



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY1002670/15787 |
|-----------------------|------------------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

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

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

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

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

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

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

Arm description:

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

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

Dosage and administration details:

2 mg, once daily

| | |
|------------------|-----------------|
| Arm title | Vilaprisan (A2) |
|------------------|-----------------|

Arm description:

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

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

Dosage and administration details:

2 mg, once daily

| | |
|------------------|-------------------------|
| Arm title | Placebo+Vilaprisan (B1) |
|------------------|-------------------------|

Arm description:

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

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-------------------------|
| Investigational medicinal product name | Vilaprisan |
| Investigational medicinal product code | BAY1002670 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 2 mg, once daily | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Once daily | |
| Arm title | Vilaprisan+Placebo (B2) |

Arm description:

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

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

Dosage and administration details:

Once daily

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

Dosage and administration details:

2 mg, once daily

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

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

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

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: In total, 93 subjects were randomized. For baseline characteristics, the full analysis set population was analysed which consists of all randomized subjects, excluding the randomized subjects who did not start treatment period (TP) 1 due to the study being temporarily on hold.

Period 2

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

Arms

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

Arm description:

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

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

Dosage and administration details:

2 mg, once daily

| | |
|------------------|-----------------|
| Arm title | Vilaprisan (A2) |
|------------------|-----------------|

Arm description:

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

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

Dosage and administration details:

2 mg, once daily

| | |
|--|-------------------------|
| Arm title | Placebo+Vilaprisan (B1) |
| Arm description: Placebo in treatment period 1 for 12 weeks, and vilaprisan (2 mg) in treatment period 2 for 12 weeks, separated by 1 bleeding episode. | |
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Once daily | |
| Investigational medicinal product name | Vilaprisan |
| Investigational medicinal product code | BAY1002670 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 2 mg, once daily | |
| Arm title | Vilaprisan+Placebo (B2) |

| | |
|---|--------------------|
| Arm description: Vilaprisan (2 mg) in treatment period 1 for 12 weeks and placebo in treatment period 2 for 12 weeks, separated by 1 bleeding episode. | |
| Arm type | Experimental |
| Investigational medicinal product name | Vilaprisan |
| Investigational medicinal product code | BAY1002670 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: 2 mg, once daily | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Once daily | |

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

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

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The primary reason for subjects who did not starting TP2 was study terminated by sponsor (i.e. closing of study with comprehensive safety follow up).

Baseline characteristics

Reporting groups

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

| Reporting group values | Vilaprisan (A1) | Vilaprisan (A2) | Placebo+Vilaprisan (B1) |
|------------------------|-----------------|-----------------|-------------------------|
| Number of subjects | 20 | 23 | 20 |
| Age categorical | | | |
| Units: Subjects | | | |

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

| Reporting group values | Vilaprisan+Placebo | Total | |
|------------------------|--------------------|-------|--|
|------------------------|--------------------|-------|--|

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

End points

End points reporting groups

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

Primary: Number of subjects with amenorrhea

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

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

Statistical analyses

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

Secondary: Time to onset of amenorrhea

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of controlled bleeding

| | |
|---|--------------------------------------|
| End point title | Time to onset of controlled bleeding |
| End point description: | |
| Onset of controlled bleeding was defined by the first day for which the MBL for all subsequent 28-day periods up to the end of a treatment period was <80.00 mL based on AH-method. For treatment period 1 and treatment period 2, "99999" indicates that the value could not be estimated due to censored data. For the treatment periods 1 and 2 combined, "99999" indicates no value because treatment group A2 is the only treatment arm, where TP1 and TP2 didn't include any break and therefore TP1 and TP2 were combined. | |
| End point type | Secondary |
| End point timeframe: | |
| In treatment period 1 (12 weeks) and in treatment period 2 (12 weeks) | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Number of subjects with heavy Menstrual Bleeding (HMB) response |
| End point description: HMB response was defined as MBL <80 mL during the last 28 days of treatment and >50% reduction from baseline based on AH-method. | |
| End point type | Secondary |
| End point timeframe: The last 28 days of treatment period 1 and treatment period 2 | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|--|
| End point title | Number of subjects with absence of bleeding (spotting allowed) |
| End point description: Absence of bleeding was defined as no scheduled or unscheduled bleeding (spotting allowed) during the last 28 days of a treatment period based on subjects' daily responses to the Uterine Fibroid Daily Bleeding Diary (UF-DBD). | |
| End point type | Secondary |
| End point timeframe: The last 28 days of treatment period 1 and treatment period 2 | |

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Number of subjects with endometrial histology findings by endometrial biopsy main results (majority read, main diagnosis) |
| End point description: Number of subjects with endometrial histology findings, e.g. benign endometrium, Malignant Neoplasm, Hyperplasia WHO 2014, no atypia or Hyperplasia WHO 2014, atypia and Endometrial Polyps. | |
| End point type | Secondary |
| End point timeframe: Up to 2 weeks after end of treatment | |

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of endometrial thickness

| | |
|--|---|
| End point title | Change from baseline of endometrial thickness |
| End point description: Ultrasound examinations were performed. Endometrial thickness was measured in the medio-sagittal section as double-layer in millimeters. Summary statistics for change from baseline in endometrial thickness was provided in below table. | |
| End point type | Secondary |
| End point timeframe: Up to 2 weeks after end of treatment and in follow-up phase | |

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

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

Notes:

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Vilaprisan - Treatment emergent AEs |
|-----------------------|-------------------------------------|

Reporting group description:

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

| | |
|-----------------------|----------------------------------|
| Reporting group title | Placebo - Treatment emergent AEs |
|-----------------------|----------------------------------|

Reporting group description:

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

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

Reporting group description:

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

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Vilaprisan (A2) - Post treatment AEs |
|-----------------------|--------------------------------------|

Reporting group description:

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

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

Reporting group description:

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

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Vilaprisan (A1) - Post treatment AEs |
|-----------------------|--------------------------------------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|---|--------------|
| 03 December 2018 | Bayer decided to temporarily pause enrollment and randomization, and to temporarily stop study treatment in already randomized patients after completion of the ongoing treatment period. | - |

Notes:

Limitations and caveats

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

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

Notes: