



Clinical trial results:

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

Summary

EudraCT number	2013-004768-72
Trial protocol	AT FI DK SE ES DE HU BG CZ PL IT
Global end of trial date	26 November 2020

Results information

Result version number	v1
This version publication date	11 November 2021
First version publication date	11 November 2021

Trial information

Trial identification

Sponsor protocol code	BAY1002670/15792
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03573336
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, 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	26 November 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

With the implementation of protocol version 4.0 dated 11-Dec-2018, no further recruitment was possible. With the data available from subjects recruited before the temporary pause the objectives above cannot be reached. Safety evaluations including the added safety evaluations of the endometrium, adrenal glands, bone, and skin may add to the understanding of the safety of vilaprisan. The original Primary objective was to assess efficacy of two doses of vilaprisan compared to placebo in women with symptomatic endometriosis.

The original secondary objective was to evaluate the safety and tolerability of two different doses of vilaprisan in women with symptomatic endometriosis.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Only after the subject voluntarily signed the informed consent form was he/she able to enter the study. If the subject was not capable of providing a signature, an oral statement of consent could have been given in the presence of a witness. Each subject was assured of the right to 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	04 July 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	Austria: 6
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Finland: 1
Worldwide total number of subjects	8
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 7 study centers worldwide, between 04-Jul-2018 (first participant first visit) and 26-Nov-2020 (last participant last visit).

Pre-assignment

Screening details:

With the implementation of protocol version 4.0 dated 11-Dec-2018, no new subjects were enrolled. The objectives of this study cannot be reached as only limited data is available from subjects recruited before the treatment stopped. Overall, 48 participants were screened, of whom 8 participants were randomized and received the study treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Vilaprisan (BAY1002670) 2 mg

Arm description:

Premenopausal women 18 years and older with endometriosis received the treatment of Vilaprisan 2 mg.

Arm type	Experimental
Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 2 mg vilaprisan tablet once daily orally for 24 weeks

Arm title	Vilaprisan (BAY1002670) 4 mg
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Arm description:

Premenopausal women 18 years and older with endometriosis received the treatment of Vilaprisan 4 mg

Arm type	Experimental
Investigational medicinal product name	Vilaprisan
Investigational medicinal product code	BAY1002670
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 4 mg vilaprisan tablet once daily orally for 24 weeks

Arm title	Placebo
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Arm description:

Premenopausal women 18 years and older with endometriosis received placebo.

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One placebo tablet matching vilaprisan once daily orally for 24 weeks

Number of subjects in period 1	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo
Started	2	4	2
Treated	2	4	2
Completed	0	0	0
Not completed	2	4	2
Study terminated	2	4	2

Baseline characteristics

Reporting groups

Reporting group title	Vilaprisan (BAY1002670) 2 mg
Reporting group description: Premenopausal women 18 years and older with endometriosis received the treatment of Vilaprisan 2 mg.	
Reporting group title	Vilaprisan (BAY1002670) 4 mg
Reporting group description: Premenopausal women 18 years and older with endometriosis received the treatment of Vilaprisan 4 mg	
Reporting group title	Placebo
Reporting group description: Premenopausal women 18 years and older with endometriosis received placebo.	

Reporting group values	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo
Number of subjects	2	4	2
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	2	4	2
>=65 years	0	0	0
Age continuous Units: years			
arithmetic mean	32.0	32.8	27.5
full range (min-max)	28 to 36	27 to 37	24 to 31
Sex: Female, Male Units: Subjects			
Female	2	4	2
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	2	4	2
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	0
Not Hispanic or Latino	2	3	2
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	8		

Age Categorical			
Units: Participants			
<=18 years	0		
Between 18 and 65 years	8		
>=65 years	0		
Age continuous			
Units: years			
arithmetic mean			
full range (min-max)	-		
Sex: Female, Male			
Units: Subjects			
Female	8		
Male	0		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	8		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	1		
Not Hispanic or Latino	7		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Vilaprisan (BAY1002670) 2 mg
Reporting group description: Premenopausal women 18 years and older with endometriosis received the treatment of Vilaprisan 2 mg.	
Reporting group title	Vilaprisan (BAY1002670) 4 mg
Reporting group description: Premenopausal women 18 years and older with endometriosis received the treatment of Vilaprisan 4 mg	
Reporting group title	Placebo
Reporting group description: Premenopausal women 18 years and older with endometriosis received placebo.	

Primary: Mean worst pelvic pain (measured on a numerical rating scale [NRS], recorded in the daily endometriosis symptom diary [ESD])

End point title	Mean worst pelvic pain (measured on a numerical rating scale [NRS], recorded in the daily endometriosis symptom diary [ESD])[¹]
End point description: Pain intensity was assessed on 11-point (0-10) NRS by ESD item 1. In ESD item 1, participants were asked to rate the worst pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. Mean 'worst pelvic pain' was calculated as the sum of the participant's daily assessments of the ESD item 1 ("worst pain" during the last 24 hours) during a study period divided by number of days with pain assessment in that study period. This was summarized by study period. No inferential statistical analysis was performed.	
End point type	Primary
End point timeframe: Screening period (up to a maximum of 75 days) + treatment period (up to a maximum of 168 days)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No inferential statistical analysis was performed due to a small population.

End point values	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	2	
Units: Scores on a scale				
arithmetic mean (full range (min-max))				
Screening period	6.0 (5.3 to 6.8)	5.8 (4.0 to 7.1)	5.6 (5.5 to 5.7)	
Treatment period	3.0 (2.0 to 4.0)	3.8 (1.9 to 5.6)	5.0 (4.1 to 5.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean worst pelvic pain (measured on a numerical rating scale [NRS],

recorded in the daily endometriosis symptom diary [ESD]) on days with/without vaginal bleeding

End point title	Mean worst pelvic pain (measured on a numerical rating scale [NRS], recorded in the daily endometriosis symptom diary [ESD]) on days with/without vaginal bleeding
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End point description:

Pain intensity was assessed on 11-point (0-10) NRS by ESD item 1. In ESD item 1, participants were asked to rate the worst pain in the target area during the past 24 hours, where 0= no pain and 10= worst imaginable pain and responses were recorded in ESD. Mean 'worst pelvic pain' on bleeding/non-bleeding days was calculated as the sum of the participant's daily assessments of the ESD item 1 ("worst pain" during the last 24 hours) on bleedings/non-bleeding days during a study period divided by number of bleeding/non-bleeding days with pain assessment in that study period. This was summarized by study period. No inferential statistical analysis was performed.

"99999" in below table stands for no data available as no subject had pain on vaginal bleeding days in the treatment period.

End point type	Secondary
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End point timeframe:

Screening period (up to a maximum of 75 days) + treatment period (up to a maximum of 168 days)

End point values	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	2	
Units: Scores on a scale				
arithmetic mean (full range (min-max))				
Screening: Worst Pain with vaginal bleeding	6.5 (4.6 to 8.4)	6.9 (4.9 to 8.4)	7.0 (6.9 to 7.0)	
Screening: Worst Pain without vaginal bleeding	5.9 (5.5 to 6.3)	5.5 (3.7 to 6.7)	5.3 (5.1 to 5.6)	
Treatment: Worst Pain with vaginal bleeding	99999 (99999 to 99999)	5.4 (3.8 to 7.0)	6.0 (5.1 to 6.9)	
Treatment: Worst Pain without vaginal bleeding	3.0 (2.0 to 4.0)	3.7 (1.8 to 5.6)	4.7 (4.0 to 5.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of tablets of rescue pain medication 1 (Ibuprofen 200 mg) taken daily for Endometriosis-associated pelvic pain (EAPP)

End point title	Mean number of tablets of rescue pain medication 1 (Ibuprofen 200 mg) taken daily for Endometriosis-associated pelvic pain (EAPP)
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End point description:

Mean number of tablets of rescue pain medication 1 (Ibuprofen 200 mg) taken daily for EAPP was calculated as the sum of the tablets taken for EAPP during a study period divided by the number of days in that study period. This was summarized by study period. No inferential statistical analysis was performed.

End point type	Secondary
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End point timeframe:

Screening period (up to a maximum of 75 days) + treatment period (up to a maximum of 168 days)

End point values	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	2	
Units: Tablets				
arithmetic mean (full range (min-max))				
Screening period	0.61 (0.35 to 0.86)	1.01 (0 to 2.14)	1.03 (0.31 to 1.74)	
Treatment period	0.09 (0.01 to 0.17)	0.16 (0.05 to 0.42)	0.81 (0.33 to 1.30)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of tablets of rescue pain medication 2 (Tramadol 50 mg) taken daily for Endometriosis-associated pelvic pain (EAPP)

End point title	Mean number of tablets of rescue pain medication 2 (Tramadol 50 mg) taken daily for Endometriosis-associated pelvic pain (EAPP)
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End point description:

Mean number of tablets of rescue pain medication 2 (Tramadol 50 mg) taken daily for EAPP was calculated as the sum of the tablets taken for EAPP during a study period divided by the number of days in that study period. This was summarized by study period. No inferential statistical analysis was performed.

End point type	Secondary
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End point timeframe:

Screening period (up to a maximum of 75 days) + treatment period (up to a maximum of 168 days)

End point values	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	2	
Units: Tablets				
arithmetic mean (full range (min-max))				
Screening period	0 (0 to 0)	0 (0 to 0)	0.17 (0 to 0.34)	
Treatment period	0.01 (0 to 0.03)	0.01 (0 to 0.05)	0.02 (0.01 to 0.02)	

Statistical analyses

No statistical analyses for this end point

Secondary: The number of participants with treatment emergent adverse events (TEAEs)

End point title	The number of participants with treatment emergent adverse events (TEAEs)
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End point description:

An adverse event (AE) is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. TEAE is defined as AE that is observed or reported after the first administration of study drug or if it starts before the first administration of study drug and the intensity/grade worsens on treatment) in this study.

End point type	Secondary
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End point timeframe:

Up to 6 months

End point values	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	2	
Units: Participants				
Non-serious TEAEs	2	3	2	
SAEs	1	3	0	
Deaths	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical significant abnormal endometrial histology findings

End point title	Number of participants with clinical significant abnormal endometrial histology findings
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End point description:

Number of participants with endometrial histology findings, e.g. hyperplasia, malignant neoplasm or endometrial polyps

End point type	Secondary
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End point timeframe:

Up to 6 months

End point values	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	2	
Units: Participants				
Endometrial hyperplasia	0	0	0	
Malignant neoplasm	0	0	0	
Endometrial polyps	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical significant abnormal ultrasound examinations

End point title	Number of participants with clinical significant abnormal ultrasound examinations
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End point description:

Ultrasound examinations (evaluated for efficacy and safety) will be performed by a qualified expert in performing gynecologic ultrasound exams. If possible, the same examiner should conduct all examinations of a subject throughout the study and the same ultrasound machine (per site) should be used throughout the study. Preferably the safety evaluation should be performed by transvaginal ultrasound (TVU). However, if deemed appropriate, transabdominal or transrectal ultrasound examinations can be performed instead. The chosen method should be used consistently throughout the study.

End point type	Secondary
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End point timeframe:

Up to 6 months

End point values	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	2	
Units: Participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical significant abnormal bone mineral density measurements

End point title	Number of participants with clinical significant abnormal bone mineral density measurements
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End point description:

A Dual-energy X-ray absorptiometry (DEXA) scan of the lumbar spine (lumbar anterior-posterior, L1-L4) and the hip/femoral neck were performed.

End point type	Secondary
End point timeframe:	
Up to 6 months	

End point values	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	2	
Units: Participants	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical significant abnormal laboratory values

End point title	Number of participants with clinical significant abnormal laboratory values
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End point description:

Clinical laboratory values including the values of hematology, general chemistry, urinalysis, coagulation, hormones, immunology and vitamins.

End point type	Secondary
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End point timeframe:

Up to 6 months

End point values	Vilaprisan (BAY1002670) 2 mg	Vilaprisan (BAY1002670) 4 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	2	
Units: Participants	0	3	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from first study medication intake until last visit of the subject.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo

Reporting group title	Vilaprisan 2mg
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Reporting group description:

Vilaprisan 2mg

Reporting group title	Vilaprisan 4mg
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Reporting group description:

Vilaprisan 4mg

Serious adverse events	Placebo	Vilaprisan 2mg	Vilaprisan 4mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	3 / 4 (75.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Endometriosis ablation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	0 / 4 (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
Eye disorders			
Retinal detachment			

subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	0 / 4 (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
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Vilaprisan 2mg	Vilaprisan 4mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	2 / 2 (100.00%)	3 / 4 (75.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal dryness			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Adenomyosis			

subjects affected / exposed occurrences (all)	2 / 2 (100.00%) 2	1 / 2 (50.00%) 1	0 / 4 (0.00%) 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Depressed mood			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Mood altered			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Adjustment disorder			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Investigations			
Cortisol increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Intraocular pressure increased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Weight increased			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Bone density decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 2 (100.00%)	1 / 2 (50.00%)	2 / 4 (50.00%)
occurrences (all)	20	6	27

<p>Eye disorders</p> <p>Dry eye</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 2 (0.00%)</p> <p>0</p>	<p>0 / 2 (0.00%)</p> <p>0</p>	<p>1 / 4 (25.00%)</p> <p>1</p>
<p>Gastrointestinal disorders</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Toothache</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 2 (0.00%)</p> <p>0</p> <p>1 / 2 (50.00%)</p> <p>1</p> <p>0 / 2 (0.00%)</p> <p>0</p>	<p>0 / 2 (0.00%)</p> <p>0</p> <p>0 / 2 (0.00%)</p> <p>0</p> <p>0 / 2 (0.00%)</p> <p>0</p>	<p>1 / 4 (25.00%)</p> <p>1</p> <p>1 / 4 (25.00%)</p> <p>1</p> <p>1 / 4 (25.00%)</p> <p>3</p>
<p>Skin and subcutaneous tissue disorders</p> <p>Acne</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hyperhidrosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 2 (0.00%)</p> <p>0</p> <p>1 / 2 (50.00%)</p> <p>1</p>	<p>0 / 2 (0.00%)</p> <p>0</p> <p>0 / 2 (0.00%)</p> <p>0</p>	<p>2 / 4 (50.00%)</p> <p>2</p> <p>0 / 4 (0.00%)</p> <p>0</p>
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bone pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 2 (0.00%)</p> <p>0</p> <p>0 / 2 (0.00%)</p> <p>0</p>	<p>0 / 2 (0.00%)</p> <p>0</p> <p>0 / 2 (0.00%)</p> <p>0</p>	<p>1 / 4 (25.00%)</p> <p>2</p> <p>1 / 4 (25.00%)</p> <p>1</p>
<p>Infections and infestations</p> <p>Bronchitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fungal skin infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gingivitis</p>	<p>1 / 2 (50.00%)</p> <p>1</p> <p>0 / 2 (0.00%)</p> <p>0</p>	<p>0 / 2 (0.00%)</p> <p>0</p> <p>0 / 2 (0.00%)</p> <p>0</p>	<p>0 / 4 (0.00%)</p> <p>0</p> <p>1 / 4 (25.00%)</p> <p>1</p>

subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 2 (50.00%)	1 / 4 (25.00%)
occurrences (all)	0	3	1
Pyelitis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vaginal infection			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 2 (50.00%)	0 / 2 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	0 / 2 (0.00%)	0 / 2 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2018	Protocol amendment 2 is based on HA's request on more robust liver safety data because of a possible liver safety signal observed with another drug in the same product group of selective progesterone receptor modulators (PRMs) as vilaprisan. The section on Adverse Events of Special Interest was updated, putting emphasis on patients proactively reporting symptoms that they perceive as unusual or of concern will result in medically meaningful interactions with the investigators.
26 June 2018	Protocol amendment 3: The purpose of this amendment is to address specific recommendations from a Health Authority for liver safety monitoring due the potential risk of liver injury observed with another drug in the same product group of selective progesterone receptor modulators (PRMs) as vilaprisan.
11 December 2018	Protocol amendment 6 triggered by Health Authority feedback based on preliminary findings from 2-year animal carcinogenicity studies (rat/mouse) with vilaprisan that were received in 2018 showed evidence of an increased incidence in endometrial and adrenal neoplasms. While these unexpected findings and their relevance for humans were further evaluated, Bayer decided to temporarily pause enrollment and randomization, and to temporarily stop study treatment in already randomized patients after completion of the ongoing treatment period. This global protocol amendment provided background, justification, as well as a detailed description of the temporary measures to be taken.
19 November 2019	Protocol amendment 7: Bayer had decided to close all clinical studies with vilaprisan. Although the outcome of the investigations regarding pre-clinical toxicology findings and their relevance to humans revealed to be of limited relevance to the human situation, Bayer decided to conduct a comprehensive safety follow up to provide additional confirmatory evidence. This amendment introduced measures and processes to prepare this study for an orderly closure, including safety follow up measures in all study participants who received at least one dose of study drug vilaprisan.
28 November 2019	Protocol amendment 8 added a clarification present in the other study protocols of the vilaprisan development project uterine fibroids, i.e. that in subjects who discontinued the study during the temporary pause and now get reconsented, conditions that newly occurred or worsened during the off-study period should be documented as AEs.
17 February 2020	Protocol amendment 9 Recently Bayer received comments from HA feedback regarding details of the safety follow-up measures introduced in the protocol amendments 7 and 8. This amendment implements these HA recommendations on eg. counselling about medical follow up.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 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.	19 November 2019

Notes:

Limitations and caveats

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

No inferential statistical analysis was performed due to a small population.

Notes: