



## Clinical trial results:

**A Phase III, randomized, controlled, single-blind, multicentre, parallel arm trial to assess the efficacy and safety of Pergoveris® (follitropin alfa and lutropin alfa) and GONAL-f® (follitropin alfa) for multifollicular development as part of an assisted reproductive technology treatment cycle in poor ovarian responders, as defined by the European Society of Human Reproduction and Embryology criteria**

### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2013-003817-16                   |
| Trial protocol           | CZ SE EE HU BE GB NL DK LV ES PL |
| Global end of trial date | 05 August 2015                   |

### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v2 (current)   |
| This version publication date     | 12 August 2017   |
| First version publication date    | 13 August 2016   |
| Version creation reason           | • Changes to summary attachments<br>Result publication to be added |
| Summary attachment (see zip file) | Publication (Humaidan et al ESPART final e-pub.pdf)                |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | EMR200061-005 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02047227 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Merck KGaA   |
| Sponsor organisation address | Frankfurter Strasse 250 , Darmstadt, Germany, 64293                                  |
| Public contact               | Communication Center Merck KGaA , Merck KGaA, +49 6151725200, service@merckgroup.com |
| Scientific contact           | Communication Center Merck KGaA , Merck KGaA, +49 6151725200, service@merckgroup.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                       | 05 August 2015 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 05 August 2015 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 05 August 2015 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate superiority of Pergoveris versus GONAL-f in poor ovarian response (POR) subjects as aligned with the 2011 Consensus Meeting of the European Society of Human Reproduction and Embryology (ESHRE)

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 30 January 2014 |
| Long term follow-up planned                               | Yes             |
| Long term follow-up rationale                             | Safety          |
| Long term follow-up duration                              | 6 Months        |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 20        |
| Country: Number of subjects enrolled | Czech Republic: 54 |
| Country: Number of subjects enrolled | Denmark: 12        |
| Country: Number of subjects enrolled | Estonia: 30        |
| Country: Number of subjects enrolled | France: 21         |
| Country: Number of subjects enrolled | Germany: 48        |
| Country: Number of subjects enrolled | Hungary: 69        |
| Country: Number of subjects enrolled | Italy: 111         |
| Country: Number of subjects enrolled | Latvia: 57         |
| Country: Number of subjects enrolled | Netherlands: 3     |
| Country: Number of subjects enrolled | Poland: 107        |
| Country: Number of subjects enrolled | Spain: 267         |
| Country: Number of subjects enrolled | Sweden: 8          |
| Country: Number of subjects enrolled | Turkey: 101        |
| Country: Number of subjects enrolled | United Kingdom: 31 |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 939 |
| EEA total number of subjects       | 838 |

Notes:

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### Subjects enrolled per age group

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|   |     |
|---|-----|
| 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)                      | 939 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study was conducted at 101 sites in 15 countries.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Single blind                   |
| Roles blinded                | Investigator <sup>[1]</sup>    |

### Arms

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

Arm description:

Pergoveris (follitropin alfa and lutropin alfa) was administered subcutaneously once daily with a starting dose of 300 International Unit (IU) recombinant human follicular stimulating hormone (rhFSH)/ 150 IU recombinant human luteinizing hormone (rhLH) after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 millimeter (mm); 250 microgram (mcg) of r-hCG (Ovidrel) was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments while maintaining the 2:1 ratio of r hFSH to r-hLH in the Pergoveris group based on the subject's response per site standard clinical practice.

|  |   |
|--|---|
| Arm type                               | Experimental                                  |
| Investigational medicinal product name | Pergoveris                                    |
| Investigational medicinal product code |   |
| Other name                             | r-hFSH/r-hLH, Follitropin alfa/Lutropin alfa  |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Subcutaneous use                              |

Dosage and administration details:

Pergoveris was administered subcutaneously once daily with a starting dose of 300 IU rhFSH/150 IU rhLH.

|  |   |
|--|---|
| Investigational medicinal product name | Recombinant human chorionic gonadotrophin (r-hCG) |
| Investigational medicinal product code |   |
| Other name                             | Ovidrel, Ovitrelle, choriogonadotropin alfa       |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe      |
| Routes of administration               | Subcutaneous use                                  |

Dosage and administration details:

250 mcg of r-hCG was administered once subcutaneously

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

Arm description:

GONAL-f (r-hFSH) was self-administered subcutaneously once daily at a starting dose of 300 IU after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 mm; 250 mcg of r-hCG was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments based on the subject's response per site standard clinical practice.

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

|  |   |
|--|---|
| Investigational medicinal product name | GONAL-f                                       |
| Investigational medicinal product code |   |
| Other name                             | r-hFSH, Follitropin alfa                      |
| Pharmaceutical forms                   | Powder and solvent for solution for injection |
| Routes of administration               | Subcutaneous use                              |

Dosage and administration details:

GONAL-f (r-hFSH) was self-administered subcutaneously once daily at a starting dose of 300 IU.

|  |   |
|--|---|
| Investigational medicinal product name | Recombinant human chorionic gonadotrophin (r-hCG) |
| Investigational medicinal product code |   |
| Other name                             | Ovidrel, Ovitrelle, choriogonadotropin alfa       |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe      |
| Routes of administration               | Subcutaneous use                                  |

Dosage and administration details:

250 mcg of r-hCG was administered once subcutaneously.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The trial was single-blinded where the Investigator and all site personnel (with the exception of the trial Nurse/Coordinator and/or Pharmacist/Pharmacy Assistant) remained blinded, throughout the course of the trial as to which treatment each subject received. The subject, however, was informed by the trial nurse or pharmacist of which treatment they were receiving.

| <b>Number of subjects in period 1</b>   | Pergoveris | GONAL-f |
|---|------------|---------|
| Started                                 | 462        | 477     |
| Completed ovarian stimulation phase     | 424        | 440     |
| Completed                               | 318        | 347     |
| Not completed                           | 144        | 130     |
| No fertilization                        | 61         | 51      |
| Intention to freeze all embryos         | 1          | -       |
| Adverse event, non-fatal                | 2          | 4       |
| All embryos discarded                   | 12         | 11      |
| No oocytes retrieved                    | 21         | 20      |
| Lack of ovarian response to stimulation | 35         | 32      |
| Unspecified                             | 10         | 9       |
| Spontaneous pregnancy                   | 1          | -       |
| Lost to follow-up                       | -          | 3       |
| Protocol deviation                      | 1          | -       |

## Baseline characteristics

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Pergoveris |
|-----------------------|------------|

Reporting group description:

Pergoveris (follitropin alfa and lutropin alfa) was administered subcutaneously once daily with a starting dose of 300 International Unit (IU) recombinant human follicular stimulating hormone (rhFSH)/ 150 IU recombinant human luteinizing hormone (rhLH) after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 millimeter (mm); 250 microgram (mcg) of r-hCG (Ovidrel) was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments while maintaining the 2:1 ratio of r hFSH to r-hLH in the Pergoveris group based on the subject's response per site standard clinical practice.

|                       |         |
|-----------------------|---------|
| Reporting group title | GONAL-f |
|-----------------------|---------|

Reporting group description:

GONAL-f (r-hFSH) was self-administered subcutaneously once daily at a starting dose of 300 IU after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 mm; 250 mcg of r-hCG was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments based on the subject's response per site standard clinical practice.

| Reporting group values             | Pergoveris | GONAL-f | Total |
|------------------------------------|------------|---------|-------|
| Number of subjects                 | 462        | 477     | 939   |
| Age categorical<br>Units: Subjects |            |         |       |

|  |       |      |     |
|--|-------|------|-----|
| Age Continuous   |       |      |     |
| All Randomized Subjects Set included all subjects who were randomized. |       |      |     |
| Units: years   |       |      |     |
| arithmetic mean  | 38.3  | 38.3 |     |
| standard deviation   | ± 2.9 | ± 3  | -   |
| Gender, Male/Female  |       |      |     |
| Units: subjects  |       |      |     |
| Female   | 462   | 477  | 939 |
| Male   | 0     | 0    | 0   |

## End points

### End points reporting groups

|  |            |
|--|------------|
| Reporting group title  | Pergoveris |
| Reporting group description:<br>Pergoveris (follitropin alfa and lutropin alfa) was administered subcutaneously once daily with a starting dose of 300 International Unit (IU) recombinant human follicular stimulating hormone (rhFSH)/ 150 IU recombinant human luteinizing hormone (rhLH) after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 millimeter (mm); 250 microgram (mcg) of r-hCG (Ovidrel) was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments while maintaining the 2:1 ratio of r hFSH to r-hLH in the Pergoveris group based on the subject's response per site standard clinical practice. |            |
| Reporting group title  | GONAL-f    |
| Reporting group description:<br>GONAL-f (r-hFSH) was self-administered subcutaneously once daily at a starting dose of 300 IU after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 mm; 250 mcg of r-hCG was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments based on the subject's response per site standard clinical practice.  |            |

### Primary: Number of oocytes retrieved

|  |                             |
|--|-----------------------------|
| End point title  | Number of oocytes retrieved |
| End point description:<br>Mean number of oocytes retrieved on the day of ovum pick up (OPU) was calculated. Oocyte retrieval was a technique used in in-vitro fertilization in order to remove oocytes from the ovary of the female, enabling fertilization outside the body. Intent-to-treat (ITT) analysis set included all subjects randomized who received at least 1 dose of GONAL-f or Pergoveris. |                             |
| End point type   | Primary                     |
| End point timeframe:<br>At approximately 34 to 38 hours after r-hCG administration   |                             |

| End point values                     | Pergoveris        | GONAL-f           |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 462               | 477               |  |  |
| Units: oocytes                       |                   |                   |  |  |
| arithmetic mean (standard deviation) | 3.3 ( $\pm$ 2.71) | 3.6 ( $\pm$ 2.82) |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Comparison between Pergoveris and Gonal f groups |
| Comparison groups          | GONAL-f v Pergoveris                             |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 939                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.054                  |
| Method                                  | Poisson Regression Model |
| Parameter estimate                      | Mean difference (net)    |
| Point estimate                          | -0.235                   |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | -0.4741                  |
| upper limit                             | 0.003                    |

### Secondary: Ongoing pregnancy rate

|   |                        |
|---|------------------------|
| End point title   | Ongoing pregnancy rate |
| End point description:  |                        |
| Ongoing pregnancy rate was defined as the percentage of subjects with a ultrasound confirmation of at least one viable fetus (positive fetal heart beat). Modified intent-to-treat (MITT) analysis set included all randomized subjects who received at least 1 dose of GONAL-f or Pergoveris and did not have spontaneous pregnancy or death at approximately 34-38 hours after rhCG administration. |                        |
| End point type  | Secondary              |
| End point timeframe:  |                        |
| 70 days after embryo transfer   |                        |

| End point values              | Pergoveris      | GONAL-f         |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 462             | 477             |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       | 11              | 12.4            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Live birth rate

|   |                 |
|---|-----------------|
| End point title   | Live birth rate |
| End point description:  |                 |
| Live birth rate was defined as the percentage of subjects with at least one live-born neonate. MITT analysis set included all randomized subjects who received at least 1 dose of GONAL-f or Pergoveris and did not have spontaneous pregnancy or death at approximately 34-38 hours after rhCG administration. |                 |
| End point type  | Secondary       |
| End point timeframe:  |                 |
| Approximately 180 days following ongoing pregnancy determination  |                 |



| End point values              | Pergoveris      | GONAL-f         |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 462             | 477             |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       | 10.6            | 11.7            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Embryo implantation rate

|  |                          |
|--|--------------------------|
| End point title  | Embryo implantation rate |
| End point description:   |                          |
| Embryo implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred per subject. MITT analysis set included all randomized subjects who received at least 1 dose of GONAL-f or Pergoveris and did not have spontaneous pregnancy or death at approximately 34-38 hours after rhCG administration. Number of subjects analysed signifies those subjects who were evaluable for this endpoint. |                          |
| End point type   | Secondary                |
| End point timeframe:   |                          |
| 2 to 3 days following oocyte retrieval   |                          |

| End point values            | Pergoveris      | GONAL-f         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 319             | 349             |  |  |
| Units: sacs/embryos/subject |                 |                 |  |  |
| number (not applicable)     | 14.7            | 15.6            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Clinical pregnancy rate

|   |                         |
|---|-------------------------|
| End point title   | Clinical pregnancy rate |
| End point description:  |                         |
| Clinical pregnancy rate defined as the percentage of subjects with a ultrasound confirmation of a gestational sac, with or without fetal heart activity. MITT analysis set included all randomized subjects who received at least 1 dose of GONAL-f or Pergoveris and did not have spontaneous pregnancy or death at approximately 34-38 hours after rhCG administration. |                         |
| End point type  | Secondary               |

End point timeframe:

35-42 days post r-hCG administration

| End point values              | Pergoveris      | GONAL-f         |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 462             | 477             |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       | 14.1            | 16.8            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Biochemical pregnancy rate

|                 |                            |
|-----------------|----------------------------|
| End point title | Biochemical pregnancy rate |
|-----------------|----------------------------|

End point description:

Biochemical pregnancy rate was defined as the percentage of subjects with a positive beta-hCG result from the serum pregnancy test. MITT Analysis Set included all randomized subjects who received at least 1 dose of GONAL-f or Pergoveris and did not have spontaneous pregnancy or death at approximately 34-38 hours after rhCG administration.

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

End point timeframe:

15 to 20 days post r-hCG administration.

| End point values              | Pergoveris      | GONAL-f         |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 462             | 477             |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       | 17.3            | 23.9            |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to 180 days after ongoing pregnancy (maximum up to 365 days)

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | Pergoveris |
|-----------------------|------------|

Reporting group description:

Pergoveris (follitropin alfa and lutropin alfa) was administered subcutaneously once daily with a starting dose of 300 IU rhFSH/150 IU rhLH after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 mm; 250 mcg of r-hCG was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments while maintaining the 2:1 ratio of r hFSH to r-hLH in the Pergoveris group based on the subject's response per site standard clinical practice.

|                       |         |
|-----------------------|---------|
| Reporting group title | GONAL-f |
|-----------------------|---------|

Reporting group description:

GONAL-f (r-hFSH) was self-administered subcutaneously once daily at a starting dose of 300 IU after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 mm; 250 mcg of r-hCG was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments based on the subject's response per site standard clinical practice.

| Serious adverse events                            | Pergoveris      | GONAL-f          |  |
|---|-----------------|------------------|--|
| Total subjects affected by serious adverse events |                 |                  |  |
| subjects affected / exposed                       | 8 / 462 (1.73%) | 17 / 477 (3.56%) |  |
| number of deaths (all causes)                     | 0               | 0                |  |
| number of deaths resulting from adverse events    | 0               | 0                |  |
| Injury, poisoning and procedural complications    |                 |                  |  |
| Overdose  |                 |                  |  |
| subjects affected / exposed                       | 0 / 462 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0            |  |
| Congenital, familial and genetic disorders        |                 |                  |  |
| Fallot's tetralogy                                |                 |                  |  |
| subjects affected / exposed                       | 0 / 462 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all   | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all        | 0 / 0           | 0 / 0            |  |
| Trisomy 21  |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Ventricular extrasystoles                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pregnancy, puerperium and perinatal conditions  |                 |                 |  |
| Abortion missed                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 3 / 477 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abortion  |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abortion spontaneous                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Premature labour                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ectopic pregnancy                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foetal death                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Hyperemesis gravidarum                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Imminent abortion                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (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                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Threatened labour                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Premature delivery                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders        |                 |                 |  |
| Ovarian cyst                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian cyst ruptured                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ovarian haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Ovarian rupture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Urticaria                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                     | Pergoveris         | GONAL-f            |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 111 / 462 (24.03%) | 151 / 477 (31.66%) |  |
| Vascular disorders                                    |                    |                    |  |
| Hot flush   |                    |                    |  |
| subjects affected / exposed                           | 19 / 462 (4.11%)   | 10 / 477 (2.10%)   |  |
| occurrences (all)                                     | 23                 | 13                 |  |
| Flushing  |                    |                    |  |
| subjects affected / exposed                           | 3 / 462 (0.65%)    | 0 / 477 (0.00%)    |  |
| occurrences (all)                                     | 3                  | 0                  |  |
| Circulatory collapse                                  |                    |                    |  |
| subjects affected / exposed                           | 1 / 462 (0.22%)    | 0 / 477 (0.00%)    |  |
| occurrences (all)                                     | 2                  | 0                  |  |
| Hypertension  |                    |                    |  |
| subjects affected / exposed                           | 1 / 462 (0.22%)    | 0 / 477 (0.00%)    |  |
| occurrences (all)                                     | 3                  | 0                  |  |
| Venous thrombosis                                     |                    |                    |  |

|  |                       |                        |  |
|--|-----------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 462 (0.00%)<br>0  | 1 / 477 (0.21%)<br>1   |  |
| Surgical and medical procedures<br>Abortion induced<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 462 (0.00%)<br>0  | 1 / 477 (0.21%)<br>1   |  |
| Pregnancy, puerperium and perinatal conditions<br>Abortion spontaneous<br>subjects affected / exposed<br>occurrences (all) | 6 / 462 (1.30%)<br>16 | 12 / 477 (2.52%)<br>12 |  |
| Abortion missed<br>subjects affected / exposed<br>occurrences (all)  | 5 / 462 (1.08%)<br>5  | 5 / 477 (1.05%)<br>5   |  |
| Abortion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 462 (0.22%)<br>1  | 1 / 477 (0.21%)<br>1   |  |
| Foetal death<br>subjects affected / exposed<br>occurrences (all)   | 0 / 462 (0.00%)<br>0  | 2 / 477 (0.42%)<br>2   |  |
| Placenta praevia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 462 (0.00%)<br>0  | 1 / 477 (0.21%)<br>1   |  |
| Vomiting in pregnancy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 462 (0.00%)<br>0  | 1 / 477 (0.21%)<br>1   |  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)        | 5 / 462 (1.08%)<br>5  | 4 / 477 (0.84%)<br>7   |  |
| Injection site erythema<br>subjects affected / exposed<br>occurrences (all)  | 4 / 462 (0.87%)<br>6  | 4 / 477 (0.84%)<br>8   |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)   | 2 / 462 (0.43%)<br>2  | 1 / 477 (0.21%)<br>1   |  |
| Chest discomfort   |                       |                        |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Gait disturbance            |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Hyperthermia                |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Injection site haematoma    |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Injection site pain         |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Malaise                     |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Oedema peripheral           |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Peripheral swelling         |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Pyrexia                     |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Immune system disorders     |                 |                 |  |
| Crying                      |                 |                 |  |
| subjects affected / exposed | 2 / 462 (0.43%) | 3 / 477 (0.63%) |  |
| occurrences (all)           | 2               | 3               |  |
| Food allergy                |                 |                 |  |
| subjects affected / exposed | 2 / 462 (0.43%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 2               | 0               |  |
| Allergy to arthropod bite   |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |



|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)       | 1 / 462 (0.22%)<br>2 | 0 / 477 (0.00%)<br>0 |  |
| Reproductive system and breast disorders                                   |                      |                      |  |
| Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all)          | 6 / 462 (1.30%)<br>7 | 6 / 477 (1.26%)<br>6 |  |
| Breast tenderness<br>subjects affected / exposed<br>occurrences (all)      | 3 / 462 (0.65%)<br>3 | 2 / 477 (0.42%)<br>2 |  |
| Vaginal haemorrhage<br>subjects affected / exposed<br>occurrences (all)    | 2 / 462 (0.43%)<br>2 | 6 / 477 (1.26%)<br>6 |  |
| Adnexa uteri pain<br>subjects affected / exposed<br>occurrences (all)      | 2 / 462 (0.43%)<br>2 | 1 / 477 (0.21%)<br>2 |  |
| Dyspareunia<br>subjects affected / exposed<br>occurrences (all)            | 0 / 462 (0.00%)<br>0 | 2 / 477 (0.42%)<br>3 |  |
| Menstruation irregular<br>subjects affected / exposed<br>occurrences (all) | 1 / 462 (0.22%)<br>1 | 1 / 477 (0.21%)<br>1 |  |
| Metrorrhagia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 462 (0.00%)<br>0 | 2 / 477 (0.42%)<br>2 |  |
| Ovarian cyst<br>subjects affected / exposed<br>occurrences (all)           | 0 / 462 (0.00%)<br>0 | 2 / 477 (0.42%)<br>2 |  |
| Uterine polyp<br>subjects affected / exposed<br>occurrences (all)          | 1 / 462 (0.22%)<br>1 | 1 / 477 (0.21%)<br>1 |  |
| Vulvovaginal dryness<br>subjects affected / exposed<br>occurrences (all)   | 0 / 462 (0.00%)<br>0 | 2 / 477 (0.42%)<br>3 |  |
| Vulvovaginal pruritus  |                      |                      |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 462 (0.22%) | 1 / 477 (0.21%) |  |
| occurrences (all)                               | 1               | 1               |  |
| Breast mass                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Nipple disorder                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Premenstrual pain                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Pelvic pain                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Vaginal inflammation                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Vulvovaginal discomfort                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Vulvovaginal burning sensation                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Breast pain                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 462 (0.43%) | 2 / 477 (0.42%) |  |
| occurrences (all)                               | 4               | 2               |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Rhinorrhoea                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 462 (0.43%) | 1 / 477 (0.21%) |  |
| occurrences (all)                               | 2               | 1               |  |
| Oropharyngeal pain                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 462 (0.65%) | 0 / 477 (0.00%) |  |
| occurrences (all)                               | 3               | 0               |  |
| Cough   |                 |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 462 (0.22%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 1               | 1               |  |
| Epistaxis                   |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences (all)           | 0               | 2               |  |
| Nasal congestion            |                 |                 |  |
| subjects affected / exposed | 2 / 462 (0.43%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 4               | 0               |  |
| Nasal discomfort            |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Dyspnoea exertional         |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Psychiatric disorders       |                 |                 |  |
| Anxiety                     |                 |                 |  |
| subjects affected / exposed | 2 / 462 (0.43%) | 3 / 477 (0.63%) |  |
| occurrences (all)           | 2               | 3               |  |
| Insomnia                    |                 |                 |  |
| subjects affected / exposed | 2 / 462 (0.43%) | 3 / 477 (0.63%) |  |
| occurrences (all)           | 5               | 3               |  |
| Mood swings                 |                 |                 |  |
| subjects affected / exposed | 3 / 462 (0.65%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 3               | 1               |  |
| Nervousness                 |                 |                 |  |
| subjects affected / exposed | 2 / 462 (0.43%) | 2 / 477 (0.42%) |  |
| occurrences (all)           | 2               | 2               |  |
| Agitation                   |                 |                 |  |
| subjects affected / exposed | 2 / 462 (0.43%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 2               | 0               |  |
| Depressive symptom          |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 1               | 1               |  |
| Depressed mood              |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| Affective disorder          |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Depression                  |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Irritability                |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Libido increased            |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Tearfulness                 |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Investigations              |                 |                 |  |
| Body temperature increased  |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 4 / 477 (0.84%) |  |
| occurrences (all)           | 1               | 4               |  |
| Weight increased            |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 2 / 477 (0.42%) |  |
| occurrences (all)           | 1               | 3               |  |
| Menstruation normal         |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 1               | 1               |  |
| Blood creatinine increased  |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Blood glucose increased     |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Blood urine present         |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Urine ketone body           |                 |                 |  |

|   |                        |                         |  |
|---|------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                          | 0 / 462 (0.00%)<br>0   | 1 / 477 (0.21%)<br>1    |  |
| Nitrite urine present<br>subjects affected / exposed<br>occurrences (all) | 1 / 462 (0.22%)<br>1   | 0 / 477 (0.00%)<br>0    |  |
| Injury, poisoning and procedural complications                            |                        |                         |  |
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)        | 1 / 462 (0.22%)<br>1   | 2 / 477 (0.42%)<br>2    |  |
| Overdose<br>subjects affected / exposed<br>occurrences (all)              | 1 / 462 (0.22%)<br>1   | 2 / 477 (0.42%)<br>2    |  |
| Procedural pain<br>subjects affected / exposed<br>occurrences (all)       | 0 / 462 (0.00%)<br>0   | 2 / 477 (0.42%)<br>2    |  |
| Animal bite<br>subjects affected / exposed<br>occurrences (all)           | 0 / 462 (0.00%)<br>0   | 1 / 477 (0.21%)<br>1    |  |
| Tooth fracture<br>subjects affected / exposed<br>occurrences (all)        | 1 / 462 (0.22%)<br>1   | 0 / 477 (0.00%)<br>0    |  |
| Cardiac disorders   |                        |                         |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)          | 2 / 462 (0.43%)<br>2   | 0 / 477 (0.00%)<br>0    |  |
| Tachycardia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 462 (0.00%)<br>0   | 1 / 477 (0.21%)<br>1    |  |
| Nervous system disorders  |                        |                         |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)              | 46 / 462 (9.96%)<br>60 | 58 / 477 (12.16%)<br>80 |  |
| Migraine<br>subjects affected / exposed<br>occurrences (all)              | 5 / 462 (1.08%)<br>7   | 2 / 477 (0.42%)<br>2    |  |
| Dizziness   |                        |                         |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 4 / 462 (0.87%)<br>4 | 8 / 477 (1.68%)<br>8 |  |
| Somnolence<br>subjects affected / exposed<br>occurrences (all)   | 3 / 462 (0.65%)<br>3 | 1 / 477 (0.21%)<br>2 |  |
| Head discomfort<br>subjects affected / exposed<br>occurrences (all)  | 1 / 462 (0.22%)<br>1 | 1 / 477 (0.21%)<br>1 |  |
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 462 (0.22%)<br>1 | 2 / 477 (0.42%)<br>2 |  |
| Disturbance in attention<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 462 (0.00%)<br>0 | 1 / 477 (0.21%)<br>1 |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 462 (0.00%)<br>0 | 1 / 477 (0.21%)<br>1 |  |
| Restless legs syndrome<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 462 (0.22%)<br>1 | 0 / 477 (0.00%)<br>0 |  |
| Sciatica<br>subjects affected / exposed<br>occurrences (all)   | 1 / 462 (0.22%)<br>1 | 0 / 477 (0.00%)<br>0 |  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)  | 0 / 462 (0.00%)<br>0 | 1 / 477 (0.21%)<br>1 |  |
| Blood and lymphatic system disorders<br>Anaemia of pregnancy<br>subjects affected / exposed<br>occurrences (all) | 0 / 462 (0.00%)<br>0 | 1 / 477 (0.21%)<br>1 |  |
| Iron deficiency anaemia<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 462 (0.00%)<br>0 | 1 / 477 (0.21%)<br>1 |  |
| Lymph node pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 462 (0.22%)<br>1 | 0 / 477 (0.00%)<br>0 |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)      | 0 / 462 (0.00%)<br>0   | 1 / 477 (0.21%)<br>1   |  |
| Ear and labyrinth disorders  |                        |                        |  |
| Ear swelling<br>subjects affected / exposed<br>occurrences (all)         | 1 / 462 (0.22%)<br>1   | 0 / 477 (0.00%)<br>0   |  |
| Vertigo<br>subjects affected / exposed<br>occurrences (all)              | 2 / 462 (0.43%)<br>2   | 0 / 477 (0.00%)<br>0   |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)             | 1 / 462 (0.22%)<br>1   | 0 / 477 (0.00%)<br>0   |  |
| Eye disorders  |                        |                        |  |
| Eye pain<br>subjects affected / exposed<br>occurrences (all)             | 1 / 462 (0.22%)<br>1   | 0 / 477 (0.00%)<br>0   |  |
| Ocular hyperaemia<br>subjects affected / exposed<br>occurrences (all)    | 1 / 462 (0.22%)<br>1   | 0 / 477 (0.00%)<br>0   |  |
| Photophobia<br>subjects affected / exposed<br>occurrences (all)          | 1 / 462 (0.22%)<br>1   | 0 / 477 (0.00%)<br>0   |  |
| Gastrointestinal disorders   |                        |                        |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)               | 15 / 462 (3.25%)<br>20 | 12 / 477 (2.52%)<br>12 |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 12 / 462 (2.60%)<br>15 | 13 / 477 (2.73%)<br>13 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 4 / 462 (0.87%)<br>4   | 7 / 477 (1.47%)<br>8   |  |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all) | 5 / 462 (1.08%)<br>5   | 5 / 477 (1.05%)<br>5   |  |
| Vomiting   |                        |                        |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed            | 4 / 462 (0.87%) | 5 / 477 (1.05%) |  |
| occurrences (all)                      | 5               | 5               |  |
| Abdominal discomfort                   |                 |                 |  |
| subjects affected / exposed            | 5 / 462 (1.08%) | 3 / 477 (0.63%) |  |
| occurrences (all)                      | 5               | 3               |  |
| Abdominal distension                   |                 |                 |  |
| subjects affected / exposed            | 1 / 462 (0.22%) | 7 / 477 (1.47%) |  |
| occurrences (all)                      | 1               | 9               |  |
| Constipation                           |                 |                 |  |
| subjects affected / exposed            | 2 / 462 (0.43%) | 1 / 477 (0.21%) |  |
| occurrences (all)                      | 2               | 1               |  |
| Toothache                              |                 |                 |  |
| subjects affected / exposed            | 1 / 462 (0.22%) | 1 / 477 (0.21%) |  |
| occurrences (all)                      | 1               | 1               |  |
| Abdominal tenderness                   |                 |                 |  |
| subjects affected / exposed            | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                      | 1               | 0               |  |
| Abdominal rigidity                     |                 |                 |  |
| subjects affected / exposed            | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                      | 1               | 0               |  |
| Anal fissure                           |                 |                 |  |
| subjects affected / exposed            | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                      | 0               | 1               |  |
| Hypoaesthesia oral                     |                 |                 |  |
| subjects affected / exposed            | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                      | 1               | 0               |  |
| Abdominal pain upper                   |                 |                 |  |
| subjects affected / exposed            | 0 / 462 (0.00%) | 4 / 477 (0.84%) |  |
| occurrences (all)                      | 0               | 5               |  |
| Skin and subcutaneous tissue disorders |                 |                 |  |
| Night sweats                           |                 |                 |  |
| subjects affected / exposed            | 2 / 462 (0.43%) | 2 / 477 (0.42%) |  |
| occurrences (all)                      | 2               | 2               |  |
| Dermatitis allergic                    |                 |                 |  |
| subjects affected / exposed            | 1 / 462 (0.22%) | 1 / 477 (0.21%) |  |
| occurrences (all)                      | 1               | 1               |  |



|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| Hyperhidrosis               |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences (all)           | 0               | 2               |  |
| Acne                        |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Dermatitis atopic           |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Erythema                    |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Papule                      |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Photosensitivity reaction   |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Pityriasis rosea            |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Pruritus                    |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Skin burning sensation      |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Solar dermatitis            |                 |                 |  |
| subjects affected / exposed | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 0               | 1               |  |
| Renal and urinary disorders |                 |                 |  |
| Leukocyturia                |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 1 / 477 (0.21%) |  |
| occurrences (all)           | 1               | 1               |  |
| Haematuria                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 462 (0.22%) | 2 / 477 (0.42%) |  |
| occurrences (all)                               | 1               | 2               |  |
| Proteinuria                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 1 / 477 (0.21%) |  |
| occurrences (all)                               | 1               | 1               |  |
| Dysuria   |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Cystitis noninfective                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Pollakiuria                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Urethral pain                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Endocrine disorders                             |                 |                 |  |
| Hypothyroidism                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 4 / 462 (0.87%) | 6 / 477 (1.26%) |  |
| occurrences (all)                               | 5               | 6               |  |
| Neck pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences (all)                               | 0               | 2               |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 462 (0.43%) | 3 / 477 (0.63%) |  |
| occurrences (all)                               | 2               | 5               |  |
| Muscle tightness                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Musculoskeletal pain                            |                 |                 |  |

|                                |                 |                 |  |
|--------------------------------|-----------------|-----------------|--|
| subjects affected / exposed    | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)              | 0               | 1               |  |
| Myalgia                        |                 |                 |  |
| subjects affected / exposed    | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)              | 0               | 1               |  |
| Pain in extremity              |                 |                 |  |
| subjects affected / exposed    | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)              | 0               | 1               |  |
| Infections and infestations    |                 |                 |  |
| Nasopharyngitis                |                 |                 |  |
| subjects affected / exposed    | 4 / 462 (0.87%) | 2 / 477 (0.42%) |  |
| occurrences (all)              | 4               | 2               |  |
| Urinary tract infection        |                 |                 |  |
| subjects affected / exposed    | 2 / 462 (0.43%) | 3 / 477 (0.63%) |  |
| occurrences (all)              | 2               | 3               |  |
| Vulvovaginal mycotic infection |                 |                 |  |
| subjects affected / exposed    | 1 / 462 (0.22%) | 3 / 477 (0.63%) |  |
| occurrences (all)              | 1               | 3               |  |
| Cystitis                       |                 |                 |  |
| subjects affected / exposed    | 0 / 462 (0.00%) | 3 / 477 (0.63%) |  |
| occurrences (all)              | 0               | 3               |  |
| Gastroenteritis                |                 |                 |  |
| subjects affected / exposed    | 1 / 462 (0.22%) | 2 / 477 (0.42%) |  |
| occurrences (all)              | 1               | 3               |  |
| Oral herpes                    |                 |                 |  |
| subjects affected / exposed    | 1 / 462 (0.22%) | 2 / 477 (0.42%) |  |
| occurrences (all)              | 1               | 2               |  |
| Sinusitis bacterial            |                 |                 |  |
| subjects affected / exposed    | 0 / 462 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences (all)              | 0               | 2               |  |
| Bacterial disease carrier      |                 |                 |  |
| subjects affected / exposed    | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)              | 0               | 1               |  |
| Bronchitis                     |                 |                 |  |
| subjects affected / exposed    | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)              | 1               | 0               |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Conjunctivitis                          |                 |                 |  |
| subjects affected / exposed             | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Herpes simplex                          |                 |                 |  |
| subjects affected / exposed             | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Genital herpes                          |                 |                 |  |
| subjects affected / exposed             | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Hordeolum                               |                 |                 |  |
| subjects affected / exposed             | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Influenza                               |                 |                 |  |
| subjects affected / exposed             | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Pharyngitis                             |                 |                 |  |
| subjects affected / exposed             | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Tonsillitis                             |                 |                 |  |
| subjects affected / exposed             | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Upper respiratory tract infection       |                 |                 |  |
| subjects affected / exposed             | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Vaginal infection                       |                 |                 |  |
| subjects affected / exposed             | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Viral upper respiratory tract infection |                 |                 |  |
| subjects affected / exposed             | 0 / 462 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences (all)                       | 0               | 1               |  |
| Vulvovaginal candidiasis                |                 |                 |  |
| subjects affected / exposed             | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)                       | 1               | 0               |  |
| Metabolism and nutrition disorders      |                 |                 |  |
| Increased appetite                      |                 |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 462 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences (all)           | 0               | 2               |  |
| Fluid retention             |                 |                 |  |
| subjects affected / exposed | 1 / 462 (0.22%) | 0 / 477 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 15 April 2014 | The following changes were made in the amended protocol: <ul style="list-style-type: none"><li>- The patient population and inclusion criteria of the trial were aligned with the 2011 Consensus Meeting of the European Society of Human Reproduction and Embryology (ESHRE)-</li><li>- Clarification was made on the emergency unblinding procedure.</li><li>- Clarification was made on the pregnancy testing criteria and embryology assessments.</li><li>- Clarification was made on the definitions of serious adverse event and last safety visit.</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported