Clinical trial results:
Randomised clinical trial comparing highly purified FSH formulation (Fostimon®) and recombinant FSH (Gonal-F®) in GnRH-antagonist controlled ovarian hyperstimulation cycles.

Summary

EudraCT number	2013-002482-19
Trial protocol	IT GB ES BE
Global end of trial date	12 August 2017

Results information

Result version number	v1 (current)
This version publication date	30 September 2018
First version publication date	30 September 2018

Trial information

Trial identification

Sponsor protocol code	13EU/FSH01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01969201
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IBSA Institut Biochimique SA
Sponsor organisation address	via del Piano, Pambio-Noranco, Switzerland, 6995
Public contact	Barbara Cometti, IBSA Institut Biochimique SA, +41 583601000, sd@ibsa.ch
Scientific contact	Barbara Cometti, IBSA Institut Biochimique SA, +41 583601000, sd@ibsa.ch

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	22 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the non-inferiority study is to evaluate the clinical efficacy and the safety of two different subcutaneous FSH preparations (Fostimon®, IBSA Institut Biochimique SA versus Gonal-F®) for controlled ovarian hyperstimulation in a GnRH-antagonist cycle

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: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 200
Country: Number of subjects enrolled	United Kingdom: 88
Country: Number of subjects enrolled	Belgium: 80
Country: Number of subjects enrolled	Italy: 179
Country: Number of subjects enrolled	Turkey: 114
Country: Number of subjects enrolled	Switzerland: 49
Worldwide total number of subjects	710
EEA total number of subjects	547

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)	710
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 17 sites randomised subjects into the trial: 4 in Spain, 6 in Italy, 1 in UK, 2 in Belgium, 2 in Switzerland, 2 in Turkey.

Pre-assignment

Screening details:

A total of 819subjects were screened in the trial, of whom 712 subjects were randomised: 354 subjects to Fostimon and 358 subjects to GONAL-F. Two subjects in the Fostimon group were randomisation failures and did not receive investigational medicinal product (IMP).

Period 1

Period 1 title	Overall trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Assessor, Investigator[2]

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 monitors and the participating subjects knew the treatment allocation once the subjects were randomised.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test product - Fostimon

Arm description:

Subject randomised and exposed to Fostimon IMP were included in this group

Arm type	Experimental
Investigational medicinal product name	Fostimon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The starting dose regimen was fixed for the first 5 days for both the study treatment: 150 IU of FSH administered daily by subcutaneous injection.

Arm title	Reference product - 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	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The starting dose regimen was fixed for the first 5 days for both the study treatment: 150 IU of FSH administered daily by subcutaneous injection.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: 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 monitors and the participating subjects knew the treatment allocation once the subjects were randomised.

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

Justification: 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 monitors and the participating subjects knew the treatment allocation once the subjects were randomised.

Number of subjects in period 1	Test product - Fostimon	Reference product - Gonal F
Started	352	358
Completed	307	313
Not completed	45	45
Embryo transfer not performed	29	29
Consent withdrawn by subject	-	1
Adverse event, non-fatal	3	5
Lack of efficacy	13	8
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Test product - Fostimon
Reporting group description:	
Subject randomised and exposed to Fostimon IMP were included in this group	
Reporting group title	Reference product - Gonal F
Reporting group description:	
Subjects randomised and exposed to Gonal F IMP were included in this group	

Reporting group values	Test product - Fostimon	Reference product - Gonal F	Total
Number of subjects	352	358	710
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)	0	0	0
From 65-84 years	352	358	710
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	32.39	32.68	
standard deviation	± 3.83	± 3.52	-
Gender categorical Units: Subjects			
Female	352	358	710
Male	0	0	0
Infertility diagnosis Units: Subjects			
Male factor	156	150	306
Tubal factor	30	32	62
Male + Tubal factor	15	13	28
Idiopathic	126	136	262
Other factors	25	27	52
BMI			
Body mass index			
Units: Kg/m2			
arithmetic mean	22.81	22.59	
standard deviation	± 2.74	± 2.87	-
Duration of infertility Units: months			
arithmetic mean	41.8	41.76	
standard deviation	± 30.15	± 27.5	-

Basal FSH Units: IU/l arithmetic mean standard deviation	 6.78 ± 1.55	 6.75 ± 1.58	 -
Basal AMH levels			
Basal anti-mullerian hormone levels			
Units: ng/ml arithmetic mean standard deviation	 2.69 ± 1.15	 2.70 ± 1.12	 -

End points

End points reporting groups

Reporting group title	Test product - Fostimon
Reporting group description:	
Subject randomised and exposed to Fostimon IMP were included in this group	
Reporting group title	Reference product - Gonal F
Reporting group description:	
Subjects randomised and exposed to Gonal F IMP were included in this group	

Primary: Clinical pregnancy rate

End point title	Clinical pregnancy rate
End point description:	
End point type	Primary
End point timeframe:	
8 weeks of gestation.	

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352[1]	358[2]		
Units: Percentage of subjects				
number (not applicable)	36.9	39.7		

Notes:

[1] - ITT population

[2] - ITT population

Statistical analyses

Statistical analysis title	Treatment comparison: clinical pregnancy rate

Statistical analysis description:

The non-inferiority of Fostimon® vs. Gonal-F® was evaluated by calculating the 95% confidence interval (CI) for the differences in pregnancy rates between the two treatment groups. If the lower bound of the 95% CI of the difference between the two proportions was greater than -0.10 (i.e. -10%), then Fostimon® was to be considered not inferior to the control treatment.

Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Treatment difference
Point estimate	-2.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.88
upper limit	4.42

Notes:

[3] - The lower bound of the 95% CI was above the pre-specified non-inferiority limit of -8.0%. Thus non inferiority of Fostimon to Gonal-F with regard to the ongoing pregnancy rate was demonstrated.

Secondary: Mean FSH dose

End point title	Mean FSH dose

End point description:

End point type	Secondary

End point timeframe:

at the end of the stimulation.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	358		
Units: IU				
median (standard deviation)	1550.6 (± 549.8)	1478.1 (± 450.0)		

Statistical analyses

Statistical analysis title	Treatment comparison: Mean FSH dose (total)
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	ANOVA

Secondary: Duration of FSH stimulation

End point title	Duration of FSH stimulation

End point description:

End point type	Secondary

End point timeframe:

At the end of the stimulation.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	358		
Units: days				
arithmetic mean (standard deviation)	9.20 (± 2.14)	9.00 (± 1.75)		

Statistical analyses

Statistical analysis title	Treatment comparison: Duration of FSH Stimulation
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.16
Method	ANOVA

Secondary: Number of follicles > 16 mm on the day of hCG

End point title	Number of follicles > 16 mm on the day of hCG

End point description:

End point type	Secondary

End point timeframe:

On the day of hCG triggering.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347[4]	350[5]		
Units: number of follicles				
arithmetic mean (standard deviation)	4.10 (± 2.47)	4.47 (± 2.33)		

Notes:

[4] - For 5 subjects, this parameter was not available.

[5] - For 8 subjects, this parameter was not available.

Statistical analyses

Statistical analysis title	Treatment comparison: Number of follicles > 16 mm
Comparison groups	Test product - Fostimon v Reference product - Gonal F

Number of subjects included in analysis	697
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.003
Method	Wilcoxon (Mann-Whitney)

Secondary: Progesterone levels on the day of hCG triggering

End point title	Progesterone levels on the day of hCG triggering

End point description:

End point type	Secondary

End point timeframe:

On the day of hCG triggering.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327[6]	336[7]		
Units: ng/ml				
arithmetic mean (standard deviation)	0.63 (± 0.93)	0.76 (± 0.99)		

Notes:

[6] - For 25 subjects, this parameter was not available or below the detection limit.

[7] - For 22 subjects, this parameter was not available or below the detection limit.

Statistical analyses

Statistical analysis title	Treatment comparison: Progesterone levels
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	ANOVA

Secondary: 17b-Estradiol levels on the day of hCG

End point title	17b-Estradiol levels on the day of hCG

End point description:

End point type	Secondary

End point timeframe:

On the day of hCG triggering

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334[8]	339[9]		
Units: pg/ml				
arithmetic mean (standard deviation)	1173.24 (± 699.06)	1311.31 (± 828.31)		

Notes:

[8] - For 18 subjects Estradiol level was not available.

[9] - For 19 subjects Estradiol levels were not available.

Statistical analyses

Statistical analysis title	Treatment comparison: Estradiol levels on hCG day
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	673
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	ANOVA

Secondary: Total number of oocytes retrieved

End point title	Total number of oocytes retrieved

End point description:

End point type	Secondary

End point timeframe:

On the day of oocytes retrieval.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337[10]	346[11]		
Units: oocytes				
arithmetic mean (standard deviation)	8.45 (± 4.72)	9.33 (± 4.90)		

Notes:

[10] - Subjects who underwent oocyte retrieval.

[11] - Subjects who underwent oocyte retrieval.

Statistical analyses

Statistical analysis title	Treatment comparison: n of oocytes retrieved.
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	683
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.02
Method	ANOVA

Secondary: Fertilisation rate

End point title	Fertilisation rate

End point description:

End point type	Secondary

End point timeframe:

Day 1 after oocytes retrieval.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331[12]	338[13]		
Units: Percentage of oocytes				
arithmetic mean (standard deviation)	73.98 (± 26.44)	75.85 (± 21.48)		

Notes:

[12] - Subjects with at least one oocyte inseminated (IVF/ICSI).

[13] - Subjects with at least one oocyte inseminated (IVF/ICSI)

Statistical analyses

Statistical analysis title	Treatment comparison: Fertilisation rate
Comparison groups	Reference product - Gonal F v Test product - Fostimon
Number of subjects included in analysis	669
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.32
Method	ANOVA

Secondary: Cleavage rate

End point title	Cleavage rate

End point description:

End point type	Secondary

End point timeframe:

Day 2 after oocytes retrieval.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331[14]	338[15]		
Units: Percentage of oocytes				
arithmetic mean (standard deviation)	59.61 (± 31.96)	61.95 (± 30.83)		

Notes:

[14] - Subjects with at least one oocyte inseminated (IVF/ICSI).

[15] - Subjects with at least one oocyte inseminated (IVF/ICSI).

Statistical analyses

Statistical analysis title	Treatment comparison: cleavage rate
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	669
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.34
Method	ANOVA

Secondary: Total number of embryos obtained

End point title	Total number of embryos obtained

End point description:

End point type	Secondary

End point timeframe:

Day 3 after oocytes retrieval.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	332[16]	338[17]		
Units: embryos				
arithmetic mean (standard deviation)	4.29 (± 2.83)	5.26 (± 3.19)		

Notes:

[16] - Subjects with at least one oocyte inseminated (IVF/ICSI).

[17] - Subjects with at least one oocyte inseminated (IVF/ICSI).

Statistical analyses

Statistical analysis title	Treatment comparison: Total n of embryos
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	670
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.0001
Method	ANOVA

Secondary: Number of transferred embryos

End point title	Number of transferred embryos

End point description:

End point type	Secondary

End point timeframe:

Day 3 after oocytes retrieval

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306[18]	314[19]		
Units: n of patients				
Single embryo transfer	144	121		
Double embryo transfer	162	193		

Notes:

[18] - Subject with at least one embryo transferred.

[19] - Subject with at least one embryo transferred.

Statistical analyses

Statistical analysis title	Treatment comparison
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.03
Method	Cochran-Mantel-Haenszel

Secondary: N of top quality of embryos transferred per patient

End point title	N of top quality of embryos transferred per patient

End point description:

End point type	Secondary

End point timeframe:
Day 3 after oocytes retrieval

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	304[20]	314[21]		
Units: top embryos				
arithmetic mean (standard deviation)	0.47 (± 0.64)	0.48 (± 0.64)		

Notes:
[20] - Subject with at least one embryo transferred, with embryo scoring available.
[21] - Subject with at least one embryo transferred, with embryo scoring available.

Statistical analyses

Statistical analysis title	Treatment comparison: Top embryos transferred
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	618
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.89
Method	ANOVA

Secondary: Positive βhCG rate

End point title	Positive βhCG rate

End point description:

End point type	Secondary

End point timeframe:
15 ± 2 days after oocytes retrieval.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	358		
Units: Percentage of subjects				
number (not applicable)	47.2	49.7		

Statistical analyses

Statistical analysis title	Treatment comparison: Positive βhCG rate
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5
Method	Fisher exact

Secondary: Implantation rate

End point title	Implantation rate

End point description:

Implantation rate defined as the number of gestational sacs divided by the number of embryos transferred.

End point type	Secondary

End point timeframe:

8 weeks of pregnancy

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306[22]	314[23]		
Units: transferred embryos				
arithmetic mean (standard deviation)	35.62 (± 43.67)	38.22 (± 45.79)		

Notes:

[22] - subjects with at least one embryo transferred.

[23] - Subjects with at least one embryo transferred.

Statistical analyses

Statistical analysis title	Treatment comparison: implantation rate
Comparison groups	Reference product - Gonal F v Test product - Fostimon
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.47
Method	Fisher exact

Secondary: Delivery rate

End point title	Delivery rate

End point description:

End point type	Secondary

End point timeframe: After delivery.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	349	357		
Units: Percentage of subjects				
number (not applicable)	34.4	36.7		

Statistical analyses

Statistical analysis title	Treatment comparison: Delivery rate
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.53
Method	Fisher exact

Secondary: Live birth rate

End point title	Live birth rate
End point description:	
End point type	Secondary
End point timeframe: after delivery.	

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	349	357		
Units: Percentage of subjects				
number (not applicable)	34.1	35.9		

Statistical analyses

Statistical analysis title	Treatment comparison: Live birth rate
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	706
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.64
Method	Fisher exact

Secondary: Cumulative pregnancy rate

End point title	Cumulative pregnancy rate

End point description:

Subjects not getting pregnant during the fresh IVF cycles, were allowed to undergo a frozen embryo transfer with the embryos frozen during the study, within one year from randomisation.

End point type	Secondary

End point timeframe:

Within 15 months from randomisation.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	358		
Units: Percentage of subjects				
number (not applicable)	45.2	52.0		

Statistical analyses

Statistical analysis title	Treatment comparison: cumulative pregnancy rate
Comparison groups	Reference product - Gonal F v Test product - Fostimon
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.07
Method	Fisher exact

Secondary: Cumulative Delivery Rate

End point title	Cumulative Delivery Rate

End point description:

Subjects not getting pregnant during the fresh IVF cycles, were allowed to undergo a frozen embryo transfer with the embryos frozen during the study, within one year from randomisation.

End point type	Secondary

End point timeframe:
Within 21 months from randomisation.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	358		
Units: Percentage of subjects				
number (not applicable)	42.0	48.3		

Statistical analyses

Statistical analysis title	Treatment comparison: cumulative delivery rate
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.1
Method	Fisher exact

Secondary: Cumulative Live birth rate

End point title	Cumulative Live birth rate

End point description:

End point type	Secondary

End point timeframe:
Within 21 months from randomisation.

End point values	Test product - Fostimon	Reference product - Gonal F		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	352	358		
Units: Percentage of patients				
number (not applicable)	42.0	47.8		

Statistical analyses

Statistical analysis title	Treatment comparison: Cumulative Live birth rate
Comparison groups	Test product - Fostimon v Reference product - Gonal F
Number of subjects included in analysis	710
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.13
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events (AEs) were recorded from signed informed consent to the end-of-trial.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19

Reporting groups	
Reporting group title	Test product - Fostimon
Reporting group description:	
Subject randomised and exposed to Fostimon IMP were included in this group	
Reporting group title	Reference product - Gonal F
Reporting group description:	
Subjects randomised and exposed to Gonal F IMP were included in this group	

Serious adverse events	Test product - Fostimon	Reference product - Gonal F	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 352 (6.82%)	31 / 358 (8.66%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 352 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			

Abortion early			
subjects affected / exposed	1 / 352 (0.28%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion incomplete			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion missed			
subjects affected / exposed	1 / 352 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	3 / 352 (0.85%)	3 / 358 (0.84%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical incompetence			
subjects affected / exposed	2 / 352 (0.57%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	3 / 352 (0.85%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gestational diabetes			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperemesis gravidarum			
subjects affected / exposed	1 / 352 (0.28%)	2 / 358 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Imminent abortion			

subjects affected / exposed	2 / 352 (0.57%)	2 / 358 (0.56%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple pregnancy			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oligohydramnios			
subjects affected / exposed	1 / 352 (0.28%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Placenta praevia haemorrage			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpartum haemorrhage			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pre-eclampsia			
subjects affected / exposed	1 / 352 (0.28%)	2 / 358 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature delivery			
subjects affected / exposed	3 / 352 (0.85%)	7 / 358 (1.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature labour			
subjects affected / exposed	1 / 352 (0.28%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature rupture of membranes			

subjects affected / exposed	2 / 352 (0.57%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Threatened labour			
subjects affected / exposed	1 / 352 (0.28%)	2 / 358 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting in pregnancy			
subjects affected / exposed	1 / 352 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain lower			
subjects affected / exposed	1 / 352 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrage			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrage			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Adnexal torsion			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 352 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ovarian hyperstimulation syndrome			
subjects affected / exposed	2 / 352 (0.57%)	4 / 358 (1.12%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 352 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine polyp			
subjects affected / exposed	1 / 352 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 352 (0.00%)	2 / 358 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 352 (0.00%)	1 / 358 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	1 / 352 (0.28%)	0 / 358 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Test product - Fostimon	Reference product - Gonal F	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 352 (21.02%)	47 / 358 (13.13%)	
Injury, poisoning and procedural complications			

Procedural pain subjects affected / exposed occurrences (all)	7 / 352 (1.99%) 7	8 / 358 (2.23%) 8	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	7 / 352 (1.99%) 7	11 / 358 (3.07%) 15	
Pregnancy, puerperium and perinatal conditions Abortion spontaneous subjects affected / exposed occurrences (all)	15 / 352 (4.26%) 15	15 / 358 (4.19%) 15	
Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all)	7 / 352 (1.99%) 8	8 / 358 (2.23%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2014	The upper limit of AMH at inclusion was enlarged to 5.6 ng/ml as it was too restrictive and the new limit was considered as safe; an upper limit (30) for the total number of antral follicles at inclusion was added to further reduce the risk of including high responder subjects (i.e. subjects at higher risk of developing OHSS);

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported