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

Summary

EudraCT number	2017-002997-38
Trial protocol	CZ BG
Global end of trial date	06 April 2022

Results information

Result version number	v1 (current)
This version publication date	31 March 2023
First version publication date	31 March 2023

Trial information

Trial identification

Sponsor protocol code	BAY1002670/15787

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03400943
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 April 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	China: 27
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	Bulgaria: 5
Worldwide total number of subjects	93
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	93
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 104 study centers in 9 countries worldwide between 17-Jan-2018 (first subject first visit) and 06-Apr-2022 (last subject last visit).

Pre-assignment

Screening details:

Overall, 646 subjects were screened. Of the 646 screened subjects, 553 (85.6%) subjects were not randomized to treatment. The majority of these (n=403) were screen failures. Of the 93 subjects who were randomized, 79 subjects received study treatment.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Vilaprisan (A1)

Arm description:

Vilaprisan (2 mg) in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks, separated by 1 bleeding episode.

Arm type	Experimental
Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg, once daily

Arm title	Vilaprisan (A2)

Arm description:

Vilaprisan (2 mg) in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks without a break.

Arm type	Experimental
Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg, once daily

Arm title	Placebo+Vilaprisan (B1)

Arm description:

Placebo in treatment period 1 for 12 weeks, and vilaprisan (2 mg) in treatment period 2 for 12 weeks, separated by 1 bleeding episode.

Arm type	Experimental

Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg, once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily

Arm title	Vilaprisan+Placebo (B2)

Arm description:

Vilaprisan (2 mg) in treatment period 1 for 12 weeks and placebo in treatment period 2 for 12 weeks, separated by 1 bleeding episode.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily

Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg, once daily

Number of subjects in period 1[1]	Vilaprisan (A1)	Vilaprisan (A2)	Placebo+Vilaprisan (B1)
Started	20	23	20
Treated	18	21	20
Completed	18	21	18
Not completed	2	2	2
Consent withdrawn by subject	-	-	2
Adverse event, non-fatal	-	-	-
Other	-	-	-
Never treated	2	2	-

Number of subjects in period 1	Vilaprisan+Placebo (B2)

[1]	
Started	21
Treated	20
Completed	18
Not completed	3
Consent withdrawn by subject	-
Adverse event, non-fatal	1
Other	1
Never treated	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: In total, 93 subjects were randomized. For baseline characteristics, the full analysis set population was analysed which consists of all randomized subjects, excluding the randomized subjects who did not start treatment period (TP) 1 due to the study being temporarily on hold.

Period 2

Period 2 title	Treatment period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Vilaprisan (A1)

Arm description:

Vilaprisan (2 mg) in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks, separated by 1 bleeding episode.

Arm type	Experimental
Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg, once daily

Arm title	Vilaprisan (A2)

Arm description:

Vilaprisan (2 mg) in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks without a break.

Arm type	Experimental
Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg, once daily

Arm title	Placebo+Vilaprisan (B1)

Arm description:

Placebo in treatment period 1 for 12 weeks, and vilaprisan (2 mg) in treatment period 2 for 12 weeks, separated by 1 bleeding episode.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily

Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg, once daily

Arm title	Vilaprisan+Placebo (B2)

Arm description:

Vilaprisan (2 mg) in treatment period 1 for 12 weeks and placebo in treatment period 2 for 12 weeks, separated by 1 bleeding episode.

Arm type	Experimental
Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg, once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Once daily

Number of subjects in period 2[2]	Vilaprisan (A1)	Vilaprisan (A2)	Placebo+Vilaprisan (B1)
Started	7	21	7
Completed	6	13	7
Not completed	1	8	0
Consent withdrawn by subject	-	1	-
Study terminated by sponsor	-	1	-
Unspecified	1	6	-

Number of subjects in period 2[2]	Vilaprisan+Placebo (B2)
Started	5
Completed	5
Not completed	0
Consent withdrawn by subject	-
Study terminated by sponsor	-
Unspecified	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The primary reason for subjects who did not starting TP2 was study terminated by sponsor (i.e. closing of study with comprehensive safety follow up).

Baseline characteristics

Reporting groups	
Reporting group title	Vilaprisan (A1)
Reporting group description:	
Vilaprisan (2 mg) in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Vilaprisan (A2)
Reporting group description:	
Vilaprisan (2 mg) in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks without a break.	
Reporting group title	Placebo+Vilaprisan (B1)
Reporting group description:	
Placebo in treatment period 1 for 12 weeks, and vilaprisan (2 mg) in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Vilaprisan+Placebo (B2)
Reporting group description:	
Vilaprisan (2 mg) in treatment period 1 for 12 weeks and placebo in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	

Reporting group values	Vilaprisan (A1)	Vilaprisan (A2)	Placebo+Vilaprisan (B1)
Number of subjects	20	23	20
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	44.0	43.4	43.0
standard deviation	± 4.9	± 5.9	± 5.1
Sex: Female, Male Units: Participants			
Female	20	23	20
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	5	9	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	6	8
White	9	6	7
More than one race	0	1	0
Unknown or Not Reported	0	1	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	2	1
Not Hispanic or Latino	15	21	19
Unknown or Not Reported	1	0	0

Reporting group values	Vilaprisan+Placebo	Total	

	(B2)		
Number of subjects	21	84	
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	43.5		
standard deviation	± 5.2	-	
Sex: Female, Male Units: Participants			
Female	21	84	
Male	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	7	26	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	10	30	
White	4	26	
More than one race	0	1	
Unknown or Not Reported	0	1	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	7	
Not Hispanic or Latino	20	75	
Unknown or Not Reported	1	2	

End points

End points reporting groups

Reporting group title	Vilaprisan (A1)
Reporting group description:	
Vilaprisan (2 mg) in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Vilaprisan (A2)
Reporting group description:	
Vilaprisan (2 mg) in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks without a break.	
Reporting group title	Placebo+Vilaprisan (B1)
Reporting group description:	
Placebo in treatment period 1 for 12 weeks, and vilaprisan (2 mg) in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Vilaprisan+Placebo (B2)
Reporting group description:	
Vilaprisan (2 mg) in treatment period 1 for 12 weeks and placebo in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Vilaprisan (A1)
Reporting group description:	
Vilaprisan (2 mg) in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Vilaprisan (A2)
Reporting group description:	
Vilaprisan (2 mg) in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks without a break.	
Reporting group title	Placebo+Vilaprisan (B1)
Reporting group description:	
Placebo in treatment period 1 for 12 weeks, and vilaprisan (2 mg) in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Vilaprisan+Placebo (B2)
Reporting group description:	
Vilaprisan (2 mg) in treatment period 1 for 12 weeks and placebo in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF consisted of all randomized subjects in the full analysis set (FAS) who took at least 1 dose of study drug.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS consists of all randomized subjects, excluding randomized subjects who did not start treatment period 1 due to the study being temporarily on hold.	

Primary: Number of subjects with amenorrhea

End point title	Number of subjects with amenorrhea
End point description:	
Amenorrhea was defined as menstrual blood loss (MBL) <2 mL during the last 28 days of treatment measured by the alkaline hematin (AH) method.	
End point type	Primary
End point timeframe:	
The last 28 days of treatment period 1	

End point values	Vilaprisan (A1)	Vilaprisan (A2)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	23	20	21
Units: Participants	16	20	4	15

Statistical analyses

Statistical analysis title	The difference in amenorrhea rates
Statistical analysis description:	
Vilaprisan (A1) and Vilaprisan+Placebo (B2) combined vs. Placebo+Vilaprisan (B1) in treatment period 1	
Comparison groups	Vilaprisan (A1) v Placebo+Vilaprisan (B1) v Vilaprisan+Placebo (B2)
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.78

Secondary: Time to onset of amenorrhea

End point title	Time to onset of amenorrhea
End point description:	
Onset of amenorrhea was defined by the first day for which the MBL for all subsequent 28-day periods up to the end of a treatment period was < 2 mL (amenorrhea defined similar to primary endpoint). For treatment period 1 and treatment period 2, "99999" indicates that the value could not be estimated due to censored data. For the treatment periods 1 and 2 combined, "99999" indicates no value because treatment group A2 is the only treatment arm, where TP1 and TP2 didn't include any break and therefore TP1 and TP2 were combined.	
End point type	Secondary
End point timeframe:	
In treatment period 1 (12 weeks) and in treatment period 2 (12 weeks)	

End point values	Vilaprisan (A1)	Vilaprisan (A2)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	23	20	21
Units: Days				
median (inter-quartile range (Q1-Q3))				
Treatment Period 1	3 (2 to 4)	99999 (99999 to 99999)	99999 (99999 to 99999)	6 (1 to 46)
Treatment Period 2	21 (2 to 32)	99999 (99999 to 99999)	2 (1 to 99999)	99999 (99999 to 99999)
Treatment periods 1 and 2 combined	99999 (99999 to 99999)	9 (3 to 107)	99999 (99999 to 99999)	99999 (99999 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of controlled bleeding

End point title	Time to onset of controlled bleeding

End point description:

Onset of controlled bleeding was defined by the first day for which the MBL for all subsequent 28-day periods up to the end of a treatment period was <80.00 mL based on AH-method. For treatment period 1 and treatment period 2, "99999" indicates that the value could not be estimated due to censored data. For the treatment periods 1 and 2 combined, "99999" indicates no value because treatment group A2 is the only treatment arm, where TP1 and TP2 didn't include any break and therefore TP1 and TP2 were combined.

End point type	Secondary

End point timeframe:

In treatment period 1 (12 weeks) and in treatment period 2 (12 weeks)

End point values	Vilaprisan (A1)	Vilaprisan (A2)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	23	20	21
Units: Days				
median (inter-quartile range (Q1-Q3))				
Treatment period 1	1 (1 to 2)	99999 (99999 to 99999)	99999 (53 to 99999)	1 (1 to 1)
Treatment period 2	1 (1 to 1)	99999 (99999 to 99999)	1 (1 to 2)	99999 (99999 to 99999)
Treatment periods 1 and 2 combined	99999 (99999 to 99999)	1 (1 to 7)	99999 (99999 to 99999)	99999 (99999 to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with heavy Menstrual Bleeding (HMB) response

End point title	Number of subjects with heavy Menstrual Bleeding (HMB) response

End point description:

HMB response was defined as MBL <80 mL during the last 28 days of treatment and >50% reduction from baseline based on AH-method.

End point type	Secondary

End point timeframe:

The last 28 days of treatment period 1 and treatment period 2

End point values	Vilaprisan (A1)	Vilaprisan (A2)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	23	20	21
Units: Participants				
Treatment period 1	17	20	8	17
Treatment period 2	6	14	6	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with absence of bleeding (spotting allowed)

End point title	Number of subjects with absence of bleeding (spotting allowed)

End point description:

Absence of bleeding was defined as no scheduled or unscheduled bleeding (spotting allowed) during the last 28 days of a treatment period based on subjects' daily responses to the Uterine Fibroid Daily Bleeding Diary (UF-DBD).

End point type	Secondary

End point timeframe:

The last 28 days of treatment period 1 and treatment period 2

End point values	Vilaprisan (A1)	Vilaprisan (A2)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	23	20	21
Units: Participants				
Treatment period 1	16	20	4	15
Treatment period 2	6	13	6	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with endometrial histology findings by endometrial biopsy main results (majority read, main diagnosis)

End point title	Number of subjects with endometrial histology findings by endometrial biopsy main results (majority read, main diagnosis)

End point description:

Number of subjects with endometrial histology findings, e.g. benign endometrium, Malignant Neoplasm, Hyperplasia WHO 2014, no atypia or Hyperplasia WHO 2014, atypia and Endometrial Polyps.

End point type	Secondary

End point timeframe:

Up to 2 weeks after end of treatment

End point values	Vilaprisan (A1)	Vilaprisan (A2)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	20	17	21[1]
Units: Participants				
Benign Endometrium	17	20	17	21
Hyperplasia WHO 2014, no atypia	0	0	0	0
Hyperplasia WHO 2014, atypia	1	0	0	0
Malignant Neoplasm	0	0	0	0
Endometrial Polyps	1	1	1	0

Notes:

[1] - Actual analysed number is 22 and result for Benign Endometrium is 22. See Limitations and caveats.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of endometrial thickness

End point title	Change from baseline of endometrial thickness

End point description:

Ultrasound examinations were performed. Endometrial thickness was measured in the medio-sagittal section as double-layer in millimeters. Summary statistics for change from baseline in endometrial thickness was provided in below table.

End point type	Secondary

End point timeframe:

Up to 2 weeks after end of treatment and in follow-up phase

End point values	Vilaprisan (A1)	Vilaprisan (A2)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	21	17	21[2]
Units: Millimeters				
arithmetic mean (standard deviation)				
Baseline	13.6 (± 7.6)	11.0 (± 5.4)	11.9 (± 6.5)	10.5 (± 3.9)
Change from baseline in Treatment phase	-2.2 (± 3.0)	-1.3 (± 4.3)	-1.8 (± 4.9)	-1.8 (± 3.4)

Change from baseline in Follow-up phase	-3.0 (± 4.6)	-0.5 (± 3.8)	-3.1 (± 4.0)	-1.8 (± 3.7)

Notes:

[2] - Actual analysed number is 23. See Limitations and caveats.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The observation period for AEs will start with signing the informed consent and will end with the last visit.

Adverse event reporting additional description:

For TEAEs: subject will be counted for both treatment groups if she received different treatments (vilaprisan or placebo) in the two treatment periods. For Post-treatment AEs: SAF was used.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Vilaprisan - Treatment emergent AEs

Reporting group description:

Participants who received the treatment of Vilaprisan in the study - Treatment emergent AEs.

Reporting group title	Placebo - Treatment emergent AEs

Reporting group description:

Participants who received placebo in the study - Treatment emergent AEs.

Reporting group title	Vilaprisan+ Placebo (B2) - Post treatment AEs

Reporting group description:

Vilaprisan (2 mg), 1 treatment period of 12 weeks, and placebo, 1 treatment period of 12 Weeks, separated by 1 bleeding episode - Post treatment AEs.

Reporting group title	Vilaprisan (A2) - Post treatment AEs

Reporting group description:

Vilaprisan (2 mg), 2 treatment periods of 12 weeks without a break - Post treatment AEs.

Reporting group title	Placebo+ Vilaprisan (B1) - Post treatment AEs

Reporting group description:

Placebo, 1 treatment period of 12 weeks, and Vilaprisan (2 mg), 1 treatment period of 12 weeks, separated by 1 bleeding episode - Post treatment AEs.

Reporting group title	Vilaprisan (A1) - Post treatment AEs

Reporting group description:

Vilaprisan (2 mg), 2 treatment periods of 12 weeks, separated by 1 bleeding episode - Post treatment AEs.

Serious adverse events	Vilaprisan - Treatment emergent AEs	Placebo - Treatment emergent AEs	Vilaprisan+ Placebo (B2) - Post treatment AEs
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 69 (2.90%)	1 / 22 (4.55%)	6 / 23 (26.09%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Cystoscopy			

subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer stage II			
subjects affected / exposed	1 / 69 (1.45%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Hysterectomy			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	2 / 23 (8.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myomectomy			

subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal lesion excision			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingectomy			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial ablation			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hysterosalpingectomy			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 69 (0.00%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menometrorrhagia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	1 / 69 (1.45%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal uterine bleeding			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal mass			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			

subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Vilaprisan (A2) - Post treatment AEs	Placebo+ Vilaprisan (B1) - Post treatment AEs	Vilaprisan (A1) - Post treatment AEs
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	3 / 17 (17.65%)	3 / 18 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Cystoscopy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	2 / 21 (9.52%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer stage II			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Palpitations			

subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Hysterectomy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myomectomy			
subjects affected / exposed	0 / 21 (0.00%)	2 / 17 (11.76%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal lesion excision			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingectomy			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial ablation			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hysterosalpingectomy			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menometrorrhagia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal uterine bleeding			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal mass			

subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Spinal osteoarthritis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Vilaprisan - Treatment emergent AEs	Placebo - Treatment emergent AEs	Vilaprisan+ Placebo (B2) - Post treatment AEs
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 69 (43.48%)	8 / 22 (36.36%)	7 / 23 (30.43%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Seborrhoeic keratosis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Fibrous histiocytoma			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Skin papilloma			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 69 (1.45%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Hot flush			
subjects affected / exposed	6 / 69 (8.70%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	6	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 69 (1.45%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	4 / 69 (5.80%)	3 / 22 (13.64%)	0 / 23 (0.00%)
occurrences (all)	5	3	0
Pyrexia			
subjects affected / exposed	1 / 69 (1.45%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences (all)	1	1	0
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Uterine polyp			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Ovarian cyst			
subjects affected / exposed	2 / 69 (2.90%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences (all)	2	1	0
Heavy menstrual bleeding			
subjects affected / exposed	0 / 69 (0.00%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Endometrial thickening			
subjects affected / exposed	4 / 69 (5.80%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences (all)	6	1	0
Fallopian tube cyst			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Vaginal haemorrhage			

subjects affected / exposed	1 / 69 (1.45%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	2
Psychiatric disorders			
Poor quality sleep			
subjects affected / exposed	1 / 69 (1.45%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Investigations			
Cortisol increased			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	2
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood testosterone increased			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Blood pressure increased			
subjects affected / exposed	1 / 69 (1.45%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 69 (13.04%)	0 / 22 (0.00%)	2 / 23 (8.70%)
occurrences (all)	10	0	2
Presyncope			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 69 (0.00%)	4 / 22 (18.18%)	3 / 23 (13.04%)
occurrences (all)	0	4	3
Eye disorders			

Eye swelling			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 69 (13.04%)	3 / 22 (13.64%)	0 / 23 (0.00%)
occurrences (all)	10	3	0
Abdominal pain			
subjects affected / exposed	4 / 69 (5.80%)	5 / 22 (22.73%)	1 / 23 (4.35%)
occurrences (all)	4	7	2
Abdominal pain lower			
subjects affected / exposed	4 / 69 (5.80%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	6	0	0
Abdominal discomfort			
subjects affected / exposed	2 / 69 (2.90%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	2 / 69 (2.90%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	2	0	0
Eczema			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 69 (5.80%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences (all)	4	1	0
Pain in extremity			
subjects affected / exposed	2 / 69 (2.90%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	3	0	1
Neck pain			

subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Onychomycosis			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	4 / 69 (5.80%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	5	0	0
Upper respiratory tract infection			
subjects affected / exposed	5 / 69 (7.25%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	6	0	2
Pyoderma			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 69 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Decreased appetite			
subjects affected / exposed	1 / 69 (1.45%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1

Non-serious adverse events	Vilaprisan (A2) - Post treatment AEs	Placebo+ Vilaprisan (B1) - Post treatment AEs	Vilaprisan (A1) - Post treatment AEs
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 21 (19.05%)	6 / 17 (35.29%)	9 / 18 (50.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Seborrhoeic keratosis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Fibrous histiocytoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

Skin papilloma			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Hot flush			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Uterine polyp			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Ovarian cyst			
subjects affected / exposed	1 / 21 (4.76%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Heavy menstrual bleeding			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	2 / 18 (11.11%)
occurrences (all)	1	0	4
Endometrial thickening			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Fallopian tube cyst			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Psychiatric disorders			
Poor quality sleep			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Investigations			
Cortisol increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Blood testosterone increased			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Presyncope			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 17 (0.00%)	4 / 18 (22.22%)
occurrences (all)	2	0	4
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Abdominal pain lower			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			

subjects affected / exposed	1 / 21 (4.76%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Neck pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Onychomycosis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0
Pyoderma			
subjects affected / exposed	0 / 21 (0.00%)	0 / 17 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	1 / 21 (4.76%)	1 / 17 (5.88%)	5 / 18 (27.78%)
occurrences (all)	1	1	5
Decreased appetite			
subjects affected / exposed	0 / 21 (0.00%)	1 / 17 (5.88%)	0 / 18 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 November 2017	- The collection period for sanitary products was extended to cover the entire study. The rationale for this change was based on the fact that the AH method was the only validated method to collect information on menstrual blood loss volume accepted by the FDA. - The statistical sections of the protocol were updated. In order to consider feedback from Authorities and to support label claims on the efficacy endpoints HMB response, time to onset of amenorrhea, and time to onset of controlled bleeding. Time to onset of amenorrhea was elevated to a secondary endpoint and all of these above-mentioned endpoints were included in the hierarchical testing strategy. Description of analyses and missing data considerations were added for these endpoints and the rationale for the study sample size was modified with respect to these changes in the testing strategy. Furthermore, the calculation of the primary efficacy variable was adapted and further efficacy variables were added to 'other' efficacy variables.
04 July 2018	- Text added describing hepatic safety signal with Esmya (ulipristal acetate), a compound that belongs to the compound group of selective PRMs, and the result of the respective PRAC review procedure including risk minimization measures. - Provided rationale that vilaprisan is structurally different from other selective PRMs. - Description of increased frequency of liver monitoring and its background in subsection "safety monitoring" added. The criterion about abnormal liver parameters was revised. The diagnosis of chronic hepatitis B / C infection was added to exclusion criteria. A description for liver symptom inquiry was included and added to all visits. More detailed instructions for the monitoring of liver parameters and liver disorders and for close observation in cases with increased liver parameters and liver disorders were added.
11 December 2018	- Introduction of measures for the temporary pause of the study: due to preliminary findings from 2-year animal carcinogenicity studies, the sponsor decided on 3 DEC 2018 that patients must not start treatment/not start a new treatment course while the preliminary findings from the carcinogenicity studies and their relevance to humans were further investigated.
21 November 2019	- Introduction of measures and processes to prepare the study for an orderly closure to allow for thorough evaluation of preclinical and clinical data prior to further decisions on the development of vilaprisan. - Information on carcinogenicity studies with vilaprisan in rodents as well as details regarding the additional safety measures were added, including adrenal monitoring, endometrial monitoring and skin monitoring. - Primary efficacy analysis limited to Treatment Period 1.
17 February 2020	- The amendment addresses comments from the FDA regarding details of the safety-follow-up measures introduced in protocol amendment 5, Version 5.0. - Described how subjects were counseled when test results (e.g., hormone, liver, physical examination) were abnormal but still below the thresholds to trigger outside evaluation in the context of the study. In such cases subjects were at least to be counseled about medical follow up according to local practice. - Revised the interval for blood sampling after intake of high doses of biotin from 8 to 72 hours. - Added glycosylated hemoglobin (HbA1c) to the parameters measured for adrenal monitoring also in subjects who had completed or discontinued the study before or during the temporary pause. - Added clarification that all randomized subjects belong to the FAS, excluding randomized subjects who did not start Treatment Period 1 due to the premature closure of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 December 2018	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.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

3 subjects who were assigned to B1, erroneously received VPR instead of placebo in TP1. 2 subjects who were assigned to B1, erroneously received placebo instead of VPR in TP2. Analysis of safety was performed by actual treatment.

Notes: