Clinical trial results:
A multicenter, randomized, partially blinded, placebo-controlled clinical trial to evaluate the effect on primary dysmenorrheal of vaginal rings with an average daily release of 700 g nomegestrol acetate (NOMAC) and 300 g estradiol (E2), or 900 g nomegestrol 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	28.7	28.7	29.1
standard deviation	± 7.5	± 8.1	± 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	28.3	28.4	
standard deviation	± 7.8	± 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	9 / 86 (10.47%)	9 / 91 (9.89%)	11 / 86 (12.79%)
occurrences (all)	13	19	13
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	5 / 86 (5.81%)	1 / 91 (1.10%)	1 / 86 (1.16%)
occurrences (all)	7	1	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 86 (1.16%)	1 / 91 (1.10%)	2 / 86 (2.33%)
occurrences (all)	1	1	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	5 / 85 (5.88%)	7 / 90 (7.78%)	
occurrences (all)	7	9	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 85 (1.18%)	2 / 90 (2.22%)	
occurrences (all)	1	3	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 85 (1.18%)	5 / 90 (5.56%)	
occurrences (all)	1	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 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