



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 standard deviation | 41.7 ± 4.9 | 42.8 ± 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 standard deviation | 173.6 ± 94.62 | 164.6 ± 78.71 | - |
| Volume of largest fibroid by US Units: millilitre(s) arithmetic mean standard deviation | 81.69 ± 85.62 | 99.03 ± 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 applicable 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) | 4.9 (-67 to 271) | | | |
| Follow-up (N=45, 48, 55, 40, 41) | 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: Assessment of interchangeability of MP and AH method

| | |
|-----------------|--|
| End point title | Assessment 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 $p(d) = E0 + Emax / \{1 + e^{[(ED50-d)/\delta]}\}$.

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 | | | |
| Total subjects affected by serious adverse events | VPR 0.5 mg | Placebo | |
| 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 occurrences (all) | 2 / 60 (3.33%) 3 | 4 / 61 (6.56%) 6 | 6 / 61 (9.84%) 6 |
| Metrorrhagia subjects affected / exposed occurrences (all) | 5 / 60 (8.33%) 7 | 7 / 61 (11.48%) 17 | 7 / 61 (11.48%) 10 |
| Ovarian cyst subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 5 | 5 / 61 (8.20%) 5 | 4 / 61 (6.56%) 6 |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 1 / 61 (1.64%) 1 | 2 / 61 (3.28%) 4 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 0 / 61 (0.00%) 0 | 0 / 61 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 6 | 4 / 61 (6.56%) 4 | 0 / 61 (0.00%) 0 |
| Infections and infestations Bacterial vaginosis subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | 1 / 61 (1.64%) 2 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 5 | 1 / 61 (1.64%) 1 | 2 / 61 (3.28%) 2 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 0 / 61 (0.00%) 0 | 1 / 61 (1.64%) 1 |
| Vulvovaginal mycotic infection subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 1 / 61 (1.64%) 1 | 4 / 61 (6.56%) 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 | <p>Following advice from FDA, the changes below were made.</p> <ul style="list-style-type: none">- 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. <p>The WHO confirmed the international nonproprietary name "vilaprisan" for BAY 1002670, which was implemented.</p> |
| 26 September 2014 | <ul style="list-style-type: none">- 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:<ul style="list-style-type: none">a. Percentage of subjects with a volume reduction of \geq 25% of the 3 largest fibroids (not the total fibroid volume) measured by MRI and ultrasoundb. 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: