

**Clinical trial results:**

A multicenter, randomized, partially blinded, placebo-controlled clinical trial to evaluate the effect on primary dysmenorrhea of vaginal rings with an average daily release of 700 g noregestrol acetate (NOMAC) and 300 g estradiol (E2), or 900 g noregestrol acetate (NOMAC) and 300 g estradiol (E2), or 100 g etonogestrel (ENG) and 300 g E2, or 125 g etonogestrel (ENG) and 300 g E2

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2012-002449-40 |
| Trial protocol | DE NO NL BE SE PL DK ES |
| Global end of trial date | 12 September 2013 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 23 May 2016 |
| First version publication date | 29 July 2015 |

Trial information**Trial identification**

| | |
|-----------------------|--------------|
| Sponsor protocol code | MK-8342B-057 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|------------------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01670656 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Schering-Plough: SCH 900432 P08257 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Merck Sharp & Dohme Corp. |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033 |
| Public contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com |
| Scientific contact | Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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 | 12 September 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 September 2013 |
| 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 identify at least one dose of progestin/estrogen amongst the 4 active doses being tested, administered as a vaginal ring, that shows clinically relevant treatment efficacy in relief of primary dysmenorrhea, as demonstrated by a statistically significantly larger reduction (as compared to baseline) in mean menstrual cramping pain score compared to placebo.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 21 January 2013 |
| 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 | Colombia: 82 |
| Country: Number of subjects enrolled | Netherlands: 33 |
| Country: Number of subjects enrolled | Norway: 25 |
| Country: Number of subjects enrolled | Poland: 167 |
| Country: Number of subjects enrolled | Spain: 5 |
| Country: Number of subjects enrolled | Sweden: 12 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Denmark: 9 |
| Country: Number of subjects enrolled | Germany: 22 |
| Country: Number of subjects enrolled | Australia: 8 |
| Country: Number of subjects enrolled | Chile: 34 |
| Country: Number of subjects enrolled | Mexico: 17 |
| Country: Number of subjects enrolled | South Africa: 9 |
| Country: Number of subjects enrolled | New Zealand: 12 |
| Worldwide total number of subjects | 439 |
| EEA total number of subjects | 277 |

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) | 439 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study enrolled adult female participants with a diagnosis of primary dysmenorrhea. Additional inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

A total of 840 subjects participants were screened to determine their eligibility for entry into the trial. A total of 439 participants were enrolled and 438 participants were treated.

Period 1

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

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | NOMAC-E2 700/300 mcg |

Arm description:

NOMAC-E2 700/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | NOMAC-E2 |
| Investigational medicinal product code | |
| Other name | SCH900121, MK-8175A |
| Pharmaceutical forms | Vaginal delivery system |
| Routes of administration | Vaginal use |

Dosage and administration details:

Nomegestrol acetate and estradiol (NOMAC-E2) contraceptive vaginal ring, at either 700 or 900 mcg NOMAC and 300 µg mcg, for two 28 day cycles

| | |
|--|-----------|
| Investigational medicinal product name | Ibuprofen |
| Investigational medicinal product code | |
| Other name | Motrin |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ibuprofen 400 mg will be dispensed throughout the entire study as needed as rescue medication for treating menstrual cramping pain. The maximum daily ibuprofen dose is 3200 mg (8 tablets).

| | |
|------------------|----------------------|
| Arm title | NOMAC-E2 900/300 mcg |
|------------------|----------------------|

Arm description:

NOMAC-E2 900/300 mcg administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | NOMAC-E2 |
| Investigational medicinal product code | |
| Other name | SCH900121, MK-8175A |
| Pharmaceutical forms | Vaginal delivery system |
| Routes of administration | Vaginal use |

Dosage and administration details:

Nomegestrol acetate and estradiol (NOMAC-E2) contraceptive vaginal ring, at either 700 or 900 mcg NOMAC and 300 mcg E2, for two 28 day cycles

| | |
|--|-----------|
| Investigational medicinal product name | Ibuprofen |
| Investigational medicinal product code | |
| Other name | Motrin |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ibuprofen 400 mg will be dispensed throughout the entire study as needed as rescue medication for treating menstrual cramping pain. The maximum daily ibuprofen dose is 3200 mg (8 tablets).

| | |
|------------------|--------------------|
| Arm title | ENG-E2 100/300 mcg |
|------------------|--------------------|

Arm description:

ENG-E2 100/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ENG-E2 |
| Investigational medicinal product code | |
| Other name | SCH900432, MK-8342B |
| Pharmaceutical forms | Vaginal delivery system |
| Routes of administration | Vaginal use |

Dosage and administration details:

Etonogestrel and estradiol (ENG-E2) contraceptive vaginal ring, at either 100 or 125 mcg ENG and 300 mcg E2, for two 28-day cycles

| | |
|--|-----------|
| Investigational medicinal product name | Ibuprofen |
| Investigational medicinal product code | |
| Other name | Motrin |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ibuprofen 400 mg will be dispensed throughout the entire study as needed as rescue medication for treating menstrual cramping pain. The maximum daily ibuprofen dose is 3200 mg (8 tablets).

| | |
|------------------|--------------------|
| Arm title | ENG-E2 125/300 mcg |
|------------------|--------------------|

Arm description:

ENG-E2 125/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ENG-E2 |
| Investigational medicinal product code | |
| Other name | SCH900432, MK-8342B |
| Pharmaceutical forms | Vaginal delivery system |
| Routes of administration | Vaginal use |

Dosage and administration details:

Etonogestrel and estradiol (ENG-E2) contraceptive vaginal ring, at either 100 or 125 mcg ENG and 300 mcg, for two 28-day cycles

| | |
|--|-----------|
| Investigational medicinal product name | Ibuprofen |
| Investigational medicinal product code | |
| Other name | Motrin |
| Pharmaceutical forms | Tablet |

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Ibuprofen 400 mg will be dispensed throughout the entire study as needed as rescue medication for treating menstrual cramping pain. The maximum daily ibuprofen dose is 3200 mg (8 tablets).

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---------|
| Investigational medicinal product name | Placebo |
|--|---------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--|
| Other name | |
|------------|--|

| | |
|----------------------|-------------------------|
| Pharmaceutical forms | Vaginal delivery system |
|----------------------|-------------------------|

| | |
|--------------------------|-------------|
| Routes of administration | Vaginal use |
|--------------------------|-------------|

Dosage and administration details:

Placebo to match vaginal ring, intravaginally for two 28-day cycles

| | |
|--|-----------|
| Investigational medicinal product name | Ibuprofen |
|--|-----------|

| | |
|--|--|
| Investigational medicinal product code | |
|--|--|

| | |
|------------|--------|
| Other name | Motrin |
|------------|--------|

| | |
|----------------------|--------|
| Pharmaceutical forms | Tablet |
|----------------------|--------|

| | |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Ibuprofen 400 mg will be dispensed throughout the entire study as needed as rescue medication for treating menstrual cramping pain. The maximum daily ibuprofen dose is 3200 mg (8 tablets).

| Number of subjects in period 1 | NOMAC-E2 700/300 mcg | NOMAC-E2 900/300 mcg | ENG-E2 100/300 mcg |
|---------------------------------------|-------------------------|-------------------------|-----------------------|
| Started | 86 | 91 | 87 |
| Completed | 83 | 84 | 79 |
| Not completed | 3 | 7 | 8 |
| Consent withdrawn by subject | 1 | 1 | 2 |
| Adverse event, non-fatal | 2 | 2 | 2 |
| Pregnancy | - | - | - |
| Non-compliance with protocol | - | 3 | 1 |
| Non-compliance with study drug | - | - | 3 |
| Subject moved | - | - | - |
| Lost to follow-up | - | - | - |
| Withdrawal by subject | - | 1 | - |

| Number of subjects in period 1 | ENG-E2 125/300 mcg | Placebo |
|---------------------------------------|-----------------------|---------|
| Started | 85 | 90 |
| Completed | 79 | 79 |
| Not completed | 6 | 11 |
| Consent withdrawn by subject | 1 | 1 |

| | | |
|--------------------------------|---|---|
| Adverse event, non-fatal | 3 | 3 |
| Pregnancy | - | 1 |
| Non-compliance with protocol | 1 | 2 |
| Non-compliance with study drug | - | 1 |
| Subject moved | 1 | - |
| Lost to follow-up | - | 3 |
| Withdrawal by subject | - | - |

Baseline characteristics

Reporting groups

| | |
|---|----------------------|
| Reporting group title | NOMAC-E2 700/300 mcg |
| Reporting group description: NOMAC-E2 700/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days. | |
| Reporting group title | NOMAC-E2 900/300 mcg |
| Reporting group description: NOMAC-E2 900/300 mcg administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days. | |
| Reporting group title | ENG-E2 100/300 mcg |
| Reporting group description: ENG-E2 100/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days. | |
| Reporting group title | ENG-E2 125/300 mcg |
| Reporting group description: ENG-E2 125/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days. | |

| Reporting group values | NOMAC-E2 700/300 mcg | NOMAC-E2 900/300 mcg | ENG-E2 100/300 mcg |
|------------------------------------|----------------------|----------------------|--------------------|
| Number of subjects | 86 | 91 | 87 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------------|---------------|---------------|
| Age continuous Units: years arithmetic mean standard deviation | 28.7 ± 7.5 | 28.7 ± 8.1 | 29.1 ± 7.7 |
| Gender categorical Units: Subjects | | | |
| Female | 86 | 91 | 87 |
| Male | 0 | 0 | 0 |

| Reporting group values | ENG-E2 125/300 mcg | Placebo | Total |
|------------------------------------|--------------------|---------|-------|
| Number of subjects | 85 | 90 | 439 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------------|---------------|---|
| Age continuous Units: years arithmetic mean standard deviation | 28.3 ± 7.8 | 28.4 ± 8.2 | - |
|---|---------------|---------------|---|

| | | | |
|--------------------|----|----|-----|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 85 | 90 | 439 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|---|----------------------|
| Reporting group title | NOMAC-E2 700/300 mcg |
| Reporting group description: NOMAC-E2 700/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days. | |
| Reporting group title | NOMAC-E2 900/300 mcg |
| Reporting group description: NOMAC-E2 900/300 mcg administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days. | |
| Reporting group title | ENG-E2 100/300 mcg |
| Reporting group description: ENG-E2 100/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days. | |
| Reporting group title | ENG-E2 125/300 mcg |
| Reporting group description: ENG-E2 125/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days. | |
| Reporting group title | Placebo |
| Reporting group description: Placebo was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days. | |

Primary: Change from Baseline in Mean Menstrual Cramping Pain Score Through Cycle 2

| | |
|---|--|
| End point title | Change from Baseline in Mean Menstrual Cramping Pain Score Through Cycle 2 |
| End point description: The Mean Menstrual Cramping Pain score was calculated as the average of the three highest menstrual pain scores on the five point scale of item #3 of the Menstrual Distress Questionnaire in the baseline cycle and treatment Cycle 2, respectively. The daily menstrual cramping pain score was based on five pain categories: none (0); mild (1); moderate (2); strong (3); and severe (4). In case of absence of withdrawal bleeding, or onset of menstruation, the mean of the three highest menstrual cramping pain scores recorded within Days 21-28 was used for analysis. This endpoint was based on the Full Analysis Set (FAS) population, which consisted of all randomized subjects, in whom a vaginal ring was inserted, with at least one baseline or one-post baseline value. | |
| End point type | Primary |
| End point timeframe: Baseline and Day 28 to 56 (Cycle 2) | |

| End point values | NOMAC-E2 700/300 mcg | NOMAC-E2 900/300 mcg | ENG-E2 100/300 mcg | ENG-E2 125/300 mcg |
|--|-------------------------|-------------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 91 | 86 | 85 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.7 (-2 to -1.5) | -1.7 (-1.9 to -1.5) | -1.9 (-2.1 to -1.7) | -1.7 (-1.9 to -1.5) |

| | | | | |
|--|---------------------|--|--|--|
| End point values | Placebo | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 90 | | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -1.2 (-1.4 to -0.9) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Chg from BL in Mean Menstrl Cramping Score thru C2 |
| Comparison groups | NOMAC-E2 700/300 mcg v Placebo |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | -0.2 |

| | |
|---|--|
| Statistical analysis title | Chg from BL in Mean Menstrl Cramping Score thru C2 |
| Comparison groups | NOMAC-E2 900/300 mcg v Placebo |
| Number of subjects included in analysis | 181 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | -0.2 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Chg from BL in Mean Menstrl Cramping Score thru C2 |
|-----------------------------------|--|

| | |
|---|------------------------------|
| Comparison groups | ENG-E2 100/300 mcg v Placebo |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | -0.4 |

| | |
|---|--|
| Statistical analysis title | Chg from BL in Mean Menstrl Cramping Score thru C2 |
| Comparison groups | ENG-E2 125/300 mcg v Placebo |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | -0.2 |

Secondary: Change from Baseline in Total Mean Impact Score Through Cycle 2

| | |
|------------------------|---|
| End point title | Change from Baseline in Total Mean Impact Score Through Cycle 2 |
| End point description: | Total Mean Impact Score, based on responses to questions 6, 8, 9, and 10 in the Dysmenorrhea Daily Diary (DysDD), measures dysmenorrhea's interference with work, physical activities, social/leisure activities, and sleep. Q6: In the past 24 hours, how much did pain or cramps in the pelvic area limit you in your paid work, work around the home, or school work? Q8: In the past 24 hours, how much did pain or cramps in the pelvic area limit you in your physical activities? Q9: In the past 24 hours, how much did pain or cramps in the pelvic area limit you in your social or leisure activities? Q10: In the past 24 hours, how much did pain or cramps in the pelvic area make it difficult for you to sleep? Each question is rated on a 5-point (0-4) scale, 0 being "Not at all" and 5 "Extremely." This endpoint was based on the FAS population, which consisted of all randomized subjects, in whom a vaginal ring was inserted, with at least one baseline or one-post baseline value. |
| End point type | Secondary |
| End point timeframe: | Baseline and Day 28 to 56 (Cycle 2) |

| End point values | NOMAC-E2 700/300 mcg | NOMAC-E2 900/300 mcg | ENG-E2 100/300 mcg | ENG-E2 125/300 mcg |
|--|-------------------------|-------------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 90 | 86 | 85 |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -4.8 (-5.6 to -4) | -5 (-5.7 to -4.2) | -4.7 (-5.5 to -3.9) | -4.3 (-5.1 to -3.5) |

| End point values | Placebo | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 90 | | | |
| Units: units on a scale | | | | |
| least squares mean (confidence interval 95%) | -3.1 (-3.9 to -2.4) | | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Change from BL in Total Mean Impact Score thru C2 |
| Comparison groups | NOMAC-E2 700/300 mcg v Placebo |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3 |
| upper limit | -0.4 |

| | |
|---|---|
| Statistical analysis title | Change from BL in Total Mean Impact Score thru C2 |
| Comparison groups | NOMAC-E2 900/300 mcg v Placebo |
| Number of subjects included in analysis | 180 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.1 |
| upper limit | -0.6 |

| | |
|---|---|
| Statistical analysis title | Change from BL in Total Mean Impact Score thru C2 |
| Comparison groups | ENG-E2 100/300 mcg v Placebo |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.9 |
| upper limit | -0.3 |

| | |
|---|---|
| Statistical analysis title | Change from BL in Total Mean Impact Score thru C2 |
| Comparison groups | ENG-E2 125/300 mcg v Placebo |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.024 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5 |
| upper limit | 0.1 |

Secondary: Change from Baseline in Number of Ibuprofen Tablets Taken Through Cycle 2

| | |
|-----------------|---|
| End point title | Change from Baseline in Number of Ibuprofen Tablets Taken Through Cycle 2 |
|-----------------|---|

End point description:

Participants were provided with ibuprofen 400 mg tablets at the screening visit to be taken throughout the study as needed as rescue medication for treating menstrual cramping pain. The maximum daily ibuprofen dose was 3200 mg (8 tablets). Participants were instructed to take the provided ibuprofen, and no other medications, for the relief of menstrual cramping pain, and to record their ibuprofen usage

in their e-Diaries. This endpoint was based on the FAS population, which consisted of all randomized subjects, in whom a vaginal ring was inserted, with at least one baseline or one-post baseline value.

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

End point timeframe:

Baseline and Day 28 to 56 (Cycle 2)

| End point values | NOMAC-E2 700/300 mcg | NOMAC-E2 900/300 mcg | ENG-E2 100/300 mcg | ENG-E2 125/300 mcg |
|--|-------------------------|-------------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 91 | 86 | 85 |
| Units: number of ibuprofen tablets taken | | | | |
| least squares mean (confidence interval 95%) | -6.4 (-7.5 to -5.3) | -6.3 (-7.4 to -5.2) | -7.1 (-8.2 to -6) | -6 (-7.1 to -4.9) |

| End point values | Placebo | | | |
|--|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 90 | | | |
| Units: number of ibuprofen tablets taken | | | | |
| least squares mean (confidence interval 95%) | -4.8 (-6 to -3.7) | | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Chg from BL in no. of ibuprofen tbs taken thru C2 |
| Comparison groups | NOMAC-E2 700/300 mcg v Placebo |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.026 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 0.2 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Chg from BL in no. of ibuprofen tbs taken thru C2 |
| Comparison groups | NOMAC-E2 900/300 mcg v Placebo |

| | |
|---|------------------------|
| Number of subjects included in analysis | 181 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.036 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.3 |
| upper limit | 0.2 |

| | |
|---|---|
| Statistical analysis title | Chg from BL in no. of ibuprofen tbs taken thru C2 |
| Comparison groups | ENG-E2 100/300 mcg v Placebo |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -2.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.1 |
| upper limit | -0.5 |

| | |
|---|---|
| Statistical analysis title | Chg from BL in no. of ibuprofen tbs taken thru C2 |
| Comparison groups | ENG-E2 125/300 mcg v Placebo |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3 |
| upper limit | 0.6 |

Secondary: Change from Baseline in Number of Days of Ibuprofen Intake Through

Cycle 2

| | |
|-----------------|--|
| End point title | Change from Baseline in Number of Days of Ibuprofen Intake Through Cycle 2 |
|-----------------|--|

End point description:

Participants were provided with ibuprofen 400 mg tablets at the screening visit to be taken throughout the study as needed as rescue medication for treating menstrual cramping pain. The maximum daily ibuprofen dose was 3200 mg (8 tablets). Participants were instructed to take the provided ibuprofen, and no other medications, for the relief of menstrual cramping pain, and to record their ibuprofen usage their e-Diaries. This endpoint was based on the FAS population, which consisted of all randomized subjects, in whom a vaginal ring was inserted, with at least one baseline or one-post baseline value.

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

End point timeframe:

Baseline and Day 28 to 56 (Cycle 2)

| End point values | NOMAC-E2 700/300 mcg | NOMAC-E2 900/300 mcg | ENG-E2 100/300 mcg | ENG-E2 125/300 mcg |
|--|-------------------------|-------------------------|-----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 85 | 91 | 86 | 85 |
| Units: Number of days of ibuprofen intake | | | | |
| least squares mean (confidence interval 95%) | -1.3 (-1.5 to -1) | -1.7 (-2 to -1.4) | -1.7 (-2 to -1.4) | -1.4 (-1.7 to -1.1) |

| End point values | Placebo | | | |
|--|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 90 | | | |
| Units: Number of days of ibuprofen intake | | | | |
| least squares mean (confidence interval 95%) | -1.1 (-1.4 to -0.9) | | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Chg frm BL in no. of days of ibprfn intake thru C2 |
| Comparison groups | NOMAC-E2 700/300 mcg v Placebo |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.477 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6 |
| upper limit | 0.3 |

| | |
|---|--|
| Statistical analysis title | Chg frm BL in no. of days of ibprfn intake thru C2 |
| Comparison groups | NOMAC-E2 900/300 mcg v Placebo |
| Number of subjects included in analysis | 181 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | -0.1 |

| | |
|---|--|
| Statistical analysis title | Chg frm BL in no. of days of ibprfn intake thru C2 |
| Comparison groups | ENG-E2 100/300 mcg v Placebo |
| Number of subjects included in analysis | 176 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.003 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | -0.1 |

| | |
|---|--|
| Statistical analysis title | Chg frm BL in no. of days of ibprfn intake thru C2 |
| Comparison groups | ENG-E2 125/300 mcg v Placebo |
| Number of subjects included in analysis | 175 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.156 |
| Method | cLDA |
| Parameter estimate | Difference in LS Means |
| Point estimate | -0.3 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.7 |
| upper limit | 0.2 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 64 days

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | NOMAC-E2 700/300 mcg |
|-----------------------|----------------------|

Reporting group description:

NOMAC-E2 700/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days

| | |
|-----------------------|----------------------|
| Reporting group title | NOMAC-E2 900/300 mcg |
|-----------------------|----------------------|

Reporting group description:

NOMAC-E2 900/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days

| | |
|-----------------------|--------------------|
| Reporting group title | ENG-E2 100/300 mcg |
|-----------------------|--------------------|

Reporting group description:

ENG-E2 100/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days

| | |
|-----------------------|--------------------|
| Reporting group title | ENG-E2 125/300 mcg |
|-----------------------|--------------------|

Reporting group description:

ENG-E2 125/300 mcg was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo was administered for two 28-day treatment periods, each period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

| Serious adverse events | NOMAC-E2 700/300 mcg | NOMAC-E2 900/300 mcg | ENG-E2 100/300 mcg |
|---|----------------------|----------------------|--------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 1 / 91 (1.10%) | 0 / 86 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 1 / 91 (1.10%) | 0 / 86 (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 |
| Psychiatric disorders | | | |
| Impulse-control disorder | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 86 (0.00%) | 1 / 91 (1.10%) | 0 / 86 (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 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 86 (0.00%) | 0 / 91 (0.00%) | 0 / 86 (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 | ENG-E2 125/300 mcg | Placebo | |
|--|--------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 90 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Impulse-control disorder | | | |
| subjects affected / exposed | 0 / 85 (0.00%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 85 (1.18%) | 0 / 90 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | NOMAC-E2 700/300 mcg | NOMAC-E2 900/300 mcg | ENG-E2 100/300 mcg |
|---|-------------------------|-------------------------|------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 12 / 86 (13.95%) | 11 / 91 (12.09%) | 14 / 86 (16.28%) |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 9 / 86 (10.47%) 13 | 9 / 91 (9.89%) 19 | 11 / 86 (12.79%) 13 |
| Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all) | 5 / 86 (5.81%) 7 | 1 / 91 (1.10%) 1 | 1 / 86 (1.16%) 1 |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 1 / 86 (1.16%) 1 | 1 / 91 (1.10%) 1 | 2 / 86 (2.33%) 2 |

| Non-serious adverse events | ENG-E2 125/300 mcg | Placebo | |
|---|-----------------------|---------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 7 / 85 (8.24%) | 11 / 90 (12.22%) | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 5 / 85 (5.88%) 7 | 7 / 90 (7.78%) 9 | |
| Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all) | 1 / 85 (1.18%) 1 | 2 / 90 (2.22%) 3 | |
| Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) | 1 / 85 (1.18%) 1 | 5 / 90 (5.56%) 7 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|--------------|--|
| 01 July 2013 | Amendment 1: Changes to the protocol included: Trial Flow Chart - addition of dispensation of ibuprofen; Inclusion Criteria/ Trial Schedule - Clarification of inclusion criterion #8 of history of regular menstrual cycles and inclusion criterion #14 baseline menstrual cycle length; Table 1 Prohibited Medications - formatted table to properly reflect 2 month wash out period, added sex hormones, and corrected bosentan to be reflected as an anti-hypertensive; Subject Exclusion Criteria - Maximum period between screening and randomization changed globally from 80 to 90 days; Non-IMP Medication - added clarifying statements regarding dispensing ibuprofen at Visit 1 and recording of ibuprofen in e-Diary following Visit 2; Dispensing - corrected training/guidance on the use of vaginal ring will be completed using a demonstration vaginal ring and not by an unblinded staff member; Events of Clinical Interest - clarified that pregnancies are to be reported on the appropriate pregnancy eCRFs ONLY. They will not be reported on the AE eCRF. Non-serious complications during pregnancy will be reported on AE eCRF; Overdose - ibuprofen overdose definition added to section; Expedited Reporting of Safety Observations by Investigator to Sponsor - removal of references to Global Safety Intake Form and corresponding Table 3; Other Endpoints - MDQ-T Correction of pain score scale from 0-5 to 0-4. Addition of intake of pain relief medications for treatment of pelvic pain as a trigger to enable questionnaire; Efficacy Endpoints - Clarification on definitions of breakthrough bleeding and breakthrough spotting; Statistical Methods for Efficacy Analysis - Daily menstrual cramping pain score item #10 of MDQ-scale corrected globally to item #3; e-Diary Ring Use Questions - Updated to reflect final approved version of ring use questions as they appear in e-Diary in addition to instructions and scenarios for triggering follow up question. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported