Clinical trial results:
A multicenter, randomized, partially-blinded, Phase IIb dose-finding study on ovarian function, vaginal bleeding pattern, and pharmacokinetics associated with the use of combined vaginal rings releasing 17-estradiol plus three different doses of either nomegestrol acetate or etonogestrel in healthy women aged 18-35 years

Summary

EudraCT number	2012-002459-41
Trial protocol	NO DE SE NL HU ES DK PL
Global end of trial date	15 October 2013

Results information

Result version number	v1
This version publication date	13 April 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	MK-8175A-012

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01709318
WHO universal trial number (UTN)	-
Other trial identifiers	Schering-Plough: SCH900121/SCH900432 P06109

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	15 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to identify at least one NGR that demonstrates inhibition of ovulation (which was considered confirmed if in the subset of participants ovulation was observed in less than 15% of the participants at any time during the 3 treatment cycles of the study) and cycle control that was non-inferior to NuvaRing®, as judged by the incidence of breakthrough bleeding and/or spotting (BTB-S) during Cycle 3.

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:

Contraception

Evidence for comparator: -

Actual start date of recruitment	12 December 2012
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	Netherlands: 163
Country: Number of subjects enrolled	Norway: 21
Country: Number of subjects enrolled	Poland: 112
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Denmark: 26
Country: Number of subjects enrolled	Germany: 298
Country: Number of subjects enrolled	Hungary: 40
Worldwide total number of subjects	666
EEA total number of subjects	666

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	666
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolled healthy female participants aged 18 to 35 years, with cycles between 24 to 35 days in length. Additional inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

Of the 757 subjects who were screened for inclusion in the trial, 666 subjects were randomized, and 660 subjects 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	Subject, Investigator

Blinding implementation details:

Note: All NOMAC-E2 and ENG-E2 treatment groups were double-blinded. The NuvaRing treatment group was open-label.

Arms

Are arms mutually exclusive?	Yes
Arm title	NOMAC-E2 500/300 mcg

Arm description:

Participants received NOMAC-E2 500/300 mcg for three treatment periods, each 28-day treatment 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	nomegestrol acetate and estradiol, MK-8175A
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Nomegestrol acetate and estradiol (NOMAC-E2), with daily release of 500, 700, or 900 mcg NOMAC, and daily release of 300 mcg E2

Arm title	NOMAC-E2 700/300 mcg

Arm description:

Participants received NOMAC-E2 700/300 mcg for three treatment periods, each 28-day treatment 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	nomegestrol acetate and estradiol, MK-8175A
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Nomegestrol acetate and estradiol (NOMAC-E2), with daily release of 500, 700, or 900 mcg NOMAC, and daily release of 300 mcg E2

Arm title	NOMAC-E2 900/300 mcg

Arm description:

Participants received NOMAC-E2 900/300 mcg for three treatment periods, each 28-day treatment 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	nomegestrol acetate and estradiol, MK-8175A
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Nomegestrol acetate and estradiol (NOMAC-E2), with daily release of 500, 700, or 900 mcg NOMAC, and daily release of 300 mcg E2

Arm title	ENG-E2 75/300 mcg

Arm description:

Participants received ENG-E2 75/300 mcg for three treatment periods, each 28-day treatment 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	etonogestrel and estradiol, MK-8342B
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Etonogestrel and estradiol (ENG-E2) contraceptive vaginal ring, with daily release of 75, 100, or 125 mcg ENG, and daily release of 300 mcg E2.

Arm title	ENG-E2 100/300 mcg

Arm description:

Participants received ENG-E2 100/300 mcg for three treatment periods, each 28-day treatment 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	etonogestrel and estradiol, MK-8342B
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Etonogestrel and estradiol (ENG-E2) contraceptive vaginal ring, with daily release of 75, 100 or 125 mcg ENG, and daily release of 300 mcg E2.

Arm title	ENG-E2 125/300 mcg

Arm description:

Participants received ENG-E2 125/300 mcg for three 28-day treatment periods, each treatment 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	etonogestrel and estradiol, MK-8342B
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

Etonogestrel and estradiol (ENG-E2) contraceptive vaginal ring, with daily release of 75, 100 or 125 mcg ENG, and daily release of 300 mcg E2.

Arm title	NuvaRing® (ENG-EE 120/15 mcg)

Arm description:

Participants received NuvaRing® for three treatment periods, each 28-day treatment period (cycle) consisting

of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

Arm type	Active comparator
Investigational medicinal product name	NuvaRing® (ENG-EE 120/15)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal delivery system
Routes of administration	Vaginal use

Dosage and administration details:

NuvaRing® (etonogestrel and ethinyl estradiol [ENG-EE]), with daily release of 120 mcg ENG, and daily release of 15 mcg EE

Number of subjects in period 1[1]	NOMAC-E2 500/300 mcg	NOMAC-E2 700/300 mcg	NOMAC-E2 900/300 mcg
Started	79	85	78
Completed	72	78	72
Not completed	7	7	6
Physician decision	-	-	-
Adverse event, non-fatal	3	4	2
Technical problems	1	-	-
Site discontinued	-	1	-
Protocol violation	-	-	-
Non-compliance with study drug	-	2	1
Lost to follow-up	2	-	-
Withdrawal by subject	1	-	3

Number of subjects in period 1[1]	ENG-E2 75/300 mcg	ENG-E2 100/300 mcg	ENG-E2 125/300 mcg
Started	77	77	86
Completed	71	74	82
Not completed	6	3	4
Physician decision	-	-	-
Adverse event, non-fatal	2	-	1
Technical problems	-	-	-
Site discontinued	-	-	-
Protocol violation	-	2	-
Non-compliance with study drug	1	-	-
Lost to follow-up	-	1	1
Withdrawal by subject	3	-	2

Number of subjects in period 1[1]	NuvaRing® (ENG-EE 120/15 mcg)
Started	178

Completed	170
Not completed	8
Physician decision	1
Adverse event, non-fatal	2
Technical problems	-
Site discontinued	-
Protocol violation	-
Non-compliance with study drug	2
Lost to follow-up	1
Withdrawal by subject	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 666 were enrolled in the study, but 6 participants who were randomized were not treated. The baseline period is based on all participants who were randomized and treated: a total of 660 participants.

Baseline characteristics

Reporting groups	
Reporting group title	NOMAC-E2 500/300 mcg
Reporting group description:	
Participants received NOMAC-E2 500/300 mcg for three treatment periods, each 28-day treatment period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.	
Reporting group title	NOMAC-E2 700/300 mcg
Reporting group description:	
Participants received NOMAC-E2 700/300 mcg for three treatment periods, each 28-day treatment 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:	
Participants received NOMAC-E2 900/300 mcg for three treatment periods, each 28-day treatment period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.	
Reporting group title	ENG-E2 75/300 mcg
Reporting group description:	
Participants received ENG-E2 75/300 mcg for three treatment periods, each 28-day treatment 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:	
Participants received ENG-E2 100/300 mcg for three treatment periods, each 28-day treatment 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:	
Participants received ENG-E2 125/300 mcg for three 28-day treatment periods, each treatment period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.	
Reporting group title	NuvaRing® (ENG-EE 120/15 mcg)
Reporting group description:	
Participants received NuvaRing® for three treatment periods, each 28-day treatment period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.	

Reporting group values	NOMAC-E2 500/300 mcg	NOMAC-E2 700/300 mcg	NOMAC-E2 900/300 mcg
Number of subjects	79	85	78
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	26.7	26.7	26.1
standard deviation	± 5	± 4.9	± 4.5
Gender categorical Units: Subjects			
Female	79	85	78
Male	0	0	0

Reporting group values	ENG-E2 75/300 mcg	ENG-E2 100/300 mcg	ENG-E2 125/300 mcg
Number of subjects	77	77	86

Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	25.5	26.1	27.1
standard deviation	± 4.9	± 4.5	± 4.6
Gender categorical Units: Subjects			
Female	77	77	86
Male	0	0	0

Reporting group values	NuvaRing® (ENG-EE 120/15 mcg)	Total	
Number of subjects	178	660	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	25.9		
standard deviation	± 4.8	-	
Gender categorical Units: Subjects			
Female	178	660	
Male	0	0	

End points

End points reporting groups

Reporting group title	NOMAC-E2 500/300 mcg
Reporting group description:	
Participants received NOMAC-E2 500/300 mcg for three treatment periods, each 28-day treatment period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.	
Reporting group title	NOMAC-E2 700/300 mcg
Reporting group description:	
Participants received NOMAC-E2 700/300 mcg for three treatment periods, each 28-day treatment 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:	
Participants received NOMAC-E2 900/300 mcg for three treatment periods, each 28-day treatment period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.	
Reporting group title	ENG-E2 75/300 mcg
Reporting group description:	
Participants received ENG-E2 75/300 mcg for three treatment periods, each 28-day treatment 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:	
Participants received ENG-E2 100/300 mcg for three treatment periods, each 28-day treatment 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:	
Participants received ENG-E2 125/300 mcg for three 28-day treatment periods, each treatment period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.	
Reporting group title	NuvaRing® (ENG-EE 120/15 mcg)
Reporting group description:	
Participants received NuvaRing® for three treatment periods, each 28-day treatment period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.	

Primary: Number of Participants with Progesterone Concentrations >16 nmol/L, by Cycle

End point title	Number of Participants with Progesterone Concentrations >16 nmol/L, by Cycle[1]
End point description:	
Inhibition of ovulation was considered confirmed if, in a subset of participants, ovulation was observed in less than 15% of the participants at any time during the 3 treatment cycles of the study. Ovulation was defined as the presence of two or more consecutive progesterone concentrations >16 nmol/L within 5 days, and supported by ultrasound evidence of ovulation. Ultrasound evidence of ovulation was defined as either follicular rupture or the preceding presence of a follicular-like structure >15 mm in size. This endpoint was based on the Per-Protocol (PP) Population, which was defined as all participants in whom vaginal rings were inserted and who did not have any major protocol violation (a protocol violation that interfered with the assessment[s] of efficacy).	
End point type	Primary
End point timeframe:	
Day 1 of Treatment Cycle 1 through Day 28 of Treatment Cycle 3 (Study Days 1-84)	

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: No pairwise comparison was performed on the primary endpoint Number of Participants With Progesterone Concentrations >16 nmol/L, by Cycle.

End point values	NOMAC-E2 500/300 mcg	NOMAC-E2 700/300 mcg	NOMAC-E2 900/300 mcg	ENG-E2 75/300 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65	73	57	60
Units: Participants				
Cycle 1 (n=18,19,19,20,19,19,21)	0	0	0	0
Cycle 2 (n=17,16,16,20,19,17,19)	0	0	0	0
Cycle 3 (n=17,15,14,17,19,17,19)	0	0	0	0

End point values	ENG-E2 100/300 mcg	ENG-E2 125/300 mcg	NuvaRing® (ENG-EE 120/15 mcg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	65	126	
Units: Participants				
Cycle 1 (n=18,19,19,20,19,19,21)	0	0	0	
Cycle 2 (n=17,16,16,20,19,17,19)	0	0	0	
Cycle 3 (n=17,15,14,17,19,17,19)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Breakthrough Bleeding and/or Spotting (BTB-S) During Cycle 3

End point title	Percentage of Participants With Breakthrough Bleeding and/or Spotting (BTB-S) During Cycle 3

End point description:

Breakthrough Bleeding and/or Spotting (BTB-S) was classified as follows: Bleeding = any bloody vaginal discharge that required one or more sanitary pads or tampons per day; Spotting = any bloody vaginal discharge that required no sanitary pads or tampons per day.

End point type	Primary

End point timeframe:

Day 1 Cycle 3 through Day 28 Cycle 3 (Study Days 57-84)

End point values	NOMAC-E2 500/300 mcg	NOMAC-E2 700/300 mcg	NOMAC-E2 900/300 mcg	ENG-E2 75/300 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	48	45	40	44
Units: percentage of participants				
number (not applicable)	14.6	13.3	17.5	13.6

End point values	ENG-E2 100/300 mcg	ENG-E2 125/300 mcg	NuvaRing® (ENG-EE 120/15 mcg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	47	97	
Units: percentage of participants				
number (not applicable)	16.3	6.4	6.2	

Statistical analyses

Statistical analysis title	Pct of participants with BTB-S during Cycle 3
Comparison groups	NOMAC-E2 500/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Difference in percentage
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	26.5

Notes:

[2] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Statistical analysis title	Pct of participants with BTB-S during Cycle 3
Comparison groups	NOMAC-E2 700/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference in percentage
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	24.8

Notes:

[3] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Statistical analysis title	Pct of participants with BTB-S during Cycle 3
Comparison groups	NOMAC-E2 900/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Difference in percentage
Point estimate	12.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	33.1

Notes:

[4] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Statistical analysis title	Pct of participants with BTB-S during Cycle 3
Comparison groups	ENG-E2 75/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Difference in percentage
Point estimate	6.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	25.4

Notes:

[5] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Statistical analysis title	Pct of participants with BTB-S during Cycle 3
Comparison groups	ENG-E2 100/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Difference in percentage
Point estimate	9.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	27.4

Notes:

[6] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Statistical analysis title	Pct of participants with BTB-S during Cycle 3
Comparison groups	ENG-E2 125/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
Parameter estimate	Difference in percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	15.9

Notes:

[7] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Secondary: Percentage of Participants With Absence of Withdrawal Bleeding and/or Spotting During Cycle 2

End point title	Percentage of Participants With Absence of Withdrawal Bleeding and/or Spotting During Cycle 2

End point description:

Withdrawal Bleeding and/or Spotting is considered any bleeding or spotting episode that starts during or continues into the expected bleeding period. Absence of Withdrawal Bleeding is no withdrawal bleeding and/or spotting episodes during an expected bleeding period. This endpoint was based on the PP Population, which was defined as all participants in whom vaginal rings were inserted and who did not have any major protocol violation (a protocol violation that interfered with the assessment[s] of efficacy).

End point type	Secondary

End point timeframe:

Day 1 Cycle 2 through Day 28 Cycle 2 (Study Days 29-56)

End point values	NOMAC-E2 500/300 mcg	NOMAC-E2 700/300 mcg	NOMAC-E2 900/300 mcg	ENG-E2 75/300 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55	53	45	51
Units: percentage of participants				
number (not applicable)	5.5	1.9	4.4	7.8

End point values	ENG-E2 100/300 mcg	ENG-E2 125/300 mcg	NuvaRing® (ENG-EE 120/15 mcg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	52	111	
Units: percentage of participants				
number (not applicable)	3.7	1.9	1.8	

Statistical analyses

Statistical analysis title	Pct of prtcpnts with absence of WB-S during C2
Comparison groups	NOMAC-E2 500/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
Parameter estimate	Difference in percentage
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	16.4

Notes:

[8] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Statistical analysis title	Pct of prtcpnts with absence of WB-S during C2
Comparison groups	NOMAC-E2 700/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
Parameter estimate	Difference in percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	11

Notes:

[9] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Statistical analysis title	Pct of prtcpnts with absence of WB-S during C2
Comparison groups	NOMAC-E2 900/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
Parameter estimate	Difference in percentage
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	17.5

Notes:

[10] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Statistical analysis title	Pct of prtcpnts with absence of WB-S during C2
Comparison groups	ENG-E2 75/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)

Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	Difference in percentage
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	18.9

Notes:

[11] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Statistical analysis title	Pct of prtcpnts with absence of WB-S during C2
Comparison groups	ENG-E2 100/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
Parameter estimate	Difference in percentage
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	13.4

Notes:

[12] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Statistical analysis title	Pct of prtcpnts with absence of WB-S during C2
Comparison groups	ENG-E2 125/300 mcg v NuvaRing® (ENG-EE 120/15 mcg)
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
Parameter estimate	Difference in percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	11

Notes:

[13] - Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is <=10%.

Secondary: Intensity of Withdrawal Bleeding During Cycle 2

End point title	Intensity of Withdrawal Bleeding During Cycle 2

End point description:

Intensity of Withdrawal Bleeding During Cycle 2 was defined as the ratio of the number of withdrawal bleeding days divided by the number of withdrawal bleeding and/or spotting days. This endpoint was based on the PP Population, which was defined as all participants in whom vaginal rings were inserted and who did not have any major protocol violation (a protocol violation that interfered with the assessment[s] of efficacy).

End point type	Secondary

End point timeframe:

Day 1 Cycle 2 through Day 28 Cycle 2 (Study Days 29-57)

End point values	NOMAC-E2 500/300 mcg	NOMAC-E2 700/300 mcg	NOMAC-E2 900/300 mcg	ENG-E2 75/300 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	52	52	43	47
Units: ratio				
arithmetic mean (standard deviation)	0.9 (± 0.2)	0.9 (± 0.2)	0.9 (± 0.2)	0.9 (± 0.2)

End point values	ENG-E2 100/300 mcg	ENG-E2 125/300 mcg	NuvaRing® (ENG-EE 120/15 mcg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	51	109	
Units: ratio				
arithmetic mean (standard deviation)	0.9 (± 0.2)	0.9 (± 0.1)	1 (± 0.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Intensity of Breakthrough Bleeding and/or Spotting During Cycle 3

End point title	Intensity of Breakthrough Bleeding and/or Spotting During Cycle 3

End point description:

Intensity of Breakthrough Bleeding and/or Spotting (BTB-S) During Cycle 3 was defined as the ratio of the number of breakthrough bleeding days divided by the number of breakthrough bleeding and/or spotting days. This endpoint was based on the PP Population, which was defined as all participants in whom vaginal rings were inserted and who did not have any major protocol violation (a protocol violation that interfered with the assessment[s] of efficacy).

End point type	Secondary

End point timeframe:

Day 1 Cycle 3 through Day 28 Cycle 3 (Study Days 57-84)

End point values	NOMAC-E2 500/300 mcg	NOMAC-E2 700/300 mcg	NOMAC-E2 900/300 mcg	ENG-E2 75/300 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	7	6
Units: ratio				
arithmetic mean (standard deviation)	0.4 (± 0.4)	0.8 (± 0.4)	0.7 (± 0.5)	0.7 (± 0.2)

End point values	ENG-E2 100/300 mcg	ENG-E2 125/300 mcg	NuvaRing® (ENG-EE 120/15 mcg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	3	6	
Units: ratio				
arithmetic mean (standard deviation)	0.7 (± 0.4)	0.3 (± 0.6)	0.7 (± 0.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Venous or Arterial Thrombotic/Thrombolic Events

End point title	Number of Participants With Venous or Arterial Thrombotic/Thrombolic Events

End point description:

This endpoint was based on the PP Population, which was defined as all participants in whom vaginal rings were inserted and who did not have any major protocol violation (a protocol violation that interfered with the assessment[s] of efficacy).

End point type	Secondary

End point timeframe:

From Cycle 1 Day 1 up to 8 days after Day 28 of Cycle 3 (Study Days 1 through 92)

End point values	NOMAC-E2 500/300 mcg	NOMAC-E2 700/300 mcg	NOMAC-E2 900/300 mcg	ENG-E2 75/300 mcg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	85	78	77
Units: Participants	0	0	0	0

End point values	ENG-E2 100/300 mcg	ENG-E2 125/300 mcg	NuvaRing® (ENG-EE 120/15 mcg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77	86	178	
Units: Participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 92 days

Adverse event reporting additional description:

The All Subjects as Treated (ASaT) population consists of all randomized subjects in whom a vaginal ring was inserted, regardless if they were randomized or not.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	NOMAC-E2 500/300 mcg

Reporting group description:

Participants received NOMAC-E2 500/300 for three treatment periods, each 28-day treatment period (cycle) consisting of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

Reporting group title	NOMAC-E2 700/300 mcg

Reporting group description:

Participants received NOMAC-E2 700/300 mcg for three treatment periods, each 28-day treatment 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:

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

Reporting group title	ENG-E2 75/300 mcg

Reporting group description:

Participants received ENG-E2 75/300 mcg for three treatment periods, each 28-day treatment 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:

Participants received ENG-E2 100/300 mcg for three treatment periods, each 28-day treatment 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:

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

Reporting group title	NuvaRing® (ENG-EE 120/15 mcg)

Reporting group description:

Participants received NuvaRing® for three treatment periods, each 28-day treatment period (cycle) consisting
of 21 days of vaginal ring use followed by 7 vaginal ring-free days.

Serious adverse events	NOMAC-E2 500/300 mcg	NOMAC-E2 700/300 mcg	NOMAC-E2 900/300 mcg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 79 (0.00%)	0 / 85 (0.00%)	0 / 78 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	ENG-E2 75/300 mcg	ENG-E2 100/300 mcg	ENG-E2 125/300 mcg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 86 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	NuvaRing® (ENG-EE 120/15 mcg)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 178 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	NOMAC-E2 500/300 mcg	NOMAC-E2 700/300 mcg	NOMAC-E2 900/300 mcg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 79 (29.11%)	20 / 85 (23.53%)	26 / 78 (33.33%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 79 (0.00%)	0 / 85 (0.00%)	4 / 78 (5.13%)
occurrences (all)	0	0	4
Headache			
subjects affected / exposed	12 / 79 (15.19%)	11 / 85 (12.94%)	14 / 78 (17.95%)
occurrences (all)	24	21	43
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 79 (2.53%)	0 / 85 (0.00%)	1 / 78 (1.28%)
occurrences (all)	2	0	2
Nausea			
subjects affected / exposed	4 / 79 (5.06%)	1 / 85 (1.18%)	2 / 78 (2.56%)
occurrences (all)	7	1	2
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	4 / 79 (5.06%)	2 / 85 (2.35%)	5 / 78 (6.41%)
occurrences (all)	5	2	5
Vaginal discharge			
subjects affected / exposed	1 / 79 (1.27%)	6 / 85 (7.06%)	4 / 78 (5.13%)
occurrences (all)	1	9	5
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 79 (5.06%)	1 / 85 (1.18%)	2 / 78 (2.56%)
occurrences (all)	5	2	2
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 79 (2.53%)	3 / 85 (3.53%)	6 / 78 (7.69%)
occurrences (all)	2	4	8
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 79 (5.06%)	0 / 85 (0.00%)	1 / 78 (1.28%)
occurrences (all)	4	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 79 (11.39%)	5 / 85 (5.88%)	11 / 78 (14.10%)
occurrences (all)	12	5	13

Non-serious adverse events	ENG-E2 75/300 mcg	ENG-E2 100/300 mcg	ENG-E2 125/300 mcg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 77 (31.17%)	22 / 77 (28.57%)	25 / 86 (29.07%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 77 (0.00%)	0 / 77 (0.00%)	0 / 86 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	13 / 77 (16.88%)	15 / 77 (19.48%)	13 / 86 (15.12%)
occurrences (all)	35	29	35
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 77 (7.79%)	1 / 77 (1.30%)	3 / 86 (3.49%)
occurrences (all)	9	1	3

Nausea			
subjects affected / exposed	4 / 77 (5.19%)	1 / 77 (1.30%)	1 / 86 (1.16%)
occurrences (all)	4	1	1
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 77 (2.60%)	3 / 77 (3.90%)	6 / 86 (6.98%)
occurrences (all)	2	3	8
Vaginal discharge			
subjects affected / exposed	4 / 77 (5.19%)	5 / 77 (6.49%)	4 / 86 (4.65%)
occurrences (all)	4	9	6
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	4 / 77 (5.19%)	1 / 77 (1.30%)	2 / 86 (2.33%)
occurrences (all)	5	1	2
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	3 / 77 (3.90%)	2 / 77 (2.60%)	6 / 86 (6.98%)
occurrences (all)	3	2	10
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 77 (1.30%)	2 / 77 (2.60%)	2 / 86 (2.33%)
occurrences (all)	2	3	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 77 (14.29%)	7 / 77 (9.09%)	8 / 86 (9.30%)
occurrences (all)	14	7	9

Non-serious adverse events	NuvaRing® (ENG-EE 120/15 mcg)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 178 (25.84%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 178 (0.00%)		
occurrences (all)	0		
Headache			

subjects affected / exposed occurrences (all)	24 / 178 (13.48%) 47		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 2 / 178 (1.12%) 3 7 / 178 (3.93%) 8		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) Vaginal discharge subjects affected / exposed occurrences (all)	 7 / 178 (3.93%) 11 3 / 178 (1.69%) 4		
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	 4 / 178 (2.25%) 4		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	 6 / 178 (3.37%) 6		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 4 / 178 (2.25%) 8		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 16 / 178 (8.99%) 18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2013	Amendment 2: Changes to the protocol included: Trial Flow Chart - screening phase changed from 60 to 80 days - randomization may occur up to 80 days after Visit 1; Table 1 - PD samples (FSH, LH, and P) and the PK should be collected in addition to the ultrasound should the subject need to return every third day until disappearance of the largest follicle that was ≥15 mm on Day 8. SHBG does not need to be repeated; Subject Inclusion Criteria - Clarification of inclusion 5: The intra-individual variation of +/- 3 days is allowed, but individual cycles should be within the 24-35 days in length - Clarification of inclusion 6: If the subject or her partner is surgically sterilized, then condoms are not required; Subjected Exclusion Criteria - Clarification of Table 2 Excluded Medications: table updated to reflect bosentan as an anti-hypertensive and not as an anti-epileptic - typographical error for carbamazepine and herbal remedies wash-out corrected - table layout streamlined to demonstrate that all medicines listed fall under the category of medicines associated with liver enzyme induction thus affecting the bioavailability of steroids.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported