# Clinical trial results:
# A controlled, assessor-blind, parallel groups, multicentre, multinational trial evaluating the immunogenicity of FE 999049 in repeated cycles of controlled ovarian stimulation in women undergoing an assisted reproductive technology programme

## Summary

| | |
|---|---|
| EudraCT number | 2013-001616-30 |
| Trial protocol | BE GB CZ DK ES PL IT |
| Global end of trial date | 03 January 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 May 2017 |
| First version publication date | 04 May 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 000071 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01956123 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Ferring Pharmaceuticals A/S |
| Sponsor organisation address | Kay Fiskers Plads 11, Copenhagen S, Denmark, 2300 |
| Public contact | Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.com |
| Scientific contact | Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 26 January 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 May 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 January 2017 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the immunogenicity of FE 999049 and GONAL-F based on the presence of anti-follicle-stimulating hormone (FSH) antibodies and their neutralising capacity in women undergoing repeated controlled ovarian stimulation (COS) cycles.

Protection of trial subjects:

The trial was performed in accordance with the Declaration of Helsinki and its amendments in force at the initiation of the trial.

Background therapy:

As concomitant therapy in the COS cycle, CETROTIDE (gonadotropin releasing hormone [GnRH] antagonist), OVITRELLE (human chorionic gonadotropin [hCG]), GONAPEPTYL (GnRH agonist), and ENDOMETRIN (progesterone) were used as non-investigational medicinal products (NIMPs).
All NIMPs were used in line with the recommendations in the respective products' labelling for the indication of assisted reproductive technologies (ART) and/or standard clinical practice and supported by literature.

Evidence for comparator:

This was a controlled trial evaluating the immunogenicity of FE 999049 during repeated exposure. GONAL-F was included as a reference group. GONAL-F is a commercially available recombinant follicle stimulating hormone (rFSH) preparation.

| | |
|---|---|
| Actual start date of recruitment | 26 March 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Brazil: 22 |
| Country: Number of subjects enrolled | Canada: 75 |
| Country: Number of subjects enrolled | Russian Federation: 17 |
| Country: Number of subjects enrolled | Poland: 49 |
| Country: Number of subjects enrolled | Spain: 201 |
| Country: Number of subjects enrolled | United Kingdom: 16 |
| Country: Number of subjects enrolled | Belgium: 15 |
| Country: Number of subjects enrolled | Czech Republic: 63 |
| Country: Number of subjects enrolled | Denmark: 37 |
| Country: Number of subjects enrolled | Italy: 18 |
| Worldwide total number of subjects | 513 |
| EEA total number of subjects | 399 |

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) | 513 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 32 investigational sites included subjects to the trial : 3 in Belgium, 3 in Brazil, 3 in Canada, 3 in the Czech Republic, 2 in Denmark, 2 in Italy, 2 in Poland, 2 in Russia, 10 in Spain and 2 in United Kingdom.

### Pre-assignment

Screening details:

Subjects who participated in Trial 000004 (COS cycle 1) and failed to achieve an ongoing pregnancy were eligible for the trial. For COS cycle 2, 520 subjects were screened, of whom 513 subjects were enrolled. For COS cycle 3, 190 subjects were screened, of whom 189 subjects were enrolled (1 subject was an enrolment failure and never exposed to IMP)

### Period 1

| | |
|---|---|
| Period 1 title | Overall Trial Period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Assessor[1] |

Blinding implementation details:

The trial was assessor-blind and all investigators, embryologists and central laboratory personnel were blinded to treatment allocation throughout the trial. The trial medication delegate at site (person responsible for investigational medicinal product [IMP]/NIMP), the trial coordinator at site (person entering data into e-CRF), the monitors and the participating subjects knew the treatment allocation. Ferring clinical trial team was blinded to treatment allocation until breaking of the blind.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | FE 999049 (COS cycle 2) |

Arm description:

Subjects randomised to FE 999049 in COS cycle 1 and enrolled and exposed in COS cycle 2 were included in this group. Subjects were exposed to the same IMP as in COS cycle 1.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FE 999049 |
| Investigational medicinal product code | |
| Other name | Follitropin delta |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

FE 999049 was administered as single daily subcutaneous injections in the abdomen. The dose was determined based on the ovarian response in COS cycle 1. The daily FE 999049 dose was fixed throughout the stimulation period and maximum allowed daily dose was 18 µg. Dosing continued until the criterion for triggering of final follicular maturation was met. Subjects could be treated for a maximum of 20 days.

| | |
|---|---|
| **Arm title** | GONAL-F (COS cycle 2) |

Arm description:

Subjects randomised to GONAL-F in COS cycle 1 and enrolled and exposed in COS cycle 2 were included in this group. Subjects were exposed to the same IMP as in COS cycle 1.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | GONAL-F |
| Investigational medicinal product code | |
| Other name | Follitropin alfa |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

GONAL-F was administered as single daily subcutaneous injections in the abdomen. The starting dose was determined based on the ovarian response in COS cycle 1. The GONAL-F starting dose was fixed for the first 5 days after which it could be adjusted by 75 IU based on the individual response. The maximum allowed daily dose was 450 IU. Dosing continued until the criterion for triggering of final follicular maturation was met. Subjects could be treated for a maximum of 20 days.

| **Arm title** | FE 999049 (COS cycle 3) |
|---|---|

Arm description:

Subjects randomised to FE 999049 in COS cycle 1 and enrolled and exposed in COS cycle 3 were included in this group. Subjects were exposed to the same IMP as in COS cycles 1 and 2.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | FE 999049 |
| Investigational medicinal product code | |
| Other name | Follitropin delta |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

FE 999049 was administered as single daily subcutaneous injections in the abdomen. The dose was determined based on the ovarian response in COS cycle 2. The daily FE 999049 dose was fixed throughout the stimulation period and maximum allowed daily dose was 24 µg. Dosing continued until the criterion for triggering of final follicular maturation was met. Subjects could be treated for a maximum of 20 days.

| **Arm title** | GONAL-F (COS cycle 3) |
|---|---|

Arm description:

Subjects randomised to GONAL-F in COS cycle 1 and enrolled and exposed in COS cycle 3 were included in this group. Subjects were exposed to the same IMP as in COS cycles 1 and 2.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | GONAL-F |
| Investigational medicinal product code | |
| Other name | Follitropin alfa |
| Pharmaceutical forms | Solution for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

GONAL-F was administered as single daily subcutaneous injections in the abdomen. The starting dose was determined based on the ovarian response in COS cycle 2. The GONAL-F starting dose was fixed for the first 5 days after which it could be adjusted by 75 IU based on the individual response. The maximum allowed daily dose was 450 IU. Dosing continued until the criterion for triggering of final follicular maturation was met. Subjects could be treated for a maximum of 20 days.

Notes:

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

Justification: Due to differences in formulation and packaging of the two IMPs, subject blinding was not feasible.

| **Number of subjects in period 1** | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) |
|---|---|---|---|
| Started | 252 | 261 | 95 |
| Completed | 238 | 254 | 89 |
| Not completed | 14 | 7 | 6 |
| Consent withdrawn by subject | 1 | - | - |
| Personal reasons | 2 | - | 1 |
| Adverse event, non-fatal | 3 | 4 | 3 |
| Protocol deviation | 8 | 3 | 2 |

| **Number of subjects in period 1** | GONAL-F (COS cycle 3) |
|---|---|
| Started | 93 |
| Completed | 91 |
| Not completed | 2 |
| Consent withdrawn by subject | 1 |
| Personal reasons | - |
| Adverse event, non-fatal | - |
| Protocol deviation | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | FE 999049 (COS cycle 2) |
| Reporting group description: | |
| Subjects randomised to FE 999049 in COS cycle 1 and enrolled and exposed in COS cycle 2 were included in this group. Subjects were exposed to the same IMP as in COS cycle 1. | |
| Reporting group title | GONAL-F (COS cycle 2) |
| Reporting group description: | |
| Subjects randomised to GONAL-F in COS cycle 1 and enrolled and exposed in COS cycle 2 were included in this group. Subjects were exposed to the same IMP as in COS cycle 1. | |
| Reporting group title | FE 999049 (COS cycle 3) |
| Reporting group description: | |
| Subjects randomised to FE 999049 in COS cycle 1 and enrolled and exposed in COS cycle 3 were included in this group. Subjects were exposed to the same IMP as in COS cycles 1 and 2. | |
| Reporting group title | GONAL-F (COS cycle 3) |
| Reporting group description: | |
| Subjects randomised to GONAL-F in COS cycle 1 and enrolled and exposed in COS cycle 3 were included in this group. Subjects were exposed to the same IMP as in COS cycles 1 and 2. | |

| Reporting group values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) |
|---|---|---|---|
| Number of subjects | 252 | 261 | 95 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 252 | 261 | 95 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 34.2 | 34 | 34.7 |
| standard deviation | ± 3.9 | ± 3.95 | ± 4.15 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 252 | 261 | 95 |
| Male | 0 | 0 | 0 |

| Reporting group values | GONAL-F (COS cycle 3) | Total | |
|---|---|---|---|
| Number of subjects | 93 | 513 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |

| | | | |
|---|---|---|---|
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 93 | 513 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 34.7 | | |
| standard deviation | ± 3.99 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 93 | 513 | |
| Male | 0 | 0 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | FE 999049 (COS cycle 2) |
| Reporting group description: | |
| Subjects randomised to FE 999049 in COS cycle 1 and enrolled and exposed in COS cycle 2 were included in this group. Subjects were exposed to the same IMP as in COS cycle 1. | |
| Reporting group title | GONAL-F (COS cycle 2) |
| Reporting group description: | |
| Subjects randomised to GONAL-F in COS cycle 1 and enrolled and exposed in COS cycle 2 were included in this group. Subjects were exposed to the same IMP as in COS cycle 1. | |
| Reporting group title | FE 999049 (COS cycle 3) |
| Reporting group description: | |
| Subjects randomised to FE 999049 in COS cycle 1 and enrolled and exposed in COS cycle 3 were included in this group. Subjects were exposed to the same IMP as in COS cycles 1 and 2. | |
| Reporting group title | GONAL-F (COS cycle 3) |
| Reporting group description: | |
| Subjects randomised to GONAL-F in COS cycle 1 and enrolled and exposed in COS cycle 3 were included in this group. Subjects were exposed to the same IMP as in COS cycles 1 and 2. | |
| Subject analysis set title | Modified intention-to-treat (mITT) analysis set |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | |
| The mITT analysis set was defined as all exposed subjects. Subjects were analysed according to actual treatment received. | |
| Subject analysis set title | Safety analysis set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The safety analysis set was defined as all exposed subjects. Subjects were analysed according to actual treatment received. The safety analysis set was identical to the mITT analysis set. | |

### Primary: Proportion of subjects with treatment-induced anti-FSH antibodies after up to two repeated COS cycles

| | |
|---|---|
| End point title | Proportion of subjects with treatment-induced anti-FSH antibodies after up to two repeated COS cycles[1][2] |
| End point description: | |
| The proportion of subjects with at least one treatment-induced anti-FSH antibody response at any time point is presented for the safety analysis set. | |
| End point type | Primary |
| End point timeframe: | |
| Stimulation day 1, 7-10 days after last FE 999049 or GONAL-F dose and 21-28 days after last FE 999049 or GONAL-F dose | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics was used to present this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The cumulative incidences in COS cycle 2 and COS cycle 3 divided by subjects in COS cycle 2 are presented. Subjects with observations in both cycles are only counted once.

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 261 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 0.79 (0.1 to 2.84) | 0.38 (0.01 to 2.12) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects with treatment-induced anti-FSH antibodies with neutralising capacity after up to two repeated COS cycles

| End point title | Proportion of subjects with treatment-induced anti-FSH antibodies with neutralising capacity after up to two repeated COS cycles[3] |
|---|---|

End point description:

The proportion of subjects with treatment-induced anti-FSH antibodies with neutralising capacity at any time point is presented for the safety analysis set.

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

End point timeframe:

Stimulation day 1, 7-10 days after last FE 999049 or GONAL-F dose and 21-28 days after last FE 999049 or GONAL-F dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The cumulative incidences in COS cycle 2 and COS cycle 3 divided by subjects in COS cycle 2 are presented. Subjects with observations in both cycles are only counted once.

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 252 | 261 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 0 (0 to 1.45) | 0 (0 to 1.4) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number and size of follicles on stimulation day 6 and end-of stimulation for each COS cycle

| End point title | Number and size of follicles on stimulation day 6 and end-of stimulation for each COS cycle |
|---|---|

End point description:

Total number of follicles with size >= 12 mm on stimulation day 6 and at end-of-stimulation are presented for the mITT analysis set.

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

End point timeframe:

Stimulation day 6 and end-of stimulation

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Number of follicles | | | | |
| arithmetic mean (standard deviation) | | | | |
| Follicles with size >=12 mm on stimulation Day 6 | 3.2 (± 2.7) | 3.2 (± 2.6) | 2.9 (± 2.6) | 2.9 (± 2.4) |
| Follicles with size >=12 mm at End-of-stimulation | 10.2 (± 5.2) | 9.9 (± 4.9) | 8.9 (± 4.5) | 9.8 (± 4.8) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects with extreme ovarian responses for each COS cycle

| End point title | Proportion of subjects with extreme ovarian responses for each COS cycle |
|---|---|

End point description:

Extreme ovarian response was defined as <4, ≥15 or ≥20 oocytes retrieved. Data are presented for the mITT analysis set.

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

End point timeframe:

Oocyte retrieval visit (36 hr [±2 hr] after triggering of final follicular maturation)

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 241[4] | 251[5] | 92[6] | 90[7] |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| <4 or >=15 oocytes retrieved | 22.4 | 19.5 | 19.6 | 20 |
| <4 or >=20 oocytes retrieved | 11.2 | 11.2 | 13 | 13.3 |

Notes:

[4] - Subjects who underwent triggering of final follicular maturation.

[5] - Subjects who underwent triggering of final follicular maturation.

[6] - Subjects who underwent triggering of final follicular maturation.

[7] - Subjects who underwent triggering of final follicular maturation.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects with early OHSS and/or preventive interventions

## for early OHSS for each COS cycle

| End point title | Proportion of subjects with early OHSS and/or preventive interventions for early OHSS for each COS cycle |
|---|---|

End point description:

The proportion of subjects with early ovarian hyperstimulation syndrome (OHSS), early OHSS of moderate or severe grade, preventive interventions for early OHSS, early OHSS and/or preventive interventions for early OHSS, and early OHSS of moderate or severe grade and/or preventive interventions for early OHSS are presented for the mITT analysis set.

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

End point timeframe:

9 days after triggering of final follicular maturation

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Early OHSS (any grade) | 0.8 | 2.3 | 1.1 | 0 |
| Early OHSS (moderate/severe) | 0 | 1.9 | 0 | 0 |
| Any preventive intervention | 1.6 | 1.9 | 0 | 1.1 |
| Early OHSS (any grade) / preventive interventions | 2 | 3.8 | 1.1 | 1.1 |
| Early OHSS (mod/severe) / preventive interventions | 1.6 | 3.8 | 0 | 1.1 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects with cycle cancellation due to poor ovarian response or excessive ovarian response for each COS cycle

| End point title | Proportion of subjects with cycle cancellation due to poor ovarian response or excessive ovarian response for each COS cycle |
|---|---|

End point description:

Proportion of subjects with cycle cancellation due to poor ovarian response, excessive ovarian response, and triggering with GnRH agonist are presented for the mITT analysis set.

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

End point timeframe:

End-of-stimulation

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Cycle cancelled due to poor ovarian response | 2 | 3.8 | 2.1 | 2.2 |
| Cycle cancelled due to excessive ovarian response | 0.4 | 0 | 0 | 0 |
| Triggering with GnRH agonist | 0.4 | 0.8 | 0 | 1.1 |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Metaphase II oocytes (inseminated through ICSI) for each COS cycle

| End point title | Metaphase II oocytes (inseminated through ICSI) for each COS cycle |
|---|---|

End point description:

Number of oocytes in metaphase II prior to intracytoplasmic sperm injection (ICSI) insemination is presented for the mITT analysis set.

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

End point timeframe:

Prior to insemination

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 219[8] | 221[9] | 87[10] | 81[11] |
| Units: Number of oocytes | | | | |
| arithmetic mean (standard deviation) | 7.1 (± 4) | 6.4 (± 3.5) | 6.5 (± 3.3) | 6.4 (± 3.6) |

Notes:

[8] - Subjects with all oocytes inseminated using ICSI.

[9] - Subjects with all oocytes inseminated using ICSI.

[10] - Subjects with all oocytes inseminated using ICSI.

[11] - Subjects with all oocytes inseminated using ICSI.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Fertilisation rate for each COS cycle

| End point title | Fertilisation rate for each COS cycle |
|---|---|

End point description:

Fertilisation rate was defined as the number of oocytes with 2 pronuclei divided by the number of oocytes retrieved. Data are presented for the mITT analysis set.

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

End point timeframe:

Day 1 after oocyte retrieval (19hr ± 2hr)

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 239[12] | 251[13] | 92[14] | 90[15] |
| Units: Percentage of oocytes | | | | |
| arithmetic mean (standard deviation) | 56.8 (± 23.5) | 52.6 (± 24.3) | 56.3 (± 20.6) | 49.7 (± 24.9) |

Notes:

[12] - Subjects with oocytes retrieved.

[13] - Subjects with oocytes retrieved.

[14] - Subjects with oocytes retrieved.

[15] - Subjects with oocytes retrieved.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number and quality of embryos on Day 3 and blastocysts on Day 5 for each COS cycle

| End point title | Number and quality of embryos on Day 3 and blastocysts on Day 5 for each COS cycle |
|---|---|

End point description:

Number and quality of embryos on Day 3 and blastocysts on Day 5 in subjects with oocytes retrieved were presented. A good-quality embryo was defined as an embryo with ≥6 blastomeres and fragmentation ≤20% on Day 3. A good-quality blastocyst was defined as a blastocyst of grade 3BB or higher. Data are presented for the mITT analysis set.

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

End point timeframe:

Day 3 and Day 5 after oocyte retrieval

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 239[16] | 251[17] | 92[18] | 90[19] |
| Units: Number of embryos/blastocyst | | | | |
| arithmetic mean (standard deviation) | | | | |
| Number of embryos on Day 3 | 5.1 (± 3.3) | 4.3 (± 2.8) | 4.4 (± 2.4) | 4.4 (± 3.3) |
| Number of good-quality embryos on Day 3 | 3.9 (± 3.1) | 3.3 (± 2.4) | 3.2 (± 2.2) | 3.3 (± 3) |
| Number of blastocysts on Day 5 | 2.8 (± 2.4) | 2.4 (± 2.1) | 2.2 (± 1.8) | 2.4 (± 2.3) |
| Number of good-quality blastocysts on Day 5 | 1.4 (± 1.7) | 1.2 (± 1.6) | 1.2 (± 1.5) | 1.2 (± 1.8) |

Notes:

[16] - Subjects with oocytes retrieved.

[17] - Subjects with oocytes retrieved.

[18] - Subjects with oocytes retrieved.

[19] - Subjects with oocytes retrieved.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Circulating concentration of FSH, and luteinising hormone (LH) for each COS cycle

| End point title | Circulating concentration of FSH, and luteinising hormone (LH) for each COS cycle |
|---|---|

End point description:

Data are presented for the mITT analysis set.

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

End point timeframe:

Stimulation day 6 and end-of-stimulation

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: IU/L | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Stimulation Day 6 - FSH | 15.3 (11.7 to 19.4) | 11.9 (9.8 to 14.6) | 17.2 (13.8 to 24.2) | 12.8 (10.3 to 17.2) |
| Stimulation Day 6 - LH | 2.7 (1.6 to 4.9) | 2.8 (1.7 to 4.7) | 2.7 (1.8 to 4) | 2.5 (1.8 to 4.4) |
| End-of-stimulation - FSH | 15.9 (11.9 to 20.5) | 14.2 (10.9 to 18.3) | 18 (13.2 to 26.1) | 15 (11.2 to 20) |
| End-of-stimulation - LH | 1.5 (0.8 to 2.4) | 1.6 (0.9 to 3.1) | 1.6 (1 to 2.9) | 1.9 (1.1 to 3.6) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Circulating concentration of estradiol for each COS cycle

| End point title | Circulating concentration of estradiol for each COS cycle |
|---|---|

End point description:

Data are presented for the mITT analysis set.

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

End point timeframe:

Stimulation day 6 and end-of-stimulation

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: pmol/L | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Stimulation Day 6 - estradiol | 1907.4 (1255.9 to 2779.2) | 1821 (1099.7 to 3125.8) | 1714.8 (958.8 to 2842.5) | 1858.4 (1128.1 to 2345.5) |
| End-of-stimulation - estradiol | 5312.5 (3766.8 to 7728.9) | 5473.6 (3590.6 to 7801) | 4757.4 (3130.7 to 6162.2) | 5348.1 (3854.2 to 7383) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Circulating concentration of progesterone for each COS cycle

| End point title | Circulating concentration of progesterone for each COS cycle |
|---|---|
| End point description: | |
| Data are presented for the mITT analysis set. | |
| End point type | Secondary |
| End point timeframe: | |
| Stimulation day 6 and end-of-stimulation | |

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: nmol/L | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Stimulation Day 6 - progesterone | 1.92 (0.8 to 2.76) | 1.89 (0.8 to 2.53) | 1.88 (0.8 to 2.69) | 1.9 (0.8 to 2.71) |
| End-of-stimulation - progesterone | 2.77 (2.06 to 3.73) | 3.03 (2.19 to 4.21) | 2.92 (2.03 to 3.99) | 3.25 (2.1 to 4.35) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Circulating concentration of Inhibin A, and Inhibin B for each COS cycle

| End point title | Circulating concentration of Inhibin A, and Inhibin B for each COS cycle |
|---|---|

End point description:

Data are presented for the mITT analysis set.

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

End point timeframe:

Stimulation day 6 and end-of-stimulation

| **End point values** | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: pg/mL | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Stimulation Day 6 - inhibin A | 104.3 (65 to 151.3) | 105.8 (62.7 to 152.6) | 91.8 (63.5 to 153) | 105 (61.7 to 148.6) |
| Stimulation Day 6 - inhibin B | 583.5 (386 to 787) | 531 (364 to 776) | 455 (291 to 709) | 491.5 (362 to 763) |
| End-of-stimulation - inhibin A | 317.9 (226.1 to 443.9) | 334.8 (222.9 to 464) | 281.3 (192 to 382.3) | 324.2 (241.8 to 409.1) |
| End-of-stimulation - inhibin B | 650 (393 to 1024) | 689 (379 to 1070) | 548 (275 to 817) | 639.5 (357.5 to 923) |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Total gonadotropin dose for each COS cycle**

| End point title | Total gonadotropin dose for each COS cycle |
|---|---|

End point description:

The total gonadotropin dose was recorded. Data are presented for the mITT analysis set.

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

End point timeframe:

End-of-stimulation

| **End point values** | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: ug | | | | |
| arithmetic mean (standard deviation) | 107.7 (± 39.22) | 121.7 (± 44.31) | 130 (± 57.53) | 132.7 (± 44.38) |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Number of stimulation days for each COS cycle

| End point title | Number of stimulation days for each COS cycle |
|---|---|

End point description:

The number of stimulation days are presented for the mITT analysis set.

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

End point timeframe:

End-of-stimulation

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | 9 (± 1.89) | 9 (± 1.84) | 8.9 (± 1.9) | 8.8 (± 1.43) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical pregnancy rate for each COS cycle

| End point title | Clinical pregnancy rate for each COS cycle |
|---|---|

End point description:

Clinical pregnancy was defined as at least one gestational sac 5-6 weeks after blastocyst transfer. Data are presented for the mITT analysis set.

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

End point timeframe:

5-6 weeks after blastocyst transfer

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 32.5 (26.8 to 38.7) | 30.3 (24.8 to 36.2) | 32.6 (23.4 to 43) | 32.3 (22.9 to 42.7) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Vital pregnancy rate for each COS cycle

| End point title | Vital pregnancy rate for each COS cycle |
|---|---|

End point description:

Vital pregnancy was defined as at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after blastocyst transfer. Data are presented for the mITT analysis set.

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

End point timeframe:

5-6 weeks after blastocyst transfer

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 29.4 (23.8 to 35.4) | 27.2 (21.9 to 33) | 27.4 (18.7 to 37.5) | 29 (20.1 to 39.4) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Implantation rate for each COS cycle

| End point title | Implantation rate for each COS cycle |
|---|---|

End point description:

Implantation rate was defined as the number of gestational sacs 5-6 weeks after transfer divided by number of blastocysts transferred. Data are presented for the mITT analysis set.

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

End point timeframe:

5-6 weeks after blastocyst transfer

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 211[20] | 221[21] | 82[22] | 75[23] |
| Units: Percentage | | | | |
| number (confidence interval 95%) | 34.6 (28.8 to 40.8) | 30.6 (25.2 to 36.5) | 28.8 (21.2 to 37.3) | 32.2 (24 to 41.3) |

Notes:

[20] - Subjects with blastocyst transfer. A total of 254 blastocysts were transferred.

[21] - Subjects with blastocyst transfer. A total of 271 blastocysts were transferred.

[22] - Subjects with blastocyst transfer. A total of 132 blastocysts were transferred.

[23] - Subjects with blastocyst transfer. A total of 121 blastocysts were transferred.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Ongoing pregnancy rate for each COS cycle

| End point title | Ongoing pregnancy rate for each COS cycle |
|---|---|

End point description:

Ongoing pregnancy rate was defined as at least one intrauterine viable fetus 10-11 weeks after blastocyst transfer. Data are presented for the mITT analysis set.

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

End point timeframe:

10-11 weeks after blastocyst transfer

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 27.8 (22.3 to 33.7) | 25.7 (20.5 to 31.4) | 27.4 (18.7 to 37.5) | 28 (19.1 to 38.2) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Ongoing implantation rate for each COS cycle

| End point title | Ongoing implantation rate for each COS cycle |
|---|---|

End point description:

Ongoing implantation rate was defined as the number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of blastocysts transferred. Data are presented for the mITT analysis set.

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

End point timeframe:

10-11 weeks after blastocyst transfer

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 211[24] | 221[25] | 82[26] | 75[27] |
| Units: Percentage | | | | |
| number (confidence interval 95%) | 28.7 (23.3 to 34.7) | 25.5 (20.4 to 31.1) | 25 (17.9 to 33.3) | 28.9 (21 to 37.9) |

Notes:

[24] - Subjects with blastocyst transfer. A total of 254 blastocysts were transferred.

[25] - Subjects with blastocyst transfer. A total of 271 blastocysts were transferred.

[26] - Subjects with blastocyst transfer. A total of 132 blastocysts were transferred.

[27] - Subjects with blastocyst transfer. A total of 121 blastocysts were transferred.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of subjects with treatment-induced anti-FSH antibodies, overall as well as with neutralising capacity, after one and after two repeated COS cycles

| End point title | Proportion of subjects with treatment-induced anti-FSH antibodies, overall as well as with neutralising capacity, after one and after two repeated COS cycles |
|---|---|

End point description:

The proportion of subjects with treatment-induced anti-FSH antibodies, overall as well as with neutralising capacity, after one and after two repeated COS cycles is presented for the safety analysis set.

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

End point timeframe:

Stimulation day 1, 7-10 days after last FE 999049 or GONAL-F dose and 21-28 days after last FE 999049 or GONAL-F dose

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| Treatment-induced anti-FSH antibodies | 0.79 (0.1 to 2.84) | 0.38 (0.01 to 2.12) | 1.05 (0.03 to 5.73) | 1.08 (0.03 to 5.85) |
| Antibodies with neutralising capacity | 0 (0 to 1.45) | 0 (0 to 1.4) | 0 (0 to 3.81) | 0 (0 to 3.89) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Positive βhCG rate for each COS cycle

| End point title | Positive βhCG rate for each COS cycle |
|---|---|

End point description:

Positive beta unit of human chorionic gonadotropin (βhCG) was confirmed by a blood test 13-15 days after blastocyst transfer. Data are presented for the mITT analysis set.

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

End point timeframe:

13-15 days after blastocyst transfer

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Percentage of subject | | | | |
| number (confidence interval 95%) | 37.7 (31.7 to 44) | 33.3 (27.6 to 39.4) | 42.1 (32 to 52.7) | 36.6 (26.8 to 47.2) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of subjects with markedly abnormal changes in clinical chemistry and haematology parameters for each COS cycle

| End point title | Proportion of subjects with markedly abnormal changes in clinical chemistry and haematology parameters for each COS cycle |
|---|---|

End point description:

Number of subjects with a markedly abnormal value at end-of-stimulation or end-of-trial after a normal baseline value, judged as clinically significant by the investigator (all parameters combined) are presented for the safety analysis set.

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

End point timeframe:

Stimulation day 1, end-of-stimulation and end-of-trial

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Clinical chemistry | 0 | 0 | 0 | 0 |
| Hematology | 0 | 0 | 0 | 0 |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Frequency of injection site reactions for each COS cycle

| End point title | Frequency of injection site reactions for each COS cycle |
|---|---|

End point description:

Subjects self-assessed injection site reactions (redness, itching, pain, swelling and bruising) immediately, 30 minutes and 24 hours after each injection. The injection site reactions were assessed as none, mild, moderate and severe. The frequency of injection site reactions (mild, moderate or severe) based on all assessment performed is presented for the safety analysis set.

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

End point timeframe:
End-of-stimulation

| End point values | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) | GONAL-F (COS cycle 3) |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 252 | 261 | 95 | 93 |
| Units: Percentage of events | | | | |
| number (not applicable) | 3 | 2.4 | 2.8 | 2.3 |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from signed informed consent to the end-of-cycle visit for COS cycle 2 and again from screening to the end-of-cycle visit for COS cycle 3.

Adverse event reporting additional description:

AEs with onset after start of first administration of IMP and before the end-of-cycle were considered treatment-emergent and are presented for the safety analysis set.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | FE 999049 (COS cycle 2) |

Reporting group description:

Subjects randomised to FE 999049 in COS cycle 1 and enrolled and exposed in COS cycle 2 were included in this group. Subjects were exposed to the same IMP as in COS cycle 1.

| | |
|---|---|
| Reporting group title | GONAL-F (COS cycle 2) |

Reporting group description:

Subjects randomised to GONAL-F in COS cycle 1 and enrolled and exposed in COS cycle 2 were included in this group. Subjects were exposed to the same IMP as in COS cycle 1.

| | |
|---|---|
| Reporting group title | FE 999049 (COS cycle 3) |

Reporting group description:

Subjects randomised to FE 999049 in COS cycle 1 and enrolled and exposed in COS cycle 3 were included in this group. Subjects were exposed to the same IMP as in COS cycles 1 and 2.

| | |
|---|---|
| Reporting group title | GONAL-F (COS cycle 3) |

Reporting group description:

Subjects randomised to GONAL-F in COS cycle 1 and enrolled and exposed in COS cycle 3 were included in this group. Subjects were exposed to the same IMP as in COS cycles 1 and 2.

| Serious adverse events | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 252 (1.59%) | 4 / 261 (1.53%) | 0 / 95 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | 2 / 261 (0.77%) | 0 / 95 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage in pregnancy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 252 (0.40%) | 1 / 261 (0.38%) | 0 / 95 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abortion spontaneous | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | 0 / 261 (0.00%) | 0 / 95 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting in pregnancy | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | 0 / 261 (0.00%) | 0 / 95 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Ovarian hyperstimulation syndrome | | | |
| subjects affected / exposed | 0 / 252 (0.00%) | 1 / 261 (0.38%) | 0 / 95 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 252 (0.40%) | 0 / 261 (0.00%) | 0 / 95 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | GONAL-F (COS cycle 3) | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Ectopic pregnancy | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage in pregnancy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting in pregnancy | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Ovarian hyperstimulation syndrome | | | |
| subjects affected / exposed | 1 / 93 (1.08%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 93 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| **Non-serious adverse events** | FE 999049 (COS cycle 2) | GONAL-F (COS cycle 2) | FE 999049 (COS cycle 3) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 118 / 252 (46.83%) | 123 / 261 (47.13%) | 46 / 95 (48.42%) |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 13 / 252 (5.16%) | 17 / 261 (6.51%) | 5 / 95 (5.26%) |
| occurrences (all) | 14 | 20 | 6 |
| Nervous system disorders | | | |
| Headache | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 19 / 252 (7.54%) | 27 / 261 (10.34%) | 11 / 95 (11.58%) |
| occurrences (all) | 24 | 34 | 12 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Biochemical pregnancy | | | |
| subjects affected / exposed | 13 / 252 (5.16%) | 8 / 261 (3.07%) | 9 / 95 (9.47%) |
| occurrences (all) | 13 | 8 | 9 |
| Haemorrhage in pregnancy | | | |
| subjects affected / exposed | 13 / 252 (5.16%) | 10 / 261 (3.83%) | 3 / 95 (3.16%) |
| occurrences (all) | 15 | 11 | 3 |
| Abortion spontaneous | | | |
| subjects affected / exposed | 10 / 252 (3.97%) | 9 / 261 (3.45%) | 5 / 95 (5.26%) |
| occurrences (all) | 10 | 9 | 5 |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 14 / 252 (5.56%) | 11 / 261 (4.21%) | 3 / 95 (3.16%) |
| occurrences (all) | 14 | 12 | 3 |
| Pelvic discomfort | | | |
| subjects affected / exposed | 6 / 252 (2.38%) | 13 / 261 (4.98%) | 0 / 95 (0.00%) |
| occurrences (all) | 6 | 14 | 0 |

| **Non-serious adverse events** | GONAL-F (COS cycle 3) | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 93 (45.16%) | | |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 8 / 93 (8.60%) | | |
| occurrences (all) | 8 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 13 / 93 (13.98%) | | |
| occurrences (all) | 15 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Biochemical pregnancy | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | | |
| occurrences (all) | 4 | | |
| Haemorrhage in pregnancy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 93 (2.15%) | | |
| occurrences (all) | 2 | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 4 / 93 (4.30%) | | |
| occurrences (all) | 4 | | |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 5 / 93 (5.38%) | | |
| occurrences (all) | 5 | | |
| Pelvic discomfort | | | |
| subjects affected / exposed | 6 / 93 (6.45%) | | |
| occurrences (all) | 7 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported