



Clinical trial results:

A multi-center, open label, single-arm study to investigate the safety and efficacy of daily oral administration of 2 mg dienogest tablets for the treatment of endometriosis in adolescents over a treatment period of 52 weeks

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2009-017169-53 |
| Trial protocol | ES FI DE AT FR CZ |
| Global end of trial date | 12 September 2013 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 04 September 2016 |
| First version publication date | 28 June 2015 |
| Version creation reason | <ul style="list-style-type: none">• New data added to full data set• Correction of full data set Bayer sponsor contact information to be updated |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | BAY86-5258/13788 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01283724 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany, |
| 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) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000147-PIP01-07 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 December 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 September 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the influence of long-term oral administration of dienogest 2 milligram (mg) once a day, on bone mineral density (BMD) of the spine, measured by dual-energy X-ray absorptiometry (DEXA) in adolescents with confirmed or clinically suspected endometriosis.

Protection of trial subjects:

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, were designed to ensure that the sponsor and investigator abide by Good Clinical Practice guidelines, the Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric population (International Conference of Harmonization [ICH] topic E11 – Committee for Medicinal Products for Human Use (CHMP)/ICH/2711/99), and under the guiding principles detailed in the Declaration of Helsinki. As applicable according to local regulations, the protocol and all protocol amendments were reviewed and approved by each pertinent Competent Authority. Each subject and legal representative(s) or proxy consentor(s) had ample time and opportunity to ask questions and was informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision. If at any time the subject had doubts or concerns regarding study procedures or investigations, the investigator had to stop the examination and had to take enough time to assess the reason and discuss the willingness of further participation with the subject. The subject entered the study only if the subject and legal representative(s) or proxy consentor(s) voluntarily agreed to sign the informed consent/ assent form and had done so. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug. The design of the study was discussed with and agreed by the Pediatric Committee of the European Medicines Agency.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 18 March 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | Austria: 13 |
| Country: Number of subjects enrolled | Czech Republic: 50 |
| Country: Number of subjects enrolled | Finland: 19 |
| Country: Number of subjects enrolled | France: 5 |

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 16 |
| Worldwide total number of subjects | 111 |
| EEA total number of subjects | 111 |

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) | 111 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 21 study centers in 6 countries: Austria, Czech Republic, Finland, France, Germany, and Spain. Girls from menarche until less than 18 years of age were considered to be appropriate with confirmed or clinically suspected endometriosis were recruited.

Pre-assignment

Screening details:

Out of 120 subjects screened, 111 were assigned to treatment and 9 were listing-only subjects (LOS) who did not receive the treatment. Of these 9 LOS, 8 were screening failures and 1 subject withdrew from the study before start of treatment.

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Overall study |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|---------------------------------|
| Arm title | Dienogest (Visanne, BAY86-5258) |
|------------------|---------------------------------|

Arm description:

Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dienogest |
| Investigational medicinal product code | BAY86-5258 |
| Other name | Visanne |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.

| Number of subjects in period 1 | Dienogest (Visanne, BAY86-5258) |
|--------------------------------|---------------------------------|
| Started | 111 |
| Received treatment | 111 |
| Entered Follow up period 1 | 111 |
| Completed treatment | 97 |
| Completed | 97 |
| Not completed | 14 |
| Consent withdrawn by subject | 6 |
| Adverse event, non-fatal | 5 |
| Noncompliance with study drug | 1 |
| Lost to follow-up | 1 |
| Lack of efficacy | 1 |

Period 2

| | |
|------------------------------|--------------------|
| Period 2 title | Follow-up period 2 |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------|---------------------------------|
| Arm title | Dienogest (Visanne, BAY86-5258) |
|------------------|---------------------------------|

Arm description:

Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dienogest |
| Investigational medicinal product code | BAY86-5258 |
| Other name | Visanne |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.

| | |
|---|---------------------------------|
| Number of subjects in period 2^[1] | Dienogest (Visanne, BAY86-5258) |
| Started | 61 |
| Completed | 61 |

Notes:

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

Justification: A total of 111 subjects started Follow-up period 1 (a follow-up assessment of 4 weeks after the end of treatment) out of which 107 subjects completed and reasons for non-completion of 4 subjects were consent withdrawn in 2 subjects and lost to follow-up in 2 subjects. A total of 61 subjects with a decrease in BMD at the end of treatment, started and completed Follow-up period 2 (a follow-up assessment for 26 weeks after the end of treatment).

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | Dienogest (Visanne, BAY86-5258) |
|-----------------------|---------------------------------|

Reporting group description:

Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks.

| Reporting group values | Dienogest (Visanne, BAY86-5258) | Total | |
|---|---------------------------------|-------|--|
| Number of subjects | 111 | 111 | |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 15.4 ± 1.3 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 111 | 111 | |
| Race Units: Subjects | | | |
| White | 105 | 105 | |
| Black or African American | 1 | 1 | |
| Not recorded | 5 | 5 | |
| Ethnicity Units: Subjects | | | |
| Not Hispanic or Latino | 105 | 105 | |
| Hispanic or Latino | 1 | 1 | |
| Not recorded | 5 | 5 | |

End points

End points reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Dienogest (Visanne, BAY86-5258) |
| Reporting group description: Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks. | |
| Reporting group title | Dienogest (Visanne, BAY86-5258) |
| Reporting group description: Subjects received Dienogest tablet orally at a dosage of 2 mg once daily over a period of 52 weeks. | |
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: FAS consisted of 111 subjects and was defined as the set of all subjects who took at least one unit of study drug and if at least one observation after drug administration was available. | |

Primary: Relative Percent Change From Baseline in Spinal Lumbar Vertebrae 2 to 4 (L2-L4) Bone Mineral Density (BMD) at Week 52 Assessed by Dual-Energy X-ray Absorptiometry (DEXA)

| | |
|---|--|
| End point title | Relative Percent Change From Baseline in Spinal Lumbar Vertebrae 2 to 4 (L2-L4) Bone Mineral Density (BMD) at Week 52 Assessed by Dual-Energy X-ray Absorptiometry (DEXA) ^[1] |
| End point description: The measurement of BMD by DEXA is the gold standard method for investigation of bone mass. | |
| End point type | Primary |
| End point timeframe: Baseline, Week 52 | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Statistical analysis was not performed since descriptive statistical analysis was only planned for this endpoint. | |

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|--------------------------------------|---------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 103 ^[2] | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -1.2 (± 2.3) | | | |

Notes:
[2] - FAS subjects with evaluable data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Relative Percent Change From Baseline in Whole Body Bone Mineral Density (BMD) at Week 52 Assessed by Dual-Energy X-ray Absorptiometry (DEXA)

| | |
|--|---|
| End point title | Relative Percent Change From Baseline in Whole Body Bone Mineral Density (BMD) at Week 52 Assessed by Dual-Energy X-ray Absorptiometry (DEXA) |
| End point description: The measurement of BMD by DEXA is the gold standard method for investigation of bone mass. | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| | | | | |
|--------------------------------------|---------------------------------------|--|--|--|
| End point values | Dienogest (Visanne, BAY86-5258) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 102 ^[3] | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 0.8 (± 1.6) | | | |

Notes:

[3] - FAS subjects with evaluable data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Spinal Lumbar Vertebrae 2 to 4 (L2-L4) Z-scores at Week 52

| | |
|-----------------|--|
| End point title | Change From Baseline in Spinal Lumbar Vertebrae 2 to 4 (L2-L4) Z-scores at Week 52 |
|-----------------|--|

End point description:

Based on the BMD values and the weight, the age-normalized percentiles (Z-scores) were determined to allow for comparison with historical control groups. "No difference" in comparison with the historical control groups was defined as a Z-score between '-0.5' and '0.5', a lower value was defined as a value below '-0.5', and a higher value above '0.5'.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 52 | |

| | | | | |
|--------------------------------------|---------------------------------------|--|--|--|
| End point values | Dienogest (Visanne, BAY86-5258) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 103 ^[4] | | | |
| Units: Z-score | | | | |
| arithmetic mean (standard deviation) | -0.3188 (± 0.2649) | | | |

Notes:

[4] - FAS subjects with evaluable data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Whole Body Z-scores at Week 52

| | |
|-----------------|--|
| End point title | Change From Baseline in Whole Body Z-scores at Week 52 |
|-----------------|--|

End point description:

Based on the BMD values and the weight, the age-normalized percentiles (Z-scores) were determined to allow for comparison with historical control groups. "No difference" in comparison with the historical control groups was defined as a Z-score between '-0.5' and '0.5', a lower value was defined as a value below '-0.5', and a higher value above '0.5'.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|--------------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 102 ^[5] | | | |
| Units: Z-score | | | | |
| arithmetic mean (standard deviation) | -0.0609 (± 0.3181) | | | |

Notes:

[5] - FAS subjects with evaluable data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Responders at Week 24

| | |
|-----------------|-------------------------------------|
| End point title | Percentage of Responders at Week 24 |
|-----------------|-------------------------------------|

End point description:

Responders were defined as subjects with reduction in pain intensity from baseline of at least 30% in the Visual Analog Scale (VAS) at Week 24. VAS consisted of a 100 unit long straight line, with verbal anchors at either end, representing a continuum of pain intensity. One end of the line with 0 score as "absence of pain" while the other end of the line with 100 score as "unbearable pain". The assessment of pelvic pain on a VAS was done once every 4 weeks till the end of the treatment (Week 52).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 24

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 ^[6] | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Yes | 81 | | | |
| No | 19 | | | |

Notes:

[6] - FAS subjects with evaluable data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Pelvic Pain Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

| | |
|-----------------|---|
| End point title | Change From Baseline in Pelvic Pain Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile |
|-----------------|---|

End point description:

The cardinal symptoms included in the modified Biberoglu and Behrman severity profile were pelvic pain, dysmenorrhea, and dyspareunia (the latter only in those subjects having sexual intercourse), analyzed at all visits with symptom severity scores from 0 (none) to 3 (severe). Negative value for change from baseline indicates an improvement. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|--------------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 ^[7] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 4 (N=107) | -0.757 (± 0.9985) | | | |
| Change at Week 8 (N=106) | -1.0094 (± 0.971) | | | |
| Change at Week 12 (N=103) | -1.0291 (± 1.0333) | | | |
| Change at Week 16 (N=100) | -1.05 (± 1.0481) | | | |
| Change at Week 20 (N=97) | -1.0825 (± 0.9754) | | | |
| Change at Week 24 (N=99) | -1.2424 (± 0.9699) | | | |
| Change at Week 28 (N=97) | -1.2062 (± 0.9889) | | | |
| Change at Week 32 (N=97) | -1.2165 (± 1.0127) | | | |
| Change at Week 36 (N=95) | -1.2421 (± 1.0181) | | | |
| Change at Week 40 (N=97) | -1.3402 (± 0.967) | | | |
| Change at Week 44 (N=94) | -1.383 (± 0.9849) | | | |
| Change at Week 48 (N=94) | -1.4255 (± 0.8858) | | | |
| Change at Week 52 (N=103) | -1.3786 (± 0.9713) | | | |

Notes:

[7] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dysmenorrhea Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

| | |
|-----------------|--|
| End point title | Change From Baseline in Dysmenorrhea Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile |
|-----------------|--|

End point description:

The cardinal symptoms included in the modified Biberoglu and Behrman severity profile were pelvic pain, dysmenorrhea, and dyspareunia (the latter only in those subjects having sexual intercourse), analyzed at all visits with symptom severity scores from 0 (none) to 3 (severe). Negative value for change from baseline indicates an improvement. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|--------------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 ^[8] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 4 (N=107) | -0.7944 (± 1.1221) | | | |
| Change at Week 8 (N=106) | -1.3208 (± 1.1343) | | | |
| Change at Week 12 (N=103) | -1.4854 (± 1.1014) | | | |
| Change at Week 16 (N=100) | -1.43 (± 1.0565) | | | |
| Change at Week 20 (N=97) | -1.5876 (± 1.0483) | | | |
| Change at Week 24 (N=99) | -1.5657 (± 1.0016) | | | |
| Change at Week 28 (N=97) | -1.5361 (± 1.0314) | | | |
| Change at Week 32 (N=97) | -1.5773 (± 1.1165) | | | |
| Change at Week 36 (N=95) | -1.5579 (± 1.1914) | | | |
| Change at Week 40 (N=97) | -1.7113 (± 1.0304) | | | |
| Change at Week 44 (N=94) | -1.7447 (± 1.0363) | | | |
| Change at Week 48 (N=94) | -1.7447 (± 1.0466) | | | |
| Change at Week 52 (N=103) | -1.7379 (± 0.9596) | | | |

Notes:

[8] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Dyspareunia Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

| | |
|-----------------|---|
| End point title | Change From Baseline in Dyspareunia Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile |
|-----------------|---|

End point description:

The cardinal symptoms included in the modified Biberoglu and Behrman severity profile were pelvic pain, dysmenorrhea, and dyspareunia (the latter only in those subjects having sexual intercourse), analyzed at all visits with symptom severity scores from 0 (none) to 3 (severe). Subjects evaluated the cardinal symptoms using modified Biberoglu and Behrman severity profile in an e-diary over the whole treatment period. Negative value for change from baseline indicates an improvement. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|--------------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 ^[9] | | | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Change at Week 4 (N=13) | -0.1538 (± 0.6887) | | | |
| Change at Week 8 (N=15) | -0.2667 (± 0.7988) | | | |
| Change at Week 12 (N=15) | -0.2667 (± 0.8837) | | | |
| Change at Week 16 (N=17) | -0.1765 (± 1.0744) | | | |
| Change at Week 20 (N=15) | -0.4 (± 0.8281) | | | |
| Change at Week 24 (N=12) | -0.25 (± 0.6216) | | | |
| Change at Week 28 (N=13) | -0.4615 (± 0.7763) | | | |
| Change at Week 32 (N=14) | -0.3571 (± 0.8419) | | | |
| Change at Week 36 (N=13) | -0.2308 (± 0.725) | | | |
| Change at Week 40 (N=14) | -0.3571 (± 0.7449) | | | |
| Change at Week 44 (N=12) | -0.5833 (± 1.0836) | | | |
| Change at Week 48 (N=13) | -0.4615 (± 1.45) | | | |
| Change at Week 52 (N=13) | -0.2308 (± 0.725) | | | |

Notes:

[9] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Pelvic Pain Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Pelvic Pain Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile |
|-----------------|---|

End point description:

In order to judge therapeutic effectiveness and to compare subjects' complaints, a severity profile score of pelvic pain was assessed using a rating scale: missing; 0 = none; 1 = mild (occasional pelvic discomfort); 2 = moderate (noticeable discomfort for most of the cycle); 3 = severe (requires strong analgesics and persists during cycle when not menstruating) based on the subject's self-assessment of symptoms. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 ^[10] | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Baseline (N=110): missing | 0 | | | |
| Baseline (N=110): none | 9.1 | | | |
| Baseline (N=110): mild | 23.6 | | | |
| Baseline (N=110): moderate | 52.7 | | | |
| Baseline (N=110): severe | 14.5 | | | |
| Week 4 (N=108): missing | 0 | | | |
| Week 4 (N=108): none | 35.2 | | | |
| Week 4 (N=108): mild | 40.7 | | | |
| Week 4 (N=108): moderate | 16.7 | | | |
| Week 4 (N=108): severe | 7.4 | | | |
| Week 8 (N=107): missing | 0 | | | |
| Week 8 (N=107): none | 44.9 | | | |
| Week 8 (N=107): mild | 42.1 | | | |
| Week 8 (N=107): moderate | 8.4 | | | |
| Week 8 (N=107): severe | 4.7 | | | |
| Week 12 (N=104): missing | 0 | | | |
| Week 12 (N=104): none | 53.8 | | | |
| Week 12 (N=104): mild | 26 | | | |
| Week 12 (N=104): moderate | 16.3 | | | |
| Week 12 (N=104): severe | 3.8 | | | |
| Week 16 (N=101): missing | 0 | | | |
| Week 16 (N=101): none | 47.5 | | | |
| Week 16 (N=101): mild | 38.6 | | | |
| Week 16 (N=101): moderate | 12.9 | | | |
| Week 16 (N=101): severe | 1 | | | |
| Week 20 (N=98): missing | 0 | | | |

| | | | | |
|---------------------------|------|--|--|--|
| Week 20 (N=98): none | 48 | | | |
| Week 20 (N=98): mild | 38.8 | | | |
| Week 20 (N=98): moderate | 13.3 | | | |
| Week 20 (N=98): severe | 0 | | | |
| Week 24 (N=100): missing | 0 | | | |
| Week 24 (N=100): none | 60 | | | |
| Week 24 (N=100): mild | 30 | | | |
| Week 24 (N=100): moderate | 7 | | | |
| Week 24 (N=100): severe | 3 | | | |
| Week 28 (N=98): missing | 0 | | | |
| Week 28 (N=98): none | 57.1 | | | |
| Week 28 (N=98): mild | 32.7 | | | |
| Week 28 (N=98): moderate | 8.2 | | | |
| Week 28 (N=98): severe | 2 | | | |
| Week 32 (N=98): missing | 0 | | | |
| Week 32 (N=98): none | 59.2 | | | |
| Week 32 (N=98): mild | 31.6 | | | |
| Week 32 (N=98): moderate | 6.1 | | | |
| Week 32 (N=98): severe | 3.1 | | | |
| Week 36 (N=96): missing | 0 | | | |
| Week 36 (N=96): none | 61.5 | | | |
| Week 36 (N=96): mild | 29.2 | | | |
| Week 36 (N=96): moderate | 7.3 | | | |
| Week 36 (N=96): severe | 2.1 | | | |
| Week 40 (N=98): missing | 0 | | | |
| Week 40 (N=98): none | 66.3 | | | |
| Week 40 (N=98): mild | 29.6 | | | |
| Week 40 (N=98): moderate | 3.1 | | | |
| Week 40 (N=98): severe | 1 | | | |
| Week 44 (N=95): missing | 0 | | | |
| Week 44 (N=95): none | 69.5 | | | |
| Week 44 (N=95): mild | 25.3 | | | |
| Week 44 (N=95): moderate | 4.2 | | | |
| Week 44 (N=95): severe | 1.1 | | | |
| Week 48 (N=95): missing | 0 | | | |
| Week 48 (N=95): none | 73.7 | | | |
| Week 48 (N=95): mild | 23.2 | | | |
| Week 48 (N=95): moderate | 3.2 | | | |
| Week 48 (N=95): severe | 0 | | | |
| Week 52 (N=104): missing | 0 | | | |
| Week 52 (N=104): none | 71.2 | | | |
| Week 52 (N=104): mild | 24 | | | |
| Week 52 (N=104): moderate | 3.8 | | | |
| Week 52 (N=104): severe | 1 | | | |

Notes:

[10] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Dysmenorrhea Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Dysmenorrhea Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile |
|-----------------|--|

End point description:

In order to judge therapeutic effectiveness and to compare subjects' complaints, a severity profile score of dysmenorrhea was assessed using a rating scale: missing; 0 = none; 1 = mild (some loss in work efficiency); 2 = moderate (in bed part of day, occasional loss of work efficiency); 3 = severe (in bed one or more days, incapacitation) based on the subject's self-assessment of symptoms. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 ^[11] | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Baseline (N=110): missing | 0 | | | |
| Baseline (N=110): none | 3.6 | | | |
| Baseline (N=110): mild | 21.8 | | | |
| Baseline (N=110): moderate | 47.3 | | | |
| Baseline (N=110): severe | 27.3 | | | |
| Week 4 (N=108): missing | 0 | | | |
| Week 4 (N=108): none | 30.6 | | | |
| Week 4 (N=108): mild | 29.6 | | | |
| Week 4 (N=108): moderate | 28.7 | | | |
| Week 4 (N=108): severe | 11.1 | | | |
| Week 8 (N=107): missing | 0 | | | |
| Week 8 (N=107): none | 57 | | | |
| Week 8 (N=107): mild | 20.6 | | | |
| Week 8 (N=107): moderate | 21.5 | | | |
| Week 8 (N=107): severe | 0.9 | | | |
| Week 12 (N=104): missing | 0 | | | |
| Week 12 (N=104): none | 62.5 | | | |
| Week 12 (N=104): mild | 27.9 | | | |
| Week 12 (N=104): moderate | 8.7 | | | |
| Week 12 (N=104): severe | 1 | | | |
| Week 16 (N=101): missing | 0 | | | |
| Week 16 (N=101): none | 61.4 | | | |
| Week 16 (N=101): mild | 25.7 | | | |
| Week 16 (N=101): moderate | 12.9 | | | |
| Week 16 (N=101): severe | 0 | | | |
| Week 20 (N=98): missing | 0 | | | |
| Week 20 (N=98): none | 73.5 | | | |
| Week 20 (N=98): mild | 18.4 | | | |
| Week 20 (N=98): moderate | 6.1 | | | |
| Week 20 (N=98): severe | 2 | | | |

| | | | | |
|---------------------------|------|--|--|--|
| Week 24 (N=100): missing | 0 | | | |
| Week 24 (N=100): none | 70 | | | |
| Week 24 (N=100): mild | 20 | | | |
| Week 24 (N=100): moderate | 8 | | | |
| Week 24 (N=100): severe | 2 | | | |
| Week 28 (N=98): missing | 0 | | | |
| Week 28 (N=98): none | 69.4 | | | |
| Week 28 (N=98): mild | 19.4 | | | |
| Week 28 (N=98): moderate | 8.2 | | | |
| Week 28 (N=98): severe | 3.1 | | | |
| Week 32 (N=98): missing | 0 | | | |
| Week 32 (N=98): none | 73.5 | | | |
| Week 32 (N=98): mild | 17.3 | | | |
| Week 32 (N=98): moderate | 6.1 | | | |
| Week 32 (N=98): severe | 3.1 | | | |
| Week 36 (N=96): missing | 0 | | | |
| Week 36 (N=96): none | 71.9 | | | |
| Week 36 (N=96): mild | 16.7 | | | |
| Week 36 (N=96): moderate | 8.3 | | | |
| Week 36 (N=96): severe | 3.1 | | | |
| Week 40 (N=98): missing | 0 | | | |
| Week 40 (N=98): none | 80.6 | | | |
| Week 40 (N=98): mild | 12.2 | | | |
| Week 40 (N=98): moderate | 6.1 | | | |
| Week 40 (N=98): severe | 1 | | | |
| Week 44 (N=95): missing | 0 | | | |
| Week 44 (N=95): none | 76.8 | | | |
| Week 44 (N=95): mild | 20 | | | |
| Week 44 (N=95): moderate | 3.2 | | | |
| Week 44 (N=95): severe | 0 | | | |
| Week 48 (N=95): missing | 0 | | | |
| Week 48 (N=95): none | 83.2 | | | |
| Week 48 (N=95): mild | 11.6 | | | |
| Week 48 (N=95): moderate | 4.2 | | | |
| Week 48 (N=95): severe | 1.1 | | | |
| Week 52 (N=104): missing | 0 | | | |
| Week 52 (N=104): none | 78.8 | | | |
| Week 52 (N=104): mild | 15.4 | | | |
| Week 52 (N=104): moderate | 5.8 | | | |
| Week 52 (N=104): severe | 0 | | | |

Notes:

[11] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Dyspareunia Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Dyspareunia Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile |
|-----------------|---|

End point description:

In order to judge therapeutic effectiveness and to compare subjects' complaints, a severity profile score of dyspareunia was assessed using a rating scale: missing; 0 = none (no pain during intercourse); 1 = mild (tolerated discomfort); 2 = moderate (intercourse painful to the point of causing interdiction); 3 = severe (avoids intercourse because of pain) based on the subject's self-assessment of symptoms. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 110 ^[12] | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Baseline (N=110): missing | 80.9 | | | |
| Baseline (N=110): none | 9.1 | | | |
| Baseline (N=110): mild | 5.5 | | | |
| Baseline (N=110): moderate | 3.6 | | | |
| Baseline (N=110): severe | 0.9 | | | |
| Week 4 (N=108): missing | 80.6 | | | |
| Week 4 (N=108): none | 12 | | | |
| Week 4 (N=108): mild | 3.7 | | | |
| Week 4 (N=108): moderate | 3.7 | | | |
| Week 4 (N=108): severe | 0 | | | |
| Week 8 (N=107): missing | 75.7 | | | |
| Week 8 (N=107): none | 15 | | | |
| Week 8 (N=107): mild | 6.5 | | | |
| Week 8 (N=107): moderate | 2.8 | | | |
| Week 8 (N=107): severe | 0 | | | |
| Week 12 (N=104): missing | 74 | | | |
| Week 12 (N=104): none | 16.3 | | | |
| Week 12 (N=104): mild | 7.7 | | | |
| Week 12 (N=104): moderate | 1.9 | | | |
| Week 12 (N=104): severe | 0 | | | |
| Week 16 (N=101): missing | 71.3 | | | |
| Week 16 (N=101): none | 16.8 | | | |
| Week 16 (N=101): mild | 6.9 | | | |
| Week 16 (N=101): moderate | 4 | | | |
| Week 16 (N=101): severe | 1 | | | |
| Week 20 (N=98): missing | 70.4 | | | |
| Week 20 (N=98): none | 19.4 | | | |
| Week 20 (N=98): mild | 7.1 | | | |
| Week 20 (N=98): moderate | 3.1 | | | |
| Week 20 (N=98): severe | 0 | | | |
| Week 24 (N=100): missing | 75 | | | |
| Week 24 (N=100): none | 18 | | | |
| Week 24 (N=100): mild | 4 | | | |
| Week 24 (N=100): moderate | 3 | | | |

| | | | | |
|---------------------------|------|--|--|--|
| Week 24 (N=100): severe | 0 | | | |
| Week 28 (N=98): missing | 73.5 | | | |
| Week 28 (N=98): none | 18.4 | | | |
| Week 28 (N=98): mild | 5.1 | | | |
| Week 28 (N=98): moderate | 3.1 | | | |
| Week 28 (N=98): severe | 0 | | | |
| Week 32 (N=98): missing | 65.3 | | | |
| Week 32 (N=98): none | 25.5 | | | |
| Week 32 (N=98): mild | 6.1 | | | |
| Week 32 (N=98): moderate | 3.1 | | | |
| Week 32 (N=98): severe | 0 | | | |
| Week 36 (N=96): missing | 63.5 | | | |
| Week 36 (N=96): none | 24 | | | |
| Week 36 (N=96): mild | 7.3 | | | |
| Week 36 (N=96): moderate | 5.2 | | | |
| Week 36 (N=96): severe | 0 | | | |
| Week 40 (N=98): missing | 68.4 | | | |
| Week 40 (N=98): none | 20.4 | | | |
| Week 40 (N=98): mild | 7.1 | | | |
| Week 40 (N=98): moderate | 2 | | | |
| Week 40 (N=98): severe | 2 | | | |
| Week 44 (N=95): missing | 63.2 | | | |
| Week 44 (N=95): none | 23.2 | | | |
| Week 44 (N=95): mild | 10.5 | | | |
| Week 44 (N=95): moderate | 2.1 | | | |
| Week 44 (N=95): severe | 1.1 | | | |
| Week 48 (N=95): missing | 64.2 | | | |
| Week 48 (N=95): none | 28.4 | | | |
| Week 48 (N=95): mild | 4.2 | | | |
| Week 48 (N=95): moderate | 1.1 | | | |
| Week 48 (N=95): severe | 2.1 | | | |
| Week 52 (N=104): missing | 66.3 | | | |
| Week 52 (N=104): none | 23.1 | | | |
| Week 52 (N=104): mild | 4.8 | | | |
| Week 52 (N=104): moderate | 3.8 | | | |
| Week 52 (N=104): severe | 1.9 | | | |

Notes:

[12] - FAS subjects with baseline data for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Pelvic Tenderness Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Pelvic Tenderness Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile |
|-----------------|---|

End point description:

In order to judge therapeutic effectiveness and to compare subjects' complaints, a severity profile score of pelvic tenderness was assessed using a rating scale: missing; 0 = none (no pain during intercourse); 1 = mild (minimal tenderness on palpation); 2 = moderate (extensive tenderness on palpation); 3 = severe (unable to palpate because of tenderness) based on the gynecological palpation by the attending physician. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 | |

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 111 ^[13] | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Baseline (N=33): missing | 0 | | | |
| Baseline (N=33): none | 63.6 | | | |
| Baseline (N=33): mild | 30.3 | | | |
| Baseline (N=33): moderate | 6.1 | | | |
| Baseline (N=33): severe | 0 | | | |
| Week 4 (N=39): missing | 0 | | | |
| Week 4 (N=39): none | 66.7 | | | |
| Week 4 (N=39): mild | 28.2 | | | |
| Week 4 (N=39): moderate | 5.1 | | | |
| Week 4 (N=39): severe | 0 | | | |
| Week 8 (N=45): missing | 0 | | | |
| Week 8 (N=45): none | 64.4 | | | |
| Week 8 (N=45): mild | 28.9 | | | |
| Week 8 (N=45): moderate | 6.7 | | | |
| Week 8 (N=45): severe | 0 | | | |
| Week 12 (N=48): missing | 0 | | | |
| Week 12 (N=48): none | 77.1 | | | |
| Week 12 (N=48): mild | 18.8 | | | |
| Week 12 (N=48): moderate | 4.2 | | | |
| Week 12 (N=48): severe | 0 | | | |
| Week 16 (N=43): missing | 0 | | | |
| Week 16 (N=43): none | 79.1 | | | |
| Week 16 (N=43): mild | 18.6 | | | |
| Week 16 (N=43): moderate | 2.3 | | | |
| Week 16 (N=43): severe | 0 | | | |
| Week 20 (N=38): missing | 0 | | | |
| Week 20 (N=38): none | 89.5 | | | |
| Week 20 (N=38): mild | 7.9 | | | |
| Week 20 (N=38): moderate | 2.6 | | | |
| Week 20 (N=38): severe | 0 | | | |
| Week 24 (N=53): missing | 0 | | | |
| Week 24 (N=53): none | 83 | | | |
| Week 24 (N=53): mild | 15.1 | | | |
| Week 24 (N=53): moderate | 1.9 | | | |
| Week 24 (N=53): severe | 0 | | | |
| Week 28 (N=40): missing | 0 | | | |
| Week 28 (N=40): none | 87.5 | | | |
| Week 28 (N=40): mild | 12.5 | | | |

| | | | | |
|--------------------------|------|--|--|--|
| Week 28 (N=40): moderate | 0 | | | |
| Week 28 (N=40): severe | 0 | | | |
| Week 32 (N=37): missing | 0 | | | |
| Week 32 (N=37): none | 91.9 | | | |
| Week 32 (N=37): mild | 8.1 | | | |
| Week 32 (N=37): moderate | 0 | | | |
| Week 32 (N=37): severe | 0 | | | |
| Week 36 (N=46): missing | 0 | | | |
| Week 36 (N=46): none | 89.1 | | | |
| Week 36 (N=46): mild | 6.5 | | | |
| Week 36 (N=46): moderate | 4.3 | | | |
| Week 36 (N=46): severe | 0 | | | |
| Week 40 (N=38): missing | 0 | | | |
| Week 40 (N=38): none | 86.8 | | | |
| Week 40 (N=38): mild | 13.2 | | | |
| Week 40 (N=38): moderate | 0 | | | |
| Week 40 (N=38): severe | 0 | | | |
| Week 44 (N=39): missing | 0 | | | |
| Week 44 (N=39): none | 87.2 | | | |
| Week 44 (N=39): mild | 10.3 | | | |
| Week 44 (N=39): moderate | 2.6 | | | |
| Week 44 (N=39): severe | 0 | | | |
| Week 48 (N=38): missing | 0 | | | |
| Week 48 (N=38): none | 94.7 | | | |
| Week 48 (N=38): mild | 5.3 | | | |
| Week 48 (N=38): moderate | 0 | | | |
| Week 48 (N=38): severe | 0 | | | |
| Week 52 (N=56): missing | 0 | | | |
| Week 52 (N=56): none | 80.4 | | | |
| Week 52 (N=56): mild | 17.9 | | | |
| Week 52 (N=56): moderate | 1.8 | | | |
| Week 52 (N=56): severe | 0 | | | |

Notes:

[13] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Induration Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Induration Over 52 Weeks Using Modified Biberoglu and Behrman Severity Profile |
|-----------------|--|

End point description:

In order to judge therapeutic effectiveness and to compare subjects' complaints, a severity profile score of induration was assessed using a rating scale: missing; 0 = none (no pain during intercourse); 1 = mild (uterus freely mobile, induration in the cul-de-sac); 2 = moderate (thickened and indurated adnexa and cul-de-sac, restricted uterine mobility); 3 = severe (nodular adnexa and cul-de-sac, uterus frequently frozen) based on the gynecological palpation by the attending physician. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 111 ^[14] | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Baseline (N=33): missing | 24.2 | | | |
| Baseline (N=33): none | 60.6 | | | |
| Baseline (N=33): mild | 15.2 | | | |
| Baseline (N=33): moderate | 0 | | | |
| Baseline (N=33): severe | 0 | | | |
| Week 4 (N=39): missing | 20.5 | | | |
| Week 4 (N=39): none | 71.8 | | | |
| Week 4 (N=39): mild | 7.7 | | | |
| Week 4 (N=39): moderate | 0 | | | |
| Week 4 (N=39): severe | 0 | | | |
| Week 8 (N=45): missing | 22.2 | | | |
| Week 8 (N=45): none | 68.9 | | | |
| Week 8 (N=45): mild | 8.9 | | | |
| Week 8 (N=45): moderate | 0 | | | |
| Week 8 (N=45): severe | 0 | | | |
| Week 12 (N=48): missing | 18.8 | | | |
| Week 12 (N=48): none | 81.3 | | | |
| Week 12 (N=48): mild | 0 | | | |
| Week 12 (N=48): moderate | 0 | | | |
| Week 12 (N=48): severe | 0 | | | |
| Week 16 (N=43): missing | 18.6 | | | |
| Week 16 (N=43): none | 79.1 | | | |
| Week 16 (N=43): mild | 2.3 | | | |
| Week 16 (N=43): moderate | 0 | | | |
| Week 16 (N=43): severe | 0 | | | |
| Week 20 (N=38): missing | 21.1 | | | |
| Week 20 (N=38): none | 78.9 | | | |
| Week 20 (N=38): mild | 0 | | | |
| Week 20 (N=38): moderate | 0 | | | |
| Week 20 (N=38): severe | 0 | | | |
| Week 24 (N=53): missing | 18.9 | | | |
| Week 24 (N=53): none | 75.5 | | | |
| Week 24 (N=53): mild | 5.7 | | | |
| Week 24 (N=53): moderate | 0 | | | |
| Week 24 (N=53): severe | 0 | | | |
| Week 28 (N=40): missing | 20 | | | |
| Week 28 (N=40): none | 80 | | | |
| Week 28 (N=40): mild | 0 | | | |
| Week 28 (N=40): moderate | 0 | | | |
| Week 28 (N=40): severe | 0 | | | |
| Week 32 (N=37): missing | 18.9 | | | |

| | | | | |
|--------------------------|------|--|--|--|
| Week 32 (N=37): none | 81.1 | | | |
| Week 32 (N=37): mild | 0 | | | |
| Week 32 (N=37): moderate | 0 | | | |
| Week 32 (N=37): severe | 0 | | | |
| Week 36 (N=46): missing | 19.6 | | | |
| Week 36 (N=46): none | 78.3 | | | |
| Week 36 (N=46): mild | 2.2 | | | |
| Week 36 (N=46): moderate | 0 | | | |
| Week 36 (N=46): severe | 0 | | | |
| Week 40 (N=38): missing | 21.1 | | | |
| Week 40 (N=38): none | 78.9 | | | |
| Week 40 (N=38): mild | 0 | | | |
| Week 40 (N=38): moderate | 0 | | | |
| Week 40 (N=38): severe | 0 | | | |
| Week 44 (N=39): missing | 20.5 | | | |
| Week 44 (N=39): none | 79.5 | | | |
| Week 44 (N=39): mild | 0 | | | |
| Week 44 (N=39): moderate | 0 | | | |
| Week 44 (N=39): severe | 0 | | | |
| Week 48 (N=38): missing | 18.4 | | | |
| Week 48 (N=38): none | 78.9 | | | |
| Week 48 (N=38): mild | 2.6 | | | |
| Week 48 (N=38): moderate | 0 | | | |
| Week 48 (N=38): severe | 0 | | | |
| Week 52 (N=56): missing | 10.7 | | | |
| Week 52 (N=56): none | 87.5 | | | |
| Week 52 (N=56): mild | 1.8 | | | |
| Week 52 (N=56): moderate | 0 | | | |
| Week 52 (N=56): severe | 0 | | | |

Notes:

[14] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Global Impression (CGI) Scores - Assessed by the Investigator

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Clinical Global Impression (CGI) Scores - Assessed by the Investigator |
|-----------------|--|

End point description:

The investigator rating scale used in this study was based on the validated CGI scale, which is widely used as a simple tool to assess the overall effect of treatments. The investigator or a sub-investigator rated the total improvement according to the following scale: Score 1 = very much improved; Score 2 = much improved; Score 3 = minimally improved; Score 4 = no change; Score 5 = minimally worse; Score 6 = much worse; Score 7 = very much worse.

None of the subjects reported Score 7. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 12, 24, 36, and 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 111 ^[15] | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 12 (N=104): Score=1 | 39.4 | | | |
| Week 12 (N=104): Score=2 | 46.2 | | | |
| Week 12 (N=104): Score=3 | 10.6 | | | |
| Week 12 (N=104): Score=4 | 2.9 | | | |
| Week 12 (N=104): Score=5 | 1 | | | |
| Week 12 (N=104): Score=6 | 0 | | | |
| Week 24 (N=102): Score=1 | 64.7 | | | |
| Week 24 (N=102): Score=2 | 27.5 | | | |
| Week 24 (N=102): Score=3 | 5.9 | | | |
| Week 24 (N=102): Score=4 | 2 | | | |
| Week 24 (N=102): Score=5 | 0 | | | |
| Week 24 (N=102): Score=6 | 0 | | | |
| Week 36 (N=98): Score=1 | 67.3 | | | |
| Week 36 (N=98): Score=2 | 24.5 | | | |
| Week 36 (N=98): Score=3 | 6.1 | | | |
| Week 36 (N=98): Score=4 | 0 | | | |
| Week 36 (N=98): Score=5 | 1 | | | |
| Week 36 (N=98): Score=6 | 1 | | | |
| Week 52 (N=109): Score=1 | 64.2 | | | |
| Week 52 (N=109): Score=2 | 25.7 | | | |
| Week 52 (N=109): Score=3 | 4.6 | | | |
| Week 52 (N=109): Score=4 | 3.7 | | | |
| Week 52 (N=109): Score=5 | 1.8 | | | |
| Week 52 (N=109): Score=6 | 0 | | | |

Notes:

[15] - FAS.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Global Impression (CGI) Scores - Assessed by the Subject

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Clinical Global Impression (CGI) Scores - Assessed by the Subject |
|-----------------|---|

End point description:

The subject rating scale used in this study was based on the validated CGI scale, which is widely used as a simple tool to assess the overall effect of treatments. The subject was asked to rate her satisfaction with the study treatment according to the following scale: Score 1 = very much satisfied; Score 2 = much satisfied; Score 3 = minimally satisfied; Score 4 = neither satisfied nor dissatisfied; Score 5 = minimally dissatisfied; Score 6 = much dissatisfied; Score 7 = very much dissatisfied. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 12, 24, 36, 40, and 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 111 ^[16] | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Week 12 (N=104): Score=1 | 27.9 | | | |
| Week 12 (N=104): Score=2 | 46.2 | | | |
| Week 12 (N=104): Score=3 | 15.4 | | | |
| Week 12 (N=104): Score=4 | 5.8 | | | |
| Week 12 (N=104): Score=5 | 1.9 | | | |
| Week 12 (N=104): Score=6 | 1.9 | | | |
| Week 12 (N=104): Score=7 | 1 | | | |
| Week 24 (N=100): Score=1 | 39 | | | |
| Week 24 (N=100): Score=2 | 45 | | | |
| Week 24 (N=100): Score=3 | 8 | | | |
| Week 24 (N=100): Score=4 | 6 | | | |
| Week 24 (N=100): Score=5 | 2 | | | |
| Week 24 (N=100): Score=6 | 0 | | | |
| Week 24 (N=100): Score=7 | 0 | | | |
| Week 36 (N=96): Score=1 | 44.8 | | | |
| Week 36 (N=96): Score=2 | 40.6 | | | |
| Week 36 (N=96): Score=3 | 10.4 | | | |
| Week 36 (N=96): Score=4 | 3.1 | | | |
| Week 36 (N=96): Score=5 | 0 | | | |
| Week 36 (N=96): Score=6 | 1 | | | |
| Week 36 (N=96): Score=7 | 0 | | | |
| Week 40 (N=1): Score=1 | 0 | | | |
| Week 40 (N=1): Score=2 | 100 | | | |
| Week 40 (N=1): Score=3 | 0 | | | |
| Week 40 (N=1): Score=4 | 0 | | | |
| Week 40 (N=1): Score=5 | 0 | | | |
| Week 40 (N=1): Score=6 | 0 | | | |
| Week 40 (N=1): Score=7 | 0 | | | |
| Week 52 (N=103): Score=1 | 47.6 | | | |
| Week 52 (N=103): Score=2 | 36.9 | | | |
| Week 52 (N=103): Score=3 | 8.7 | | | |
| Week 52 (N=103): Score=4 | 4.9 | | | |
| Week 52 (N=103): Score=5 | 0 | | | |
| Week 52 (N=103): Score=6 | 1.9 | | | |
| Week 52 (N=103): Score=7 | 0 | | | |

Notes:

[16] - FAS.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Safety-related Findings

| | |
|-----------------|-----------------------------------|
| End point title | Number of Safety-related Findings |
|-----------------|-----------------------------------|

End point description:

Safety-related findings such as blood pressure, heart rate, body weight, and laboratory examinations, were listed as adverse events.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline up to 2 days after last dose of study drug (approximately 52 weeks)

| | | | | |
|-----------------------------|---------------------------------------|--|--|--|
| End point values | Dienogest (Visanne, BAY86-5258) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 0 ^[17] | | | |
| Units: Findings | | | | |

Notes:

[17] - Data for this endpoint were reported in adverse event (AE) section of the study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Vaginal Bleeding Events by 90-day Reference Period

| | |
|-----------------|--|
| End point title | Vaginal Bleeding Events by 90-day Reference Period |
|-----------------|--|

End point description:

Bleeding episodes were described using the reference period (RP) method recommended by the World Health Organization over a RP of 90 days. Each subject recorded the vaginal bleeding patterns in their e-diaries. In the listed categories, 'N' signifies those subjects who were evaluable for this measure.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline up to Week 52

| | | | | |
|---|---------------------------------------|--|--|--|
| End point values | Dienogest (Visanne, BAY86-5258) | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 111 ^[18] | | | |
| Units: Events | | | | |
| arithmetic mean (standard deviation) | | | | |
| Bleeding /spotting episodes in RP-1 (N=64) | 3.1 (± 2.3) | | | |
| Bleeding /spotting episodes in RP-2 (N=51) | 1.9 (± 2.1) | | | |
| Bleeding /spotting episodes in RP-3 (N=55) | 1.5 (± 2.1) | | | |

| | | | | |
|---|-----------|--|--|--|
| Bleeding /spotting episodes in RP-4 (N=44) | 1.6 (± 2) | | | |
|---|-----------|--|--|--|

Notes:

[18] - FAS.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Women With Pregnancy Test Result Over 52 Weeks

| | |
|-----------------|--|
| End point title | Number of Women With Pregnancy Test Result Over 52 Weeks |
|-----------------|--|

End point description:

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, unscheduled visit, and 52

| End point values | Dienogest (Visanne, BAY86-5258) | | | |
|-----------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 111 ^[19] | | | |
| Units: Subjects | | | | |
| Baseline (N=111): Positive | 0 | | | |
| Baseline (N=111): Negative | 111 | | | |
| Week 4 (N=110): Positive | 0 | | | |
| Week 4 (N=110): Negative | 110 | | | |
| Week 8 (N=107): Positive | 0 | | | |
| Week 8 (N=107): Negative | 107 | | | |
| Week 12 (N=104): Positive | 0 | | | |
| Week 12 (N=104): Negative | 104 | | | |
| Week 16 (N=103): Positive | 0 | | | |
| Week 16 (N=103): Negative | 103 | | | |
| Week 20 (N=100): Positive | 0 | | | |
| Week 20 (N=100): Negative | 100 | | | |
| Week 24 (N=102): Positive | 0 | | | |
| Week 24 (N=102): Negative | 102 | | | |
| Week 28 (N=100): Positive | 0 | | | |
| Week 28 (N=100): Negative | 100 | | | |
| Week 32 (N=97): Positive | 0 | | | |
| Week 32 (N=97): Negative | 97 | | | |
| Week 36 (N=99): Positive | 0 | | | |
| Week 36 (N=99): Negative | 99 | | | |
| Week 40 (N=97): Positive | 0 | | | |
| Week 40 (N=97): Negative | 97 | | | |
| Week 44 (N=97): Positive | 0 | | | |
| Week 44 (N=97): Negative | 97 | | | |
| Week 48 (N=95): Positive | 0 | | | |

| | | | | |
|-----------------------------------|-----|--|--|--|
| Week 48 (N=95): Negative | 95 | | | |
| Unscheduled visit (N=4): Positive | 1 | | | |
| Unscheduled visit (N=4): Negative | 3 | | | |
| Week 52 (N=108): Positive | 0 | | | |
| Week 52 (N=108): Negative | 108 | | | |

Notes:

[19] - FAS.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 2 days after last dose of study drug (approximately 52 weeks)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Dienogest (BAY 86-5258) |
|-----------------------|-------------------------|

Reporting group description:

Subjects received Dienogest orally at a dosage of 2 mg once daily over a period of 52 weeks.

| Serious adverse events | Dienogest (BAY 86-5258) | | |
|---|-------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 111 (4.50%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Spinal column injury | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Ovarian cyst ruptured | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Adenomyosis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ovarian adhesion | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| | | | |
|---|-------------------------|--|--|
| Non-serious adverse events | Dienogest (BAY 86-5258) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 92 / 111 (82.88%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Anogenital warts | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Surgical and medical procedures | | | |
| Dental operation | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|-----------------|--|--|
| Orthodontic procedure | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Tooth repair | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Tonsillectomy | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Wisdom teeth removal | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Chills | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Discomfort | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Medical device pain | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | | |
| occurrences (all) | 6 | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Malaise | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Irritability | | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 111 (0.90%) 3 | | |
| Influenza like illness subjects affected / exposed occurrences (all) | 1 / 111 (0.90%) 1 | | |
| Feeling cold subjects affected / exposed occurrences (all) | 1 / 111 (0.90%) 1 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 1 / 111 (0.90%) 1 | | |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 4 / 111 (3.60%) 4 | | |
| Reproductive system and breast disorders Amenorrhoea subjects affected / exposed occurrences (all) | 2 / 111 (1.80%) 2 | | |
| Polycystic ovaries subjects affected / exposed occurrences (all) | 1 / 111 (0.90%) 1 | | |
| Pelvic pain subjects affected / exposed occurrences (all) | 4 / 111 (3.60%) 4 | | |
| Ovarian cyst subjects affected / exposed occurrences (all) | 1 / 111 (0.90%) 1 | | |
| Metrorrhagia subjects affected / exposed occurrences (all) | 7 / 111 (6.31%) 8 | | |
| Breast enlargement subjects affected / exposed occurrences (all) | 2 / 111 (1.80%) 2 | | |
| Menorrhagia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 111 (3.60%) | | |
| occurrences (all) | 4 | | |
| Endometriosis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Endometrial hypertrophy | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Breast pain | | | |
| subjects affected / exposed | 8 / 111 (7.21%) | | |
| occurrences (all) | 9 | | |
| Menstruation irregular | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Vulvovaginal pruritus | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Vaginal inflammation | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 4 / 111 (3.60%) | | |
| occurrences (all) | 7 | | |
| Vaginal discharge | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 3 | | |
| Oropharyngeal pain | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 6 / 111 (5.41%) | | |
| occurrences (all) | 12 | | |
| Nasal inflammation | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Cough | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | | |
| occurrences (all) | 7 | | |
| Psychiatric disorders | | | |
| Major depression | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Tearfulness | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Panic disorder | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Mood swings | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 7 | | |
| Mood altered | | | |
| subjects affected / exposed | 4 / 111 (3.60%) | | |
| occurrences (all) | 4 | | |
| Depression | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Depressed mood | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 10 | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Libido decreased | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|------------------|--|--|
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 3 | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Body temperature increased | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 3 | | |
| Blood sodium increased | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Weight increased | | | |
| subjects affected / exposed | 10 / 111 (9.01%) | | |
| occurrences (all) | 10 | | |
| White blood cell count increased | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Face injury | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Muscle strain | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 3 | | |
| Excoriation | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Sunburn | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Ligament sprain | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Ligament injury | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Hand fracture | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Arthropod bite | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Post-traumatic pain | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Tooth fracture | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Limb injury | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 3 | | |
| Cardiac disorders | | | |
| Tachycardia | | | |

| | | | |
|--------------------------------------|-------------------|--|--|
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Poor quality sleep | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 3 | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Migraine | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 7 | | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 2 | | |
| Headache | | | |
| subjects affected / exposed | 36 / 111 (32.43%) | | |
| occurrences (all) | 75 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Blood and lymphatic system disorders | | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Lymphadenitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|--|--|--|--|
| Ear pain subjects affected / exposed occurrences (all) | 1 / 111 (0.90%) 1 | | |
| Eye disorders Eye pruritus subjects affected / exposed occurrences (all) Myopia subjects affected / exposed occurrences (all) | 1 / 111 (0.90%) 1 1 / 111 (0.90%) 1 | | |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Haematochezia subjects affected / exposed occurrences (all) Glossitis subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Gastritis subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain upper | 2 / 111 (1.80%) 2 1 / 111 (0.90%) 1 1 / 111 (0.90%) 1 2 / 111 (1.80%) 2 1 / 111 (0.90%) 1 8 / 111 (7.21%) 9 9 / 111 (8.11%) 9 2 / 111 (1.80%) 2 | | |

| | | | |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 5 / 111 (4.50%) | | |
| occurrences (all) | 6 | | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 7 / 111 (6.31%) | | |
| occurrences (all) | 10 | | |
| Flatulence | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Plicated tongue | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Odynophagia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 13 / 111 (11.71%) | | |
| occurrences (all) | 18 | | |
| Hyperchlorhydria | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Gastric disorder | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Vomiting | | | |
| subjects affected / exposed | 16 / 111 (14.41%) | | |
| occurrences (all) | 22 | | |
| Toothache | | | |
| subjects affected / exposed | 4 / 111 (3.60%) | | |
| occurrences (all) | 5 | | |
| Hepatobiliary disorders | | | |

| | | | |
|--|-----------------|--|--|
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 5 / 111 (4.50%) | | |
| occurrences (all) | 6 | | |
| Seborrhoea | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Rash | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 3 | | |
| Alopecia | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Eczema | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Cafe au lait spots | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Blister | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|--|--|
| Dysuria | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Torticollis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Neck pain | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 3 | | |
| Back pain | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | | |
| occurrences (all) | 12 | | |
| Tendonitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Acute tonsillitis | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 3 | | |
| Bronchitis | | | |
| subjects affected / exposed | 6 / 111 (5.41%) | | |
| occurrences (all) | 6 | | |
| Candidiasis | | | |

| | | | |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Cystitis | | | |
| subjects affected / exposed | 8 / 111 (7.21%) | | |
| occurrences (all) | 8 | | |
| Ear infection | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 4 | | |
| Fungal skin infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Influenza | | | |
| subjects affected / exposed | 16 / 111 (14.41%) | | |
| occurrences (all) | 17 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 35 / 111 (31.53%) | | |
| occurrences (all) | 61 | | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Otitis media | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 2 | | |
| Gingivitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Periodontitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 7 / 111 (6.31%) | | |
| occurrences (all) | 8 | | |
| Gastroenteritis | | | |

| | | | |
|-----------------------------------|-------------------|--|--|
| subjects affected / exposed | 4 / 111 (3.60%) | | |
| occurrences (all) | 5 | | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Otitis media acute | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 5 / 111 (4.50%) | | |
| occurrences (all) | 8 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Rhinitis | | | |
| subjects affected / exposed | 3 / 111 (2.70%) | | |
| occurrences (all) | 3 | | |
| Scarlet fever | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Sinusitis | | | |
| subjects affected / exposed | 5 / 111 (4.50%) | | |
| occurrences (all) | 5 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 12 / 111 (10.81%) | | |
| occurrences (all) | 13 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Vaginal infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Varicella | | | |

| | | | |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Adenovirus infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Helminthic infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 3 | | |
| Vulvitis | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Vulvovaginal candidiasis | | | |
| subjects affected / exposed | 2 / 111 (1.80%) | | |
| occurrences (all) | 4 | | |
| Burn infection | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Tinea versicolour | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Viral infection | | | |
| subjects affected / exposed | 5 / 111 (4.50%) | | |
| occurrences (all) | 8 | | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 111 (0.90%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|----------------------|--|--|
| Lactose intolerance subjects affected / exposed occurrences (all) | 1 / 111 (0.90%) 1 | | |
|---|----------------------|--|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 02 December 2010 | In the initial study protocol, the study phase was termed as "Phase IV". The Austrian Health Authority (AGES) recommended a change of the study phase as "Phase II" in order to increase the focus on the latter aspects of the trial design. |
| 19 May 2011 | The following modifications were done in this protocol amendment: 1. Country specific change of inclusion criterion for Finland included study enrolment of 12 – 14 years old adolescents whose diagnosis of endometriosis had been confirmed by laparoscopy 2. Country specific change of requirements to perform gynecological examination in subjects below 15 years of age and written authorization of investigators |
| 16 August 2012 | Subjects with a decrease in BMD between baseline and end of treatment were invited for a follow-up scan of 6 months after the end of treatment in order to assess development of BMD after stopping study treatment. Data related to potential confounding parameters (height, weight, diet and medication) were also collected. A newly introduced Visit 17 was only to take place if there was a decrease in the lumbar spine BMD observed between Baseline (Visit 2) and End of Treatment (Visit 15). Introduced with this amendment, additional diagnostic procedures including a further BMD measurement of 12 months after end of treatment, and treatments were initiated as deemed necessary by the investigator. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported