



## Clinical trial results:

### A Multicenter, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2015-003150-40       |
| Trial protocol           | CZ HU SE FI PL DE BE |
| Global end of trial date | 17 October 2018      |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 11 May 2019  |
| First version publication date | 11 May 2019  |

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | MIT-Es0001-C301 |
|-----------------------|-----------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |                                                                                                                  |
|------------------------------|------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Mithra Pharmaceuticals                                                                                           |
| Sponsor organisation address | Rue Saint Georges 5-7, Liège, Belgium, 4000                                                                      |
| Public contact               | Mithra Pharmaceuticals SA Pharma Department, Mithra Pharmaceuticals SA, +32 43492822, clinical.trials@mithra.com |
| Scientific contact           | Mithra Pharmaceuticals SA Pharma Department, Mithra Pharmaceuticals SA, +32 43492822, clinical.trials@mithra.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                       | 26 April 2018   |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 26 April 2018   |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 17 October 2018 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the contraceptive efficacy of 15 mg estetrol (E4)/ 3 mg drospirenone (DRSP) using the Pearl Index in participants aged 18 to 35 years.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki in place at the time of study conduct. The study was conducted in compliance with the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) (Committee for Proprietary Medicinal Products [CPMP] guideline CPMP/ICH/135/95), and compliant with the European Union Clinical Trial Directive (EU CTD): Directive 2001/20/EC.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 28 June 2016 |
| 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 | Finland: 181            |
| Country: Number of subjects enrolled | Czech Republic: 335     |
| Country: Number of subjects enrolled | Germany: 141            |
| Country: Number of subjects enrolled | Hungary: 190            |
| Country: Number of subjects enrolled | Norway: 108             |
| Country: Number of subjects enrolled | Poland: 221             |
| Country: Number of subjects enrolled | Russian Federation: 280 |
| Country: Number of subjects enrolled | Belgium: 87             |
| Country: Number of subjects enrolled | Sweden: 10              |
| Worldwide total number of subjects   | 1553                    |
| EEA total number of subjects         | 1273                    |

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)                     | 1553 |
| From 65 to 84 years                      | 0    |
| 85 years and over                        | 0    |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 1,744 participants aged 18-50 years were screened. Of these, 1,577 participants were enrolled in the study: 1,373 participants aged 18 to 35 years and 204 participants aged > 35 years. Of the 1577 enrolled participants, 1553 participants were treated in the study (1,353 participants aged 18-35 years and 200 participants aged > 35 years)

### Period 1

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

### Arms

|                  |                                                          |
|------------------|----------------------------------------------------------|
| <b>Arm title</b> | 15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age) |
|------------------|----------------------------------------------------------|

Arm description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population.

|                                        |                                   |
|----------------------------------------|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | 15 mg estetrol/ 3 mg drospirenone |
| Investigational medicinal product code | E4/ DRSP                          |
| Other name                             |                                   |
| Pharmaceutical forms                   | Tablet                            |
| Routes of administration               | Oral use                          |

Dosage and administration details:

15 mg estetrol/ 3 mg drospirenone was administered once daily for 24 consecutive days followed by placebo once daily for 4 consecutive days.

|                                       |                                                          |
|---------------------------------------|----------------------------------------------------------|
| <b>Number of subjects in period 1</b> | 15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age) |
| Started                               | 1553                                                     |
| Completed                             | 1218                                                     |
| Not completed                         | 335                                                      |
| Consent withdrawn by subject          | 78                                                       |
| Adverse event not related to bleeding | 104                                                      |
| Pregnancy                             | 7                                                        |
| Adverse event related to bleeding     | 53                                                       |
| Unspecified                           | 26                                                       |
| Lost to follow-up                     | 41                                                       |
| Pregnancy wish                        | 15                                                       |
| Protocol deviation                    | 11                                                       |



## Baseline characteristics

### Reporting groups

|                       |                                                          |
|-----------------------|----------------------------------------------------------|
| Reporting group title | 15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age) |
|-----------------------|----------------------------------------------------------|

Reporting group description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population.

| Reporting group values | 15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age) | Total |  |
|------------------------|----------------------------------------------------------|-------|--|
| Number of subjects     | 1553                                                     | 1553  |  |
| Age categorical        |                                                          |       |  |
| Units: Subjects        |                                                          |       |  |

|                    |        |      |  |
|--------------------|--------|------|--|
| Age continuous     |        |      |  |
| Units: years       |        |      |  |
| arithmetic mean    | 27.1   |      |  |
| standard deviation | ± 6.86 | -    |  |
| Gender categorical |        |      |  |
| Units: Subjects    |        |      |  |
| Female             | 1553   | 1553 |  |

|      |  |  |  |
|------|--|--|--|
| Race |  |  |  |
|------|--|--|--|

Participants who did not receive the investigational product have been disclosed as not reported

|                           |      |      |  |
|---------------------------|------|------|--|
| Units: Subjects           |      |      |  |
| White                     | 1532 | 1532 |  |
| Black or African American | 8    | 8    |  |
| Asian                     | 10   | 10   |  |
| Other                     | 3    | 3    |  |

|           |  |  |  |
|-----------|--|--|--|
| Ethnicity |  |  |  |
|-----------|--|--|--|

Participants who did not receive the investigational product have been disclosed as not reported

|                        |      |      |  |
|------------------------|------|------|--|
| Units: Subjects        |      |      |  |
| Hispanic or Latino     | 13   | 13   |  |
| Not Hispanic or Latino | 1540 | 1540 |  |

|                    |         |   |  |
|--------------------|---------|---|--|
| Weight             |         |   |  |
| Units: kilogram(s) |         |   |  |
| arithmetic mean    | 63.83   |   |  |
| standard deviation | ± 10.53 | - |  |

|                    |         |   |  |
|--------------------|---------|---|--|
| Height             |         |   |  |
| Units: cm          |         |   |  |
| arithmetic mean    | 166.53  |   |  |
| standard deviation | ± 6.234 | - |  |

|                          |         |   |  |
|--------------------------|---------|---|--|
| BMI                      |         |   |  |
| Units: kg/m <sup>2</sup> |         |   |  |
| arithmetic mean          | 23      |   |  |
| standard deviation       | ± 3.469 | - |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                  |                                                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                            | 15 mg estetrol/ 3 mg drospirenone (18 - 50 years of age) |
| Reporting group description:<br>All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population.                                                                      |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                       | 15 mg estetrol/ 3 mg drospirenone (18 - 35 years of age) |
| Subject analysis set type                                                                                                                                                                                                                                        | Sub-group analysis                                       |
| Subject analysis set description:<br>All participants between 18 and 35 years of age, inclusive, at the time of screening in the 15 mg estetrol/ 3 mg drospirenone intention-to-treat population.                                                                |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                       | Endometrial biopsy baseline results                      |
| Subject analysis set type                                                                                                                                                                                                                                        | Sub-group analysis                                       |
| Subject analysis set description:<br>All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/ 3 mg drospirenone intention-to-treat population with an endometrial biopsy at the screening visit and visit 7a. |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                       | Endometrial biopsy visit 7a results                      |
| Subject analysis set type                                                                                                                                                                                                                                        | Sub-group analysis                                       |
| Subject analysis set description:<br>All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/ 3 mg drospirenone intention-to-treat population with an endometrial biopsy at the screening visit and visit 7a. |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                       | Unscheduled bleeding analysis                            |
| Subject analysis set type                                                                                                                                                                                                                                        | Intention-to-treat                                       |
| Subject analysis set description:<br>All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/ 3 mg drospirenone intention-to-treat population with at least 1 evaluable cycle for the bleeding analysis.      |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                       | Unscheduled spotting analysis                            |
| Subject analysis set type                                                                                                                                                                                                                                        | Intention-to-treat                                       |
| Subject analysis set description:<br>All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/ 3 mg drospirenone intention-to-treat population with at least 1 evaluable cycle for the bleeding analysis.      |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                       | Q-LES-Q-SF baseline results                              |
| Subject analysis set type                                                                                                                                                                                                                                        | Intention-to-treat                                       |
| Subject analysis set description:<br>All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with baseline Q-LES-Q-SF results.                                |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                       | Q-LES-Q-SF end of treatment results                      |
| Subject analysis set type                                                                                                                                                                                                                                        | Intention-to-treat                                       |
| Subject analysis set description:<br>All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with end of treatment Q-LES-Q-SF results.                        |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                       | MDQ baseline results                                     |
| Subject analysis set type                                                                                                                                                                                                                                        | Intention-to-treat                                       |
| Subject analysis set description:<br>All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with baseline MDQ results.                                       |                                                          |
| Subject analysis set title                                                                                                                                                                                                                                       | MDQ end of treatment results                             |
| Subject analysis set type                                                                                                                                                                                                                                        | Intention-to-treat                                       |

Subject analysis set description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with end of treatment MDQ results.

|                            |                                       |
|----------------------------|---------------------------------------|
| Subject analysis set title | Physical examination baseline results |
| Subject analysis set type  | Intention-to-treat                    |

Subject analysis set description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with baseline physical examination results.

|                            |                                               |
|----------------------------|-----------------------------------------------|
| Subject analysis set title | Physical examination end of treatment results |
| Subject analysis set type  | Intention-to-treat                            |

Subject analysis set description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with end of treatment physical examination results.

|                            |                                            |
|----------------------------|--------------------------------------------|
| Subject analysis set title | Gynecological examination baseline results |
| Subject analysis set type  | Intention-to-treat                         |

Subject analysis set description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with baseline gynecological examination results.

|                            |                                                    |
|----------------------------|----------------------------------------------------|
| Subject analysis set title | Gynecological examination end of treatment results |
| Subject analysis set type  | Intention-to-treat                                 |

Subject analysis set description:

All participants between 18 and 50 years of age, inclusive, at the time of screening in the 15 mg estetrol/3 mg drospirenone intention-to-treat population with end of treatment gynecological examination results.

### **Primary: Primary Pearl Index of participants between 18 and 35 years of age**

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Primary Pearl Index of participants between 18 and 35 years of age <sup>[1]</sup> |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment was calculated as: Pearl Index = (1300\*number of on-treatment pregnancies)/number of women 28-day equivalent cycles of treatment. Only at-risk cycles were included in the denominator of the Pearl Index calculation.

At-risk-cycles were defined as cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary and during which the subject confirmed that sexual intercourse had occurred.

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

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

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 additional statistical analysis was planned for this endpoint.

|                                  |                                                                      |  |  |  |
|----------------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 35 years<br>of age) |  |  |  |
| Subject group type               | Subject analysis set                                                 |  |  |  |
| Number of subjects analysed      | 1313 <sup>[2]</sup>                                                  |  |  |  |
| Units: Pearl Index               |                                                                      |  |  |  |
| number (confidence interval 95%) | 0.47 (0.15 to<br>1.11)                                               |  |  |  |

Notes:

[2] - Participants aged 18 to 35 years, inclusive, at screening with at least 1 at-risk cycle

## Statistical analyses

No statistical analyses for this end point

### Secondary: Modified Pearl Index of participants between 18 and 35 years of age

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Modified Pearl Index of participants between 18 and 35 years of age |
|-----------------|---------------------------------------------------------------------|

End point description:

The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment was calculated as: Pearl Index = (1300\*number of on-treatment pregnancies)/number of women 28-day equivalent cycles of treatment. Only modified at-risk cycles were included in the denominator of the Pearl Index calculation. Modified at-risk cycles were cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary, regardless of whether or not the subject reported intercourse during the cycle.

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

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

|                                  |                                                                      |  |  |  |
|----------------------------------|----------------------------------------------------------------------|--|--|--|
| End point values                 | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 35 years<br>of age) |  |  |  |
| Subject group type               | Subject analysis set                                                 |  |  |  |
| Number of subjects analysed      | 1343 <sup>[3]</sup>                                                  |  |  |  |
| Units: Pearl Index               |                                                                      |  |  |  |
| number (confidence interval 95%) | 0.44 (0.14 to<br>1.03)                                               |  |  |  |

Notes:

[3] - Participants aged 18 to 35 years, inclusive, at screening with at least 1 modified at-risk cycle

## Statistical analyses

No statistical analyses for this end point

### Secondary: Primary method failure Pearl Index of participants between 18 and 35 years of age

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Primary method failure Pearl Index of participants between 18 and 35 years of age |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

The method failure Pearl Index (also referred to as "perfect-use" Pearl Index) was calculated using the same method as the Pearl Index, but included only those pregnancies that were classified as method failure and not the pregnancies due to user failure, i.e incorrect intake of the contraceptive method. Only at-risk cycles were included in the denominator of the Pearl Index calculation.

At-risk-cycles were defined as cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary and during which the subject confirmed that sexual intercourse had occurred.

|                                      |           |
|--------------------------------------|-----------|
| End point type                       | Secondary |
| End point timeframe:                 |           |
| Day 1 to End of Cycle 13 (12 months) |           |

|                                   |                                                                      |  |  |  |
|-----------------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 35 years<br>of age) |  |  |  |
| Subject group type                | Subject analysis set                                                 |  |  |  |
| Number of subjects analysed       | 1313 <sup>[4]</sup>                                                  |  |  |  |
| Units: Method failure Pearl Index |                                                                      |  |  |  |
| number (confidence interval 95%)  | 0.29 (0.06 to<br>0.83)                                               |  |  |  |

Notes:

[4] - Participants aged 18 to 35 years, inclusive, at screening with at least 1 at-risk cycle

## Statistical analyses

No statistical analyses for this end point

## Secondary: Modified method failure Pearl Index of participants between 18 and 35 years of age

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Modified method failure Pearl Index of participants between 18 and 35 years of age |
|-----------------|------------------------------------------------------------------------------------|

End point description:

The method failure Pearl Index (also referred to as "perfect use" Pearl Index) was calculated using the same method as the Pearl Index, but included only those pregnancies that were classified as method failure and not the pregnancies due to user failure, i.e incorrect intake of the contraceptive method. Only modified at-risk cycles were included in the denominator of the method failure Pearl Index calculation. Modified at-risk cycles were cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary, regardless of whether or not the subject reported intercourse during the cycle.

|                                      |           |
|--------------------------------------|-----------|
| End point type                       | Secondary |
| End point timeframe:                 |           |
| Day 1 to End of Cycle 13 (12 months) |           |

|                                   |                                                                      |  |  |  |
|-----------------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 35 years<br>of age) |  |  |  |
| Subject group type                | Subject analysis set                                                 |  |  |  |
| Number of subjects analysed       | 1343 <sup>[5]</sup>                                                  |  |  |  |
| Units: Method failure Pearl Index |                                                                      |  |  |  |
| number (confidence interval 95%)  | 0.26 (0.05 to<br>0.77)                                               |  |  |  |

Notes:

[5] - Participants aged 18 to 35 years, inclusive, at screening with at least 1 modified at-risk cycle

## Statistical analyses

No statistical analyses for this end point

### Secondary: Cumulative on-treatment pregnancy rate of participants between 18 and 35 years of age

|                                                                                                       |                                                                                       |
|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| End point title                                                                                       | Cumulative on-treatment pregnancy rate of participants between 18 and 35 years of age |
| End point description:<br>Cumulative pregnancy rate was calculated per year using life-table methods. |                                                                                       |
| End point type                                                                                        | Secondary                                                                             |
| End point timeframe:<br>Day 1 to End of Cycle 13 (12 months)                                          |                                                                                       |

|                                  |                                                                      |  |  |  |
|----------------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 35 years<br>of age) |  |  |  |
| Subject group type               | Subject analysis set                                                 |  |  |  |
| Number of subjects analysed      | 1353 <sup>[6]</sup>                                                  |  |  |  |
| Units: Percent                   |                                                                      |  |  |  |
| number (confidence interval 95%) | 0.45 (0.19 to<br>1.09)                                               |  |  |  |

Notes:

[6] - Participants aged 18 to 35 years, inclusive, at screening, who received at least one dose of IP

## Statistical analyses

No statistical analyses for this end point

### Secondary: Modified Pearl Index of participants between 18 and 50 years of age

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Modified Pearl Index of participants between 18 and 50 years of age |
| End point description:<br>The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment was calculated as: Pearl Index = (1300*number of on-treatment pregnancies)/number of women 28-day equivalent cycles of treatment. Only modified at-risk cycles were included in the denominator of the Pearl Index calculation. Modified at-risk cycles were cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary, regardless of whether or not the subject reported intercourse during the cycle. |                                                                     |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Secondary                                                           |
| End point timeframe:<br>Day 1 to End of Cycle 13 (12 months)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                     |

|                                  |                                                                      |  |  |  |
|----------------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
| Subject group type               | Reporting group                                                      |  |  |  |
| Number of subjects analysed      | 1542 <sup>[7]</sup>                                                  |  |  |  |
| Units: Pearl Index               |                                                                      |  |  |  |
| number (confidence interval 95%) | 0.38 (0.12 to<br>0.89)                                               |  |  |  |

Notes:

[7] - Participants aged 18 to 50 years, inclusive, at screening with at least 1 modified at-risk cycle

## Statistical analyses

No statistical analyses for this end point

### Secondary: Primary method failure Pearl Index of participants between 18 and 50 years of age

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Primary method failure Pearl Index of participants between 18 and 50 years of age |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

The method failure Pearl Index (also referred to as "perfect-use" Pearl Index) was calculated using the same method as the Pearl Index, but included only those pregnancies that were classified as method failure and not the pregnancies due to user failure, i.e incorrect intake of the contraceptive method. Only at-risk cycles were included in the denominator of the Pearl Index calculation.

At-risk-cycles were defined as cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary and during which the subject confirmed that sexual intercourse had occurred.

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

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

|                                   |                                                                      |  |  |  |
|-----------------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
| Subject group type                | Reporting group                                                      |  |  |  |
| Number of subjects analysed       | 1510 <sup>[8]</sup>                                                  |  |  |  |
| Units: Method failure Pearl Index |                                                                      |  |  |  |
| number (confidence interval 95%)  | 0.25 (0.05 to<br>0.72)                                               |  |  |  |

Notes:

[8] - Participants aged 18 to 50 years, inclusive, at screening with at least one at-risk cycle

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Primary Pearl Index of participants between 18 and 50 years of age**

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|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Primary Pearl Index of participants between 18 and 50 years of age |
|-----------------|--------------------------------------------------------------------|

End point description:

The Pearl Index, defined as the number of pregnancies per 100 women-years of treatment was calculated as: Pearl Index = (1300\*number of on-treatment pregnancies)/number of women 28-day equivalent cycles of treatment. Only at-risk cycles were included in the denominator of the Pearl Index calculation.

At-risk-cycles were defined as cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary and during which the subject confirmed that sexual intercourse had occurred.

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

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

---

|                                  |                                                                      |  |  |  |
|----------------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
| Subject group type               | Reporting group                                                      |  |  |  |
| Number of subjects analysed      | 1510 <sup>[9]</sup>                                                  |  |  |  |
| Units: Pearl Index               |                                                                      |  |  |  |
| number (confidence interval 95%) | 0.41 (0.13 to<br>0.96)                                               |  |  |  |

Notes:

[9] - Participants aged 18 to 50 years, inclusive, at screening with at least one at-risk cycle

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Cumulative on-treatment pregnancy rate of participants between 18 and 50 years of age**

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|                 |                                                                                       |
|-----------------|---------------------------------------------------------------------------------------|
| End point title | Cumulative on-treatment pregnancy rate of participants between 18 and 50 years of age |
|-----------------|---------------------------------------------------------------------------------------|

End point description:

Cumulative pregnancy rate was calculated per year using life-table methods.

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

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

---

|                                  |                                                                      |  |  |  |
|----------------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>          | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
| Subject group type               | Reporting group                                                      |  |  |  |
| Number of subjects analysed      | 1553 <sup>[10]</sup>                                                 |  |  |  |
| Units: Percent                   |                                                                      |  |  |  |
| number (confidence interval 95%) | 0.39 (0.16 to<br>0.94)                                               |  |  |  |

Notes:

[10] - Participants aged 18 to 50 years, inclusive, at screening, who received at least one dose of IP

### Statistical analyses

No statistical analyses for this end point

### Secondary: Modified method failure Pearl Index of participants between 18 and 50 years of age

|                 |                                                                                    |
|-----------------|------------------------------------------------------------------------------------|
| End point title | Modified method failure Pearl Index of participants between 18 and 50 years of age |
|-----------------|------------------------------------------------------------------------------------|

End point description:

The method failure Pearl Index (also referred to as "perfect use" Pearl Index) was calculated using the same method as the Pearl Index, but included only those pregnancies that were classified as method failure and not the pregnancies due to user failure, i.e incorrect intake of the contraceptive method. Only modified at-risk cycles were included in the denominator of the method failure Pearl Index calculation. Modified at-risk cycles were cycles in which no other methods of birth control (including condoms) were used by the subject as confirmed in the subject diary, regardless of whether or not the subject reported intercourse during the cycle.

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

End point timeframe:

Day 1 to End of Cycle 13 (12 months)

|                                   |                                                                      |  |  |  |
|-----------------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>           | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
| Subject group type                | Reporting group                                                      |  |  |  |
| Number of subjects analysed       | 1542 <sup>[11]</sup>                                                 |  |  |  |
| Units: Method failure Pearl Index |                                                                      |  |  |  |
| number (confidence interval 95%)  | 0.23 (0.05 to<br>0.67)                                               |  |  |  |

Notes:

[11] - Participants aged 18 to 50 years, inclusive, at screening with at least 1 modified at-risk cycle

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants experiencing unscheduled bleeding and/ or spotting episodes per cycle

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Number of participants experiencing unscheduled bleeding and/ |
|-----------------|---------------------------------------------------------------|

|                                |
|--------------------------------|
| or spotting episodes per cycle |
|--------------------------------|

End point description:

Participants with evaluable cycles for the bleeding analysis from Cycle 1 to Cycle 12: 1507, 1465, 1436, 1409, 1361, 1331, 1287, 1277, 1245, 1236, 1209, 1183.

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

End point timeframe:

Day 1 to End of Cycle 12 (approximately 11 months)

|                             |                                                                      |  |  |  |
|-----------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>     | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
| Subject group type          | Reporting group                                                      |  |  |  |
| Number of subjects analysed | 1507 <sup>[12]</sup>                                                 |  |  |  |
| Units: Participants         |                                                                      |  |  |  |
| Cycle 1                     | 354                                                                  |  |  |  |
| Cycle 2                     | 282                                                                  |  |  |  |
| Cycle 3                     | 250                                                                  |  |  |  |
| Cycle 4                     | 249                                                                  |  |  |  |
| Cycle 5                     | 238                                                                  |  |  |  |
| Cycle 6                     | 207                                                                  |  |  |  |
| Cycle 7                     | 170                                                                  |  |  |  |
| Cycle 8                     | 202                                                                  |  |  |  |
| Cycle 9                     | 182                                                                  |  |  |  |
| Cycle 10                    | 168                                                                  |  |  |  |
| Cycle 11                    | 155                                                                  |  |  |  |
| Cycle 12                    | 154                                                                  |  |  |  |

Notes:

[12] - Participants aged 18 to 50 years, inclusive, at screening, with evaluable cycle 1 data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of unscheduled bleeding and spotting days per cycle

|                 |                                                            |
|-----------------|------------------------------------------------------------|
| End point title | Number of unscheduled bleeding and spotting days per cycle |
|-----------------|------------------------------------------------------------|

End point description:

Participants with evaluable cycles for the bleeding analysis from Cycle 1 to Cycle 12: 1507, 1465, 1436, 1409, 1361, 1331, 1287, 1277, 1245, 1236, 1209, 1183.

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

End point timeframe:

Day 1 to End of Cycle 12 (approximately 11 months)

| End point values                     | Unscheduled bleeding analysis | Unscheduled spotting analysis |  |  |
|--------------------------------------|-------------------------------|-------------------------------|--|--|
| Subject group type                   | Subject analysis set          | Subject analysis set          |  |  |
| Number of subjects analysed          | 1507 <sup>[13]</sup>          | 1507 <sup>[14]</sup>          |  |  |
| Units: Days                          |                               |                               |  |  |
| arithmetic mean (standard deviation) |                               |                               |  |  |
| Cycle 1                              | 0.2 (± 0.89)                  | 0.8 (± 1.99)                  |  |  |
| Cycle 2                              | 0.1 (± 0.66)                  | 0.5 (± 1.50)                  |  |  |
| Cycle 3                              | 0.1 (± 0.67)                  | 0.5 (± 1.46)                  |  |  |
| Cycle 4                              | 0.2 (± 0.79)                  | 0.5 (± 1.55)                  |  |  |
| Cycle 5                              | 0.1 (± 0.70)                  | 0.5 (± 1.35)                  |  |  |
| Cycle 6                              | 0.1 (± 0.80)                  | 0.4 (± 1.24)                  |  |  |
| Cycle 7                              | 0.1 (± 0.68)                  | 0.4 (± 1.17)                  |  |  |
| Cycle 8                              | 0.1 (± 0.72)                  | 0.4 (± 1.19)                  |  |  |
| Cycle 9                              | 0.1 (± 0.70)                  | 0.4 (± 1.13)                  |  |  |
| Cycle 10                             | 0.1 (± 0.61)                  | 0.4 (± 1.25)                  |  |  |
| Cycle 11                             | 0.1 (± 0.72)                  | 0.3 (± 1.18)                  |  |  |
| Cycle 12                             | 0.1 (± 0.68)                  | 0.4 (± 1.23)                  |  |  |

Notes:

[13] - Participants aged 18 to 50 years, inclusive, at screening, with evaluable cycle 1 data

[14] - Participants aged 18 to 50 years, inclusive, at screening, with evaluable cycle 1 data

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants not experiencing scheduled bleeding and/ or spotting per cycle

|                 |                                                                                       |
|-----------------|---------------------------------------------------------------------------------------|
| End point title | Number of participants not experiencing scheduled bleeding and/ or spotting per cycle |
|-----------------|---------------------------------------------------------------------------------------|

End point description:

Participants with evaluable cycles for the bleeding analysis from Cycle 1 to Cycle 12: 1507, 1465, 1436, 1409, 1361, 1331, 1287, 1277, 1245, 1236, 1209, 1183.

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

End point timeframe:

Day 1 to End of Cycle 12 (approximately 11 months)

| End point values            | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
|-----------------------------|----------------------------------------------------------------------|--|--|--|
| Subject group type          | Reporting group                                                      |  |  |  |
| Number of subjects analysed | 1507 <sup>[15]</sup>                                                 |  |  |  |
| Units: Participants         |                                                                      |  |  |  |
| Cycle 1                     | 84                                                                   |  |  |  |
| Cycle 2                     | 90                                                                   |  |  |  |
| Cycle 3                     | 105                                                                  |  |  |  |
| Cycle 4                     | 83                                                                   |  |  |  |
| Cycle 5                     | 91                                                                   |  |  |  |
| Cycle 6                     | 91                                                                   |  |  |  |

|          |     |  |  |  |
|----------|-----|--|--|--|
| Cycle 7  | 90  |  |  |  |
| Cycle 8  | 103 |  |  |  |
| Cycle 9  | 92  |  |  |  |
| Cycle 10 | 89  |  |  |  |
| Cycle 11 | 80  |  |  |  |
| Cycle 12 | 94  |  |  |  |

Notes:

[15] - Participants aged 18 to 50 years, inclusive, at screening, with evaluable cycle 1 data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of scheduled bleeding and/ or spotting days per cycle

|                 |                                                              |
|-----------------|--------------------------------------------------------------|
| End point title | Number of scheduled bleeding and/ or spotting days per cycle |
|-----------------|--------------------------------------------------------------|

End point description:

Participants with evaluable cycles for the bleeding analysis from Cycle 1 to Cycle 12: 1507, 1465, 1436, 1409, 1361, 1331, 1287, 1277, 1245, 1236, 1209, 1183.

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

End point timeframe:

Day 1 to End of Cycle 12 (approximately 11 months)

|                                      |                                                                      |  |  |  |
|--------------------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>              | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
| Subject group type                   | Reporting group                                                      |  |  |  |
| Number of subjects analysed          | 1507 <sup>[16]</sup>                                                 |  |  |  |
| Units: Days                          |                                                                      |  |  |  |
| arithmetic mean (standard deviation) |                                                                      |  |  |  |
| Cycle 1                              | 6.1 (± 4.95)                                                         |  |  |  |
| Cycle 2                              | 5.3 (± 3.62)                                                         |  |  |  |
| Cycle 3                              | 5.2 (± 3.99)                                                         |  |  |  |
| Cycle 4                              | 5.0 (± 3.14)                                                         |  |  |  |
| Cycle 5                              | 4.9 (± 3.43)                                                         |  |  |  |
| Cycle 6                              | 4.9 (± 3.34)                                                         |  |  |  |
| Cycle 7                              | 4.7 (± 2.80)                                                         |  |  |  |
| Cycle 8                              | 4.8 (± 3.85)                                                         |  |  |  |
| Cycle 9                              | 4.7 (± 2.87)                                                         |  |  |  |
| Cycle 10                             | 4.6 (± 2.69)                                                         |  |  |  |
| Cycle 11                             | 4.7 (± 3.16)                                                         |  |  |  |
| Cycle 12                             | 4.6 (± 2.97)                                                         |  |  |  |

Notes:

[16] - Participants aged 18 to 50 years, inclusive, at screening, with evaluable cycle 1 data

## Statistical analyses

No statistical analyses for this end point

**Secondary: Number of participants with abnormal laboratory assessment results**

|                 |                                                                    |
|-----------------|--------------------------------------------------------------------|
| End point title | Number of participants with abnormal laboratory assessment results |
|-----------------|--------------------------------------------------------------------|

End point description:

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

End point timeframe:

Screening to End of Treatment (12 months)

|                             |                                                                      |  |  |  |
|-----------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>     | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
| Subject group type          | Reporting group                                                      |  |  |  |
| Number of subjects analysed | 1553 <sup>[17]</sup>                                                 |  |  |  |
| Units: Participants         | 55                                                                   |  |  |  |

Notes:

[17] - Participants aged 18 to 50 years, inclusive, at screening, who received at least one dose of IP

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of participants with abnormal vital signs**

|                 |                                                  |
|-----------------|--------------------------------------------------|
| End point title | Number of participants with abnormal vital signs |
|-----------------|--------------------------------------------------|

End point description:

All abnormal findings in vital signs that were considered by the Investigator to be clinically significant were recorded as adverse events.

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

End point timeframe:

Screening to End of Treatment (12 months)

|                             |                                                                      |  |  |  |
|-----------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>     | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
| Subject group type          | Reporting group                                                      |  |  |  |
| Number of subjects analysed | 1553 <sup>[18]</sup>                                                 |  |  |  |
| Units: Participants         | 15                                                                   |  |  |  |

Notes:

[18] - Participants aged 18 to 50 years, inclusive, at screening, who received at least one dose of IP

**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Number of participants with abnormal physical examination results**

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|                 |                                                                   |
|-----------------|-------------------------------------------------------------------|
| End point title | Number of participants with abnormal physical examination results |
|-----------------|-------------------------------------------------------------------|

End point description:

Physical examinations included the body as a whole, skin, head (eyes, ears, nose and throat), neck, cardiovascular system, respiratory system, musculoskeletal system, neurological system, lymphatic/thyroid system and the abdomen

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

End point timeframe:

Screening to End of Treatment (12 months)

---

| End point values                  | Physical examination baseline results | Physical examination end of treatment results |  |  |
|-----------------------------------|---------------------------------------|-----------------------------------------------|--|--|
| Subject group type                | Subject analysis set                  | Subject analysis set                          |  |  |
| Number of subjects analysed       | 1553 <sup>[19]</sup>                  | 1498 <sup>[20]</sup>                          |  |  |
| Units: Participants               |                                       |                                               |  |  |
| Body as a whole                   | 5                                     | 5                                             |  |  |
| Skin                              | 16                                    | 22                                            |  |  |
| Head, eyes, ears, nose and throat | 10                                    | 3                                             |  |  |
| Neck                              | 1                                     | 1                                             |  |  |
| Cardiovascular                    | 0                                     | 1                                             |  |  |
| Respiratory                       | 2                                     | 1                                             |  |  |
| Musculoskeletal                   | 0                                     | 1                                             |  |  |
| Neurologic                        | 0                                     | 2                                             |  |  |
| Lymphatic/Thyroid                 | 2                                     | 1                                             |  |  |
| Abdomen                           | 0                                     | 1                                             |  |  |

Notes:

[19] - Participants aged 18 to 50 years, inclusive, at screening with baseline PE results

[20] - Participants aged 18 to 50 years, inclusive at screening with end of treatment PE results

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Number of participants with abnormal gynecological examination results**

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|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Number of participants with abnormal gynecological examination results |
|-----------------|------------------------------------------------------------------------|

End point description:

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

End point timeframe:

Screening to End of Cycle 13 (12 months)

---

| End point values               | Gynecological examination baseline results | Gynecological examination end of treatment results |  |  |
|--------------------------------|--------------------------------------------|----------------------------------------------------|--|--|
| Subject group type             | Subject analysis set                       | Subject analysis set                               |  |  |
| Number of subjects analysed    | 1553 <sup>[21]</sup>                       | 1499 <sup>[22]</sup>                               |  |  |
| Units: Participants            |                                            |                                                    |  |  |
| Cervix examination             | 21                                         | 13                                                 |  |  |
| Breast examination             | 8                                          | 8                                                  |  |  |
| Vagina examination             | 8                                          | 8                                                  |  |  |
| Uterus examination             | 11                                         | 6                                                  |  |  |
| Adnexa examination             | 4                                          | 2                                                  |  |  |
| External genitalia examination | 1                                          | 1                                                  |  |  |

Notes:

[21] - Participants aged 18 to 50 years, inclusive at screening with baseline gynecological results

[22] - Participants aged 18 to 50 years, inclusive at screening with end of treatment gynecological results

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of participants experiencing common treatment emergent adverse events related to the investigational product

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants experiencing common treatment emergent adverse events related to the investigational product |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

Common treatment emergent adverse events occur in more than 1% of trial participants.

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

End point timeframe:

Day 1 to End of Treatment (13 months)

| End point values               | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
|--------------------------------|----------------------------------------------------------------------|--|--|--|
| Subject group type             | Reporting group                                                      |  |  |  |
| Number of subjects analysed    | 1553 <sup>[23]</sup>                                                 |  |  |  |
| Units: Percent of participants |                                                                      |  |  |  |
| number (not applicable)        |                                                                      |  |  |  |
| Metrorrhagia                   | 5.0                                                                  |  |  |  |
| Vaginal haemorrhage            | 4.3                                                                  |  |  |  |
| Breast pain                    | 2.4                                                                  |  |  |  |
| Dysmenorrhoea                  | 2.1                                                                  |  |  |  |
| Menorrhagia                    | 1.0                                                                  |  |  |  |
| Libido decreased               | 2.2                                                                  |  |  |  |
| Mood altered                   | 1.0                                                                  |  |  |  |
| Mood swings                    | 1.0                                                                  |  |  |  |
| Acne                           | 3.8                                                                  |  |  |  |
| Headache                       | 2.8                                                                  |  |  |  |

|                  |     |  |  |  |
|------------------|-----|--|--|--|
| Weight increased | 1.7 |  |  |  |
|------------------|-----|--|--|--|

Notes:

[23] - Participants aged 18 to 50 years, inclusive, at screening, who received at least one dose of IP

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants who experience at least one treatment emergent serious adverse event

|                 |                                                                                             |
|-----------------|---------------------------------------------------------------------------------------------|
| End point title | Number of participants who experience at least one treatment emergent serious adverse event |
|-----------------|---------------------------------------------------------------------------------------------|

End point description:

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

End point timeframe:

Day 1 to End of Treatment (13 months)

|                             |                                                                      |  |  |  |
|-----------------------------|----------------------------------------------------------------------|--|--|--|
| <b>End point values</b>     | 15 mg estetrol/<br>3 mg<br>drospirenone<br>(18 - 50 years<br>of age) |  |  |  |
| Subject group type          | Reporting group                                                      |  |  |  |
| Number of subjects analysed | 1553 <sup>[24]</sup>                                                 |  |  |  |
| Units: Participants         | 13                                                                   |  |  |  |

Notes:

[24] - Participants aged 18 to 50 years, inclusive, at screening, who received at least one dose of IP

## Statistical analyses

No statistical analyses for this end point

## Secondary: Endometrial biopsy histology at screening and end of treatment

|                 |                                                                |
|-----------------|----------------------------------------------------------------|
| End point title | Endometrial biopsy histology at screening and end of treatment |
|-----------------|----------------------------------------------------------------|

End point description:

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

End point timeframe:

Screening to End of Cycle 13 (12 months)

| End point values               | Endometrial biopsy baseline results | Endometrial biopsy visit 7a results |  |  |
|--------------------------------|-------------------------------------|-------------------------------------|--|--|
| Subject group type             | Subject analysis set                | Subject analysis set                |  |  |
| Number of subjects analysed    | 108                                 | 108                                 |  |  |
| Units: Percent of participants |                                     |                                     |  |  |
| number (not applicable)        |                                     |                                     |  |  |
| Proliferative (weakly)         | 30                                  | 10                                  |  |  |
| Proliferative (active)         | 24                                  | 1                                   |  |  |
| Proliferative (disordered)     | 22                                  | 11                                  |  |  |
| Secretory (cyclic)             | 16                                  | 1                                   |  |  |
| Secretory (progestational)     | 6                                   | 4                                   |  |  |
| Inactive                       | 7                                   | 61                                  |  |  |
| Atrophic                       | 2                                   | 11                                  |  |  |
| Insufficient tissue            | 1                                   | 9                                   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Quality of life enjoyment and satisfaction questionnaire – short form (Q-LES-Q-SF) at screening and end of treatment

|                 |                                                                                                                      |
|-----------------|----------------------------------------------------------------------------------------------------------------------|
| End point title | Quality of life enjoyment and satisfaction questionnaire – short form (Q-LES-Q-SF) at screening and end of treatment |
|-----------------|----------------------------------------------------------------------------------------------------------------------|

End point description:

Participants were asked to rate a series of different items from 1 (very poor) to 5 (very good). The total score of the Q-LES-Q-SF was derived by summing the first 14 items to obtain the raw total score, then transformed into a percentage maximum using the following formula: (raw score – 14)/56. A positive change from baseline indicated the participant had experienced improved overall life satisfaction and contentment during the previous week.

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

End point timeframe:

Day 1 to End of Treatment (12 months)

| End point values                             | Q-LES-Q-SF baseline results | Q-LES-Q-SF end of treatment results |  |  |
|----------------------------------------------|-----------------------------|-------------------------------------|--|--|
| Subject group type                           | Subject analysis set        | Subject analysis set                |  |  |
| Number of subjects analysed                  | 1379 <sup>[25]</sup>        | 1406 <sup>[26]</sup>                |  |  |
| Units: Percent                               |                             |                                     |  |  |
| arithmetic mean (standard deviation)         |                             |                                     |  |  |
| Percentage maximum                           | 73.4 (± 12.77)              | 73.8 (± 12.82)                      |  |  |
| Satisfaction with medicine                   | 4.0 (± 0.78)                | 4.0 (± 0.77)                        |  |  |
| Overall life satisfaction over the past week | 4.0 (± 0.68)                | 4.0 (± 0.70)                        |  |  |

Notes:

[25] - Participants aged 18 to 50 years, inclusive, at screening with baseline Q-LES-Q-SF results

[26] - Participants aged 18 to 50 years, inclusive, at screening with end of treatment Q-LES-Q-SF

results.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Menstrual distress questionnaire (MDQ) at screening and end of treatment

|                 |                                                                          |
|-----------------|--------------------------------------------------------------------------|
| End point title | Menstrual distress questionnaire (MDQ) at screening and end of treatment |
|-----------------|--------------------------------------------------------------------------|

End point description:

The participant rated common symptoms and feelings associated with menstruation from 0 (no experience of symptom) to 4 (present, severe) pre-menstruation, during menstruation and after menstruation. An overall positive change from baseline represents an increase in symptom or feeling severity.

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

End point timeframe:

Day 1 to End of Treatment (12 months)

| End point values                        | MDQ baseline results | MDQ end of treatment results |  |  |
|-----------------------------------------|----------------------|------------------------------|--|--|
| Subject group type                      | Subject analysis set | Subject analysis set         |  |  |
| Number of subjects analysed             | 1526 <sup>[27]</sup> | 1412 <sup>[28]</sup>         |  |  |
| Units: Result                           |                      |                              |  |  |
| arithmetic mean (standard deviation)    |                      |                              |  |  |
| Pain (Intermenstrual)                   | 1.8 (± 2.62)         | 1.6 (± 2.46)                 |  |  |
| Pain (Premenstrual)                     | 2.8 (± 3.01)         | 2.6 (± 3.09)                 |  |  |
| Pain (Menstrual)                        | 4.0 (± 3.71)         | 3.5 (± 3.73)                 |  |  |
| Water retention (Intermenstrual)        | 1.0 (± 1.73)         | 1.0 (± 1.69)                 |  |  |
| Water retention (Premenstrual)          | 2.2 (± 2.45)         | 2.1 (± 2.44)                 |  |  |
| Water retention (Menstrual)             | 2.2 (± 2.47)         | 2.1 (± 2.55)                 |  |  |
| Autonomic reactions (Intermenstrual)    | 0.4 (± 1.08)         | 0.3 (± 1.02)                 |  |  |
| Autonomic reactions (Premenstrual)      | 0.5 (± 1.18)         | 0.4 (± 1.11)                 |  |  |
| Autonomic reactions (Menstrual)         | 0.7 (± 1.41)         | 0.5 (± 1.32)                 |  |  |
| Negative affect (Intermenstrual)        | 2.0 (± 3.66)         | 1.8 (± 3.62)                 |  |  |
| Negative affect (Premenstrual)          | 3.9 (± 4.90)         | 3.5 (± 4.80)                 |  |  |
| Negative affect (Menstrual)             | 3.9 (± 4.89)         | 3.5 (± 4.84)                 |  |  |
| Impaired concentration (Intermenstrual) | 1.1 (± 2.25)         | 1.0 (± 2.13)                 |  |  |
| Impaired concentration (Premenstrual)   | 1.4 (± 2.60)         | 1.3 (± 2.50)                 |  |  |
| Impaired concentration (Menstrual)      | 1.4 (± 2.63)         | 1.4 (± 2.69)                 |  |  |
| Behaviour change (Intermenstrual)       | 0.9 (± 1.90)         | 0.9 (± 1.83)                 |  |  |
| Behaviour change (Premenstrual)         | 1.5 (± 2.40)         | 1.4 (± 2.34)                 |  |  |
| Behaviour change (Menstrual)            | 1.9 (± 2.86)         | 1.7 (± 2.73)                 |  |  |
| Arousal (Intermenstrual)                | 3.7 (± 4.22)         | 3.4 (± 3.88)                 |  |  |
| Arousal (Premenstrual)                  | 3.3 (± 3.80)         | 3.0 (± 3.57)                 |  |  |

|                          |              |              |  |  |
|--------------------------|--------------|--------------|--|--|
| Arousal (Menstrual)      | 3.2 (± 3.68) | 2.9 (± 3.43) |  |  |
| Control (Intermenstrual) | 0.5 (± 1.38) | 0.5 (± 1.37) |  |  |
| Control (Premenstrual)   | 0.6 (± 1.47) | 0.5 (± 1.36) |  |  |
| Control (Menstrual)      | 0.6 (± 1.41) | 0.6 (± 1.42) |  |  |

Notes:

[27] - Participants aged 18 to 50 years, inclusive, at screening, with baseline MDQ results

[28] - Participants aged 18 to 50 years, inclusive, at screening, with end of treatment MDQ results

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Screening to End of Treatment (13 months)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

Participants aged 18 to 50 years, inclusive, at screening

| Serious adverse events                            | Overall Study     |  |  |
|---------------------------------------------------|-------------------|--|--|
| Total subjects affected by serious adverse events |                   |  |  |
| subjects affected / exposed                       | 13 / 1553 (0.84%) |  |  |
| number of deaths (all causes)                     | 0                 |  |  |
| number of deaths resulting from adverse events    | 0                 |  |  |
| Injury, poisoning and procedural complications    |                   |  |  |
| Spinal column injury                              |                   |  |  |
| subjects affected / exposed                       | 1 / 1553 (0.06%)  |  |  |
| occurrences causally related to treatment / all   | 0 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Concussion                                        |                   |  |  |
| subjects affected / exposed                       | 1 / 1553 (0.06%)  |  |  |
| occurrences causally related to treatment / all   | 0 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Upper limb fracture                               |                   |  |  |
| subjects affected / exposed                       | 1 / 1553 (0.06%)  |  |  |
| occurrences causally related to treatment / all   | 0 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |
| Vascular disorders                                |                   |  |  |
| Venous thrombosis                                 |                   |  |  |
| subjects affected / exposed                       | 1 / 1553 (0.06%)  |  |  |
| occurrences causally related to treatment / all   | 1 / 1             |  |  |
| deaths causally related to treatment / all        | 0 / 0             |  |  |

|                                                                                                                                                                                                        |                                            |  |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|--|--|
| Pregnancy, puerperium and perinatal conditions<br>Abortion spontaneous<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | <br><br>1 / 1553 (0.06%)<br>0 / 1<br>0 / 0 |  |  |
| Nervous system disorders<br>Migraine without aura<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                      | <br><br>1 / 1553 (0.06%)<br>0 / 1<br>0 / 0 |  |  |
| General disorders and administration site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all        | <br><br>1 / 1553 (0.06%)<br>0 / 1<br>0 / 0 |  |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                 | <br><br>1 / 1553 (0.06%)<br>0 / 1<br>0 / 0 |  |  |
| Gastrointestinal disorders<br>Colitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | <br><br>1 / 1553 (0.06%)<br>0 / 1<br>0 / 0 |  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                                         | <br><br>1 / 1553 (0.06%)<br>0 / 1<br>0 / 0 |  |  |
| Reproductive system and breast disorders<br>Haemorrhagic ovarian cyst<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all  | <br><br>1 / 1553 (0.06%)<br>0 / 1<br>0 / 0 |  |  |

|                                                                                                                                                                             |                                    |  |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|--|--|
| Infections and infestations<br>Appendicitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 2 / 1553 (0.13%)<br>0 / 2<br>0 / 0 |  |  |
| Abscess limb<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                | 1 / 1553 (0.06%)<br>0 / 1<br>0 / 0 |  |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                                                                                                                                               | Overall Study                                        |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                                                                            | 784 / 1553<br>(50.48%)                               |  |  |
| Investigations<br>Low density lipoprotein increased<br>subjects affected / exposed<br>occurrences (all)<br>Weight increased<br>subjects affected / exposed<br>occurrences (all) | 18 / 1553 (1.16%)<br>19<br>36 / 1553 (2.32%)<br>36   |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                       | 120 / 1553 (7.73%)<br>171<br>19 / 1553 (1.22%)<br>24 |  |  |
| Reproductive system and breast disorders<br>Vaginal haemorrhage<br>subjects affected / exposed<br>occurrences (all)<br>Dysmenorrhoea                                            | 74 / 1553 (4.76%)<br>151                             |  |  |

|                                                 |                   |  |  |
|-------------------------------------------------|-------------------|--|--|
| subjects affected / exposed                     | 47 / 1553 (3.03%) |  |  |
| occurrences (all)                               | 74                |  |  |
| Metrorrhagia                                    |                   |  |  |
| subjects affected / exposed                     | 85 / 1553 (5.47%) |  |  |
| occurrences (all)                               | 156               |  |  |
| Menorrhagia                                     |                   |  |  |
| subjects affected / exposed                     | 15 / 1553 (0.97%) |  |  |
| occurrences (all)                               | 17                |  |  |
| Breast pain                                     |                   |  |  |
| subjects affected / exposed                     | 42 / 1553 (2.70%) |  |  |
| occurrences (all)                               | 51                |  |  |
| Vaginal discharge                               |                   |  |  |
| subjects affected / exposed                     | 16 / 1553 (1.03%) |  |  |
| occurrences (all)                               | 19                |  |  |
| Gastrointestinal disorders                      |                   |  |  |
| Diarrhoea                                       |                   |  |  |
| subjects affected / exposed                     | 25 / 1553 (1.61%) |  |  |
| occurrences (all)                               | 45                |  |  |
| Abdominal pain                                  |                   |  |  |
| subjects affected / exposed                     | 36 / 1553 (2.32%) |  |  |
| occurrences (all)                               | 48                |  |  |
| Vomiting                                        |                   |  |  |
| subjects affected / exposed                     | 27 / 1553 (1.74%) |  |  |
| occurrences (all)                               | 49                |  |  |
| Nausea                                          |                   |  |  |
| subjects affected / exposed                     | 20 / 1553 (1.29%) |  |  |
| occurrences (all)                               | 25                |  |  |
| Respiratory, thoracic and mediastinal disorders |                   |  |  |
| Oropharyngeal pain                              |                   |  |  |
| subjects affected / exposed                     | 15 / 1553 (0.97%) |  |  |
| occurrences (all)                               | 16                |  |  |
| Skin and subcutaneous tissue disorders          |                   |  |  |
| Acne                                            |                   |  |  |
| subjects affected / exposed                     | 65 / 1553 (4.19%) |  |  |
| occurrences (all)                               | 69                |  |  |
| Psychiatric disorders                           |                   |  |  |

|                                                                                                                  |                         |  |  |
|------------------------------------------------------------------------------------------------------------------|-------------------------|--|--|
| Mood altered<br>subjects affected / exposed<br>occurrences (all)                                                 | 19 / 1553 (1.22%)<br>19 |  |  |
| Libido decreased<br>subjects affected / exposed<br>occurrences (all)                                             | 38 / 1553 (2.45%)<br>43 |  |  |
| Mood swings<br>subjects affected / exposed<br>occurrences (all)                                                  | 18 / 1553 (1.16%)<br>18 |  |  |
| Irritability<br>subjects affected / exposed<br>occurrences (all)                                                 | 18 / 1553 (1.16%)<br>18 |  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 19 / 1553 (1.22%)<br>20 |  |  |
| Infections and infestations<br>Tonsillitis<br>subjects affected / exposed<br>occurrences (all)                   | 29 / 1553 (1.87%)<br>31 |  |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                              | 52 / 1553 (3.35%)<br>63 |  |  |
| Vulvovaginal mycotic infection<br>subjects affected / exposed<br>occurrences (all)                               | 17 / 1553 (1.09%)<br>22 |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                      | 30 / 1553 (1.93%)<br>35 |  |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                                                   | 15 / 1553 (0.97%)<br>16 |  |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                                                    | 28 / 1553 (1.80%)<br>30 |  |  |
| Vaginal infection                                                                                                |                         |  |  |

|                             |                   |  |  |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 29 / 1553 (1.87%) |  |  |
| occurrences (all)           | 33                |  |  |
| Sinusitis                   |                   |  |  |
| subjects affected / exposed | 17 / 1553 (1.09%) |  |  |
| occurrences (all)           | 19                |  |  |
| Respiratory tract infection |                   |  |  |
| subjects affected / exposed | 18 / 1553 (1.16%) |  |  |
| occurrences (all)           | 19                |  |  |
| Cystitis                    |                   |  |  |
| subjects affected / exposed | 24 / 1553 (1.55%) |  |  |
| occurrences (all)           | 29                |  |  |
| Vulvovaginal candidiasis    |                   |  |  |
| subjects affected / exposed | 20 / 1553 (1.29%) |  |  |
| occurrences (all)           | 23                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 01 September 2016 | - In line with the urgent safety memo issued on 04 August 2016, the requirement to use condoms for the first 7 days after switching from an intrauterine or dermally implantable contraceptive was added to the instructions for starting the first pack of tablets.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 06 February 2017  | <ul style="list-style-type: none"><li>- "Nicotine-containing products" was added to the exclusion criteria #7 to clarify that this criterion includes cigarettes, e-cigarettes and cigars but not marijuana.</li><li>- Instructions for the participant to contact the site immediately if the participant decided to discontinue the investigational product and, if possible, to not discontinue the investigational product before contacting the site in order to minimize the likelihood of the participant discontinuing study product use without notifying the Investigator. This allowed alternative contraception to be instituted if desired and a discontinuation visit to be scheduled.</li><li>- Clarification was added for participants participating in the Endometrial Safety Sub-study (Finland, Germany, and Poland only) and desiring to discontinue the study. In that case, the second biopsy planned at Visit 7a could be done for participants who discontinue after the completion of the 10th treatment cycle and if she was still under treatment i.e., Cycle 11 or 12.</li><li>- Clarification was added to describe how to handle scheduling the Early Termination Visit for a subject, whether or not she had started study product, who desired early discontinuation from the study.</li><li>- Clarification was added that the information about pregnancy follow-up applied to all enrolled participants who started study product. In the rare circumstance that an enrolled participant became pregnant and claimed she never started study product, the pregnancy did not have to be followed if she could prove she never started study product by returning all of the study product she had received.</li><li>- Text regarding the withdrawal of participants was modified to clarify that any participant who underwent Visit 2 and was withdrawn from the study prior or after the investigational product intake should have participated in an Early Termination Visit and should have been immediately counseled about alternative contraception.</li></ul> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported