Clinical trial results:
A randomized, parallel-group, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of different doses of BAY 1002670 in subjects with uterine fibroids over 3 months

Summary

EudraCT number	2013-003945-40
Trial protocol	SE FI NO HU CZ BE ES BG
Global end of trial date	04 May 2016

Results information

Result version number	v1 (current)
This version publication date	19 May 2017
First version publication date	19 May 2017

Trial information

Trial identification

Sponsor protocol code	BAY1002670/15788

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02131662
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, 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	04 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 May 2016
Global end of trial reached?	Yes
Global end of trial date	04 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the dose-response relationship of vilaprisan (VPR) in subjects with uterine fibroids.

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. Before entering the study, the informed consent form was read by and explained to all 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 May 2014
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	Norway: 34
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Sweden: 38
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Bulgaria: 44
Country: Number of subjects enrolled	Czech Republic: 40
Country: Number of subjects enrolled	Finland: 47
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Japan: 98
Country: Number of subjects enrolled	United States: 306
Country: Number of subjects enrolled	Canada: 27
Worldwide total number of subjects	748
EEA total number of subjects	317

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)	748
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in 12 countries worldwide between 15 May 2014 (first subject first visit) and 04 May 2016 (last subject last visit).

Pre-assignment

Screening details:

748 subjects were enrolled; 439 subjects were not randomized, the majority was screen failures. Therefore, 309 subjects were randomized. 9 randomized subjects were not treated. 14 subjects prematurely discontinued study treatment. Overall, 93% of randomized subjects completed the treatment period; 79% of subjects completed the follow-up period.

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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	VPR 4 mg

Arm description:

Subjects received 4 milligram (mg) VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.

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

Dosage and administration details:

Subjects received treatment with VPR 4 mg, one tablet taken orally daily about the same time every day. Treatment started during the first week of the menstrual cycle following randomization. The treatment period was 12 weeks (84 days).

Arm title	VPR 2 mg

Arm description:

Subjects received 2 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.

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

Dosage and administration details:

Subjects received treatment with VPR 2 mg, one tablet taken orally daily about the same time every day. Treatment started during the first week of the menstrual cycle following randomization. The treatment period was 12 weeks (84 days).

Arm title	VPR 1 mg

Arm description:

Subjects received 1 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the

menstrual cycle following randomization.

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

Dosage and administration details:

Subjects received treatment with either VPR (0.5 mg, 1 mg, 2 mg, or 4 mg) or matching placebo, one tablet taken orally daily about the same time every day. Treatment started during the first week of the menstrual cycle following randomization. The treatment period was 12 weeks (84 days).

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

Dosage and administration details:

Subjects received treatment with VPR 1 mg, one tablet taken orally daily about the same time every day. Treatment started during the first week of the menstrual cycle following randomization. The treatment period was 12 weeks (84 days).

Arm title	VPR 0.5 mg

Arm description:

Subjects received 0.5 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.

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

Dosage and administration details:

Subjects received treatment with VPR 0.5 mg, one tablet taken orally daily about the same time every day. Treatment started during the first week of the menstrual cycle following randomization. The treatment period was 12 weeks (84 days).

Arm title	Placebo

Arm description:

Subjects received matching placebo tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.

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

Dosage and administration details:

Subjects received treatment with matching placebo, one tablet taken orally daily about the same time every day. Treatment started during the first week of the menstrual cycle following randomization. The treatment period was 12 weeks (84 days).

Number of subjects in period 1[1]	VPR 4 mg	VPR 2 mg	VPR 1 mg
Started	60	61	61
Treated	60	61	61
Completed treatment	57	60	61
Completed follow-up	54	47	56
Completed	54	47	56
Not completed	6	14	5
Wish for pregnancy	-	-	-
Other	2	4	3
Pregnancy	-	1	-
Adverse event	-	1	1
Lost to follow-up	1	3	-
Protocol deviation	1	-	-
Withdrawal by subject	1	5	1
Lack of efficacy	1	-	-

Number of subjects in period 1[1]	VPR 0.5 mg	Placebo
Started	60	58
Treated	60	58
Completed treatment	56	52
Completed follow-up	42	44
Completed	41	43
Not completed	19	15
Wish for pregnancy	-	1
Other	3	4
Pregnancy	1	-
Adverse event	1	3
Lost to follow-up	9	-
Protocol deviation	-	-
Withdrawal by subject	5	6
Lack of efficacy	-	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: Not all enrolled subjects received treatment. Only treated subjects were included in the baseline period. There were 2 subjects (1 subject in VPR 0.5 mg group and 1 subject in placebo group) who did not complete treatment period but completed follow-up period according to protocol. These 2 subjects were considered not completed for overall study.

Baseline characteristics

Reporting groups	
Reporting group title	VPR 4 mg
Reporting group description:	
Subjects received 4 milligram (mg) VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	VPR 2 mg
Reporting group description:	
Subjects received 2 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	VPR 1 mg
Reporting group description:	
Subjects received 1 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	VPR 0.5 mg
Reporting group description:	
Subjects received 0.5 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	

Reporting group values	VPR 4 mg	VPR 2 mg	VPR 1 mg
Number of subjects	60	61	61
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	43.5	43	41.9
standard deviation	± 4.2	± 4.6	± 4.5
Gender categorical Units: Subjects			
Female	60	61	61
Male	0	0	0
Baseline menstrual blood loss by MP Units: millilitre(s)			
arithmetic mean	172.3	176.9	178.2
standard deviation	± 111.86	± 128.71	± 116.64
Volume of largest fibroid by US Units: millilitre(s)			
arithmetic mean	78.92	77.66	74.55
standard deviation	± 95.644	± 91.605	± 88.397

Reporting group values	VPR 0.5 mg	Placebo	Total
Number of subjects	60	58	300

Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	41.7	42.8	
standard deviation	± 4.9	± 5.1	-
Gender categorical Units: Subjects			
Female	60	58	300
Male	0	0	0
Baseline menstrual blood loss by MP Units: millilitre(s)			
arithmetic mean	173.6	164.6	
standard deviation	± 94.62	± 78.71	-
Volume of largest fibroid by US Units: millilitre(s)			
arithmetic mean	81.69	99.03	
standard deviation	± 85.62	± 117.379	-

End points

End points reporting groups

Reporting group title	VPR 4 mg
Reporting group description:	
Subjects received 4 milligram (mg) VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	VPR 2 mg
Reporting group description:	
Subjects received 2 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	VPR 1 mg
Reporting group description:	
Subjects received 1 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	VPR 0.5 mg
Reporting group description:	
Subjects received 0.5 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS (N=300) included all subjects who took at least 1 dose of study drug.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAF (N= 300) included all subjects who took at least 1 dose of study drug.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
PPS (N=221) included all subjects in the FAS without any major protocol deviation.	
Subject analysis set title	Method interchange analysis set
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Method interchange analysis set (N=399) for the assessment of the interchangeability of the menstrual pictogram (MP) and the alkaline hematin (AH) method to judge menstrual blood loss (MBL) included subjects with sanitary product data for which there was a matching pair of MP score and AH value available.	

Primary: Percentage of subjects with amenorrhea, defined as no scheduled or unscheduled bleeding/spotting after the end of the initial bleeding episode until end of treatment

End point title	Percentage of subjects with amenorrhea, defined as no scheduled or unscheduled bleeding/spotting after the end of the initial bleeding episode until end of treatment
End point description:	
Amenorrhea was defined as no scheduled or unscheduled bleeding/spotting after the end of the initial bleeding episode until end of treatment. Dose-response curve was estimated based on the primary endpoint. The 4 parameters characterizing the dose-response curve were reported in other pre-specified endpoints below.	
End point type	Primary

End point timeframe:

After end of the initial bleeding episode until the end of treatment

End point values	VPR 4 mg	VPR 2 mg	VPR 1 mg	VPR 0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	61	61	60
Units: Percentage				
number (not applicable)	60	54.1	55.7	30

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: Percentage				
number (not applicable)	1.7			

Statistical analyses

Statistical analysis title	Placebo-adjusted amenorrhea rate of VPR 4 mg

Statistical analysis description:

The placebo-adjusted amenorrhea rate was summarized by dose with unconditional 2-sided 95% confidence intervals for each active treatment group. This unconditional confidence interval was calculated by inverting 2 separate one-sided tests of half the nominal significance level each.

Comparison groups	VPR 4 mg v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Proportion difference
Point estimate	58.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	44.55
upper limit	70.94

Statistical analysis title	Placebo-adjusted amenorrhea rate of VPR 2 mg

Statistical analysis description:

The placebo-adjusted amenorrhea rate was summarized by dose with unconditional 2-sided 95% confidence intervals for each active treatment group. This unconditional confidence interval was calculated by inverting 2 separate one-sided tests of half the nominal significance level each.

Comparison groups	VPR 2 mg v Placebo

Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Proportion difference
Point estimate	52.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	38.8
upper limit	65.42

Statistical analysis title	Placebo-adjusted amenorrhea rate of VPR 1 mg

Statistical analysis description:

The placebo-adjusted amenorrhea rate was summarized by dose with unconditional 2-sided 95% confidence intervals for each active treatment group. This unconditional confidence interval was calculated by inverting 2 separate one-sided tests of half the nominal significance level each.

Comparison groups	VPR 1 mg v Placebo
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Proportion difference
Point estimate	54.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	40.41
upper limit	66.95

Statistical analysis title	Placebo-adjusted amenorrhea rate of VPR 0.5 mg

Statistical analysis description:

The placebo-adjusted amenorrhea rate was summarized by dose with unconditional 2-sided 95% confidence intervals for each active treatment group. This unconditional confidence interval was calculated by inverting 2 separate one-sided tests of half the nominal significance level each.

Comparison groups	VPR 0.5 mg v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Proportion difference
Point estimate	28.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.92
upper limit	41.5

Secondary: Change in volume of menstrual blood loss per 28 days from baseline during treatment by reference period (assessed by Alkaline Hematin method)

End point title	Change in volume of menstrual blood loss per 28 days from baseline during treatment by reference period (assessed by Alkaline Hematin method)

End point description:

In the below table, "N" signifies subjects who were evaluable for the specific parameter at that timepoint for each arm, respectively.

End point type	Secondary

End point timeframe:

From baseline to end of follow-up

End point values	VPR 4 mg	VPR 2 mg	VPR 1 mg	VPR 0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	61	61	60
Units: mL				
arithmetic mean (standard deviation)				
1st period (N=46, 46, 47, 45, 45)	-79.83 (± 234.22)	-30.18 (± 106.82)	-55.42 (± 109.29)	-44.14 (± 110.61)
2ndperiod (N=44, 45, 47, 44, 44)	-203.43 (± 215.23)	-166.71 (± 149.57)	-181.76 (± 111.98)	-146.32 (± 136.97)
3rd period (N=43, 45, 47, 43, 40)	-205.08 (± 214.8)	-173.38 (± 153.37)	-185.77 (± 106.91)	-147.55 (± 138.4)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: mL				
arithmetic mean (standard deviation)				
1st period (N=46, 46, 47, 45, 45)	17.22 (± 124.14)			
2ndperiod (N=44, 45, 47, 44, 44)	-28.42 (± 113.93)			
3rd period (N=43, 45, 47, 43, 40)	-36.69 (± 117.98)			

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 (assessed by MP, Version 2014) for all subsequent 28-day periods up to the end of the treatment period was less than 80 mL. Kaplan-Meier estimated time to onset of controlled bleeding (days) was reported. Number of bleeding events was 59, 61, 59, 53, 26 for VPR 4 mg, VPR 2 mg, VPR 1 mg, VPR 0.5 mg and placebo

respectively. '99999' indicates that the data were not appilcable for that specific reporting group.

End point type	Secondary

End point timeframe:

During treatment period

End point values	VPR 4 mg	VPR 2 mg	VPR 1 mg	VPR 0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	61	59[1]	53[2]
Units: Days				
median (inter-quartile range (Q1-Q3))	2 (1 to 3)	2 (1 to 3)	3 (1 to 3)	2 (1 to 4)

Notes:

[1] - Only subjects with valid data for this assessment were included

[2] - Only subjects with valid data for this assessment were included

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	26[3]			
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (32 to 99999)			

Notes:

[3] - Only subjects with valid data for this assessment were included

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in volume of largest fibroid compared to baseline measured by MRI

End point title	Percent change in volume of largest fibroid compared to baseline measured by MRI

End point description:

Pelvic Magnetic resonance imagings (MRI), without contrast agents, were performed for volume measurements of the uterus and fibroids preferably using 1.5 Tesla scanners or higher. Images were sent to the imaging core laboratory for evaluation. Volume measurements of the uterus and fibroids were performed centrally by independent radiologist(s).

End point type	Secondary

End point timeframe:

From baseline to end of follow-up period

End point values	VPR 4 mg	VPR 2 mg	VPR 1 mg	VPR 0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	61	61	60
Units: mL				
median (full range (min-max))				
End of treatment (N=47, 52, 58, 47, 48)	-41.4 (-98 to 10)	-27.2 (-81 to 47)	-18.9 (-85 to 11314)	-14.9 (-68 to 74)

Follow-up (N=45, 48, 55, 40, 41)	-26.9 (-94 to 18)	-15 (-82 to 52)	-9.7 (-79 to 437)	-9.3 (-96 to 91)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: mL				
median (full range (min-max))				
End of treatment (N=47, 52, 58, 47, 48) Follow-up (N=45, 48, 55, 40, 41)	4.9 (-67 to 271) 5.1 (-59 to 364)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Exposure-response analysis of Vilaprisan - number of subjects achieving maximum effect (Emax) of induced amenorrhea

End point title	Exposure-response analysis of Vilaprisan - number of subjects achieving maximum effect (Emax) of induced amenorrhea

End point description:

Maximum effect of vilaprisan on induced amenorrhea during treatment period. Induced amenorrhea was defined as number of subjects with amenorrhea (that is, all days with bleeding intensity 1 = none) , i.e. no bleeding or spotting allowed after initial bleeding episode until end of treatment.

End point type	Other pre-specified

End point timeframe:

From start of the study treatment to Day 84 (treatment period)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	267[4]			
Units: Percentage of subjects				
number (confidence interval 95%)	59 (49 to 68)			

Notes:

[4] - Only subjects with valid data for this assessment were included.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Steady-state exposure achieving half-maximal effect (EAUC50) of induced amenorrhea during treatment period of Vilaprisan

End point title	Steady-state exposure achieving half-maximal effect (EAUC50) of induced amenorrhea during treatment period of Vilaprisan

End point description:

Area-under-the-curve (AUC) of vilaprisan between 0 and 24 hours post-dose at steady-state achieving 50% of maximum effect of vilaprisan on induced amenorrhea during treatment period. Induced amenorrhea was defined as number of subjects with induced-amenorrhea (that is, all days with bleeding intensity 1 = none) , i.e. no bleeding or spotting allowed after initial bleeding episode until end of treatment.

End point type	Other pre-specified

End point timeframe:

From start of the study treatment to Day 84 (treatment period)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	267[5]			
Units: mcg*h/L				
number (confidence interval 95%)	36.93 (27.69 to 48.69)			

Notes:

[5] - Only subjects with valid data for this assessment were included.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Exposure-response analysis of Vilaprisan - Predicted fraction of subjects below 90% of the maximum probability of induced amenorrhea

End point title	Exposure-response analysis of Vilaprisan - Predicted fraction of subjects below 90% of the maximum probability of induced amenorrhea

End point description:

Exposure-response model predicted fraction of subjects below 90% of the maximum probability of induced amenorrhea (that is, all days with bleeding intensity 1 = none) , i.e. no bleeding or spotting allowed after initial bleeding episode until end of treatment.

End point type	Other pre-specified

End point timeframe:

From start of the study treatment to Day 84 (treatment period)

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	267[6]			
Units: Percentage of subjects				
number (not applicable)				
1 mg	36			
2 mg	2			
3 mg	1			

Notes:

[6] - Only subjects with valid data for this assessment were included.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Assement of interchangeability of MP and AH method

End point title	Assement of interchangeability of MP and AH method

End point description:

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of MP method for detecting heavy menstrual bleeding at baseline were calculated against the AH method.

End point type	Other pre-specified

End point timeframe:

From baseline to treatment period

End point values	Method interchange analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	399			
Units: Percentage				
number (not applicable)				
Version 2014: Sensitivity	83.3			
Version 2014: Specificity	77.3			
Version 2014: PPV	82.1			
Version 2014: NPV	78.7			
Version 2016: Sensitivity	89.7			
Version 2016: Specificity	54.5			
Version 2016: PPV	70.6			
Version 2016: NPV	81.4			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects with Amenorrhea (defined as MBL < 2 mL) during the last 28 days of treatment

End point title	Percentage of subjects with Amenorrhea (defined as MBL < 2 mL) during the last 28 days of treatment

End point description:

End point type	Other pre-specified

End point timeframe:

After end of the initial bleeding episode until the end of treatment

End point values	VPR 4 mg	VPR 2 mg	VPR 1 mg	VPR 0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	61	61	60
Units: Percentage of subjects				
number (not applicable)	83.33	88.52	85.25	65

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: Percentage of subjects				
number (not applicable)	8.62			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of subjects with HMB response during the last 28 days of treatment

End point title	Percentage of subjects with HMB response during the last 28 days of treatment

End point description:

End point type	Other pre-specified

End point timeframe:

After end of the initial bleeding episode until the end of treatment

End point values	VPR 4 mg	VPR 2 mg	VPR 1 mg	VPR 0.5 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	61	61	60
Units: Percentage of subjects				
number (not applicable)	93.33	96.72	93.44	81.67

End point values	Placebo			

Subject group type	Reporting group			
Number of subjects analysed	58			
Units: Percentage of subjects				
number (not applicable)	29.31			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Estimated dose-response curve based on amenorrhea - E0 and Emax

End point title	Estimated dose-response curve based on amenorrhea - E0 and Emax

End point description:

The primary objective was to estimate the dose-response curve based on the primary endpoint: subjects with amenorrhea. The number of subjects with amenorrhea was assumed to be binomial distributed. A 4 parameters logistic model was used to fit the observed data for characterizing the dose-response curve: E0, Emax, ED50 and δ. The model is defined as p(d)=E0 + Emax/{1+ e^[{ED50-d)/δ]}.
E0 is the amenorrhea rate for placebo; Emax is the maximum effect attributable to the drug (compared with the basal effect with dose at d=0 [placebo group], the maximum increase of drug effect).

End point type	Other pre-specified

End point timeframe:

After end of the initial bleeding episode until the end of treatment

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	300			
Units: Percentage				
number (not applicable)				
E0	0.0082			
Emax	0.57			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Estimated dose-response curve based on amenorrhea - ED50

End point title	Estimated dose-response curve based on amenorrhea - ED50

End point description:

ED50 is the dose at which 50% of Emax were achieved.

End point type	Other pre-specified

End point timeframe:

After end of the initial bleeding episode until the end of treatment

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	300			
Units: mg				
number (not applicable)	0.5			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Estimated dose-response curve based on amenorrhea - δ

End point title	Estimated dose-response curve based on amenorrhea - δ

End point description:

δ is hill slope parameter for characterizing the dose-response curve.

End point type	Other pre-specified

End point timeframe:

After end of the initial bleeding episode until the end of treatment

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	300			
Units: not applicable				
number (not applicable)	0.145			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study treatment until the end of the 6-month follow-up period	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	VPR 4 mg
Reporting group description:	
Subjects received 4 milligram (mg) VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	VPR 2 mg
Reporting group description:	
Subjects received 2 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	VPR 1 mg
Reporting group description:	
Subjects received 1 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	VPR 0.5 mg
Reporting group description:	
Subjects received 0.5 mg VPR tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	
Reporting group title	Placebo
Reporting group description:	
Subjects matching placebo tablet once daily orally for 12 weeks (84 days) from the first week of the menstrual cycle following randomization.	

Serious adverse events	VPR 4 mg	VPR 2 mg	VPR 1 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 60 (3.33%)	4 / 61 (6.56%)	3 / 61 (4.92%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 61 (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
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 61 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	0 / 61 (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
Metastases to ovary			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 61 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous complete			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 61 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 61 (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
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 61 (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			
Menorrhagia			

subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	0 / 61 (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
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 61 (1.64%)
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			
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 61 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	VPR 0.5 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 60 (3.33%)	2 / 58 (3.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to ovary			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 60 (1.67%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous complete			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			

subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 60 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	VPR 4 mg	VPR 2 mg	VPR 1 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 60 (51.67%)	30 / 61 (49.18%)	31 / 61 (50.82%)
Investigations			
Weight increased			
subjects affected / exposed	4 / 60 (6.67%)	1 / 61 (1.64%)	1 / 61 (1.64%)
occurrences (all)	4	1	1
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 60 (13.33%)	5 / 61 (8.20%)	5 / 61 (8.20%)
occurrences (all)	8	5	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 60 (5.00%)	0 / 61 (0.00%)	0 / 61 (0.00%)
occurrences (all)	5	0	0
Headache			
subjects affected / exposed	5 / 60 (8.33%)	5 / 61 (8.20%)	7 / 61 (11.48%)
occurrences (all)	8	6	13
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 60 (5.00%)	3 / 61 (4.92%)	3 / 61 (4.92%)
occurrences (all)	3	3	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 60 (6.67%)	0 / 61 (0.00%)	1 / 61 (1.64%)
occurrences (all)	9	0	1
Nausea			
subjects affected / exposed	3 / 60 (5.00%)	3 / 61 (4.92%)	0 / 61 (0.00%)
occurrences (all)	4	3	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 60 (3.33%)	2 / 61 (3.28%)	1 / 61 (1.64%)
occurrences (all)	2	2	1
Menorrhagia			

subjects affected / exposed	2 / 60 (3.33%)	4 / 61 (6.56%)	6 / 61 (9.84%)
occurrences (all)	3	6	6
Metrorrhagia			
subjects affected / exposed	5 / 60 (8.33%)	7 / 61 (11.48%)	7 / 61 (11.48%)
occurrences (all)	7	17	10
Ovarian cyst			
subjects affected / exposed	4 / 60 (6.67%)	5 / 61 (8.20%)	4 / 61 (6.56%)
occurrences (all)	5	5	6
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 60 (5.00%)	1 / 61 (1.64%)	2 / 61 (3.28%)
occurrences (all)	3	1	4
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 60 (5.00%)	0 / 61 (0.00%)	0 / 61 (0.00%)
occurrences (all)	3	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 60 (6.67%)	4 / 61 (6.56%)	0 / 61 (0.00%)
occurrences (all)	6	4	0
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	1 / 61 (1.64%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	3 / 60 (5.00%)	1 / 61 (1.64%)	2 / 61 (3.28%)
occurrences (all)	5	1	2
Urinary tract infection			
subjects affected / exposed	3 / 60 (5.00%)	0 / 61 (0.00%)	1 / 61 (1.64%)
occurrences (all)	3	0	1
Vulvovaginal mycotic infection			
subjects affected / exposed	3 / 60 (5.00%)	1 / 61 (1.64%)	4 / 61 (6.56%)
occurrences (all)	3	1	4

Non-serious adverse events	VPR 0.5 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 60 (53.33%)	32 / 58 (55.17%)	

Investigations Weight increased subjects affected / exposed occurrences (all)	 0 / 60 (0.00%) 0	 0 / 58 (0.00%) 0	
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	 6 / 60 (10.00%) 8	 4 / 58 (6.90%) 4	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 0 / 60 (0.00%) 0 5 / 60 (8.33%) 9	 1 / 58 (1.72%) 1 7 / 58 (12.07%) 11	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 2 / 60 (3.33%) 2	 5 / 58 (8.62%) 5	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 0 / 60 (0.00%) 0 2 / 60 (3.33%) 2	 3 / 58 (5.17%) 3 0 / 58 (0.00%) 0	
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) Menorrhagia subjects affected / exposed occurrences (all) Metrorrhagia subjects affected / exposed occurrences (all) Ovarian cyst	 4 / 60 (6.67%) 5 3 / 60 (5.00%) 4 4 / 60 (6.67%) 5	 1 / 58 (1.72%) 1 4 / 58 (6.90%) 6 1 / 58 (1.72%) 1	

subjects affected / exposed occurrences (all)	15 / 60 (25.00%) 16	5 / 58 (8.62%) 7	
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	 1 / 60 (1.67%) 1	 0 / 58 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 0 / 60 (0.00%) 0	 0 / 58 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 2 / 60 (3.33%) 2	 2 / 58 (3.45%) 2	
Infections and infestations Bacterial vaginosis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	 3 / 60 (5.00%) 3 4 / 60 (6.67%) 4 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0	 2 / 58 (3.45%) 2 7 / 58 (12.07%) 7 3 / 58 (5.17%) 3 1 / 58 (1.72%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2014	Following advice from FDA, the changes below were made. - Stratification of the treatment groups by baseline hemoglobin level was added. - A requirement for an immediate unscheduled endometrial biopsy was added in the event of endometrial thickness (double layer) > 18 mm or a suspicious bleeding pattern was detected. Prior to this, subjects were to be followed, and an unscheduled biopsy was to be conducted after 1 month if not resolved. - The requirement of using a non-hormonal barrier method of contraception during the study was changed to a double-barrier method. * Rationale was added explaining the expectation that 17% of subjects would be excluded from the PPS.. - The WHO confirmed the international nonproprietary name "vilaprisan" for BAY 1002670, which was implemented. The WHO confirmed the international nonproprietary name "vilaprisan" for BAY 1002670, which was implemented.
26 September 2014	- Per a request from the Swedish authorities, examples of diseases, conditions, and concomitant medications that would exclude a subject from participating in the study were added. - Allowance to include subjects with prior dilation and curettage and myomectomy was added based on feedback from the investigators meeting and an ethics committee. - Changes for statistical analyses were introduced for following exploratory efficacy variables: a. Percentage of subjects with a volume reduction of >/= 25% of the 3 largest fibroids (not the total fibroid volume) measured by MRI and ultrasound b. Evaluation of the CGI-C/PGI-C not only at EoT, but also during the follow-up period. c.Based upon newly available data from PK investigations, the exclusion of grapefruit and grapefruit juice during treatment was added. d. The exclusion of solarium visits during treatment was added. e. Instructions were added to avoid screening subjects who were unlikely to meet the inclusion criterion on heavy bleeding. f. If PAECs were detected in the biopsy at FUP 3, a recommendation to take a new biopsy was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

'99999' in the posting indicates that data were not available. Decimal places were automatically truncated if last decimal equals zero.

Notes: