

**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 | 22 October 2013         |

**Results information**

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v2 (current)    |
| This version publication date  | 26 January 2020 |
| First version publication date | 01 August 2015  |
| Version creation reason        |                 |

**Trial information****Trial identification**

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | P06109 |
|-----------------------|--------|

**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.,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>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                       | 22 October 2013 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 22 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                          | 11 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 | Norway: 21       |
| Country: Number of subjects enrolled | Netherlands: 163 |
| 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 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)                     | 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                  |
| <b>Arm title</b>             | 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

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | 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

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | 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

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | 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.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | 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.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | 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.

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 1</b> | NOMAC-E2 500/300 mcg | NOMAC-E2 700/300 mcg | NOMAC-E2 900/300 mcg |
|---------------------------------------|----------------------|----------------------|----------------------|
| Started                               | 82                   | 85                   | 77                   |
| Treated                               | 79                   | 85                   | 77                   |
| Completed                             | 73                   | 78                   | 71                   |
| Not completed                         | 9                    | 7                    | 6                    |
| Physician decision                    | -                    | -                    | -                    |
| Adverse event, non-fatal              | 3                    | 4                    | 2                    |
| Technical problems                    | 1                    | -                    | -                    |
| Protocol violation                    | -                    | -                    | -                    |
| Other protocol specified criteria     | -                    | 1                    | -                    |
| Pregnancy                             | -                    | -                    | -                    |
| Non-compliance with study drug        | -                    | 2                    | 1                    |
| Lost to follow-up                     | 2                    | -                    | -                    |
| Withdrawal by subject                 | 3                    | -                    | 3                    |

| <b>Number of subjects in period 1</b> | ENG-E2 75/300 mcg | ENG-E2 100/300 mcg | ENG-E2 125/300 mcg |
|---------------------------------------|-------------------|--------------------|--------------------|
| Started                               | 78                | 78                 | 84                 |
| Treated                               | 77                | 77                 | 84                 |
| Completed                             | 72                | 74                 | 80                 |
| Not completed                         | 6                 | 4                  | 4                  |
| Physician decision                    | -                 | -                  | -                  |
| Adverse event, non-fatal              | -                 | -                  | 1                  |
| Technical problems                    | -                 | -                  | -                  |
| Protocol violation                    | 2                 | 2                  | -                  |
| Other protocol specified criteria     | -                 | -                  | -                  |
| Pregnancy                             | -                 | 1                  | -                  |
| Non-compliance with study drug        | 1                 | -                  | -                  |
| Lost to follow-up                     | -                 | 1                  | 1                  |
| Withdrawal by subject                 | 3                 | -                  | 2                  |

|                                       |                               |
|---------------------------------------|-------------------------------|
| <b>Number of subjects in period 1</b> | NuvaRing® (ENG-EE 120/15 mcg) |
|---------------------------------------|-------------------------------|

|                                   |     |
|-----------------------------------|-----|
| Started                           | 182 |
| Treated                           | 178 |
| Completed                         | 171 |
| Not completed                     | 11  |
| Physician decision                | 1   |
| Adverse event, non-fatal          | 2   |
| Technical problems                | -   |
| Protocol violation                | 1   |
| Other protocol specified criteria | -   |
| Pregnancy                         | -   |
| Non-compliance with study drug    | 2   |
| Lost to follow-up                 | 1   |
| Withdrawal by subject             | 4   |

## 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                        | 82                   | 85                   | 77                   |
| Age categorical<br>Units: Subjects        |                      |                      |                      |
| Age continuous<br>Units: years            |                      |                      |                      |
| arithmetic mean                           | 26.6                 | 26.7                 | 26.1                 |
| standard deviation                        | ± 5.0                | ± 4.9                | ± 4.4                |
| Gender categorical<br>Units: Subjects     |                      |                      |                      |
| Female                                    | 82                   | 85                   | 77                   |
| Male                                      | 0                    | 0                    | 0                    |
| Race<br>Units: Subjects                   |                      |                      |                      |
| Asian                                     | 0                    | 1                    | 0                    |
| Native Hawaiian or Other Pacific Islander | 0                    | 0                    | 0                    |
| Black or African American                 | 1                    | 1                    | 0                    |

|                    |    |    |    |
|--------------------|----|----|----|
| White              | 80 | 83 | 75 |
| More than one race | 1  | 0  | 2  |

| <b>Reporting group values</b>      | ENG-E2 75/300 mcg | ENG-E2 100/300 mcg | ENG-E2 125/300 mcg |
|------------------------------------|-------------------|--------------------|--------------------|
| Number of subjects                 | 78                | 78                 | 84                 |
| Age categorical<br>Units: Subjects |                   |                    |                    |

|   |       |       |       |
|---|-------|-------|-------|
| Age continuous<br>Units: years            |       |       |       |
| arithmetic mean                           | 25.5  | 26.0  | 26.9  |
| standard deviation                        | ± 4.8 | ± 4.5 | ± 4.5 |
| Gender categorical<br>Units: Subjects     |       |       |       |
| Female                                    | 78    | 78    | 84    |
| Male                                      | 0     | 0     | 0     |
| Race<br>Units: Subjects                   |       |       |       |
| Asian                                     | 0     | 0     | 0     |
| Native Hawaiian or Other Pacific Islander | 1     | 0     | 0     |
| Black or African American                 | 1     | 0     | 0     |
| White                                     | 74    | 78    | 83    |
| More than one race                        | 2     | 0     | 1     |

| <b>Reporting group values</b>      | NuvaRing® (ENG-EE 120/15 mcg) | Total |  |
|------------------------------------|-------------------------------|-------|--|
| Number of subjects                 | 182                           | 666   |  |
| Age categorical<br>Units: Subjects |                               |       |  |

|   |       |     |  |
|---|-------|-----|--|
| Age continuous<br>Units: years            |       |     |  |
| arithmetic mean                           | 26.0  | -   |  |
| standard deviation                        | ± 4.9 |     |  |
| Gender categorical<br>Units: Subjects     |       |     |  |
| Female                                    | 182   | 666 |  |
| Male                                      | 0     | 0   |  |
| Race<br>Units: Subjects                   |       |     |  |
| Asian                                     | 1     | 2   |  |
| Native Hawaiian or Other Pacific Islander | 0     | 1   |  |
| Black or African American                 | 1     | 4   |  |
| White                                     | 178   | 651 |  |
| More than one race                        | 2     | 8   |  |

## End points

### End points reporting groups

|   |                               |
|---|-------------------------------|
| Reporting group title   | NOMAC-E2 500/300 mcg          |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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.                 |                               |
| Subject analysis set title  | NOMAC-E2 500/300 mcg          |
| Subject analysis set type   | Intention-to-treat            |
| Subject analysis set description:<br>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. |                               |
| Subject analysis set title  | NOMAC-E2 700/300 mcg          |
| Subject analysis set type   | Intention-to-treat            |
| Subject analysis set description:<br>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. |                               |
| Subject analysis set title  | NOMAC-E2 900/300 mcg          |
| Subject analysis set type   | Intention-to-treat            |
| Subject analysis set description:<br>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. |                               |
| Subject analysis set title  | ENG-E2 75/300 mcg             |
| Subject analysis set type   | Intention-to-treat            |
| Subject analysis set description:<br>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.    |                               |
| Subject analysis set title  | ENG-E2 100/300 mcg            |
| Subject analysis set type   | Intention-to-treat            |

Subject analysis set 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.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | ENG-E2 125/300 mcg |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set 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.

|                            |                               |
|----------------------------|-------------------------------|
| Subject analysis set title | NuvaRing® (ENG-EE 120/15 mcg) |
| Subject analysis set type  | Intention-to-treat            |

Subject analysis set description:

Participants received NuvaRing® (ENG-EE 120/15 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.

### Primary: Percentage of Participants with Ovulation Incidence, by Cycle

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with Ovulation Incidence, by Cycle <sup>[1]</sup> |
|-----------------|--|

End point description:

Ovulation was defined as having 2 or more consecutive progesterone concentrations >16 nmol/L within 5 days, confirmed by ultrasound evidence of ovulation (follicular rupture or preceding presence of a follicle-like structure >15 mm in size). The analysis population included all participants in whom vaginal rings were inserted and received ultrasound and hormonal assessments, excluding participants who were protocol violators in terms of ring use, daily diary entry or prohibited medications.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 of Treatment Cycle 1 through Day 28 of Treatment Cycle 3 (Up to ~92 days)

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 between-group statistical analysis was performed for this end point.

| End point values   | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|--|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type   | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed                                  | 65                      | 73                      | 57                      | 60                   |
| Units: Percentage of Participants<br>number (not applicable) |                         |                         |                         |                      |
| Cycle 1  | 0                       | 0                       | 0                       | 0                    |
| Cycle 2  | 0                       | 0                       | 0                       | 0                    |
| Cycle 3  | 0                       | 0                       | 0                       | 0                    |

| End point values   | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|--|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type   | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| Number of subjects analysed                                  | 63                    | 65                    | 126                                 |  |
| Units: Percentage of Participants<br>number (not applicable) |                       |                       |                                     |  |
| Cycle 1  | 0                     | 0                     | 0                                   |  |
| Cycle 2  | 0                     | 0                     | 0                                   |  |
| Cycle 3  | 0                     | 0                     | 0                                   |  |

## Statistical analyses

No statistical analyses for this end point

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

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with Progesterone Concentrations >16 nmol/L, by Cycle <sup>[2]</sup> |
|-----------------|---|

End point description:

Maximum progesterone (Max P) was defined as the maximum progesterone value. Ovulation was defined as 2 or more consecutive progesterone concentrations >16 nmol/L within 5 days during the 3 treatment cycles, supported by ultrasound evidence of ovulation. The Max P values greater than 16 nmol/L are presented by vaginal ring group and cycle. The analysis population included all participants in whom vaginal rings were inserted and received hormonal assessment for progesterone concentration, excluding participants who were protocol violators in terms of ring use, daily diary entry or prohibited medications.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 of Treatment Cycle 1 through Day 28 of Treatment Cycle 3 (Up to ~92 days)

Notes:

[2] - 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 between-group statistical analysis was performed for this end point.

| End point values                                     | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|--|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type                                   | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed                          | 65 <sup>[3]</sup>       | 73 <sup>[4]</sup>       | 57 <sup>[5]</sup>       | 60 <sup>[6]</sup>    |
| Units: Percentage of Participants                    |                         |                         |                         |                      |
| number (not applicable)                              |                         |                         |                         |                      |
| Cycle 1 Max P >16 nmol/L<br>(N=18,19,19,20,19,19,21) | 0                       | 0                       | 0                       | 0                    |
| Cycle 2 Max P >16 nmol/L<br>(N=17,16,16,20,19,17,19) | 0                       | 0                       | 0                       | 0                    |
| Cycle 3 Max P >16 nmol/L<br>(N=17,15,14,17,19,17,19) | 0                       | 0                       | 0                       | 0                    |

Notes:

[3] - The denominator N used for this outcome measure varied by cycle and is provided in column 1.

[4] - The denominator N used for this outcome measure varied by cycle and is provided in column 1.

[5] - The denominator N used for this outcome measure varied by cycle and is provided in column 1.

[6] - The denominator N used for this outcome measure varied by cycle and is provided in column 1.

| End point values                  | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |
|-----------------------------------|-----------------------|-----------------------|-------------------------------------|
| Subject group type                | Subject analysis set  | Subject analysis set  | Subject analysis set                |
| Number of subjects analysed       | 63 <sup>[7]</sup>     | 65 <sup>[8]</sup>     | 126 <sup>[9]</sup>                  |
| Units: Percentage of Participants |                       |                       |                                     |
| number (not applicable)           |                       |                       |                                     |

|  |   |   |   |  |
|--|---|---|---|--|
| Cycle 1 Max P >16 nmol/L<br>(N=18,19,19,20,19,19,21) | 0 | 0 | 0 |  |
| Cycle 2 Max P >16 nmol/L<br>(N=17,16,16,20,19,17,19) | 0 | 0 | 0 |  |
| Cycle 3 Max P >16 nmol/L<br>(N=17,15,14,17,19,17,19) | 0 | 0 | 0 |  |

Notes:

[7] - The denominator N used for this outcome measure varied by cycle and is provided in column 1.

[8] - The denominator N used for this outcome measure varied by cycle and is provided in column 1.

[9] - The denominator N used for this outcome measure varied by cycle and is provided in column 1.

## Statistical analyses

No statistical analyses for this end point

## Primary: Percentage of Participants With Breakthrough Bleeding and/or Spotting During Cycle 3

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With Breakthrough Bleeding and/or Spotting During Cycle 3 |
|-----------------|--|

End point description:

Breakthrough bleeding and/or spotting (BTB-S) is defined as any bleeding or spotting episode that occurred during the expected non-bleeding period that was neither an early nor a continued withdrawal bleeding. 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. The analysis population included all participants in whom vaginal rings were inserted and had an evaluable cycle with non-missing bleeding data in the respective cycle, excluding participants who were protocol violators in terms of ring use, daily diary entry or prohibited medications.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 1 Cycle 3 through Day 28 Cycle 3 (Up to ~28 days)

| End point values                  | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|-----------------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type                | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed       | 48 <sup>[10]</sup>      | 45 <sup>[11]</sup>      | 40 <sup>[12]</sup>      | 44 <sup>[13]</sup>   |
| Units: Percentage of Participants |                         |                         |                         |                      |
| number (not applicable)           | 14.6                    | 13.3                    | 17.5                    | 13.6                 |

Notes:

[10] - % of participants with breakthrough bleeding and/or spotting during Cycle 3.

[11] - % of participants with breakthrough bleeding and/or spotting during Cycle 3.

[12] - % of participants with breakthrough bleeding and/or spotting during Cycle 3.

[13] - % of participants with breakthrough bleeding and/or spotting during Cycle 3.

| End point values                  | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|-----------------------------------|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type                | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| Number of subjects analysed       | 49 <sup>[14]</sup>    | 47 <sup>[15]</sup>    | 97 <sup>[16]</sup>                  |  |
| Units: Percentage of Participants |                       |                       |                                     |  |
| number (not applicable)           | 16.3                  | 6.4                   | 6.2                                 |  |

Notes:

[14] - % of participants with breakthrough bleeding and/or spotting during Cycle 3.

[15] - % of participants with breakthrough bleeding and/or spotting during Cycle 3.

[16] - % of participants with breakthrough bleeding and/or spotting during Cycle 3.

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[17]</sup>                      |
| Parameter estimate                      | Difference in Percent                                |
| Point estimate                          | 8.3  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -4.3   |
| upper limit                             | 26.5   |

Notes:

[17] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[18]</sup>                      |
| Parameter estimate                      | Difference in Percent                                |
| Point estimate                          | 6.5  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -5.7   |
| upper limit                             | 24.8   |

Notes:

[18] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[19]</sup>                      |
| Parameter estimate                      | Difference in Percent                                |
| Point estimate                          | 12.3   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -1.7    |
| upper limit         | 33.1    |

Notes:

[19] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[20]</sup>                   |
| Parameter estimate                      | Difference in Percent                             |
| Point estimate                          | 6.6   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -5.7  |
| upper limit                             | 25.4  |

Notes:

[20] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[21]</sup>                    |
| Parameter estimate                      | Difference in Percent                              |
| Point estimate                          | 9.3  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -3.5   |
| upper limit                             | 27.4   |

Notes:

[21] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[22]</sup> |
| Parameter estimate                      | Difference in Percent           |
| Point estimate                          | 0                               |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -10.7                           |
| upper limit                             | 15.9                            |

Notes:

[22] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnnett).

### 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 (i.e., when the ring has been removed the last week of the cycle). Absence of withdrawal bleeding is no withdrawal bleeding and/or spotting episodes during an expected bleeding period when the ring has been removed. The analysis population included all participants in whom vaginal rings were inserted and had an evaluable cycle with non-missing bleeding data in the respective cycle, excluding participants who were protocol violators in terms of ring use, daily diary entry or prohibited medications.

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

End point timeframe:

Day 1 Cycle 2 through Day 28 Cycle 2 (Up to ~28 days)

| End point values                  | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|-----------------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type                | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed       | 55 <sup>[23]</sup>      | 53 <sup>[24]</sup>      | 45 <sup>[25]</sup>      | 51 <sup>[26]</sup>   |
| Units: Percentage of Participants |                         |                         |                         |                      |
| number (not applicable)           | 5.5                     | 1.9                     | 4.4                     | 7.8                  |

Notes:

[23] - % of participants with absence of withdrawal bleeding and/or spotting during Cycle 2.

[24] - % of participants with absence of withdrawal bleeding and/or spotting during Cycle 2.

[25] - % of participants with absence of withdrawal bleeding and/or spotting during Cycle 2.

[26] - % of participants with absence of withdrawal bleeding and/or spotting during Cycle 2.

| End point values                  | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|-----------------------------------|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type                | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| Number of subjects analysed       | 54 <sup>[27]</sup>    | 52 <sup>[28]</sup>    | 111 <sup>[29]</sup>                 |  |
| Units: Percentage of Participants |                       |                       |                                     |  |
| number (not applicable)           | 3.7                   | 1.9                   | 1.8                                 |  |

Notes:

[27] - % of participants with absence of withdrawal bleeding and/or spotting during Cycle 2.

[28] - % of participants with absence of withdrawal bleeding and/or spotting during Cycle 2.

[29] - % of participants with absence of withdrawal bleeding and/or spotting during Cycle 2.

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[30]</sup>                      |
| 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:

[30] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[31]</sup>                      |
| Parameter estimate                      | Difference in percentage                             |
| Point estimate                          | 0  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -6.2   |
| upper limit                             | 11   |

Notes:

[31] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[32]</sup>                      |
| Parameter estimate                      | Difference in percentage                             |
| Point estimate                          | 3  |

| Confidence interval |         |
|---------------------|---------|
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -3.8    |
| upper limit         | 17.5    |

Notes:

[32] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

| <b>Statistical analysis title</b>       | 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 <sup>[33]</sup>                   |
| 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:

[33] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

| <b>Statistical analysis title</b>       | 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 <sup>[34]</sup>                    |
| Parameter estimate                      | Difference in percentage                           |
| Point estimate                          | 1.4  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -5   |
| upper limit                             | 13.4   |

Notes:

[34] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[35]</sup> |
| Parameter estimate                      | Difference in percentage        |
| Point estimate                          | 0                               |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -6.2                            |
| upper limit                             | 11                              |

Notes:

[35] - Based on a longitudinal data analysis (LDA) model with terms for treatment, cycle and the interaction cycle by treatment and stratum:starter/switcher followed by Miettinen and Nurminen's method. Non-inferiority criterion was met if the upper bound of the 95% CI of the difference is less than or equal to 10%. 95% CI is adjusted for multiplicity (Dunnett).

## 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. Withdrawal bleeding and/or spotting is considered any bleeding or spotting episode that starts during or continues into the expected bleeding period (i.e., when the ring has been removed the last week of the cycle). Absence of withdrawal bleeding is no withdrawal bleeding and/or spotting episodes during an expected bleeding period when the ring has been removed. The analysis population included all participants in whom vaginal rings were inserted and had an evaluable cycle with non-missing bleeding data in the respective cycle, and with at least one withdrawal bleeding or spotting day, excluding participants who were protocol violators in terms of ring use, daily diary entry or prohibited medications.

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

End point timeframe:

Day 1 Cycle 2 through Day 28 Cycle 2 (Up to ~28 days)

| End point values                     | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|--------------------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type                   | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed          | 52 <sup>[36]</sup>      | 52 <sup>[37]</sup>      | 43 <sup>[38]</sup>      | 47 <sup>[39]</sup>   |
| Units: Ratio                         |                         |                         |                         |                      |
| arithmetic mean (standard deviation) | 0.87 (± 0.25)           | 0.92 (± 0.17)           | 0.86 (± 0.19)           | 0.90 (± 0.18)        |

Notes:

[36] - Ratio of withdrawal bleeding days divided by the number of withdrawal bleeding/spotting days.

[37] - Ratio of withdrawal bleeding days divided by the number of withdrawal bleeding/spotting days.

[38] - Ratio of withdrawal bleeding days divided by the number of withdrawal bleeding/spotting days.

[39] - Ratio of withdrawal bleeding days divided by the number of withdrawal bleeding/spotting days.

| End point values                     | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|--------------------------------------|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type                   | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| Number of subjects analysed          | 52 <sup>[40]</sup>    | 51 <sup>[41]</sup>    | 109 <sup>[42]</sup>                 |  |
| Units: Ratio                         |                       |                       |                                     |  |
| arithmetic mean (standard deviation) | 0.92 (± 0.18)         | 0.93 (± 0.14)         | 0.95 (± 0.12)                       |  |

Notes:

[40] - Ratio of withdrawal bleeding days divided by the number of withdrawal bleeding/spotting days.

[41] - Ratio of withdrawal bleeding days divided by the number of withdrawal bleeding/spotting days.

[42] - Ratio of withdrawal bleeding days divided by the number of withdrawal bleeding/spotting days.

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Intensity of Withdrawal Bleeding During Cycle 2      |
| Comparison groups                       | NOMAC-E2 500/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 161  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | other <sup>[43]</sup>                                |
| P-value                                 | = 0.096  |
| Method                                  | LDA  |
| Parameter estimate                      | Diff of Least Squares (LS) Mean: -0.08               |

Notes:

[43] - Based on longitudinal data analysis (LDA) model: generalized linear mixed model with terms for stratum, ring group, cycle (and the interaction of cycle by ring group), and continuous response variable.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Intensity of Withdrawal Bleeding During Cycle 2      |
| Comparison groups                       | NOMAC-E2 700/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 161  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.993  |
| Method                                  | LDA  |
| Parameter estimate                      | Difference of LS Mean: -0.03                         |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Intensity of Withdrawal Bleeding During Cycle 2      |
| Comparison groups                       | NOMAC-E2 900/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 152  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.124  |
| Method                                  | LDA  |
| Parameter estimate                      | Difference of LS Mean: -0.08                         |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Intensity of Withdrawal Bleeding During Cycle 2   |
| Comparison groups                 | ENG-E2 75/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |

|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 156                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           |                              |
| P-value                                 | = 0.845                      |
| Method                                  | LDA                          |
| Parameter estimate                      | Difference of LS Mean: -0.05 |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Intensity of Withdrawal Bleeding During Cycle 2    |
| Comparison groups                       | ENG-E2 100/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 161  |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           |  |
| P-value                                 | = 0.976  |
| Method                                  | LDA  |
| Parameter estimate                      | Difference of LS Mean: -0.04                       |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Intensity of Withdrawal Bleeding During Cycle 2    |
| Comparison groups                       | ENG-E2 125/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 160  |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           |  |
| P-value                                 | = 0.995  |
| Method                                  | LDA  |
| Parameter estimate                      | Difference of LS Mean: -0.03                       |

### **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. Breakthrough bleeding and/or spotting (BTB-S) is defined as any bleeding or spotting episode that occurred during the expected non-bleeding period that was neither an early nor a continued withdrawal bleeding. 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 | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 Cycle 3 through Day 28 Cycle 3 (Up to ~ 28 days)

| <b>End point values</b>              | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|--------------------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type                   | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed          | 7 <sup>[44]</sup>       | 6 <sup>[45]</sup>       | 7 <sup>[46]</sup>       | 6 <sup>[47]</sup>    |
| Units: Ratio                         |                         |                         |                         |                      |
| arithmetic mean (standard deviation) | 0.42 (± 0.45)           | 0.80 (± 0.40)           | 0.68 (± 0.47)           | 0.73 (± 0.16)        |

Notes:

[44] - Ratio of breakthrough bleeding days divided by the number of breakthrough bleeding/spotting days.

[45] - Ratio of breakthrough bleeding days divided by the number of breakthrough bleeding/spotting days.

[46] - Ratio of breakthrough bleeding days divided by the number of breakthrough bleeding/spotting days.

[47] - Ratio of breakthrough bleeding days divided by the number of breakthrough bleeding/spotting days.

| <b>End point values</b>              | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|--------------------------------------|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type                   | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| Number of subjects analysed          | 8 <sup>[48]</sup>     | 3 <sup>[49]</sup>     | 6 <sup>[50]</sup>                   |  |
| Units: Ratio                         |                       |                       |                                     |  |
| arithmetic mean (standard deviation) | 0.67 (± 0.43)         | 0.33 (± 0.58)         | 0.67 (± 0.52)                       |  |

Notes:

[48] - Ratio of breakthrough bleeding days divided by the number of breakthrough bleeding/spotting days.

[49] - Ratio of breakthrough bleeding days divided by the number of breakthrough bleeding/spotting days.

[50] - Ratio of breakthrough bleeding days divided by the number of breakthrough bleeding/spotting days.

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Breakthrough Bleeding/Spotting During Cycle 3        |
| Comparison groups                       | NOMAC-E2 500/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 13   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 1  |
| Method                                  | LDA  |
| Parameter estimate                      | Difference of LS Mean: -0.01                         |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Breakthrough Bleeding/Spotting During Cycle 3        |
| Comparison groups                       | NOMAC-E2 700/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 12   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 0.996  |
| Method                                  | LDA  |
| Parameter estimate                      | Difference of LS Mean: 0.19                          |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Breakthrough Bleeding/Spotting During Cycle 3        |
| Comparison groups                       | NOMAC-E2 900/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 13   |
| Analysis specification                  | Pre-specified  |
| Analysis type                           |  |
| P-value                                 | = 1  |
| Method                                  | LDA  |
| Parameter estimate                      | Difference of LS Mean: -0.06                         |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Breakthrough Bleeding/Spotting During Cycle 3     |
| Comparison groups                       | ENG-E2 75/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 12  |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           |   |
| P-value                                 | = 1   |
| Method                                  | LDA   |
| Parameter estimate                      | Difference of LS Mean: -0.04                      |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Breakthrough Bleeding/Spotting During Cycle 3      |
| Comparison groups                       | ENG-E2 100/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 14   |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           |  |
| P-value                                 | = 1  |
| Method                                  | LDA  |
| Parameter estimate                      | Difference of LS Mean: 0.09                        |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Breakthrough Bleeding/Spotting During Cycle 3      |
| Comparison groups                       | ENG-E2 125/300 mcg v NuvaRing® (ENG-EE 120/15 mcg) |
| Number of subjects included in analysis | 9  |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           |  |
| P-value                                 | = 0.998  |
| Method                                  | LDA  |
| Parameter estimate                      | Difference of LS Mean: -0.24                       |

### **Secondary: Percentage of Participants Who Experienced At Least One Adverse Event**

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Who Experienced At Least One Adverse Event |
|-----------------|---|

End point description:

An adverse event (AE) is defined as any unfavorable and unintended sign (including an abnormal

laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not it is considered related to the study drug. The analysis population included all randomized participants in whom a vaginal ring was inserted.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to ~92 days       |           |

| <b>End point values</b>           | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|-----------------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type                | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed       | 79                      | 85                      | 78                      | 77                   |
| Units: Percentage of Participants |                         |                         |                         |                      |
| number (not applicable)           | 43.0                    | 40.0                    | 43.6                    | 37.7                 |

| <b>End point values</b>           | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|-----------------------------------|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type                | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| Number of subjects analysed       | 77                    | 86                    | 178                                 |  |
| Units: Percentage of Participants |                       |                       |                                     |  |
| number (not applicable)           | 39.0                  | 46.5                  | 39.3                                |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants Who Experienced At Least One Serious Adverse Event

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants Who Experienced At Least One Serious Adverse Event |
|-----------------|---|

End point description:

A serious adverse event (SAE) is an AE that results in death, is life threatening, requires or prolongs an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is a cancer, is associated with an overdose; or is another important medical event deemed such by medical or scientific judgment. The analysis population included all randomized participants in whom a vaginal ring was inserted.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to ~92 days       |           |

| <b>End point values</b>           | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|-----------------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type                | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed       | 79                      | 85                      | 78                      | 77                   |
| Units: Percentage of Participants |                         |                         |                         |                      |
| number (not applicable)           | 0.0                     | 0.0                     | 0.0                     | 0.0                  |

| <b>End point values</b>           | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|-----------------------------------|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type                | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| Number of subjects analysed       | 77                    | 86                    | 178                                 |  |
| Units: Percentage of Participants |                       |                       |                                     |  |
| number (not applicable)           | 0.0                   | 0.0                   | 0.0                                 |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Who Experienced At Least One Drug-Related Adverse Event

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants Who Experienced At Least One Drug-Related Adverse Event |
|-----------------|--|

End point description:

An adverse event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not it is considered related to the study drug. A drug-related AE was defined as any AE for which there is reasonable possibility of drug relationship as assessed by the Investigator. The analysis population included all randomized participants in whom a vaginal ring was inserted.

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

End point timeframe:

Up to ~92 days

| <b>End point values</b>           | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|-----------------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type                | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed       | 79                      | 85                      | 78                      | 77                   |
| Units: Percentage of Participants |                         |                         |                         |                      |
| number (not applicable)           | 26.6                    | 23.5                    | 26.9                    | 29.9                 |

| <b>End point values</b>     | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|-----------------------------|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type          | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| Number of subjects analysed | 77                    | 86                    | 178                                 |  |

|                                   |      |      |      |  |
|-----------------------------------|------|------|------|--|
| Units: Percentage of Participants |      |      |      |  |
| number (not applicable)           | 26.0 | 31.4 | 20.8 |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants With Any Drug-Related Serious Adverse Event

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With Any Drug-Related Serious Adverse Event |
|-----------------|--|

End point description:

A serious adverse event (SAE) is an AE that results in death, is life threatening, requires or prolongs an existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is a cancer, is associated with an overdose; or is another important medical event deemed such by medical or scientific judgment. A drug-related SAE was defined as any SAE for which there is reasonable possibility of drug relationship as assessed by the Investigator. The analysis population included all randomized participants in whom a vaginal ring was inserted.

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

End point timeframe:

Up to ~92 days

| End point values                  | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|-----------------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type                | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed       | 79                      | 85                      | 78                      | 77                   |
| Units: Percentage of Participants |                         |                         |                         |                      |
| number (not applicable)           | 0.0                     | 0.0                     | 0.0                     | 0.0                  |

| End point values                  | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|-----------------------------------|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type                | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| Number of subjects analysed       | 77                    | 86                    | 178                                 |  |
| Units: Percentage of Participants |                       |                       |                                     |  |
| number (not applicable)           | 0.0                   | 0.0                   | 0.0                                 |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Participants Who Discontinued Study Drug Due to an Adverse Event

|                        |  |
|------------------------|--|
| End point title        | Percentage of Participants Who Discontinued Study Drug Due to an Adverse Event   |
| End point description: | An adverse event (AE) is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not it is considered related to the study drug. The analysis population included all randomized participants in whom a vaginal ring was inserted. |
| End point type         | Secondary  |
| End point timeframe:   | Up to ~92 days   |

| End point values                  | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|-----------------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type                | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed       | 79                      | 85                      | 78                      | 77                   |
| Units: Percentage of Participants |                         |                         |                         |                      |
| number (not applicable)           | 3.8                     | 4.7                     | 2.6                     | 2.6                  |

| End point values                  | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|-----------------------------------|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type                | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| Number of subjects analysed       | 77                    | 86                    | 178                                 |  |
| Units: Percentage of Participants |                       |                       |                                     |  |
| number (not applicable)           | 0.0                   | 1.2                   | 1.1                                 |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: 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: | Venous or arterial thrombotic/thrombo-embolic events, (VTEs or ATEs) (e.g., deep venous thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident) were assessed. The analysis population included all randomized participants in whom a vaginal ring was inserted. |
| End point type         | Other pre-specified   |
| End point timeframe:   | From Cycle 1 Day 1 up to 8 days after Day 28 of Cycle 3 (Up to ~92 days)  |

| <b>End point values</b>     | NOMAC-E2<br>500/300 mcg | NOMAC-E2<br>700/300 mcg | NOMAC-E2<br>900/300 mcg | ENG-E2 75/300<br>mcg |
|-----------------------------|-------------------------|-------------------------|-------------------------|----------------------|
| Subject group type          | Subject analysis set    | Subject analysis set    | Subject analysis set    | Subject analysis set |
| Number of subjects analysed | 79                      | 85                      | 78                      | 77                   |
| Units: Participants         | 0                       | 0                       | 0                       | 0                    |

| <b>End point values</b>     | ENG-E2<br>100/300 mcg | ENG-E2<br>125/300 mcg | NuvaRing®<br>(ENG-EE<br>120/15 mcg) |  |
|-----------------------------|-----------------------|-----------------------|-------------------------------------|--|
| Subject group type          | Subject analysis set  | Subject analysis set  | Subject analysis set                |  |
| 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 analysis population consisted of all randomized participants in whom a vaginal ring was inserted..

|                 |            |
|-----------------|------------|
| 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.

| <b>Serious adverse events</b>                     | 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    |                      |                      |                      |

| <b>Serious adverse events</b>                     | 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    |                   |                    |                    |

| <b>Serious adverse events</b>                     | 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 %

| <b>Non-serious adverse events</b>                     | 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<br>subjects affected / exposed<br>occurrences (all)   | 1 / 79 (1.27%)<br>1   | 6 / 85 (7.06%)<br>9 | 4 / 78 (5.13%)<br>5    |
| Respiratory, thoracic and mediastinal disorders<br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 4 / 79 (5.06%)<br>5   | 1 / 85 (1.18%)<br>2 | 2 / 78 (2.56%)<br>2    |
| Skin and subcutaneous tissue disorders<br>Acne<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 79 (2.53%)<br>2   | 3 / 85 (3.53%)<br>4 | 6 / 78 (7.69%)<br>8    |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all)          | 4 / 79 (5.06%)<br>4   | 0 / 85 (0.00%)<br>0 | 1 / 78 (1.28%)<br>1    |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                        | 9 / 79 (11.39%)<br>12 | 5 / 85 (5.88%)<br>5 | 11 / 78 (14.10%)<br>13 |

| <b>Non-serious adverse events</b>   | ENG-E2 75/300 mcg      | ENG-E2 100/300 mcg     | ENG-E2 125/300 mcg     |
|---|------------------------|------------------------|------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed        | 24 / 77 (31.17%)       | 22 / 77 (28.57%)       | 25 / 86 (29.07%)       |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 0 / 77 (0.00%)<br>0    | 0 / 77 (0.00%)<br>0    | 0 / 86 (0.00%)<br>0    |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                | 13 / 77 (16.88%)<br>35 | 15 / 77 (19.48%)<br>29 | 13 / 86 (15.12%)<br>35 |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | 6 / 77 (7.79%)<br>9    | 1 / 77 (1.30%)<br>1    | 3 / 86 (3.49%)<br>3    |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                  | 4 / 77 (5.19%)<br>4    | 1 / 77 (1.30%)<br>1    | 1 / 86 (1.16%)<br>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              |

|   |                                  |  |  |
|---|----------------------------------|--|--|
| <b>Non-serious adverse events</b>                     | NuvaRing® (ENG-EE<br>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                           | 24 / 178 (13.48%)                |  |  |
| occurrences (all)                                     | 47                               |  |  |
| Gastrointestinal disorders                            |                                  |  |  |
| Diarrhoea   |                                  |  |  |

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date        | Amendment  |
|-------------|--|
| 26 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 $\geq 15$ 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported