



## Clinical trial results: Assisted reproduction and the early luteal phase The effect of ovulation induction on the endocrine profile

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-003304-39 |
| Trial protocol           | DK             |
| Global end of trial date | 28 August 2020 |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 21 January 2022 |
| First version publication date | 21 January 2022 |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 13.010 |
|-----------------------|--------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Odense University Hospital  |
| Sponsor organisation address | Kløvervænget 23, Odense, Denmark,   |
| Public contact               | Fertilitycenter, Odense University Hospital, 0045 20342687, Peter.Humaidan@midt.rm.dk |
| Scientific contact           | Fertilitycenter, Odense University Hospital, 0045 20342687, Peter.Humaidan@midt.rm.dk |

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                       | 30 November 2021 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 28 August 2020   |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 28 August 2020   |
| Was the trial ended prematurely?                     | No               |

Notes:

---

**General information about the trial**

---

Main objective of the trial:

To investigate the endocrine hormone levels in the luteal phase during fertility treatment.

Protection of trial subjects:

Ethics Committee of Southern of Denmark, the Danish Health and Medicines Authority, the Danish Data Protection Agency and Local Good Clinical Practice Unit.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 14 December 2014 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

---

**Population of trial subjects**

---

**Subjects enrolled per country**

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Denmark: 222 |
| Worldwide total number of subjects   | 222          |
| EEA total number of subjects         | 222          |

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)                      | 222 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Fertility Clinic, Patients in fertility treatment.

### Pre-assignment

Screening details:

Healthy women in infertility treatment, 18-40 years, healthy with normal screening blood samples  
RCT I: In total  $\leq 11$  follicles  $\leq 12$  mm, on both ovaries at the last ultrasonography before oocyte retrieval

RCT II: In total  $\geq 12$  or  $\leq 25$  follicles  $\leq 12$  mm, on both ovaries at the last ultrasonography before oocyte retrieval

### Period 1

|                              |                         |
|------------------------------|-------------------------|
| Period 1 title               | overall periode         |
| Is this the baseline period? | Yes                     |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

### Arms

|                              |                |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes            |
| <b>Arm title</b>             | RCT I, group 1 |

Arm description:

5.000 IU (urinary hCG) + 17 $\alpha$  OH P4

|  |   |
|--|---|
| Arm type                               | Active comparator                       |
| Investigational medicinal product name | Lentogest                               |
| Investigational medicinal product code | G03DA03                                 |
| Other name                             |   |
| Pharmaceutical forms                   | Suspension for suspension for injection |
| Routes of administration               | Intramuscular use                       |

Dosage and administration details:

341 mg every 3.th day

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | RCT I, group 2 |
|------------------|----------------|

Arm description:

6.500 IU (recombinant hCG) + 17 $\alpha$  OH P4

|  |   |
|--|---|
| Arm type                               | Active comparator                       |
| Investigational medicinal product name | Lentogest                               |
| Investigational medicinal product code | G03DA03                                 |
| Other name                             |   |
| Pharmaceutical forms                   | Suspension for suspension for injection |
| Routes of administration               | Intramuscular use                       |

Dosage and administration details:

341 mg every 3.th day

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | RCT I, group 3 |
|------------------|----------------|

Arm description:

10.000 IU (urinary hCG) + 17 $\alpha$  OH P4

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

|  |   |
|--|---|
| Investigational medicinal product name   | Lentogest                               |
| Investigational medicinal product code   | G03DA03                                 |
| Other name   |   |
| Pharmaceutical forms   | Suspension for suspension for injection |
| Routes of administration   | Intramuscular use                       |
| Dosage and administration details:<br>341 mg every 3.th day  |   |
| <b>Arm title</b>   | RCT I, group 4                          |
| Arm description:<br>6500 IU (recombinant hCG) + P4   |   |
| Arm type   | control                                 |
| Investigational medicinal product name   | Progesterone, Crinone                   |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Vaginal gel                             |
| Routes of administration   | Vaginal use                             |
| Dosage and administration details:<br>180 mg every day   |   |
| <b>Arm title</b>   | RCT II, group 1                         |
| Arm description:<br>Trigger: 6.500 IU hCG. Luteal support: P4  |   |
| Arm type   | control                                 |
| Investigational medicinal product name   | Progesterone, Crinone                   |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Vaginal gel                             |
| Routes of administration   | Vaginal use                             |
| Dosage and administration details:<br>180 mg every day   |   |
| <b>Arm title</b>   | RCT II, group 2                         |
| Arm description:<br>Trigger: GnRh agonist 0.5 mg. Luteal support: 1500 IU hCG at OPU, P4                       |   |
| Arm type   | Active comparator                       |
| Investigational medicinal product name   | Progesterone, Crinone                   |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Vaginal gel                             |
| Routes of administration   | Vaginal use                             |
| Dosage and administration details:<br>180 mg every day   |   |
| <b>Arm title</b>   | RCT II, group 3                         |
| Arm description:<br>Trigger: GnRha agonist 0.5 mg. Luteal support: 1000 IU hCG at OPU, 500 IU hCG at OPU+5, P4 |   |
| Arm type   | Active comparator                       |
| Investigational medicinal product name   | Progesterone, Crinone                   |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Vaginal gel                             |
| Routes of administration   | Vaginal use                             |

Dosage and administration details:  
180 mg every day

| Number of subjects in period 1 | RCT I, group 1 | RCT I, group 2 | RCT I, group 3 |
|--------------------------------|----------------|----------------|----------------|
| Started                        | 30             | 33             | 32             |
| Completed                      | 21             | 22             | 25             |
| Not completed                  | 9              | 11             | 7              |
| Consent withdrawn by subject   | 1              | 1              | 1              |
| missed blood samples           | 1              | 1              | -              |
| Adverse event, non-fatal       | -              | -              | 1              |
| missing ovary                  | -              | -              | -              |
| total freeze                   | -              | 2              | 1              |
| wrong medicine                 | -              | -              | -              |
| no oocytes                     | 2              | 1              | 1              |
| cancelled transfer             | -              | 3              | 3              |
| endocrinological diseases      | -              | 3              | -              |
| transfer cancelled             | 5              | -              | -              |

| Number of subjects in period 1 | RCT I, group 4 | RCT II, group 1 | RCT II, group 2 |
|--------------------------------|----------------|-----------------|-----------------|
| Started                        | 32             | 33              | 32              |
| Completed                      | 26             | 25              | 22              |
| Not completed                  | 6              | 8               | 10              |
| Consent withdrawn by subject   | 1              | 1               | -               |
| missed blood samples           | 1              | -               | 1               |
| Adverse event, non-fatal       | -              | -               | -               |
| missing ovary                  | -              | -               | 1               |
| total freeze                   | 3              | 1               | 5               |
| wrong medicine                 | -              | -               | 1               |
| no oocytes                     | -              | -               | -               |
| cancelled transfer             | 1              | 6               | 2               |
| endocrinological diseases      | -              | -               | -               |
| transfer cancelled             | -              | -               | -               |

| Number of subjects in period 1 | RCT II, group 3 |
|--------------------------------|-----------------|
| Started                        | 30              |

|                              |    |
|------------------------------|----|
| Completed                    | 22 |
| Not completed                | 8  |
| Consent withdrawn by subject | -  |
| missed blood samples         | 3  |
| Adverse event, non-fatal     | -  |
| missing ovary                | -  |
| total freeze                 | 1  |
| wrong medicine               | -  |
| no oocytes                   | 1  |
| cancelled transfer           | 3  |
| endocrinological diseases    | -  |
| transfer cancelled           | -  |

## Baseline characteristics

### Reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | RCT I, group 1  |
| Reporting group description:<br>5.000 IU (urinary hCG) + 17α OH P4   |                 |
| Reporting group title  | RCT I, group 2  |
| Reporting group description:<br>6.500 IU (recombinant hCG) + 17α OH P4   |                 |
| Reporting group title  | RCT I, group 3  |
| Reporting group description:<br>10.000 IU (urinary hCG) + 17α OH P4  |                 |
| Reporting group title  | RCT I, group 4  |
| Reporting group description:<br>6500 IU (recombinant hCG) + P4   |                 |
| Reporting group title  | RCT II, group 1 |
| Reporting group description:<br>Trigger: 6.500 IU hCG. Luteal support: P4  |                 |
| Reporting group title  | RCT II, group 2 |
| Reporting group description:<br>Trigger: GnRh agonist 0.5 mg. Luteal support: 1500 IU hCG at OPU, P4                       |                 |
| Reporting group title  | RCT II, group 3 |
| Reporting group description:<br>Trigger: GnRha agonist 0.5 mg. Luteal support: 1000 IU hCG at OPU, 500 IU hCG at OPU+5, P4 |                 |

| Reporting group values             | RCT I, group 1 | RCT I, group 2 | RCT I, group 3 |
|------------------------------------|----------------|----------------|----------------|
| Number of subjects                 | 30             | 33             | 32             |
| Age categorical<br>Units: Subjects |                |                |                |

|                                       |       |        |       |
|---------------------------------------|-------|--------|-------|
| Age continuous<br>Units: years        |       |        |       |
| arithmetic mean                       | 29.1  | 31.1   | 30.1  |
| standard deviation                    | ± 5.0 | ± 4.44 | ± 4.4 |
| Gender categorical<br>Units: Subjects |       |        |       |
| Female                                | 30    | 33     | 32    |
| Male                                  | 0     | 0      | 0     |

| Reporting group values             | RCT I, group 4 | RCT II, group 1 | RCT II, group 2 |
|------------------------------------|----------------|-----------------|-----------------|
| Number of subjects                 | 32             | 33              | 32              |
| Age categorical<br>Units: Subjects |                |                 |                 |

|                                |      |      |      |
|--------------------------------|------|------|------|
| Age continuous<br>Units: years |      |      |      |
| arithmetic mean                | 31.7 | 30.9 | 31.0 |

|                    |       |       |       |
|--------------------|-------|-------|-------|
| standard deviation | ± 4.3 | ± 3.6 | ± 4.2 |
|--------------------|-------|-------|-------|

|                                       |    |    |    |
|---------------------------------------|----|----|----|
| Gender categorical<br>Units: Subjects |    |    |    |
| Female                                | 32 | 33 | 32 |
| Male                                  | 0  | 0  | 0  |

|                                    |                 |       |  |
|------------------------------------|-----------------|-------|--|
| <b>Reporting group values</b>      | RCT II, group 3 | Total |  |
| Number of subjects                 | 30              | 222   |  |
| Age categorical<br>Units: Subjects |                 |       |  |

|   |               |     |  |
|---|---------------|-----|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 30.1<br>± 3.9 | -   |  |
| Gender categorical<br>Units: Subjects                                   |               |     |  |
| Female  | 30            | 222 |  |
| Male  | 0             | 0   |  |



## End points

### End points reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | RCT I, group 1  |
| Reporting group description:<br>5.000 IU (urinary hCG) + 17α OH P4   |                 |
| Reporting group title  | RCT I, group 2  |
| Reporting group description:<br>6.500 IU (recombinant hCG) + 17α OH P4   |                 |
| Reporting group title  | RCT I, group 3  |
| Reporting group description:<br>10.000 IU (urinary hCG) + 17α OH P4  |                 |
| Reporting group title  | RCT I, group 4  |
| Reporting group description:<br>6500 IU (recombinant hCG) + P4   |                 |
| Reporting group title  | RCT II, group 1 |
| Reporting group description:<br>Trigger: 6.500 IU hCG. Luteal support: P4  |                 |
| Reporting group title  | RCT II, group 2 |
| Reporting group description:<br>Trigger: GnRh agonist 0.5 mg. Luteal support: 1500 IU hCG at OPU, P4                       |                 |
| Reporting group title  | RCT II, group 3 |
| Reporting group description:<br>Trigger: GnRha agonist 0.5 mg. Luteal support: 1000 IU hCG at OPU, 500 IU hCG at OPU+5, P4 |                 |

### Primary: Progesterone

|  |              |
|--|--------------|
| End point title                          | Progesterone |
| End point description:                   |              |
| End point type                           | Primary      |
| End point timeframe:<br>At randomization |              |

| End point values                      | RCT I, group 1   | RCT I, group 2   | RCT I, group 3   | RCT I, group 4   |
|---------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type                    | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed           | 20               | 22               | 25               | 25               |
| Units: nmol/l                         |                  |                  |                  |                  |
| median (inter-quartile range (Q1-Q3)) | 1.9 (1.5 to 2.3) | 2.1 (1.3 to 2.9) | 1.6 (1.0 to 2.4) | 2.3 (1.6 to 2.7) |

|                  |                 |                 |                 |  |
|------------------|-----------------|-----------------|-----------------|--|
| End point values | RCT II, group 1 | RCT II, group 2 | RCT II, group 3 |  |
|------------------|-----------------|-----------------|-----------------|--|

|                                       |                  |                  |                  |  |
|---------------------------------------|------------------|------------------|------------------|--|
| Subject group type                    | Reporting group  | Reporting group  | Reporting group  |  |
| Number of subjects analysed           | 25               | 22               | 22               |  |
| Units: nmol/l                         |                  |                  |                  |  |
| median (inter-quartile range (Q1-Q3)) | 2.5 (2.0 to 3.9) | 2.7 (1.7 to 3.5) | 2.9 (2.1 to 3.6) |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | progesterone levels   |
| Comparison groups                       | RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3 |
| Number of subjects included in analysis | 161   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | < 0.05  |
| Method                                  | Mixed models analysis   |

## Primary: Progesterone

|                        |              |
|------------------------|--------------|
| End point title        | Progesterone |
| End point description: |              |
| End point type         | Primary      |
| End point timeframe:   |              |
| Oocyte pick up (OPU)   |              |

|                                       |                   |                     |                     |                     |
|---------------------------------------|-------------------|---------------------|---------------------|---------------------|
| <b>End point values</b>               | RCT I, group 1    | RCT I, group 2      | RCT I, group 3      | RCT I, group 4      |
| Subject group type                    | Reporting group   | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed           | 21                | 22                  | 25                  | 26                  |
| Units: nmol/l                         |                   |                     |                     |                     |
| median (inter-quartile range (Q1-Q3)) | 20.4 (15.7 to 28) | 21.4 (17.7 to 35.0) | 16.8 (11.1 to 25.7) | 21.0 (17.3 to 31.0) |

|                                       |                     |                     |                     |  |
|---------------------------------------|---------------------|---------------------|---------------------|--|
| <b>End point values</b>               | RCT II, group 1     | RCT II, group 2     | RCT II, group 3     |  |
| Subject group type                    | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed           | 25                  | 22                  | 22                  |  |
| Units: nmol/l                         |                     |                     |                     |  |
| median (inter-quartile range (Q1-Q3)) | 35.0 (27.2 to 38.5) | 17.3 (14.5 to 27.8) | 23.4 (17.2 to 26.1) |  |

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | progesterone levels   |
| Comparison groups                       | RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3 |
| Number of subjects included in analysis | 163   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | < 0.05  |
| Method                                  | Mixed models analysis   |

## Primary: Progesterone

|                        |              |
|------------------------|--------------|
| End point title        | Progesterone |
| End point description: |              |
| End point type         | Primary      |
| End point timeframe:   |              |
| OPU+2                  |              |

|                                       |                      |                       |                      |                       |
|---------------------------------------|----------------------|-----------------------|----------------------|-----------------------|
| <b>End point values</b>               | RCT I, group 1       | RCT I, group 2        | RCT I, group 3       | RCT I, group 4        |
| Subject group type                    | Reporting group      | Reporting group       | Reporting group      | Reporting group       |
| Number of subjects analysed           | 21                   | 21                    | 25                   | 26                    |
| Units: nmol/l                         |                      |                       |                      |                       |
| median (inter-quartile range (Q1-Q3)) | 79.5 (60.7 to 110.0) | 104.0 (74.4 to 168.0) | 94.1 (58.2 to 177.0) | 125.5 (70.0 to 246.0) |

|                                       |                        |                        |                        |  |
|---------------------------------------|------------------------|------------------------|------------------------|--|
| <b>End point values</b>               | RCT II, group 1        | RCT II, group 2        | RCT II, group 3        |  |
| Subject group type                    | Reporting group        | Reporting group        | Reporting group        |  |
| Number of subjects analysed           | 25                     | 22                     | 22                     |  |
| Units: nmol/l                         |                        |                        |                        |  |
| median (inter-quartile range (Q1-Q3)) | 208.0 (114.0 to 266.0) | 204.5 (113.0 to 261.0) | 241.0 (119.0 to 282.0) |  |

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | progesterone levels   |
| Comparison groups                 | RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3 |

|   |                       |
|---|-----------------------|
| Number of subjects included in analysis | 162                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other                 |
| P-value                                 | < 0.05                |
| Method                                  | Mixed models analysis |

### Primary: Progesterone

|                        |              |
|------------------------|--------------|
| End point title        | Progesterone |
| End point description: |              |
| End point type         | Primary      |
| End point timeframe:   |              |
| OPU+4                  |              |

| End point values                      | RCT I, group 1       | RCT I, group 2       | RCT I, group 3         | RCT I, group 4         |
|---------------------------------------|----------------------|----------------------|------------------------|------------------------|
| Subject group type                    | Reporting group      | Reporting group      | Reporting group        | Reporting group        |
| Number of subjects analysed           | 20                   | 21                   | 24                     | 26                     |
| Units: nmol/l                         |                      |                      |                        |                        |
| median (inter-quartile range (Q1-Q3)) | 122 (105.0 to 281.0) | 228 (104.0 to 287.0) | 234.5 (120.0 to 364.0) | 286.5 (125.0 to 382.0) |

| End point values                      | RCT II, group 1        | RCT II, group 2        | RCT II, group 3        |  |
|---------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type                    | Reporting group        | Reporting group        | Reporting group        |  |
| Number of subjects analysed           | 25                     | 21                     | 22                     |  |
| Units: nmol/l                         |                        |                        |                        |  |
| median (inter-quartile range (Q1-Q3)) | 385.0 (290.0 to 442.0) | 363.0 (256.0 to 385.0) | 278.0 (186.0 to 417.0) |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | progesterone levels   |
| Comparison groups                       | RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3 |
| Number of subjects included in analysis | 159   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | < 0.05  |
| Method                                  | Mixed models analysis   |

**Primary: Progesterone**

|                 |              |
|-----------------|--------------|
| End point title | Progesterone |
|-----------------|--------------|

|                        |
|------------------------|
| End point description: |
|------------------------|

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

|                      |
|----------------------|
| End point timeframe: |
|----------------------|

|       |
|-------|
| OPU+6 |
|-------|

| End point values                      | RCT I, group 1       | RCT I, group 2        | RCT I, group 3       | RCT I, group 4        |
|---------------------------------------|----------------------|-----------------------|----------------------|-----------------------|
| Subject group type                    | Reporting group      | Reporting group       | Reporting group      | Reporting group       |
| Number of subjects analysed           | 20                   | 22                    | 25                   | 26                    |
| Units: nmol/l                         |                      |                       |                      |                       |
| median (inter-quartile range (Q1-Q3)) | 61.7 (36.0 to 181.0) | 171.5 (89.7 to 285.0) | 216 (125.0 to 299.0) | 207.0 (82.7 to 278.0) |

| End point values                      | RCT II, group 1        | RCT II, group 2       | RCT II, group 3        |  |
|---------------------------------------|------------------------|-----------------------|------------------------|--|
| Subject group type                    | Reporting group        | Reporting group       | Reporting group        |  |
| Number of subjects analysed           | 24                     | 22                    | 22                     |  |
| Units: nmol/l                         |                        |                       |                        |  |
| median (inter-quartile range (Q1-Q3)) | 234.0 (183.0 to 300.0) | 112.5 (57.9 to 236.0) | 354.5 (177.0 to 541.0) |  |

**Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | progesterone levels   |
| Comparison groups                       | RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3 |
| Number of subjects included in analysis | 161   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | < 0.05  |
| Method                                  | Mixed models analysis   |

**Primary: progesterone**

|                 |              |
|-----------------|--------------|
| End point title | progesterone |
|-----------------|--------------|

|                        |
|------------------------|
| End point description: |
|------------------------|

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

|                      |
|----------------------|
| End point timeframe: |
|----------------------|

|       |
|-------|
| OPU+8 |
|-------|

| <b>End point values</b>               | RCT I, group 1    | RCT I, group 2      | RCT I, group 3       | RCT I, group 4      |
|---------------------------------------|-------------------|---------------------|----------------------|---------------------|
| Subject group type                    | Reporting group   | Reporting group     | Reporting group      | Reporting group     |
| Number of subjects analysed           | 21                | 22                  | 25                   | 26                  |
| Units: nmol/l                         |                   |                     |                      |                     |
| median (inter-quartile range (Q1-Q3)) | 8.4 (6.4 to 24.5) | 19.1 (13.0 to 59.1) | 47.4 (31.4 to 116.0) | 47.2 (33.1 to 63.6) |

| <b>End point values</b>               | RCT II, group 1     | RCT II, group 2     | RCT II, group 3       |  |
|---------------------------------------|---------------------|---------------------|-----------------------|--|
| Subject group type                    | Reporting group     | Reporting group     | Reporting group       |  |
| Number of subjects analysed           | 24                  | 21                  | 21                    |  |
| Units: nmol/l                         |                     |                     |                       |  |
| median (inter-quartile range (Q1-Q3)) | 46.1 (34.7 to 55.8) | 42.0 (34.0 to 46.7) | 230.0 (75.7 to 321.0) |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | progesterone levels   |
|---|---|
| Comparison groups                       | RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3 |
| Number of subjects included in analysis | 160   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | < 0.05  |
| Method                                  | Mixed models analysis   |

### Primary: progesterone

|                        |              |
|------------------------|--------------|
| End point title        | progesterone |
| End point description: |              |
| End point type         | Primary      |
| End point timeframe:   |              |
| OPU+10                 |              |

| End point values                      | RCT I, group 1   | RCT I, group 2    | RCT I, group 3     | RCT I, group 4      |
|---------------------------------------|------------------|-------------------|--------------------|---------------------|
| Subject group type                    | Reporting group  | Reporting group   | Reporting group    | Reporting group     |
| Number of subjects analysed           | 21               | 22                | 24                 | 24                  |
| Units: nmol/l                         |                  |                   |                    |                     |
| median (inter-quartile range (Q1-Q3)) | 3.8 (1.2 to 7.4) | 5.8 (3.5 to 10.4) | 11.7 (7.1 to 56.0) | 36.1 (28.0 to 45.8) |

| End point values                      | RCT II, group 1     | RCT II, group 2     | RCT II, group 3      |  |
|---------------------------------------|---------------------|---------------------|----------------------|--|
| Subject group type                    | Reporting group     | Reporting group     | Reporting group      |  |
| Number of subjects analysed           | 23                  | 22                  | 21                   |  |
| Units: nmol/l                         |                     |                     |                      |  |
| median (inter-quartile range (Q1-Q3)) | 30.7 (26.2 to 45.1) | 31.9 (27.0 to 51.2) | 42.9 (32.4 to 252.0) |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | progesterone levels   |
| Comparison groups                       | RCT I, group 2 v RCT I, group 1 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3 |
| Number of subjects included in analysis | 157   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | < 0.05  |
| Method                                  | Mixed models analysis   |

## Primary: Progesterone

|                        |              |
|------------------------|--------------|
| End point title        | Progesterone |
| End point description: |              |
| End point type         | Primary      |
| End point timeframe:   |              |
| OPU+14                 |              |

| End point values                      | RCT I, group 1   | RCT I, group 2   | RCT I, group 3    | RCT I, group 4      |
|---------------------------------------|------------------|------------------|-------------------|---------------------|
| Subject group type                    | Reporting group  | Reporting group  | Reporting group   | Reporting group     |
| Number of subjects analysed           | 21               | 20               | 23                | 25                  |
| Units: nmol/l                         |                  |                  |                   |                     |
| median (inter-quartile range (Q1-Q3)) | 1.6 (1.2 to 7.4) | 1.5 (1.1 to 4.4) | 2.6 (1.1 to 90.3) | 34.0 (27.1 to 48.0) |

| <b>End point values</b>               | RCT II, group 1     | RCT II, group 2     | RCT II, group 3      |  |
|---------------------------------------|---------------------|---------------------|----------------------|--|
| Subject group type                    | Reporting group     | Reporting group     | Reporting group      |  |
| Number of subjects analysed           | 24                  | 22                  | 21                   |  |
| Units: nmol/l                         |                     |                     |                      |  |
| median (inter-quartile range (Q1-Q3)) | 31.3 (25.3 to 53.8) | 33.2 (25.5 to 58.8) | 29.1 (24.0 to 461.0) |  |

### Statistical analyses

| <b>Statistical analysis title</b>       | progesterone levels   |
|---|---|
| Comparison groups                       | RCT I, group 1 v RCT I, group 2 v RCT I, group 3 v RCT I, group 4 v RCT II, group 1 v RCT II, group 2 v RCT II, group 3 |
| Number of subjects included in analysis | 156   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other   |
| P-value                                 | < 0.05  |
| Method                                  | Mixed models analysis   |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

14 dec. 2014 until 29. aug 2020, for each patient from randomization until OPU+14 or ultrasonography in gestational week 7.

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

### Dictionary used

|                 |      |
|-----------------|------|
| Dictionary name | none |
|-----------------|------|

|                    |   |
|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | RCT I |
|-----------------------|-------|

Reporting group description:

Group 1, 2, 3, 4

|                       |        |
|-----------------------|--------|
| Reporting group title | RCT II |
|-----------------------|--------|

Reporting group description:

Group 5, 6, 7

| Serious adverse events                            | RCT I           | RCT II         |  |
|---|-----------------|----------------|--|
| Total subjects affected by serious adverse events |                 |                |  |
| subjects affected / exposed                       | 0 / 127 (0.00%) | 0 / 95 (0.00%) |  |
| number of deaths (all causes)                     | 0               | 0              |  |
| number of deaths resulting from adverse events    | 0               | 0              |  |

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

| Non-serious adverse events                            | RCT I   | RCT II           |  |
|---|---|------------------|--|
| Total subjects affected by non-serious adverse events |   |                  |  |
| subjects affected / exposed                           | 27 / 127 (21.26%)   | 20 / 95 (21.05%) |  |
| General disorders and administration site conditions  |   |                  |  |
| Local reaction  | Additional description: Pain at the injection site        |                  |  |
| subjects affected / exposed                           | 13 / 127 (10.24%)   | 0 / 95 (0.00%)   |  |
| occurrences (all)                                     | 13  | 0                |  |
| OHSS  | Additional description: ovarian hyperstimulation syndrome |                  |  |
| subjects affected / exposed                           | 5 / 127 (3.94%)   | 7 / 95 (7.37%)   |  |
| occurrences (all)                                     | 5   | 7                |  |
| bloated stomach                                       |   |                  |  |

|   |                      |                       |  |
|---|----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 8 / 127 (6.30%)<br>3 | 12 / 95 (12.63%)<br>8 |  |
| Endocrine disorders<br>sore breasts<br>subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1 | 5 / 95 (5.26%)<br>3   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 08 December 2015  | Before randomization of the first patient into group 4-5-6-7, Prolutex was changed to Crinone. It was not possible to have Prolutex for all the patients. It didn't affect the study outcome. |
| 11 September 2017 | extension of the inclusion periode  |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported