Clinical trial results:
A Phase II, Multicentre, Multinational, Randomised, Assessor-Blind Trial to Investigate the Efficacy and Safety of Various Dosages of FSH-GEX™ in Comparison With 150 IU Gonal-f® in Women Undergoing ICSI Treatment

Summary

EudraCT number	2012-003006-27
Trial protocol	HU DE
Global end of trial date	30 July 2013

Results information

Result version number	v1 (current)
This version publication date	21 June 2020
First version publication date	21 June 2020

Trial information

Trial identification

Sponsor protocol code	GEXGP24201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01794208
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Glycotope GmbH
Sponsor organisation address	Robert Roessle St 10, Berlin, Germany, 13125
Public contact	Reception, Glycotope GmbH, +49 3094892600, Trials@glycotope.com
Scientific contact	Reception, Glycotope GmbH, +49 3094892600, Trials@glycotope.com
Sponsor organisation name	Glycotope GmbH
Sponsor organisation address	Robert Roessle St 10, Berlin, Germany, 13125
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Scientific contact	Lars Stoeckl, PhD, Glycotope GmbH, +49 3094892600, Lars.Stoeckl@glycotope.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	27 August 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 July 2013
Global end of trial reached?	Yes
Global end of trial date	30 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is the determination of the recommended standard treatment dose of FSH-GEX™ as assessed by follicle growth dynamics in women between 18 and 37 years of age undergoing intracytoplasmic sperm injection (ICSI) treatment.

Protection of trial subjects:

Patients were closely monitored and seen daily or every-other day by their Investigators.

Background therapy:

Triptorelin acetate (Decapeptyl® in Germany, Gonapeptyl® in Hungary), a gonadotropin releasing hormone agonist, was administered to all patients for down-regulation. Triptorelin acetate (100 µg) was administered once daily subcutaneously.
Recombinant hCG:
A human recombinant chorionic gonadotropin (Ovitrelle® in Germany and Hungary) was administered to all patients for stimulation of follicle maturation prior to IVF procedures. Recombinant hCG (250 µg) was administered as one single dose subcutaneously according to the instructions of the investigator.
Progesterone:
A progesterone derivative (Crinone® in Germany and Hungary) was administered to all patients for luteal support. Progesterone (90 mg) gel was administered once daily by vaginal application.

Evidence for comparator:

Gonal-f®, a recombinant human FSH, was the comparator drug used in this study.
Gonal-f® has been used as comparator in the two Phase 1 studies. It is widely used and comprises a broad documentation of efficacy and safety.

Actual start date of recruitment	08 January 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	Germany: 147
Country: Number of subjects enrolled	Hungary: 120
Worldwide total number of subjects	267
EEA total number of subjects	267

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)	267
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

During the study period from 08-Jan-2013 to 30-Jul-2013, a total of 267 patients were enrolled in six study centers in Germany and in two centers in Hungary.

Pre-assignment

Screening details:

Of the 267 patients enrolled, 9 were screening failures: 5 patients violated inclusion criterion 4 (AMH level of 1 to 4 ng/mL), 1 patient violated inclusion criterion 6 (BMI 18.5-30 kg/m²), 1 patient fulfilled exclusion criterion 14 (history of thrombosis or other risk factors), and 2 patients violated inclusion criterion 10 (comply with protocol)

Pre-assignment period milestones

Number of subjects started	267
Intermediate milestone: Number of subjects	Starting Down-regulation: 258
Number of subjects completed	247

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 2
Reason: Number of subjects	pregnancy: 4
Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	non-compliance: 1
Reason: Number of subjects	treatment failure: 2
Reason: Number of subjects	Protocol deviation: 9

Period 1

Period 1 title	Assessor-blind treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

Blinding of the patient was not possible. Study blind was maintained using an “independent” third party; the drug administrators in each center, e.g. a physician or nurse, who was not involved in any study assessments, received the randomization information regarding the treatment allocation. Investigator, who was performing all assessments, and the embryologist, who was performing the counting of the oocytes as well as evaluating the oocyte maturity and quality, were blinded during the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment 1

Arm description:

Patients received FSH-GEX: 52.5 IU QD

Arm type	Experimental

Investigational medicinal product name	FSH-GEX
Investigational medicinal product code	
Other name	follitropin epsilon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage: 52.5 IU QD
Dosage form: Solution for subcutaneous injection, provided in single-use vials.
Strength: 750 IU/ml.
Volume:0.5 ml/vial (375 IU/vial).
Excipients: Sucrose, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, methionine, and poloxamer 1886

Arm title	Treatment 2

Arm description:

Patients received FSH-GEX: 75 IU QD

Arm type	Experimental
Investigational medicinal product name	FSH-GEX
Investigational medicinal product code	
Other name	follitropin epsilon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage: FSH-GEX: 52.5 IU QD
Dosage form: Solution for subcutaneous injection, provided in single-use vials.
Strength: 750 IU/ml.
Volume:0.5 ml/vial (375 IU/vial).
Excipients: Sucrose, disodium phosphate dihydrate, sodium dihydrogen phosphate monohydrate, methionine, and poloxamer 1886

Arm title	Treatment 3

Arm description:

Patients received FSH-GEX: 112.5 IU QD

Arm type	Experimental
Investigational medicinal product name	FSH-GEX
Investigational medicinal product code	
Other name	follitropin epsilon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage 112.5 IU QD

Arm title	Treatment 4

Arm description:

Patients received FSH-GEX:150 IU QD

Arm type	Experimental
Investigational medicinal product name	FSH-GEX
Investigational medicinal product code	
Other name	follitropin epsilon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dosage: 150 IU QD

Arm title	Treatment 5

Arm description: Patients received FSH-GEX: 150 IU QAD	
Arm type	Experimental
Investigational medicinal product name	FSH-GEX
Investigational medicinal product code	
Other name	follitropin epsilon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Dosage: 150 IU QAD	
Arm title	Treatment 6
Arm description: Patients received Gonal-f: 150 IU QD	
Arm type	Active comparator
Investigational medicinal product name	Gonal-f
Investigational medicinal product code	
Other name	follitropin alfa
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Dosage 150 IU QD Dosage form: Powder and solvent for solution for injection. Appearance of powder: Lyophilized white pellet, provided in vials (glass). Appearance of solvent: Clear colorless solution, provided in pre-filled syringe (glass). Excipients: Powder: sucrose, sodium dihydrogen phosphate monohydrate, disodium phosphate dehydrate, methionine, polysorbate 20, phosphoric acid (concentrated), sodium hydroxide, and solvent: water for injections	

Notes:

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

Justification: Blinding of the patient was not possible. Study blind was maintained using an "independent" third party; the drug administrators in each center, e.g. a physician or nurse, who was not involved in any study assessments, received the randomization information regarding the treatment allocation. Investigator, who was performing all assessments, and the embryologist, who was performing the counting of the oocytes as well as evaluating the oocyte maturity and quality, were blinded during the study.

Number of subjects in period 1[2]	Treatment 1	Treatment 2	Treatment 3
Started	41	42	40
Meeting hCG criteria	38	40	38
Completed	38	40	38
Not completed	3	2	2
Physician decision	1	1	1
Adverse event, non-fatal	-	1	-
Lack of efficacy	2	-	1

Number of subjects in period 1[2]	Treatment 4	Treatment 5	Treatment 6
Started	43	42	39
Meeting hCG criteria	41	41	37

Completed	41	41	37
Not completed	2	1	2
Physician decision	-	-	-
Adverse event, non-fatal	-	-	1
Lack of efficacy	2	1	1

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: Baseline values were only taken from patients who fulfilled criteria for starting with experimental treatment

Baseline characteristics

Reporting groups	
Reporting group title	Treatment 1
Reporting group description:	
Patients received FSH-GEX: 52.5 IU QD	
Reporting group title	Treatment 2
Reporting group description:	
Patients received FSH-GEX: 75 IU QD	
Reporting group title	Treatment 3
Reporting group description:	
Patients received FSH-GEX: 112.5 IU QD	
Reporting group title	Treatment 4
Reporting group description:	
Patients received FSH-GEX:150 IU QD	
Reporting group title	Treatment 5
Reporting group description:	
Patients received FSH-GEX: 150 IU QAD	
Reporting group title	Treatment 6
Reporting group description:	
Patients received Gonal-f: 150 IU QD	

Reporting group values	Treatment 1	Treatment 2	Treatment 3
Number of subjects	41	42	40
Age categorical			
Age at screening			
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)	41	42	40
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Only female patients aged 18 to 37 years at Screening were enrolled			
Units: years			
arithmetic mean	32.54	31.86	31.88
standard deviation	± 3.769	± 3.339	± 3.897
Gender categorical			
Population			
Units: Subjects			
Female	41	42	40
Male	0	0	0

Reporting group values	Treatment 4	Treatment 5	Treatment 6
Number of subjects	43	42	39
Age categorical			
Age at screening			
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)	43	42	39
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Only female patients aged 18 to 37 years at Screening were enrolled			
Units: years			
arithmetic mean	32.28	32.07	32.10
standard deviation	± 2.865	± 2.709	± 2.683
Gender categorical			
Population			
Units: Subjects			
Female	43	42	39
Male	0	0	0

Reporting group values	Total		
Number of subjects	247		
Age categorical			
Age at screening			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	247		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Only female patients aged 18 to 37 years at Screening were enrolled			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Population			
Units: Subjects			
Female	247		

Male	0		

Subject analysis sets

Subject analysis set title	Intent-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT consisted of all randomized patients who received at least one dose of randomized study medication (IMP). The ITT was the primary population for the efficacy analysis.

Reporting group values	Intent-to-treat		
Number of subjects	247		
Age categorical			
Age at screening			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	247		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Only female patients aged 18 to 37 years at Screening were enrolled			
Units: years			
arithmetic mean	32.07		
standard deviation	± 3.226		
Gender categorical			
Population			
Units: Subjects			
Female	247		
Male	0		

End points

End points reporting groups

Reporting group title	Treatment 1
Reporting group description: Patients received FSH-GEX: 52.5 IU QD	
Reporting group title	Treatment 2
Reporting group description: Patients received FSH-GEX: 75 IU QD	
Reporting group title	Treatment 3
Reporting group description: Patients received FSH-GEX: 112.5 IU QD	
Reporting group title	Treatment 4
Reporting group description: Patients received FSH-GEX:150 IU QD	
Reporting group title	Treatment 5
Reporting group description: Patients received FSH-GEX: 150 IU QAD	
Reporting group title	Treatment 6
Reporting group description: Patients received Gonal-f: 150 IU QD	
Subject analysis set title	Intent-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT consisted of all randomized patients who received at least one dose of randomized study medication (IMP). The ITT was the primary population for the efficacy analysis.	

Primary: number of follicles with a diameter of ≥ 12 mm

End point title	number of follicles with a diameter of ≥ 12 mm
End point description: The primary efficacy variable was the number of follicles with a diameter of ≥ 12 mm on the day of r hCG injection or the day before.	
End point type	Primary
End point timeframe: Assessor-blind Treatment period	

End point values	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	42	40	43
Units: Number				
arithmetic mean (standard deviation)	11.2 (± 4.61)	13.0 (± 4.16)	13.9 (± 4.35)	13.7 (± 4.18)

End point values	Treatment 5	Treatment 6	Intent-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	39	247	

Units: Number				
arithmetic mean (standard deviation)	12.8 (± 3.84)	12.4 (± 5.14)	12.8 (± 4.43)	

Statistical analyses

Statistical analysis title	number of follicles with a diameter of ≥ 12 mm

Statistical analysis description:

H0(1): μ (FSH-GEX™ 150 IU quaque die [QD]) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(1): μ (FSH-GEX™ 150 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 4 v Treatment 6
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	≤ 0.025 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	3.37
Variability estimate	Standard deviation
Dispersion value	0.2

Notes:

[1] - The primary analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.

[2] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	number of follicles with a diameter of ≥ 12 mm

Statistical analysis description:

H0(2): μ (FSH-GEX™ 112.5 IU QD) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(2): μ (FSH-GEX™ 112.5 IU QD) > μ (Gonal-f® 150 IU QD)

Comparison groups	Treatment 6 v Treatment 3
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	≤ 0.025 [4]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	3.36
Variability estimate	Standard deviation
Dispersion value	0.16

Notes:

[3] - The primary analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[4] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	Copy of number of follicles with a diameter of ...

Statistical analysis description:

H0(3): μ (FSH-GEX™ 75 IU QD) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(3): μ (FSH-GEX™ 75 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 2 v Treatment 6
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	≤ 0.025 [6]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.42
upper limit	2.45
Variability estimate	Standard deviation
Dispersion value	0.17

Notes:

[5] - The primary analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[6] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	Copy of number of follicles with a diameter of ...

Statistical analysis description:

H0(4): μ (FSH-GEX™ 52.5 IU QD) ≤ μ (Gonal-f®) 150 IU QD vs.
H1(4): μ (FSH-GEX™ 52.5 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 1

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	≤ 0.025 [8]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.43
upper limit	0.8
Variability estimate	Standard deviation
Dispersion value	0.17

Notes:

[7] - The primary analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[8] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Secondary: Number of retrieved COCs

End point title	Number of retrieved COCs
End point description:	
Number of retrieved COCs	
End point type	Secondary
End point timeframe:	
Day of follicle puncture	

End point values	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	41	40	41
Units: number				
arithmetic mean (standard deviation)	10.2 (± 6.97)	12.6 (± 5.03)	14.5 (± 5.84)	12.6 (± 5.69)

End point values	Treatment 5	Treatment 6	Intent-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	38	243	
Units: number				
arithmetic mean (standard deviation)	13.4 (± 5.69)	11.1 (± 5.39)	12.4 (± 5.91)	

Statistical analyses

Statistical analysis title	Number of retrieved COCs T1 vs T6

Statistical analysis description:

H0(4): μ (FSH-GEX™ 52.5 IU QD) ≤ μ (Gonal-f®) 150 IU QD vs.
H1(4): μ (FSH-GEX™ 52.5 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 1
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	≤ 0.025 [10]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.73
upper limit	1.88
Variability estimate	Standard deviation
Dispersion value	0.23

Notes:

[9] - The primary analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[10] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	Copy of Number of retrieved COCs T3 vs T6

Statistical analysis description:

H0(2): μ (FSH-GEX™ 112.5 IU QD) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(2): μ (FSH-GEX™ 112.5 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 3 v Treatment 6
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	≤ 0.025 [12]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	3.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	5.72
Variability estimate	Standard deviation
Dispersion value	0.2

Notes:

[11] - The primary analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.

[12] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	Copy of Copy of Number of retrieved COCs T2 vs T6

Statistical analysis description:

H0(3): μ (FSH-GEX™ 75 IU QD) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(3): μ (FSH-GEX™ 75 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 2
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	≤ 0.025 [14]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	3.71
Variability estimate	Standard deviation
Dispersion value	0.19

Notes:

[13] - The primary analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[14] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	Copy of Number of retrieved COCs T4 vs T6

Statistical analysis description:

H0(1): μ (FSH-GEX™ 150 IU quaque die [QD]) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(1): μ (FSH-GEX™ 150 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 4
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	≤ 0.025 [16]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	4.05
Variability estimate	Standard deviation
Dispersion value	0.24

Notes:

[15] - The primary analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.

[16] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Secondary: Number of Metaphase II Oocytes

End point title	Number of Metaphase II Oocytes
End point description:	
Number of Metaphase II Oocytes Retrieved	
End point type	Secondary
End point timeframe:	
After follicle puncture	

End point values	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	41	40	41
Units: number				
arithmetic mean (standard deviation)	7.9 (± 4.99)	9.4 (± 4.76)	10.7 (± 4.94)	8.8 (± 4.60)

End point values	Treatment 5	Treatment 6	Intent-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	38	243	
Units: number				
arithmetic mean (standard deviation)	10.1 (± 3.97)	8.6 (± 4.40)	9.2 (± 4.67)	

Statistical analyses

Statistical analysis title	Number of metaphase II oocytes

Statistical analysis description:

H0(1): μ (FSH-GEX™ 150 IU quaque die [QD]) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(1): μ (FSH-GEX™ 150 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 4
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	≤ 0.025 [18]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.87
upper limit	2.14
Variability estimate	Standard deviation
Dispersion value	0.19

Notes:

[17] - The analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[18] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	Number of metaphase II oocytes

Statistical analysis description:

H0(2): μ (FSH-GEX™ 112.5 IU QD) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(2): μ (FSH-GEX™ 112.5 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 3
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	≤ 0.025 [20]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	3.88
Variability estimate	Standard deviation
Dispersion value	0.15

Notes:

[19] - The analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[20] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	Number of metaphase II oocytes

Statistical analysis description:

H0(3): μ (FSH-GEX™ 75 IU QD) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(3): μ (FSH-GEX™ 75 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 2

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	≤ 0.025 [22]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.19
upper limit	2.7
Variability estimate	Standard deviation
Dispersion value	0.16

Notes:

[21] - The analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[22] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	Number of metaphase II oocytes

Statistical analysis description:

H0(4): μ (FSH-GEX™ 52.5 IU QD) ≤ μ (Gonal-f®) 150 IU QD vs.
H1(4): μ (FSH-GEX™ 52.5 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 1
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	≤ 0.025 [24]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.89
upper limit	1.18
Variability estimate	Standard deviation
Dispersion value	0.16

Notes:

[23] - The analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[24] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Secondary: Number of 2PN Oocytes

End point title	Number of 2PN Oocytes

End point description:

Number of 2PN Oocytes one Day after Follicle Puncture

End point type	Secondary

End point timeframe:
One Day after Follicle Puncture

End point values	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	41	39	41
Units: Number				
arithmetic mean (standard deviation)	6.0 (± 4.60)	7.3 (± 3.99)	7.5 (± 3.99)	6.6 (± 3.66)

End point values	Treatment 5	Treatment 6	Intent-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	42	38	241	
Units: Number				
arithmetic mean (standard deviation)	7.5 (± 4.62)	6.2 (± 3.81)	6.9 (± 4.14)	

Statistical analyses

Statistical analysis title	Number of 2PN oocytes

Statistical analysis description:

H0(1): μ (FSH-GEX™ 150 IU quaque die [QD]) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(1): μ (FSH-GEX™ 150 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 4
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	≤ 0.025 [26]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	2.03
Variability estimate	Standard deviation
Dispersion value	0.16

Notes:

[25] - The analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[26] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	Number of 2PN oocytes

Statistical analysis description:

H0(2): μ (FSH-GEX™ 112.5 IU QD) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(2): μ (FSH-GEX™ 112.5 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 3
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	≤ 0.025 [28]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	3.06
Variability estimate	Standard deviation
Dispersion value	0.15

Notes:

[27] - The analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[28] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Statistical analysis title	Number of 2PN oocytes

Statistical analysis description:

H0(3): μ (FSH-GEX™ 75 IU QD) ≤ μ (Gonal-f® 150 IU QD) vs.
H1(3): μ (FSH-GEX™ 75 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 2
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	≤ 0.025 [30]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.64
upper limit	2.75
Variability estimate	Standard deviation
Dispersion value	0.14

Notes:

[29] - The analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.
[30] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as

one-sided tests at a significance level of 0.025.

Statistical analysis title	Number of 2PN oocytes

Statistical analysis description:

H0(4): μ (FSH-GEX™ 52.5 IU QD) ≤ μ (Gonal-f®) 150 IU QD vs.
H1(4): μ (FSH-GEX™ 52.5 IU QD) > μ (Gonal-f® 150 IU QD).

Comparison groups	Treatment 6 v Treatment 1
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	≤ 0.025 [32]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	1.62
Variability estimate	Standard deviation
Dispersion value	0.15

Notes:

[31] - The analysis was conducted based on the ITT population using sequential (hierarchical) testing for the pair-wise comparison of the four FSH-GEX™ daily dosing regimens with Gonal-f® 150 IU per day. Each of these comparisons was performed using an analysis of covariance (ANCOVA) model, which included treatment (two levels) and site as factors and age as a covariate.

[32] - Given the one sided hypotheses to be tested, the analysis of treatment effects was performed as one-sided tests at a significance level of 0.025.

Secondary: Estradiol concentration

End point title	Estradiol concentration

End point description:

Pharmacodynamic effect of FSH-GEX and Gonal-f on Estradiol

End point type	Secondary

End point timeframe:

The pharmacodynamic effect of FSH-GEX™ and Gonal-f on Estradiol was measured on the day of HCG injection or the day before.

End point values	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	42	40	43
Units: pmol/L				
arithmetic mean (standard deviation)	8425.7 (± 9665.14)	11157.3 (± 7794.47)	13692.8 (± 8945.99)	13014.0 (± 9462.37)

End point values	Treatment 5	Treatment 6		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: pmol/L				
arithmetic mean (standard deviation)	11991.1 (± 9127.09)	8405.6 (± 5677.45)		

Statistical analyses

Statistical analysis title	Estradiol T1 vs T6
Statistical analysis description:	
Comparison of FSH-GEX 52.5 IU QD versus Gonal-f 150 IU QD	
Comparison groups	Treatment 1 v Treatment 6
Number of subjects included in analysis	80
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	p-value
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	1

Statistical analysis title	Estradiol T2 vs T6
Statistical analysis description:	
Comparison of FSH.GEX 75 IU QD versus Gonal-f 150 IU QD	
Comparison groups	Treatment 2 v Treatment 6
Number of subjects included in analysis	81
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	p-value
Point estimate	0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	1

Statistical analysis title	Estradiol T3 vs T6

Statistical analysis description:	
Comparison of FSH-GEX 112.5 IU QD versus Gonal-f 150 IU QD	
Comparison groups	Treatment 3 v Treatment 6
Number of subjects included in analysis	79
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	p-value
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	1

Statistical analysis title	Estradiol T4 vs T6
Statistical analysis description:	
Comparison of FSH-GEX 150 IU QD versus Gonal-f 150 IU QD	
Comparison groups	Treatment 4 v Treatment 6
Number of subjects included in analysis	82
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	p-value
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	1

Statistical analysis title	Estradiol T5 vs T6
Statistical analysis description:	
Comparison of FSH-GEX 150 IU QAD vs 150 IU QD	
Comparison groups	Treatment 5 v Treatment 6
Number of subjects included in analysis	81
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	p-value
Point estimate	0.474

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	1

Secondary: Inhibin B concentration

End point title	Inhibin B concentration

End point description:

Pharmacodynamic effect of FSH-GEX and Gonal-f on Inhibin B

End point type	Secondary

End point timeframe:

The pharmacodynamic effect of FSH-GEX™ and Gonal-f on Inhibin B was measured on the day of HCG injection or the day before.

End point values	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	42	40	43
Units: U/L				
arithmetic mean (standard deviation)	883.3 (± 631.41)	902.0 (± 461.87)	871.4 (± 428.93)	724.2 (± 465.30)

End point values	Treatment 5	Treatment 6		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	39		
Units: U/L				
arithmetic mean (standard deviation)	998.7 (± 496.53)	694.5 (± 420.11)		

Statistical analyses

Statistical analysis title	Inhibin B T1 vs T6

Statistical analysis description:

Comparison of 52.5 IU QD versus Gonal-f 150 IU QD

Comparison groups	Treatment 1 v Treatment 6
Number of subjects included in analysis	80
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	p-value
Point estimate	0.166

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	1

Statistical analysis title	Inhibin B T2 vs T6
Statistical analysis description:	
Comparison of FSH-GEX 75 IU QD versus Gonal-f 150 IU QD	
Comparison groups	Treatment 2 v Treatment 6
Number of subjects included in analysis	81
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	p-value
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	1

Statistical analysis title	Inhibin B T3 vs T6
Statistical analysis description:	
Comparison of FSH-GEX 112.5 IU QD vs Gonal-f 150 IU QD	
Comparison groups	Treatment 3 v Treatment 6
Number of subjects included in analysis	79
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	p-value
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	1

Statistical analysis title	Inhibin B T4 vs T6
Statistical analysis description:	
Comparison of FSH-GEX 150 IU QD versus Gonal-f 150 IU QD	
Comparison groups	Treatment 4 v Treatment 6

Number of subjects included in analysis	82
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	p-value
Point estimate	0.956
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	1

Statistical analysis title	Inhibin B T5 vs T6
Statistical analysis description:	
Comparison of FSH-GEX 150 IU QAD versus Gonal-f 150 IU QD	
Comparison groups	Treatment 5 v Treatment 6
Number of subjects included in analysis	81
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	p-value
Point estimate	0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	1

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment-emergent AEs were defined as AEs occurring or worsening with an onset at the time of or following the first administration of IMP (FSH-GEX or Gonal-f).	
Adverse event reporting additional description:	
FSH (both FSH-GEX and Gonal-f) was to be administered once daily for a maximum duration of 18 days, with the exception of the FSH-GEX 150 IU QAD group, where patient were to receive treatment every second day.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Treatment 1
Reporting group description:	
Patients received FSH-GEX: 52.5 IU QD	
Reporting group title	Treatment 2
Reporting group description:	
Patients received FSH-GEX: 75 IU QD	
Reporting group title	Treatment 3
Reporting group description:	
Patients received FSH-GEX: 112.5 IU QD	
Reporting group title	Treatment 4
Reporting group description:	
Patients received FSH-GEX:150 IU QD	
Reporting group title	Treatment 5
Reporting group description:	
Patients received FSH-GEX: 150 IU QAD	
Reporting group title	Treatment 6
Reporting group description:	
Patients received Gonal-f: 150 IU QD	

Serious adverse events	Treatment 1	Treatment 2	Treatment 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 40 (2.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 41 (0.00%)	0 / 42 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Treatment 4	Treatment 5	Treatment 6
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	1 / 39 (2.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Treatment 1	Treatment 2	Treatment 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 41 (39.02%)	13 / 42 (30.95%)	16 / 40 (40.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 41 (21.95%)	5 / 42 (11.90%)	6 / 40 (15.00%)
occurrences (all)	36	36	36
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	2 / 40 (5.00%)
occurrences (all)	3	3	3
Ectopic pregnancy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 42 (2.38%)	0 / 40 (0.00%)
occurrences (all)	2	2	2
Abortion imminent			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	1	1
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	3 / 41 (7.32%)	2 / 42 (4.76%)	1 / 40 (2.50%)
occurrences (all)	13	13	13
Injection site pain			
subjects affected / exposed	3 / 41 (7.32%)	1 / 42 (2.38%)	0 / 40 (0.00%)
occurrences (all)	11	11	11
Injection site swelling			
subjects affected / exposed	2 / 41 (4.88%)	0 / 42 (0.00%)	0 / 40 (0.00%)
occurrences (all)	7	7	7
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 41 (9.76%)	1 / 42 (2.38%)	2 / 40 (5.00%)
occurrences (all)	16	16	16
Abdominal discomfort			
subjects affected / exposed	1 / 41 (2.44%)	0 / 42 (0.00%)	4 / 40 (10.00%)
occurrences (all)	7	7	7
Nausea			

subjects affected / exposed	3 / 41 (7.32%)	2 / 42 (4.76%)	1 / 40 (2.50%)
occurrences (all)	10	10	10
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	2 / 41 (4.88%)	2 / 42 (4.76%)	1 / 40 (2.50%)
occurrences (all)	11	11	11
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 41 (0.00%)	2 / 42 (4.76%)	0 / 40 (0.00%)
occurrences (all)	7	7	7

Non-serious adverse events	Treatment 4	Treatment 5	Treatment 6
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 43 (34.88%)	19 / 42 (45.24%)	11 / 39 (28.21%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 43 (9.30%)	8 / 42 (19.05%)	4 / 39 (10.26%)
occurrences (all)	36	36	36
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 39 (0.00%)
occurrences (all)	3	3	3
Ectopic pregnancy			
subjects affected / exposed	1 / 43 (2.33%)	0 / 42 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	2	2
Abortion imminent			
subjects affected / exposed	0 / 43 (0.00%)	0 / 42 (0.00%)	0 / 39 (0.00%)
occurrences (all)	1	1	1
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	4 / 43 (9.30%)	2 / 42 (4.76%)	1 / 39 (2.56%)
occurrences (all)	13	13	13
Injection site pain			
subjects affected / exposed	4 / 43 (9.30%)	2 / 42 (4.76%)	1 / 39 (2.56%)
occurrences (all)	11	11	11
Injection site swelling			

subjects affected / exposed	3 / 43 (6.98%)	2 / 42 (4.76%)	0 / 39 (0.00%)
occurrences (all)	7	7	7
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 43 (6.98%)	3 / 42 (7.14%)	3 / 39 (7.69%)
occurrences (all)	16	16	16
Abdominal discomfort			
subjects affected / exposed	0 / 43 (0.00%)	1 / 42 (2.38%)	1 / 39 (2.56%)
occurrences (all)	7	7	7
Nausea			
subjects affected / exposed	1 / 43 (2.33%)	1 / 42 (2.38%)	2 / 39 (5.13%)
occurrences (all)	10	10	10
Reproductive system and breast disorders			
Ovarian hyperstimulation syndrome			
subjects affected / exposed	1 / 43 (2.33%)	2 / 42 (4.76%)	3 / 39 (7.69%)
occurrences (all)	11	11	11
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 43 (4.65%)	2 / 42 (4.76%)	1 / 39 (2.56%)
occurrences (all)	7	7	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2013	The Sponsor amended the protocol in order to 1. determine the FSH concentration in serum during the FSH treatment period in order to ex-plore the exposure-response relationship. Blood sampling for the analysis of FSH serum concentrations should be performed on Day 1 and Day 2 of FSH treatment and at least every second day thereafter as well as on visit 4 (record of hCG criterion). Since these sampling timepoints corresponded to serum samples taken for the central lab un-der the current protocol (version 1.0) no additional blood sampling was required. Also, no in-crease in blood sampling volumes, either of individual samples or in total, was required.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31982355