Clinical trial results:
A randomised, controlled, assessor-blind, parallel groups, multicentre, multinational trial comparing the efficacy and safety of FE 999049 with follitropin alfa (GONAL-F) in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme

Summary

EudraCT number	2013-001669-17
Trial protocol	BE GB CZ DK PL ES 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	000004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01956110
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	11 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 demonstrate non-inferiority of FE 999049 compared with GONAL-F with respect to ongoing pregnancy rate and ongoing implantation rate in the fresh cycle in women undergoing controlled ovarian stimulation.

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 controlled ovarian stimulation 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 randomised, controlled trial with GONAL-F as the comparator to adequately document the efficacy and safety of FE 999049. GONAL-F is a commercially available recombinant follicle stimulating hormone (rFSH) preparation.

Actual start date of recruitment	08 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 58
Country: Number of subjects enrolled	Canada: 152
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	Poland: 117
Country: Number of subjects enrolled	Spain: 510
Country: Number of subjects enrolled	United Kingdom: 44
Country: Number of subjects enrolled	Belgium: 78
Country: Number of subjects enrolled	Czech Republic: 161
Country: Number of subjects enrolled	Denmark: 64
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Italy: 64

Worldwide total number of subjects	1329
EEA total number of subjects	1047

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)	1329
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 37 sites randomised subjects into the trial : 3 in Belgium, 3 in Brazil, 3 in Canada, 4 in the Czech Republic, 2 in Denmark, 2 in France, 2 in Italy, 2 in Poland, 4 in Russia, 10 in Spain and 2 in United Kingdom.

Pre-assignment

Screening details:

A total of 1501 subjects were screened in the trial, of whom 1329 subjects were randomised: 666 subjects to FE 999049 and 663 subjects to GONAL-F. Three subjects were randomisation failures and did not receive investigational medicinal product (IMP); 1 in the FE 999049 group and 2 in the GONAL-F group.

Period 1

Period 1 title	Overall Trial Period (overall period)
Is this the baseline period?	Yes
Allocation method	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 during the trial. The trial medication delegate at site (person responsible for IMP/NIMP), the trial coordinator at site (person entering data into e-CRF), the monitors and the participating subjects knew the treatment allocation once the subjects were randomised. The Ferring clinical trial team was blinded to treatment allocation until breaking of the blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	FE 999049

Arm description:

Subjects randomised and exposed to FE 999049 IMP were included in this group.

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. Subjects randomised to FE 999049 had their individual dose determined on the basis of their anti-Müllerian hormone (AMH) level at screening and their body weight at randomisation. The daily FE 999049 dose was fixed throughout the stimulation period and maximum allowed daily dose was 12 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

Arm description:

Subjects randomised and exposed to GONAL-F IMP were included in this group.

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 of GONAL-F was 150 international units (IU) and fixed for the first five stimulation 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[2]	FE 999049	GONAL-F
Started	665	661
Completed	630	639
Not completed	35	22
Personal reasons	1	1
Adverse event, non-fatal	9	10
Protocol deviation	25	11

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Three subjects were randomisation failures and did not receive IMP; 1 in the FE 999049 group and 2 in the GONAL-F group.

Baseline characteristics

Reporting groups	
Reporting group title	FE 999049
Reporting group description:	
Subjects randomised and exposed to FE 999049 IMP were included in this group.	
Reporting group title	GONAL-F
Reporting group description:	
Subjects randomised and exposed to GONAL-F IMP were included in this group.	

Reporting group values	FE 999049	GONAL-F	Total
Number of subjects	665	661	1326
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)	665	661	1326
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	33.4	33.2	
standard deviation	± 3.89	± 3.85	-
Gender categorical Units: Subjects			
Female	665	661	1326
Male	0	0	0

End points

End points reporting groups

Reporting group title	FE 999049
Reporting group description:	
Subjects randomised and exposed to FE 999049 IMP were included in this group.	
Reporting group title	GONAL-F
Reporting group description:	
Subjects randomised and exposed to GONAL-F IMP were included in this group.	
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 randomised and 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 randomised and exposed subjects. Subjects were analysed according to actual treatment received. The safety analysis set was identical to the mITT analysis set.	

Primary: Ongoing pregnancy rate

End point title	Ongoing pregnancy rate
End point description:	
Ongoing pregnancy 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	Primary
End point timeframe:	
10-11 weeks after blastocyst transfer	

End point values	FE 999049	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: Percentage of subjects				
number (not applicable)	30.7	31.6		

Statistical analyses

Statistical analysis title	Treatment comparison: Ongoing pregnancy rate
Statistical analysis description:	
The pre-specified non-inferiority margin was -8.0% (absolute). Non-inferiority was evaluated based on a two-sided 95% confidence interval derived based on the asymptotic normal distribution. The treatment comparison was adjusted for age (<35, 35-37 and 38-40 years) by using the Mantel-Haenszel method to combine results across age-strata.	
Comparison groups	FE 999049 v GONAL-F

Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Treatment difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	4.1

Notes:

[1] - The lower bound of the 95% CI was well above the pre-specified non-inferiority limit of -8.0%. Thus, non-inferiority of FE 999049 to GONAL-F with regard to ongoing pregnancy rate was demonstrated.

Primary: Ongoing implantation rate

End point title	Ongoing implantation rate

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	Primary

End point timeframe:

10-11 weeks after blastocyst transfer

End point values	FE 999049	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	562[2]	560[3]		
Units: Percentage				
number (not applicable)	35.2	35.8		

Notes:

[2] - Subjects with blastocyst transfer. A total of 585 blastocysts were transferred

[3] - Subjects with blastocyst transfer. A total of 584 blastocysts were transferred.

Statistical analyses

Statistical analysis title	Treatment comparison: Ongoing implantation rate

Statistical analysis description:

The pre-specified non-inferiority margin was -8.0% (absolute). Non-inferiority was evaluated based on a two-sided 95% confidence interval derived based on the asymptotic normal distribution. The treatment comparison was adjusted for age (<35, 35-37 and 38-40 years) by using the Mantel-Haenszel method to combine results across age-strata.

Comparison groups	GONAL-F v FE 999049
Number of subjects included in analysis	1122
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Treatment difference
Point estimate	-0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.1
upper limit	4.8

Notes:

[4] - The lower bound of the 95% CI was well above the pre-specified non-inferiority limit of -8.0%. Thus, non-inferiority of FE 999049 to GONAL-F with regard to ongoing implantation rate was demonstrated.

Secondary: Positive βhCG rate

End point title	Positive βhCG rate

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: Percentage of subject				
number (not applicable)	38.6	40.2		

Statistical analyses

Statistical analysis title	Treatment comparison: Positive βhCG rate

Statistical analysis description:

Treatment groups were compared using a two-sided 95% confidence interval derived based on the asymptotic normal distribution. The treatment comparison was adjusted for age (<35, 35-37 and 38-40 years) by using the Mantel-Haenszel method to combine results across age-strata.

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Treatment difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	3.7

Secondary: Clinical pregnancy rate

End point title	Clinical pregnancy rate

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: Percentage of subjects				
number (not applicable)	34.9	36.5		

Statistical analyses

Statistical analysis title	Treatment comparison: Clinical pregnancy rate

Statistical analysis description:

Treatment groups were compared using a two-sided 95% confidence interval derived based on the asymptotic normal distribution. The treatment comparison was adjusted for age (<35, 35-37 and 38-40 years) by using the Mantel-Haenszel method to combine results across age-strata.

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Treatment difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	3.6

Secondary: Vital pregnancy rate

End point title	Vital pregnancy rate

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: Percentage of subjects				
number (not applicable)	31.7	33.4		

Statistical analyses

Statistical analysis title	Treatment comparison: Vital pregnancy rate

Statistical analysis description:

Treatment groups were compared using a two-sided 95% confidence interval derived based on the asymptotic normal distribution. The treatment comparison was adjusted for age (<35, 35-37 and 38-40 years) by using the Mantel-Haenszel method to combine results across age-strata.

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Treatment difference
Point estimate	-1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	3.4

Secondary: Implantation rate

End point title	Implantation rate

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	562[5]	560[6]		
Units: Percentage				
number (not applicable)	39.8	41.3		

Notes:

[5] - Subjects with blastocyst transfer. A total of 585 blastocysts were transferred.

[6] - Subjects with blastocyst transfer. A total of 584 blastocysts were transferred.

Statistical analyses

Statistical analysis title	Treatment comparison: Implantation rate

Statistical analysis description:

Treatment groups were compared using a two-sided 95% confidence interval derived based on the asymptotic normal distribution. The treatment comparison was adjusted for age (<35, 35-37 and 38-40 years) by using the Mantel-Haenszel method to combine results across age-strata.

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1122
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Treatment difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	4.2

Secondary: Proportion of subjects with extreme ovarian responses

End point title	Proportion of subjects with extreme ovarian responses

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	635[7]	643[8]		
Units: Percentage of subjects				
number (not applicable)				
<4 or >=15 oocytes retrieved	26.6	31.3		
<4 or >=20 oocytes retrieved	14.5	18.4		

Notes:

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

[8] - Subjects who underwent triggering of follicular maturation.

Statistical analyses

Statistical analysis title	Treatment comparison: <4 or >=15 oocytes retrieved

Statistical analysis description:

Nested logistic regression models were compared using the likelihood ratio test. The full logistic regression model included treatment as factor, AMH as covariate and the interaction term. The nested model did not include the interaction term.

Comparison groups	FE 999049 v GONAL-F

Number of subjects included in analysis	1278
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.001
Method	Likelihood ratio test

Statistical analysis title	Treatment comparison: <4 or >=20 oocytes retrieved

Statistical analysis description:

Nested logistic regression models were compared using the likelihood ratio test. The full logistic regression model included treatment as factor, AMH as covariate and the interaction term. The nested model did not include the interaction term.

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1278
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.002
Method	Likelihood ratio test

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

End point title	Proportion of subjects with early OHSS and/or preventive interventions for early OHSS

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: Percentage of subjects				
number (not applicable)				
Early OHSS (any grade)	2.6	3		
Early OHSS (moderate/severe)	1.4	1.4		
Any preventive intervention	2.3	4.5		
Early OHSS (any grade) / preventive interventions	4.7	6.2		
Early OHSS (mod/severe) / preventive interventions	3.6	5.1		

Statistical analyses

Statistical analysis title	Treatment comparison: Early OHSS (any grade)

Statistical analysis description:

Nested logistic regression models were compared using the likelihood ratio test. The full logistic regression model included treatment as factor, AMH as covariate and the interaction term. The nested model did not include the interaction term.

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.291
Method	Likelihood ratio test

Statistical analysis title	Treatment comparison: Early OHSS (mod/sev)

Statistical analysis description:

Nested logistic regression models were compared using the likelihood ratio test. The full logistic regression model included treatment as factor, AMH as covariate and the interaction term. The nested model did not include the interaction term.

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.644
Method	Likelihood ratio test

Statistical analysis title	Treatment comparison: Preventive interventions

Statistical analysis description:

Nested logistic regression models were compared using the likelihood ratio test. The full logistic regression model included treatment as factor, AMH as covariate and the interaction term. The nested model did not include the interaction term.

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.005
Method	Likelihood ratio test

Statistical analysis title	Treatment comp: Early OHSS (any grade)/preventive

Statistical analysis description:

Nested logistic regression models were compared using the likelihood ratio test. The full logistic regression model included treatment as factor, AMH as covariate and the interaction term. The nested model did not include the interaction term.

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.046
Method	Likelihood ratio test

Statistical analysis title	Treatment comp: Early OHSS (mod/sev)/preventive

Statistical analysis description:

Nested logistic regression models were compared using the likelihood ratio test. The full logistic regression model included treatment as factor, AMH as covariate and the interaction term. The nested model did not include the interaction term.

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.019
Method	Likelihood ratio test

Secondary: Proportion of subjects with cycle cancellation due to poor or excessive ovarian response

End point title	Proportion of subjects with cycle cancellation due to poor or excessive ovarian response

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: Percentage of subjects				
number (not applicable)				
Cycle cancelled due to poor ovarian response	3.8	2.7		
Cycle cancelled due to excessive ovarian response	0	0		
Triggering with GnRH agonist	1.5	3.5		

Statistical analyses

Statistical analysis title	Treatment comp: Cycle cancelled due to poor resp.
Statistical analysis description:	
Treatment groups were compared using a logistic regression model with treatment and age (<35, 35-37, and 38-40 years) as factors.	
Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.302
Method	Likelihood ratio test
Parameter estimate	Odds ratio (OR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	2.57

Statistical analysis title	Treatment comparison:Triggering with GnRH agonist
Statistical analysis description:	
Treatment groups were compared using a logistic regression model with treatment and age (<35, 35-37, and 38-40 years) as factors.	
Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.019
Method	Likelihood ratio test
Parameter estimate	Odds ratio (OR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.9

Secondary: Number and size of follicles on stimulation day 6 and end-of-stimulation

End point title	Number and size of follicles on stimulation day 6 and end-of-stimulation

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-stimulaition

End point values	FE 999049	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: Number of follicles				
arithmetic mean (standard deviation)				
Follicles with size >= 12 mm on stimulation Day 6	3.3 (± 2.7)	3.6 (± 3)		
Follicles with size >= 12 mm at End-of-stimulation	10.8 (± 5.4)	11.1 (± 6)		

Statistical analyses

Statistical analysis title	Treatment comparison: Follicles on Day 6

Statistical analysis description:

Treatment groups were compared using the van Elteren test adjusted for age (<35, 35-37, and 38-40 years).

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.076
Method	van Elteren

Statistical analysis title	Treatment comp: Follicles at end-of-stimulation

Statistical analysis description:

Treatment groups were compared using the van Elteren test adjusted for age (<35, 35-37, and 38-40 years).

Comparison groups	GONAL-F v FE 999049
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.954
Method	van Elteren

Secondary: Metaphase II oocytes (inseminated through ICSI)

End point title	Metaphase II oocytes (inseminated through ICSI)

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	531[9]	522[10]		
Units: Number of oocytes				
arithmetic mean (standard deviation)	7.4 (± 4.3)	7.7 (± 5.2)		

Notes:

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

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

Statistical analyses

Statistical analysis title	Treatment comparison: No. of metaphase II oocytes

Statistical analysis description:

Treatment groups were compared using the van Elteren test adjusted for age (<35, 35-37, and 38-40 years).

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1053
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.909
Method	van Elteren

Secondary: Fertilisation rate

End point title	Fertilisation rate

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 (19 hr ± 2 hr)

End point values	FE 999049	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	634[11]	640[12]		
Units: Percentage of oocytes				
arithmetic mean (standard deviation)	56 (± 24.5)	57 (± 23.8)		

Notes:

[11] - Subjects with oocytes retrieved.

[12] - Subjects with oocytes retrieved.

Statistical analyses

Statistical analysis title	Treatment comparison: Fertilisation rate

Statistical analysis description:

Treatment groups were compared using the van Elteren test adjusted for age (<35, 35-37, and 38-40 years).

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.53
Method	van Elteren

Secondary: Number and quality of embryos on Day 3

End point title	Number and quality of embryos on Day 3

End point description:

Number of embryos (total and good-quality) on Day 3 are presented. A good-quality embryo was defined as an embryo with ≥6 blastomeres and fragmentation ≤20% on Day 3. Data are presented for the mITT analysis set.

End point type	Secondary

End point timeframe:

Day 3 after oocyte retrieval

End point values	FE 999049	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	634[13]	640[14]		
Units: Number of embryos				
arithmetic mean (standard deviation)				
Number of embryos	5.4 (± 3.7)	5.7 (± 4.3)		
Number of good-quality embryos	4.2 (± 3.3)	4.5 (± 3.7)		

Notes:

[13] - Subjects with oocytes retrieved.

[14] - Subjects with oocytes retrieved.

Statistical analyses

Statistical analysis title	Treatment comparison: Number of embryos

Statistical analysis description:

Treatment groups were compared using the van Elteren test adjusted for age (<35, 35-37, and 38-40 years).

Comparison groups	GONAL-F v FE 999049
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.59
Method	van Elteren

Statistical analysis title	Treatment comparison: Good quality embryos

Statistical analysis description:

Treatment groups were compared using the van Elteren test adjusted for age (<35, 35-37, and 38-40 years).

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.414
Method	van Elteren

Secondary: Number and quality of blastocysts on Day 5

End point title	Number and quality of blastocysts on Day 5

End point description:

Number of blastocysts (total and good-quality) on Day 5 are presented. 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 5 after oocyte retrieval

End point values	FE 999049	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	634[15]	640[16]		
Units: Number of blastocyst				
arithmetic mean (standard deviation)				
Number of blastocysts	3.3 (± 2.8)	3.5 (± 3.2)		
Number of good-quality blastocysts	2 (± 2.2)	2.1 (± 2.4)		

Notes:

[15] - Subjects with oocytes retrieved.

[16] - Subjects with oocytes retrieved.

Statistical analyses

Statistical analysis title	Treatment comparison: Number of blastocysts
Statistical analysis description:	
Treatment groups were compared using the van Elteren test adjusted for age (<35, 35-37, and 38-40 years).	
Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.344
Method	van Elteren

Statistical analysis title	Treatment comparison: Good-quality blastocysts
Statistical analysis description:	
Treatment groups were compared using the van Elteren test adjusted for age (<35, 35-37, and 38-40 years).	
Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1274
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.58
Method	van Elteren

Secondary: Circulating concentration of FSH, LH, estradiol, progesterone, inhibin A, and inhibin B

End point title	Circulating concentration of FSH, LH, estradiol, progesterone, inhibin A, and inhibin B
End point description:	
Ratio of circulating concentrations of hormones; follicle stimulating hormone (FSH), luteinising hormone (LH), estradiol, progesterone, inhibin A, and inhibin B are presented for the mITT analysis set.	
End point type	Secondary
End point timeframe:	
Stimulation day 6 and end-of-stimulation	

End point values	Modified intention-to-treat (mITT) analysis set			
Subject group type	Subject analysis set			
Number of subjects analysed	1326			
Units: Ratio				
number (confidence interval 95%)				
Stimulation Day 6 - FSH	1.15 (1.11 to 1.19)			
Stimulation Day 6 - LH	0.94 (0.86 to 1.03)			

Stimulation Day 6 - estradiol	0.92 (0.85 to 0.99)			
Stimulation Day 6 - progesterone	0.97 (0.9 to 1.03)			
Stimulation Day 6 - inhibin A	0.92 (0.85 to 0.99)			
Stimulation Day 6 - inhibin B	0.95 (0.89 to 1.02)			
End-of-stimulation - FSH	1.1 (1.07 to 1.14)			
End-of-stimulation - LH	0.95 (0.86 to 1.04)			
End-of-stimulation - estradiol	0.95 (0.89 to 1.03)			
End-of-stimulation - progesterone	0.95 (0.89 to 1.01)			
End-of-stimulation - inhibin A	0.92 (0.86 to 0.99)			
End-of-stimulation - inhibin B	0.95 (0.88 to 1.03)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total gonadotropin dose

End point title	Total gonadotropin dose

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: ug				
arithmetic mean (standard deviation)	90 (± 25.3)	103.7 (± 33.6)		

Statistical analyses

Statistical analysis title	Treatment comparison: Total gonadotropin dose

Statistical analysis description:

Treatment groups were compared using the van Elteren test adjusted for age (<35, 35-37, and 38-40 years).

Comparison groups	FE 999049 v GONAL-F

Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	van Elteren

Secondary: Number of stimulation days

End point title	Number of stimulation days

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: Days				
arithmetic mean (standard deviation)	8.9 (± 1.9)	8.6 (± 1.7)		

Statistical analyses

Statistical analysis title	Treatment comparison: Number of stimulation days

Statistical analysis description:

Treatment groups were compared using the van Elteren test adjusted for age (<35, 35-37, and 38-40 years).

Comparison groups	FE 999049 v GONAL-F
Number of subjects included in analysis	1326
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.062
Method	van Elteren

Secondary: Proportion of subjects with markedly abnormal changes in clinical chemistry and haematology parameters

End point title	Proportion of subjects with markedly abnormal changes in clinical chemistry and haematology parameters

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: Percentage of subjects				
number (not applicable)				
Clinical chemistry	0.15	0		
Hematology	0.3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of injection site reactions

End point title	Frequency of injection site reactions

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	GONAL-F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	665	661		
Units: Percentage of events				
number (not applicable)	3.4	3.5		

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-trial.

Adverse event reporting additional description:

AEs with onset after start of first administration of IMP 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

Reporting group description:

Subjects randomised and exposed to FE 999049 IMP were included in this group.

Reporting group title	GONAL-F

Reporting group description:

Subjects randomised and exposed to GONAL-F IMP were included in this group.

Serious adverse events	FE 999049	GONAL-F	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 665 (2.41%)	10 / 661 (1.51%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	2 / 665 (0.30%)	0 / 661 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Haemorrhage in pregnancy			
subjects affected / exposed	5 / 665 (0.75%)	1 / 661 (0.15%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	2 / 665 (0.30%)	1 / 661 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Biochemical pregnancy			
subjects affected / exposed	1 / 665 (0.15%)	2 / 661 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion threatened			
subjects affected / exposed	1 / 665 (0.15%)	0 / 661 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperemesis gravidarum			
subjects affected / exposed	0 / 665 (0.00%)	1 / 661 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	1 / 665 (0.15%)	0 / 661 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	3 / 665 (0.45%)	6 / 661 (0.91%)	
occurrences causally related to treatment / all	2 / 3	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adnexal torsion			
subjects affected / exposed	1 / 665 (0.15%)	0 / 661 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Affect lability			
subjects affected / exposed	1 / 665 (0.15%)	0 / 661 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Post procedural infection			

subjects affected / exposed	0 / 665 (0.00%)	1 / 661 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FE 999049	GONAL-F	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	356 / 665 (53.53%)	330 / 661 (49.92%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	49 / 665 (7.37%)	52 / 661 (7.87%)	
occurrences (all)	51	54	
Nervous system disorders			
Headache			
subjects affected / exposed	97 / 665 (14.59%)	88 / 661 (13.31%)	
occurrences (all)	131	110	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	46 / 665 (6.92%)	41 / 661 (6.20%)	
occurrences (all)	54	59	
Pelvic discomfort			
subjects affected / exposed	38 / 665 (5.71%)	25 / 661 (3.78%)	
occurrences (all)	46	31	

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