



## Clinical trial results:

### **A Double-Blind, Double-Dummy, Randomized, Two-arm, Multicenter Study Comparing the Efficacy, Safety, and Tolerability of Oral Dydrogesterone 30 mg Daily Versus Intravaginal Micronized Progesterone Capsules 600 mg Daily for Luteal Support in In-Vitro Fertilization (LOTUS I)**

#### **Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-002215-26 |
| Trial protocol           | BE AT ES FI    |
| Global end of trial date | 23 March 2016  |

#### **Results information**

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 18 July 2019 |
| First version publication date | 18 July 2019 |

#### **Trial information**

##### **Trial identification**

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | M13-563 |
|-----------------------|---------|

##### **Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01850030 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### **Sponsors**

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Abbott Laboratories GmbH  |
| Sponsor organisation address | Freundallee 9A, Hannover, Germany, 30173  |
| Public contact               | Senior Global Medical Director, Abbott Laboratories GmbH,<br>claire.pexman-fieth@abbott.com |
| Scientific contact           | Senior Global Medical Director, Abbott Laboratories GmbH,<br>claire.pexman-fieth@abbott.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                       | 23 March 2016 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 23 March 2016 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the non-inferiority of oral dydrogesterone 10 milligrams (mg) three times daily (TID) versus micronized progesterone vaginal capsules 200 mg TID. The primary efficacy variable was the presence of fetal heartbeats at 12 weeks gestation determined by transvaginal ultrasound.

Protection of trial subjects:

The study was conducted in compliance with Good Clinical Practice and the applicable national regulations to assure that the rights, safety, and well-being of the participating study subjects were protected, consistent with the ethical principles that have their origin in the Declaration of Helsinki. All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 26 August 2013 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Austria: 15             |
| Country: Number of subjects enrolled | Belgium: 390            |
| Country: Number of subjects enrolled | Finland: 10             |
| Country: Number of subjects enrolled | Germany: 136            |
| Country: Number of subjects enrolled | Israel: 144             |
| Country: Number of subjects enrolled | Russian Federation: 216 |
| Country: Number of subjects enrolled | Spain: 120              |
| Worldwide total number of subjects   | 1031                    |
| EEA total number of subjects         | 671                     |

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          | 0 |

|                           |      |
|---------------------------|------|
| months)                   |      |
| Children (2-11 years)     | 0    |
| Adolescents (12-17 years) | 0    |
| Adults (18-64 years)      | 1031 |
| From 65 to 84 years       | 0    |
| 85 years and over         | 0    |

## Subject disposition

### Recruitment

Recruitment details:

Adult female subjects aged >18 and <42 years entered this randomized, double-blind, double-dummy multicenter study from August 2013. The study was conducted at 38 sites in Europe, Russia and Israel. The study completed in March 2016.

### Pre-assignment

Screening details:

Subjects were premenopausal and had a documented history of infertility, with a clinically indicated protocol for induction of in vitro fertilization with a fresh embryo.

### Period 1

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

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | Oral Dydrogesterone |

Arm description:

Subjects were randomized to receive oral dydrogesterone 10 mg tablets TID (30 mg daily) and placebo intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) from Visit 2 (Day 1). At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta human chorionic gonadotropin (beta-hCG) or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Placebo intravaginal micronized progesterone capsules |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Vaginal capsule                                       |
| Routes of administration               | Vaginal use   |

Dosage and administration details:

Subjects received placebo intravaginal micronized progesterone 200 mg capsules TID from Day 1 to Week 10 (if pregnancy confirmed at Visit 4).

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Dydrogesterone     |
| Investigational medicinal product code |                    |
| Other name                             | Duphaston          |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subjects received oral dydrogesterone 10 mg tablets TID from Day 1 to Week 10 (if pregnancy confirmed at Visit 4).

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Intravaginal Micronized Progesterone |
|------------------|--------------------------------------|

Arm description:

Subjects were randomized to receive intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) and placebo oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1). At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta-hCG or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |                        |
|--|------------------------|
| Investigational medicinal product name | Placebo dydrogesterone |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Film-coated tablet     |
| Routes of administration               | Oral use               |

Dosage and administration details:

Subjects received placebo dydrogesterone 10 mg tablets TID from Day 1 to Week 10 (if pregnancy confirmed at Visit 4).

|  |   |
|--|---|
| Investigational medicinal product name | Intravaginal micronized progesterone capsules |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Vaginal capsule                               |
| Routes of administration               | Vaginal use                                   |

Dosage and administration details:

Subjects received intravaginal micronized progesterone 200 mg capsules TID from Day 1 to Week 10 (if pregnancy confirmed at Visit 4).

| Number of subjects in period 1    | Oral Dydrogesterone | Intravaginal Micronized Progesterone |
|-----------------------------------|---------------------|--------------------------------------|
|                                   |                     |                                      |
| Started                           | 520                 | 511                                  |
| Confirmed pregnancy at Day 15     | 234                 | 217                                  |
| Ongoing pregnancy at Week 6       | 197                 | 169                                  |
| Confirmed pregnancy at Week 10    | 187                 | 158                                  |
| Giving live birth(s)              | 172 <sup>[1]</sup>  | 142                                  |
| Completed                         | 173                 | 142                                  |
| Not completed                     | 347                 | 369                                  |
| Pregnancy not confirmed at Day 15 | 248                 | 249                                  |
| Consent withdrawn by subject      | 3                   | 4                                    |
| Adverse event, non-fatal          | 64                  | 82                                   |
| Lost to follow-up                 | 5                   | 5                                    |
| Lack of efficacy                  | 3                   | 1                                    |
| Protocol deviation                | 24                  | 28                                   |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: One subject was recorded as lost to follow-up and was recorded as having a live birth.

## Baseline characteristics

### Reporting groups

|  |                                      |
|--|--------------------------------------|
| Reporting group title  | Oral Dydrogesterone                  |
| Reporting group description:   |                                      |
| Subjects were randomized to receive oral dydrogesterone 10 mg tablets TID (30 mg daily) and placebo intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) from Visit 2 (Day 1). At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta human chorionic gonadotropin (beta-hCG) or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10). |                                      |
| Reporting group title  | Intravaginal Micronized Progesterone |
| Reporting group description:   |                                      |
| Subjects were randomized to receive intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) and placebo oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1). At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta-hCG or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).                                     |                                      |

| Reporting group values                             | Oral Dydrogesterone | Intravaginal Micronized Progesterone | Total |
|--|---------------------|--------------------------------------|-------|
| Number of subjects                                 | 520                 | 511                                  | 1031  |
| Age categorical<br>Units: Subjects                 |                     |                                      |       |
| In utero   | 0                   | 0                                    | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                   | 0                                    | 0     |
| Newborns (0-27 days)                               | 0                   | 0                                    | 0     |
| Infants and toddlers (28 days-23 months)           | 0                   | 0                                    | 0     |
| Children (2-11 years)                              | 0                   | 0                                    | 0     |
| Adolescents (12-17 years)                          | 0                   | 0                                    | 0     |
| Adults (18-64 years)                               | 520                 | 511                                  | 1031  |
| From 65-84 years                                   | 0                   | 0                                    | 0     |
| 85 years and over                                  | 0                   | 0                                    | 0     |
| Gender categorical<br>Units: Subjects              |                     |                                      |       |
| Female   | 520                 | 511                                  | 1031  |
| Male   | 0                   | 0                                    | 0     |

## End points

### End points reporting groups

|   |                                      |
|---|--------------------------------------|
| Reporting group title   | Oral Dydrogesterone                  |
| Reporting group description:<br>Subjects were randomized to receive oral dydrogesterone 10 mg tablets TID (30 mg daily) and placebo intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) from Visit 2 (Day 1).<br>At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta human chorionic gonadotropin (beta-hCG) or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10). |                                      |
| Reporting group title   | Intravaginal Micronized Progesterone |
| Reporting group description:<br>Subjects were randomized to receive intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) and placebo oral dydrogesterone 10 mg tablets TID (30 mg daily) from Visit 2 (Day 1).<br>At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta-hCG or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).                                     |                                      |

### Primary: Pregnancy Rate at Visit 6 (Week 10): Per Protocol (PP) Subject Sample

|   |   |
|---|---|
| End point title   | Pregnancy Rate at Visit 6 (Week 10): Per Protocol (PP) Subject Sample |
| End point description:<br>The pregnancy rate, defined as the percentage of subjects for whom a fetal heartbeat was detected by transvaginal ultrasound at Visit 6 (Week 10) (12 weeks gestation), in the PP Subject Sample is presented. The PP Subject Sample consisted of all subjects who were allocated to treatment who received at least one administration of study drug, had a successful single or dual embryo transfer at Visit 3 (Day 3 to 6) and did not have any major protocol deviations unrelated to treatment. Subjects who prematurely discontinued after having a pregnancy test were counted as failures if the test was negative or if the test was positive but the reason for discontinuation was related to study drug or pregnancy related issues. |   |
| End point type  | Primary   |
| End point timeframe:<br>At Visit 6 (Week 10).   |   |

| End point values                 | Oral Dydrogesterone | Intravaginal Micronized Progesterone |  |  |
|----------------------------------|---------------------|--------------------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group                      |  |  |
| Number of subjects analysed      | 492                 | 475                                  |  |  |
| Units: Percentage of subjects    |                     |                                      |  |  |
| number (confidence interval 95%) | 37.6 (33.3 to 42.1) | 33.1 (28.8 to 37.5)                  |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Treatment difference: PP Subject Sample                    |
| Comparison groups          | Oral Dydrogesterone v Intravaginal Micronized Progesterone |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 967                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[1]</sup> |
| Method                                  | Cochran-Mantel-Haenszel        |
| Parameter estimate                      | Treatment difference (%)       |
| Point estimate                          | 4.7                            |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.2                           |
| upper limit                             | 10.6                           |

Notes:

[1] - To show that oral dydrogesterone was non-inferior to intravaginal micronized progesterone, a two-sided 95% confidence interval (CI) with a non-inferiority margin of 10% for the difference in pregnancy rates was used.

### Primary: Pregnancy Rate at Visit 6 (Week 10): Full Analysis (FA) Subject Sample

|                 |  |
|-----------------|--|
| End point title | Pregnancy Rate at Visit 6 (Week 10): Full Analysis (FA) Subject Sample |
|-----------------|--|

End point description:

The pregnancy rate, defined as the percentage of subjects for whom a fetal heartbeat was detected by transvaginal ultrasound at Visit 6 (Week 10) (12 weeks gestation), in the FA Subject Sample is presented. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues. Subjects who prematurely discontinued after having a pregnancy test were counted as failures if the test was negative or if the test was positive but the reason for discontinuation was related to study drug or pregnancy related issues.

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

End point timeframe:

At Visit 6 (Week 10).

| End point values                 | Oral<br>Dydrogesterone | Intravaginal<br>Micronized<br>Progesterone |  |  |
|----------------------------------|------------------------|--|--|--|
| Subject group type               | Reporting group        | Reporting group                            |  |  |
| Number of subjects analysed      | 497                    | 477  |  |  |
| Units: Percentage of subjects    |                        |  |  |  |
| number (confidence interval 95%) | 37.6 (33.4 to 42.1)    | 33.1 (28.9 to 37.6)                        |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Treatment difference: FA Subject Sample                    |
| Comparison groups          | Oral Dydrogesterone v Intravaginal Micronized Progesterone |



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 974                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[2]</sup> |
| Method                                  | Cochran-Mantel-Haenszel        |
| Parameter estimate                      | Treatment difference (%)       |
| Point estimate                          | 4.7                            |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.2                           |
| upper limit                             | 10.6                           |

Notes:

[2] - To show that oral dydrogesterone was non-inferior to intravaginal micronized progesterone, a two-sided 95% CI with a non-inferiority margin of 10% for the difference in pregnancy rates was used.

### Secondary: Pregnancy Rate at Visit 4 (Day 15)

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Pregnancy Rate at Visit 4 (Day 15) |
|-----------------|------------------------------------|

End point description:

The percentage of subjects who were pregnant at Visit 4 (Day 15) as determined by a positive beta-hCG serum test are presented for the FA Subject Sample. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues.

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

End point timeframe:

At Visit 4 (Day 15).

| End point values                 | Oral<br>Dydrogesterone | Intravaginal<br>Micronized<br>Progesterone |  |  |
|----------------------------------|------------------------|--|--|--|
| Subject group type               | Reporting group        | Reporting group                            |  |  |
| Number of subjects analysed      | 497                    | 477  |  |  |
| Units: Percentage of subjects    |                        |  |  |  |
| number (confidence interval 95%) | 47.1 (42.6 to 51.6)    | 45.5 (41.0 to 50.1)                        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pregnancy Rate at Visit 5 (Week 6)

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Pregnancy Rate at Visit 5 (Week 6) |
|-----------------|------------------------------------|

End point description:

Ongoing pregnancy at Visit 5 (Week 6) was confirmed based on clinical evidence. The percentage of subjects in the FA Subject Sample who had pregnancy confirmed at Visit 5 are presented. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues.

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

End point timeframe:

At Visit 5 (Week 6).

| End point values                 | Oral<br>Dydrogesterone | Intravaginal<br>Micronized<br>Progesterone |  |  |
|----------------------------------|------------------------|--|--|--|
| Subject group type               | Reporting group        | Reporting group                            |  |  |
| Number of subjects analysed      | 497                    | 477  |  |  |
| Units: Percentage of subjects    |                        |  |  |  |
| number (confidence interval 95%) | 39.6 (35.3 to 44.1)    | 35.4 (31.1 to 39.9)                        |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Abortion Rate

|                 |               |
|-----------------|---------------|
| End point title | Abortion Rate |
|-----------------|---------------|

End point description:

The percentage of subjects in the FA Subject Sample who had an abortion (abortion rate) is presented. Subjects with abortions reported from Visit 5 (Week 6) onwards were included, since abortions reported before Visit 5 (Week 6) were considered biochemical pregnancies and were therefore not to be considered in the efficacy analysis of abortion rate. The Investigator determined whether the subject had an abortion. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues.

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

End point timeframe:

From Visit 5 (Week 6) up to 20-24 weeks gestation (18-22 weeks pregnancy).

| End point values                 | Oral<br>Dydrogesterone | Intravaginal<br>Micronized<br>Progesterone |  |  |
|----------------------------------|------------------------|--|--|--|
| Subject group type               | Reporting group        | Reporting group                            |  |  |
| Number of subjects analysed      | 497                    | 477  |  |  |
| Units: Percentage of subjects    |                        |  |  |  |
| number (confidence interval 95%) | 1.6 (0.7 to 3.2)       | 2.1 (1.0 to 3.8)                           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Preterm Birth Rate

|   |                    |
|---|--------------------|
| End point title   | Preterm Birth Rate |
| End point description:  |                    |
| The percentage of subjects in the FA Subject Sample who had a preterm birth (preterm birth rate) is presented. The Investigator determined whether the subject had a preterm birth. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues. |                    |
| End point type  | Secondary          |
| End point timeframe:  |                    |
| Up to 37 weeks of gestation (35 weeks of pregnancy).  |                    |

| End point values                 | Oral Dydrogesterone | Intravaginal Micronized Progesterone |  |  |
|----------------------------------|---------------------|--------------------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group                      |  |  |
| Number of subjects analysed      | 497                 | 477                                  |  |  |
| Units: Percentage of subjects    |                     |                                      |  |  |
| number (confidence interval 95%) | 7.9 (5.6 to 10.6)   | 5.2 (3.4 to 7.6)                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Live Birth Rate

|   |                 |
|---|-----------------|
| End point title   | Live Birth Rate |
| End point description:  |                 |
| The percentage of subjects in the FA Subject Sample who had at least one live birth (live birth rate) are presented. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug, had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues. |                 |
| End point type  | Secondary       |
| End point timeframe:  |                 |
| After delivery (up to approximately 9 months after embryo transfer).  |                 |

| End point values                 | Oral Dydrogesterone | Intravaginal Micronized Progesterone |  |  |
|----------------------------------|---------------------|--------------------------------------|--|--|
| Subject group type               | Reporting group     | Reporting group                      |  |  |
| Number of subjects analysed      | 497                 | 477                                  |  |  |
| Units: Percentage of subjects    |                     |                                      |  |  |
| number (confidence interval 95%) | 34.6 (30.4 to 39.0) | 29.8 (25.7 to 34.1)                  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Healthy Newborn Rate

|                 |                      |
|-----------------|----------------------|
| End point title | Healthy Newborn Rate |
|-----------------|----------------------|

End point description:

The percentage of subjects in the FA Subject Sample who gave birth to at least one healthy newborn (healthy newborn rate) is presented. The FA Subject Sample consisted of all subjects allocated to treatment who received at least one administration of study drug and had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or did not prematurely discontinue prior to embryo transfer at Visit 3 due to non-study drug related issues.

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

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer).

| End point values                 | Oral<br>Dydrogesterone | Intravaginal<br>Micronized<br>Progesterone |  |  |
|----------------------------------|------------------------|--|--|--|
| Subject group type               | Reporting group        | Reporting group                            |  |  |
| Number of subjects analysed      | 497                    | 477  |  |  |
| Units: Percentage of subjects    |                        |  |  |  |
| number (confidence interval 95%) | 32.0 (27.9 to 36.3)    | 27.7 (23.7 to 31.9)                        |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Gender of the Newborn

|                 |                       |
|-----------------|-----------------------|
| End point title | Gender of the Newborn |
|-----------------|-----------------------|

End point description:

The number of male and female live newborns is presented for the FA Subject Sample.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

After delivery (up to approximately 9 months after embryo transfer).

| End point values            | Oral<br>Dydrogesterone | Intravaginal<br>Micronized<br>Progesterone |  |  |
|-----------------------------|------------------------|--|--|--|
| Subject group type          | Reporting group        | Reporting group                            |  |  |
| Number of subjects analysed | 497                    | 477  |  |  |
| Units: Newborns             |                        |  |  |  |
| Male                        | 120                    | 88   |  |  |
| Female                      | 93                     | 70   |  |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the start of treatment (Day 1) to the follow-up phone call at Visit 10 (30 days after delivery).

Adverse event reporting additional description:

The Safety Subject Sample consists of all subjects who were allocated to treatment and received at least one administration of study drug.

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

### Dictionary used

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

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

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Oral Dydrogesterone |
|-----------------------|---------------------|

Reporting group description:

Subjects were randomized to receive oral dydrogesterone 20 mg tablets TID (30 mg daily) and placebo intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) from Visit 2 (Day 1).

At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta-hCG or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Intravaginal Micronized Progesterone |
|-----------------------|--------------------------------------|

Reporting group description:

Subjects were randomized to receive intravaginal micronized progesterone 200 mg capsules TID (600 mg daily) and placebo oral dydrogesterone 20 mg tablets TID (30 mg daily) from Visit 2 (Day 1).

At Visit 3 (Day 3 to Day 6) subjects received a single or dual fresh embryo transfer. Pregnancy was confirmed at Visit 4 (Day 15 [+/- 3 days]) by a serum beta-hCG or urine strip test. If positive, luteal support continued up to Visit 6 (Week 10).

| Serious adverse events                            | Oral Dydrogesterone | Intravaginal Micronized Progesterone |  |
|---|---------------------|--------------------------------------|--|
| Total subjects affected by serious adverse events |                     |                                      |  |
| subjects affected / exposed                       | 56 / 518 (10.81%)   | 68 / 511 (13.31%)                    |  |
| number of deaths (all causes)                     | 0                   | 0                                    |  |
| number of deaths resulting from adverse events    | 0                   | 0                                    |  |
| Vascular disorders                                |                     |                                      |  |
| Deep vein thrombosis                              |                     |                                      |  |
| subjects affected / exposed                       | 1 / 518 (0.19%)     | 0 / 511 (0.00%)                      |  |
| occurrences causally related to treatment / all   | 0 / 1               | 0 / 0                                |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0                                |  |
| Jugular vein thrombosis                           |                     |                                      |  |
| subjects affected / exposed                       | 0 / 518 (0.00%)     | 1 / 511 (0.20%)                      |  |
| occurrences causally related to treatment / all   | 0 / 0               | 0 / 1                                |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0                                |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| Hypertension                                    |                 |                  |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 1 / 511 (0.20%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Haemorrhage                                     |                 |                  |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Surgical and medical procedures                 |                 |                  |  |
| Abortion induced                                |                 |                  |  |
| subjects affected / exposed                     | 2 / 518 (0.39%) | 3 / 511 (0.59%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Selective abortion                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 1 / 511 (0.20%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Labour induction                                |                 |                  |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pregnancy, puerperium and perinatal conditions  |                 |                  |  |
| Abortion spontaneous                            |                 |                  |  |
| subjects affected / exposed                     | 9 / 518 (1.74%) | 15 / 511 (2.94%) |  |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 15           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Abortion threatened                             |                 |                  |  |
| subjects affected / exposed                     | 2 / 518 (0.39%) | 1 / 511 (0.20%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Abortion missed                                 |                 |                  |  |
| subjects affected / exposed                     | 6 / 518 (1.16%) | 9 / 511 (1.76%)  |  |
| occurrences causally related to treatment / all | 0 / 6           | 3 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Abortion  |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abortion complete                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abortion of ectopic pregnancy                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ectopic pregnancy                               |                 |                 |  |
| subjects affected / exposed                     | 4 / 518 (0.77%) | 4 / 511 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cervical incompetence                           |                 |                 |  |
| subjects affected / exposed                     | 3 / 518 (0.58%) | 3 / 511 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperemesis gravidarum                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Premature labour                                |                 |                 |  |
| subjects affected / exposed                     | 4 / 518 (0.77%) | 2 / 511 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Premature rupture of membranes                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 2 / 511 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Premature delivery                              |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 518 (0.19%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Threatened labour                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foetal death                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 6 / 511 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foetal distress syndrome                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 2 / 511 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foetal disorder                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foetal hypokinesia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pre-eclampsia                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 518 (0.39%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| HELLP syndrome                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 2 / 511 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oligohydramnios                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 518 (0.39%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Polyhydramnios                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Premature baby                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 518 (0.39%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Premature separation of placenta                |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhage in pregnancy                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retroplacental haematoma                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pregnancy of unknown location                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Uterine contractions during pregnancy           |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical cord around neck                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical cord vascular disorder                |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blighted ovum                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foetal growth restriction                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retained placenta or membranes                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postpartum haemorrhage                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Ovarian hyperstimulation syndrome               |                 |                 |  |
| subjects affected / exposed                     | 8 / 518 (1.54%) | 5 / 511 (0.98%) |  |
| occurrences causally related to treatment / all | 1 / 8           | 1 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Adnexal torsion                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian haemorrhage                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shortened cervix                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian cyst                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metrorrhagia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Genital haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vaginal haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Foetal heart rate abnormal                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| C-reactive protein increased<br>subjects affected / exposed | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural<br>complications           |                 |                 |  |
| Fall  |                 |                 |  |
| subjects affected / exposed                                 | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           |  |
| Procedural pain   |                 |                 |  |
| subjects affected / exposed                                 | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           |  |
| Bladder injury  |                 |                 |  |
| subjects affected / exposed                                 | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic<br>disorders               |                 |                 |  |
| Trisomy 21  |                 |                 |  |
| subjects affected / exposed                                 | 1 / 518 (0.19%) | 2 / 511 (0.39%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 2           |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           |  |
| Trisomy 13  |                 |                 |  |
| subjects affected / exposed                                 | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           |  |
| Pulmonary artery atresia                                    |                 |                 |  |
| subjects affected / exposed                                 | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           |  |
| Univentricular heart  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital tricuspid valve atresia              |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spina bifida                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital hydrocephalus                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Turner's Syndrome                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Foetal heart rate deceleration                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foetal heart rate disorder                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Orthostatic intolerance                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epilepsy  |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 3 / 511 (0.59%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain lower                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Diverticulitis                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus infection                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 518 (0.00%) | 1 / 511 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 518 (0.19%) | 0 / 511 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Oral Dydrogesterone | Intravaginal Micronized Progesterone |  |
|---|---------------------|--------------------------------------|--|
| Total subjects affected by non-serious adverse events |                     |                                      |  |
| subjects affected / exposed                           | 156 / 518 (30.12%)  | 147 / 511 (28.77%)                   |  |
| Injury, poisoning and procedural complications        |                     |                                      |  |
| Procedural pain                                       |                     |                                      |  |
| subjects affected / exposed                           | 39 / 518 (7.53%)    | 40 / 511 (7.83%)                     |  |
| occurrences (all)                                     | 40                  | 41                                   |  |
| Pregnancy, puerperium and perinatal conditions        |                     |                                      |  |
| Pregnancy of unknown location                         |                     |                                      |  |



|  |  |  |  |
|--|--|--|--|
| subjects affected / exposed<br>occurrences (all)   | 19 / 518 (3.67%)<br>19                               | 29 / 511 (5.68%)<br>29                               |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)   | 27 / 518 (5.21%)<br>31                               | 32 / 511 (6.26%)<br>36                               |  |
| Reproductive system and breast disorders<br>Vaginal haemorrhage<br>subjects affected / exposed<br>occurrences (all)  | 60 / 518 (11.58%)<br>74                              | 46 / 511 (9.00%)<br>54                               |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all) | 24 / 518 (4.63%)<br>25<br><br>44 / 518 (8.49%)<br>46 | 31 / 511 (6.07%)<br>33<br><br>26 / 511 (5.09%)<br>27 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 22 April 2013    | Implemented a change in the time for embryo transfer at Visit 3 from 'Day2/3' to 'Day 2 to Day 5'.  |
| 24 November 2015 | The definition and AE/serious AE reporting requirements of a biochemical pregnancy and clinical pregnancy were clarified. Clarified that pregnancy was to be confirmed according to clinical evidence. The definition of miscarriage and explanatory text on the expectedness of early miscarriages before Week 10 of pregnancy (12 weeks gestation) were also added. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported