for SAE reporting for endometrial biopsies, adrenal tumors, and malignant skin tumors	To address FDA request.
9.6.1.6 AEs of special interest	New AESIs added for adrenal and skin disorders, relevant loss of BMD, and liver disorder	To address FDA request.
9.6.3.1 Endometrial biopsies and subsections	Content reorganized from Section 9.7.2 Timing of last endometrial biopsy described, algorithm updated newly created section with	Extended safety monitoring to address FDA request, measures at close-out of the study, to facilitate investigators' and HA´s review

Section # and Name	**Description of Major Changes**	**Brief Rationale**
	consolidated content to clarify and describe in greater detail process for abnormal endometrial biopsies follow up within study framework with multi-reader assessment.	
9.6.3.3 Laboratory evaluations	Added more details for laboratory parameters associated with adrenal disorder	To address FDA request on extended safety monitoring (adrenal monitoring)
9.6.3.2 Bone mineral density and 9.6.3.6 Ultrasound	Content of Section 9.6.2 and 9.6.3 shifted to Section 9.6.3.5 Ultrasound and 9.6.3.6 and revised to reflect collection of parameters at the safety closeout visit	To facilitate investigators' and health authority (HA)´s review, update necessary due to new visit structure
9.6.3.1.7 Heavy menstrual bleeding	Content reorganized from Section 9.7.3. New section of Standard criteria and evaluation plan for patients with unusual HMB or new onset bleeding pattern added.	To facilitate investigators' and HA´s review of previous and newly introduced measurements
9.6.3.8 Adrenal monitoring	New section to describe adrenal monitoring (MRI, laboratory investigations and symptom inquiry) and findings that require referral to expert	To address FDA request
9.6.3.9 Liver monitoring	Combined descriptions of liver monitoring from previous locations (e.g., in Section 9.6.1.6)	To facilitate investigators' and HA´s review of previous and newly introduced measurements of improved liver monitoring
9.6.3.10 Skin monitoring	New section to describe skin exam	To address FDA request
10. Statistical Methods and determination of sample size	Deletion of all statistical analyses and summary statistics	To reflect that only few subjects were randomized to treatment

Minor changes and typo corrections are not mentioned in this compilation.

15.5 Overview of changes of AMD 8

Modification:

This amendment (Protocol Amendment no.8) adds a clarification present in the other study protocols of the vilaprisan development project uterine fibroids, i.e. that in subjects who discontinued the study during the temporary pause and now get reconsented, conditions that newly occurred or worsened during the off-study period should be documented as AEs.

A separate document with tracked changes as against the last integrated protocol version (AMD 3) is available on request.

Section # and Name	**Description of Major Changes**	**Brief Rationale**
9.6.1.1 Definitions	In subjects who discontinued the study during the temporary pause and now get reconsented, conditions that newly occurred or worsened during the off-study period should be documented as AEs	For alignment with the other protocols of the uterine fibroids indication of vilaprisan.

15.6 Overview of changes of AMD 9

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

16. Appendices

16.1 CYP3A4 inhibitors

Table 16–1: Strong CYP3A4 inhibitors

Substance name	Inhibitor strength
Boceprevir	Strong
Clarithromycin	Strong
Grapefruit juice	Depend on dose: Moderate or strong
Cobicistat	Strong
Conivaptan	Strong
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 CYP3A4 inducers

Table 16–2: Strong CYP3A4 inducers

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