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 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 Units: years			
arithmetic mean	34.2	34	34.7
standard deviation	± 3.9	± 3.95	± 4.15
Gender categorical 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 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