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

Summary

EudraCT number	2016-003561-26
Trial protocol	CZ
Global end of trial date	30 June 2021

Results information

Result version number	v1 (current)
This version publication date	09 June 2022
First version publication date	09 June 2022

Trial information

Trial identification

Sponsor protocol code	BAY1002670/15790

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03400956
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, 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	30 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objective was to show superiority in 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	24 January 2018
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	United States: 40
Country: Number of subjects enrolled	Japan: 33
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Ukraine: 3
Worldwide total number of subjects	96
EEA total number of subjects	5

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)	96
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 87 study centers in USA, Japan, Czech Republic, Russia, and Ukraine between 24-Jan-2018 (first subject first visit) and 30-Jun-2021 (last subject last visit).

Pre-assignment

Screening details:

Overall, 481 subjects were screened, of them, 378 (78.6%) subjects were not randomized to treatment. The majority of these (n=286) were screen failures. Of the 103 subjects who were randomized, 91 subjects received study treatment. Full analysis set (FAS) included 96 subjects.

Period 1

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

Arms

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

Arm description:

Vilaprisan 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:

Vilaprisan 2 mg in treatment period 1 for 12 weeks.

Arm title	Placebo+Vilaprisan (B1)

Arm description:

Placebo in treatment period 1 for 12 weeks, and vilaprisan 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:

Placebo in treatment period 1 for 12 weeks.

Arm title	Vilaprisan+Placebo (B2)

Arm description:

Vilaprisan 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:

Vilaprisan 2 mg in treatment period 1 for 12 weeks.

Number of subjects in period 1	Vilaprisan (A1)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)
Started	32	33	31
Treated	31	30	30
Completed	31	26	25
Not completed	1	7	6
Consent withdrawn by subject	-	2	3
Adverse event, non-fatal	-	1	-
Unspecified	1	2	2
Lost to follow-up	-	-	1
Protocol deviation	-	2	-

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, Carer, Data analyst, Assessor

Arms

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

Arm description:

Vilaprisan 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:

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

Arm title	Placebo+Vilaprisan (B1)

Arm description:

Placebo in treatment period 1 for 12 weeks, and vilaprisan 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:

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

Arm title	Vilaprisan+Placebo (B2)

Arm description:

Vilaprisan 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:

Placebo in treatment period 2 for 12 weeks, separated by 1 bleeding episode from treatment period 1.

Number of subjects in period 2[1]	Vilaprisan (A1)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)
Started	9	10	9
Completed	5	7	5
Not completed	4	3	4
Consent withdrawn by subject	-	-	3
Adverse event, non-fatal	2	1	1
Unspecified	1	1	-
Lost to follow-up	1	1	-

Notes:

[1] - 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: Not all the subjects completing the period 1 entered the period 2 due to early termination.

Baseline characteristics

Reporting groups	
Reporting group title	Vilaprisan (A1)
Reporting group description:	
Vilaprisan in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Placebo+Vilaprisan (B1)
Reporting group description:	
Placebo in treatment period 1 for 12 weeks, and vilaprisan in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Vilaprisan+Placebo (B2)
Reporting group description:	
Vilaprisan 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)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)
Number of subjects	32	33	31
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	43.1	42.7	43.8
standard deviation	± 5.5	± 6.0	± 4.3
Sex: Female, Male Units: Subjects			
Female	32	33	31
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	11	11	11
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	7	8
White	13	15	10
More than one race	0	0	0
Unknown or Not Reported	2	0	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	3	5
Not Hispanic or Latino	30	30	26
Unknown or Not Reported	0	0	0
Endometrial thickness			
Ultrasound examinations were performed. Endometrial thickness was measured in the medio-sagittal section as double-layer in millimeters. Baseline data of endometrial thickness is provided in below table.			
Units: Millimeters			
arithmetic mean	12.8	12.8	11.9
standard deviation	± 4.5	± 2.9	± 3.9

Reporting group values	Total		
Number of subjects	96		
Age categorical Units: Subjects			

Age Continuous Units: Years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: Subjects			
Female	96		
Male	0		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	33		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	21		
White	38		
More than one race	0		
Unknown or Not Reported	4		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	10		
Not Hispanic or Latino	86		
Unknown or Not Reported	0		
Endometrial thickness			
Ultrasound examinations were performed. Endometrial thickness was measured in the medio-sagittal section as double-layer in millimeters. Baseline data of endometrial thickness is provided in below table.			
Units: Millimeters arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Vilaprisan (A1)
Reporting group description:	
Vilaprisan in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Placebo+Vilaprisan (B1)
Reporting group description:	
Placebo in treatment period 1 for 12 weeks, and vilaprisan in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Vilaprisan+Placebo (B2)
Reporting group description:	
Vilaprisan 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 in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Placebo+Vilaprisan (B1)
Reporting group description:	
Placebo in treatment period 1 for 12 weeks, and vilaprisan in treatment period 2 for 12 weeks, separated by 1 bleeding episode.	
Reporting group title	Vilaprisan+Placebo (B2)
Reporting group description:	
Vilaprisan 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	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set (FAS) consisted of all randomized subjects, excluding randomized subjects who did not start treatment period 1 (never received study drug) due to the study being closed prematurely (7 [6.8%]), and included 96 (93.2%) subjects.	

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. The evaluation of MBL was based on 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)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	33	31	
Units: Subjects	29	1	25	

Statistical analyses

Statistical analysis title	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	96
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	0.93

Notes:

[1] - Number of subjects per treatment: 63 (Vilaprisan) / 33 (Placebo).

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 was defined as MBL <80.00 mL during the last 28 days of treatment and >50% reduction compared to baseline (assessed by the AH method).	
End point type	Secondary
End point timeframe:	
The last 28 days of treatment period (TP) 1 and treatment period 2	

End point values	Vilaprisan (A1)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	33	31	
Units: Subjects				
Number of subjects analyzed in TP1	32	33	31	
Treatment period 1	30	7	26	
Number of subjects analysed in TP2	8	10	8	
Treatment period 2	6	9	1	

Statistical analyses

No statistical analyses for this end point

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 and assessed by the AH method).
99999 denotes value could not be calculated because less than 50% of subjects in group showed response.

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)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32[2]	33[3]	31[4]	
Units: Days				
median (inter-quartile range (Q1-Q3))				
Treatment period 1	3 (2 to 4)	99999 (99999 to 99999)	3 (1 to 9)	
Treatment period 2	3 (2 to 20)	4 (3 to 99999)	99999 (99999 to 99999)	

Notes:

[2] - TP 1: 32
TP 2: 8
[3] - TP 1: 33
TP 2: 10
[4] - TP 1: 31
TP 2: 8

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 (assessed by the AH method).
99999 denotes value could not be calculated because less than 50% of subjects in group showed response.

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)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32[5]	33[6]	31[7]	
Units: Days				
median (inter-quartile range (Q1-Q3))				
Treatment period 1	1 (1 to 1)	99999 (99999 to 99999)	1 (1 to 2)	
Treatment period 2	1.5 (1 to 1.9)	1 (1 to 2)	99999 (99999 to 99999)	

Notes:

[5] - TP 1: 32
TP 2: 8
[6] - TP 1: 33
TP 2: 10
[7] - TP 1: 31
TP 2: 8

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 UF-DBD (Uterine Fibroid Daily Bleeding Diary).

End point type	Secondary

End point timeframe:

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

End point values	Vilaprisan (A1)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	33	31	
Units: Subjects				
Number of subjects analysed in TP1	32	33	31	
Treatment period 1	29	2	25	
Number of subjects analysed in TP2	8	10	8	
Treatment period 2	6	8	1	

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects 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 2014, no atypia or Hyperplasia 2014, atypia and Endometrial Polyps.

End point type	Secondary

End point timeframe:

Up to 36 weeks

End point values	Vilaprisan (A1)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	30	30	
Units: Subjects				
Adequate endometrial tissue	31	30	26	
Benign Endometrium	31	30	26	
Hyperplasia WHO 2014, no atypia	0	0	0	
Hyperplasia WHO 2014, atypia	0	0	0	
Malignant Neoplasm	0	0	0	
Endometrial Polyps	2	0	1	

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:

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

End point values	Vilaprisan (A1)	Placebo+Vilaprisan (B1)	Vilaprisan+Placebo (B2)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31[8]	30[9]	30[10]	
Units: Millimeters				
arithmetic mean (standard deviation)				
Treatment period (TP) 1	-2.5 (± 4.1)	-2.8 (± 2.6)	-3.1 (± 3.7)	
Treatment period 2	-5.3 (± 7.6)	-3.5 (± 4.1)	-0.4 (± 4.1)	

Notes:

[8] - TP 1: 30
TP 2: 7
[9] - TP 1: 30
TP 2: 10
[10] - TP 1: 29
TP 2: 7

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The observation period for AEs started with signing the informed consent and ended with the last visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Vilaprisan (A1) - Treatment emergent AEs

Reporting group description:

Vilaprisan in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks, separated by 1 bleeding episode. TEAEs: defined as AEs that "started from the first application of study medication up to 60 calendar days after end of treatment with study medication".

Reporting group title	Placebo+Vilaprisan (B1) - Treatment emergent AEs

Reporting group description:

Placebo in treatment period 1 for 12 weeks, and vilaprisan in treatment period 2 for 12 weeks, separated by 1 bleeding episode. TEAEs: defined as AEs that "started from the first application of study medication up to 60 calendar days after end of treatment with study medication".

Reporting group title	Vilaprisan +Placebo (B2) - Treatment emergent AEs

Reporting group description:

Vilaprisan in treatment period 1 for 12 weeks, and placebo in treatment period 2 for 12 weeks, separated by 1 bleeding episode. TEAEs: defined as AEs that "started from the first application of study medication up to 60 calendar days after end of treatment with study medication".

Reporting group title	Vilaprisan (A1) - Post treatment AEs

Reporting group description:

Vilaprisan in treatment period 1 for 12 weeks and in treatment period 2 for 12 weeks, separated by 1 bleeding episode. Post-treatment AEs: defined as all AEs that started from Day 61 after the end of treatment with study medication. (All AEs identified during the safety follow-up are included in this portion).

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

Reporting group description:

Placebo in treatment period 1 for 12 weeks, and vilaprisan in treatment period 2 for 12 weeks, separated by 1 bleeding episode. Post-treatment AEs: defined as all AEs that started from Day 61 after the end of treatment with study medication. (All AEs identified during the safety follow-up are included in this portion).

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

Reporting group description:

Vilaprisan in treatment period 1 for 12 weeks, and placebo in treatment period 2 for 12 weeks, separated by 1 bleeding episode. Post-treatment AEs: defined as all AEs that started from Day 61 after the end of treatment with study medication. (All AEs identified during the safety follow-up are included in this portion).

Serious adverse events	Vilaprisan (A1) - Treatment emergent AEs	Placebo+Vilaprisan (B1) - Treatment emergent AEs	Vilaprisan +Placebo (B2) - Treatment emergent AEs
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 31 (3.23%)	4 / 30 (13.33%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Investigations			
Liver function test increased			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (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)			
Breast cancer			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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 neoplasm			
subjects affected / exposed	1 / 31 (3.23%)	0 / 30 (0.00%)	0 / 30 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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
Adrenal adenoma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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
Bile duct cancer			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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
Myomectomy			

subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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
Hysterosalpingo-oophorectomy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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
Urinary cystectomy			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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 dilation and curettage			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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
Endometriosis ablation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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 leiomyoma embolisation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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			
Anaemia			

subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (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
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	0 / 31 (0.00%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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			
Tendonitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (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
Rheumatoid arthritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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 (A1) - Post treatment AEs	Placebo+Vilaprisan (B1) - Post	Vilaprisan+Placebo (B2) - Post

		treatment AEs	treatment AEs
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 31 (22.58%)	8 / 30 (26.67%)	3 / 30 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Liver function test increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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)			
Breast cancer			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial neoplasm			
subjects affected / exposed	1 / 31 (3.23%)	0 / 30 (0.00%)	0 / 30 (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 leiomyoma			
subjects affected / exposed	2 / 31 (6.45%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal adenoma			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (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
Bile duct cancer			
subjects affected / exposed	1 / 31 (3.23%)	0 / 30 (0.00%)	0 / 30 (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
Surgical and medical procedures			
Hysterectomy			

subjects affected / exposed	1 / 31 (3.23%)	3 / 30 (10.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myomectomy			
subjects affected / exposed	1 / 31 (3.23%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingectomy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (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
Hysterosalpingo-oophorectomy			
subjects affected / exposed	1 / 31 (3.23%)	0 / 30 (0.00%)	0 / 30 (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
Urinary cystectomy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (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
Hysterosalpingectomy			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine dilation and curettage			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis ablation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (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
Uterine leiomyoma embolisation			

subjects affected / exposed	1 / 31 (3.23%)	0 / 30 (0.00%)	0 / 30 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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			
Heavy menstrual bleeding			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 30 (0.00%)	0 / 30 (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
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	1 / 31 (3.23%)	0 / 30 (0.00%)	0 / 30 (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
Musculoskeletal and connective tissue disorders			
Tendonitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (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
Rheumatoid arthritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (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
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (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

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

Non-serious adverse events	Vilaprisan (A1) - Treatment emergent AEs	Placebo+Vilaprisan (B1) - Treatment emergent AEs	Vilaprisan +Placebo (B2) - Treatment emergent AEs
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 31 (58.06%)	19 / 30 (63.33%)	16 / 30 (53.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hot flush			
subjects affected / exposed	4 / 31 (12.90%)	2 / 30 (6.67%)	1 / 30 (3.33%)
occurrences (all)	4	2	1
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 31 (0.00%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	0	2	2
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 31 (3.23%)	4 / 30 (13.33%)	0 / 30 (0.00%)
occurrences (all)	2	5	0
Premenstrual syndrome			
subjects affected / exposed	0 / 31 (0.00%)	3 / 30 (10.00%)	0 / 30 (0.00%)
occurrences (all)	0	3	0
Uterine haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	3	0

Endometrial thickening			
subjects affected / exposed	3 / 31 (9.68%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Genital haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	2 / 30 (6.67%)	1 / 30 (3.33%)
occurrences (all)	0	3	1
Intermenstrual bleeding			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 31 (12.90%)	1 / 30 (3.33%)	4 / 30 (13.33%)
occurrences (all)	6	1	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 31 (3.23%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Iron deficiency anaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 31 (6.45%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 31 (6.45%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Dyspepsia			

subjects affected / exposed	0 / 31 (0.00%)	2 / 30 (6.67%)	2 / 30 (6.67%)
occurrences (all)	0	2	2
Nausea			
subjects affected / exposed	3 / 31 (9.68%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	3	1	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 31 (6.45%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	2 / 31 (6.45%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Influenza			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	3 / 31 (9.68%)	3 / 30 (10.00%)	4 / 30 (13.33%)
occurrences (all)	3	3	4
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 31 (6.45%)	0 / 30 (0.00%)	1 / 30 (3.33%)
occurrences (all)	3	0	1
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Vilaprisan (A1) - Post treatment AEs	Placebo+Vilaprisan (B1) - Post treatment AEs	Vilaprisan+Placebo (B2) - Post treatment AEs

Total subjects affected by non-serious adverse events subjects affected / exposed	10 / 31 (32.26%)	12 / 30 (40.00%)	12 / 30 (40.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Uterine leiomyoma subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 30 (0.00%) 0	3 / 30 (10.00%) 3
Hypertension subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	2 / 30 (6.67%) 2	1 / 30 (3.33%) 1
General disorders and administration site conditions Malaise subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Reproductive system and breast disorders Ovarian cyst subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	2 / 30 (6.67%) 2	0 / 30 (0.00%) 0
Premenstrual syndrome subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Uterine haemorrhage subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Endometrial thickening subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Genital haemorrhage subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Intermenstrual bleeding subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	2 / 30 (6.67%) 2	1 / 30 (3.33%) 1

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	1 / 30 (3.33%) 2	0 / 30 (0.00%) 0
Investigations Blood pressure increased subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 30 (0.00%) 0	1 / 30 (3.33%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Iron deficiency anaemia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2 0 / 31 (0.00%) 0	2 / 30 (6.67%) 3 3 / 30 (10.00%) 3	1 / 30 (3.33%) 1 2 / 30 (6.67%) 2
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0	0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 0 / 30 (0.00%) 0	0 / 30 (0.00%) 0 0 / 30 (0.00%) 0 1 / 30 (3.33%) 1
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 30 (0.00%) 0	0 / 30 (0.00%) 0
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 31 (0.00%)	2 / 30 (6.67%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 31 (3.23%)	1 / 30 (3.33%)	2 / 30 (6.67%)
occurrences (all)	1	2	3
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Influenza			
subjects affected / exposed	0 / 31 (0.00%)	1 / 30 (3.33%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	5 / 31 (16.13%)	1 / 30 (3.33%)	5 / 30 (16.67%)
occurrences (all)	9	1	5
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 30 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	2 / 31 (6.45%)	4 / 30 (13.33%)	3 / 30 (10.00%)
occurrences (all)	2	4	3

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 whole treatment period.
04 July 2018	1) Text added describing hepatic safety signal with Esmya (ulipristal acetate), a compound that belongs to the compound group of selective PRMs, and the result of the respective PRAC review procedure including risk minimization measures. 2) Provided rationale that vilaprisan is structurally different from other selective PRMs. 3) 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.
20 November 2019	1) 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. 2) 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. 3) Primary efficacy analysis limited to Treatment Period 1.
17 February 2020	1) The amendment addresses comments from the FDA regarding details of the safety-follow-up measures introduced in protocol amendment 5, Version 5.0. 2) 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. 3) Revised the interval for blood sampling after intake of high doses of biotin from 8 to 72 hours. 4) 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. 5) 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.

- The trial was terminated earlier than planned. It was sufficiently advanced to allow for meaningful analysis.
- In many subjects, follow up phase was longer than the planned one.
- Safety evaluations were not limited to the planned timepoints.

Notes: