Clinical trial results:
A Phase III, randomized, controlled, single-blind, multicentre, parallel arm trial to assess the efficacy and safety of Pergoveris® (follitropin alfa and lutropin alfa) and GONAL-f® (follitropin alfa) for multifollicular development as part of an assisted reproductive technology treatment cycle in poor ovarian responders, as defined by the European Society of Human Reproduction and Embryology criteria

Summary

EudraCT number	2013-003817-16
Trial protocol	CZ SE EE HU BE GB NL DK LV ES PL
Global end of trial date	05 August 2015

Results information

Result version number	v1
This version publication date	13 August 2016
First version publication date	13 August 2016

Trial information

Trial identification

Sponsor protocol code	EMR200061-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02047227
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250 , Darmstadt, Germany, 64293
Public contact	Communication Center Merck KGaA , Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Center Merck KGaA , Merck KGaA, +49 6151725200, service@merckgroup.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	05 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 August 2015
Global end of trial reached?	Yes
Global end of trial date	05 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superiority of Pergoveris versus GONAL-f in poor ovarian response (POR) subjects as aligned with the 2011 Consensus Meeting of the European Society of Human Reproduction and Embryology (ESHRE)

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Czech Republic: 54
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Estonia: 30
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Hungary: 69
Country: Number of subjects enrolled	Italy: 111
Country: Number of subjects enrolled	Latvia: 57
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 107
Country: Number of subjects enrolled	Spain: 267
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Turkey: 101
Country: Number of subjects enrolled	United Kingdom: 31
Worldwide total number of subjects	939
EEA total number of subjects	838

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)	939
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at 101 sites in 15 countries.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pergoveris

Arm description:

Pergoveris (follitropin alfa and lutropin alfa) was administered subcutaneously once daily with a starting dose of 300 International Unit (IU) recombinant human follicular stimulating hormone (rhFSH)/ 150 IU recombinant human luteinizing hormone (rhLH) after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 millimeter (mm); 250 microgram (mcg) of r-hCG (Ovidrel) was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments while maintaining the 2:1 ratio of r hFSH to r-hLH in the Pergoveris group based on the subject's response per site standard clinical practice.

Arm type	Experimental
Investigational medicinal product name	Pergoveris
Investigational medicinal product code	
Other name	r-hFSH/r-hLH, Follitropin alfa/Lutropin alfa
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Pergoveris was administered subcutaneously once daily with a starting dose of 300 IU rhFSH/150 IU rhLH.

Investigational medicinal product name	Recombinant human chorionic gonadotrophin (r-hCG)
Investigational medicinal product code	
Other name	Ovidrel, Ovitrelle, choriogonadotropin alfa
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

250 mcg of r-hCG was administered once subcutaneously

Arm title	GONAL-f

Arm description:

GONAL-f (r-hFSH) was self-administered subcutaneously once daily at a starting dose of 300 IU after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 mm; 250 mcg of r-hCG was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments based on the subject's response per site standard clinical practice.

Arm type	Active comparator

Investigational medicinal product name	GONAL-f
Investigational medicinal product code	
Other name	r-hFSH, Follitropin alfa
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

GONAL-f (r-hFSH) was self-administered subcutaneously once daily at a starting dose of 300 IU.

Investigational medicinal product name	Recombinant human chorionic gonadotrophin (r-hCG)
Investigational medicinal product code	
Other name	Ovidrel, Ovitrelle, choriogonadotropin alfa
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

250 mcg of r-hCG was administered once subcutaneously.

Notes:

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

Justification: The trial was single-blinded where the Investigator and all site personnel (with the exception of the trial Nurse/Coordinator and/or Pharmacist/Pharmacy Assistant) remained blinded, throughout the course of the trial as to which treatment each subject received. The subject, however, was informed by the trial nurse or pharmacist of which treatment they were receiving.

Number of subjects in period 1	Pergoveris	GONAL-f
Started	462	477
Completed ovarian stimulation phase	424	440
Completed	318	347
Not completed	144	130
No fertilization	61	51
Intention to freeze all embryos	1	-
Adverse event, non-fatal	2	4
All embryos discarded	12	11
No oocytes retrieved	21	20
Lack of ovarian response to stimulation	35	32
Unspecified	10	9
Spontaneous pregnancy	1	-
Lost to follow-up	-	3
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Pergoveris

Reporting group description:

Pergoveris (follitropin alfa and lutropin alfa) was administered subcutaneously once daily with a starting dose of 300 International Unit (IU) recombinant human follicular stimulating hormone (rhFSH)/ 150 IU recombinant human luteinizing hormone (rhLH) after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 millimeter (mm); 250 microgram (mcg) of r-hCG (Ovidrel) was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments while maintaining the 2:1 ratio of r hFSH to r-hLH in the Pergoveris group based on the subject's response per site standard clinical practice.

Reporting group title	GONAL-f

Reporting group description:

GONAL-f (r-hFSH) was self-administered subcutaneously once daily at a starting dose of 300 IU after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 mm; 250 mcg of r-hCG was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments based on the subject's response per site standard clinical practice.

Reporting group values	Pergoveris	GONAL-f	Total
Number of subjects	462	477	939
Age categorical Units: Subjects			

Age Continuous			
All Randomized Subjects Set included all subjects who were randomized.			
Units: years			
arithmetic mean	38.3	38.3	
standard deviation	± 2.9	± 3	-
Gender, Male/Female Units: subjects			
Female	462	477	939
Male	0	0	0

End points

End points reporting groups

Reporting group title	Pergoveris

Reporting group description:

Pergoveris (follitropin alfa and lutropin alfa) was administered subcutaneously once daily with a starting dose of 300 International Unit (IU) recombinant human follicular stimulating hormone (rhFSH)/ 150 IU recombinant human luteinizing hormone (rhLH) after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 millimeter (mm); 250 microgram (mcg) of r-hCG (Ovidrel) was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments while maintaining the 2:1 ratio of r hFSH to r-hLH in the Pergoveris group based on the subject's response per site standard clinical practice.

Reporting group title	GONAL-f

Reporting group description:

GONAL-f (r-hFSH) was self-administered subcutaneously once daily at a starting dose of 300 IU after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 mm; 250 mcg of r-hCG was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments based on the subject's response per site standard clinical practice.

Primary: Number of oocytes retrieved

End point title	Number of oocytes retrieved

End point description:

Mean number of oocytes retrieved on the day of ovum pick up (OPU) was calculated. Oocyte retrieval was a technique used in in-vitro fertilization in order to remove oocytes from the ovary of the female, enabling fertilization outside the body. Intent-to-treat (ITT) analysis set included all subjects randomized who received at least 1 dose of GONAL-f or Pergoveris.

End point type	Primary

End point timeframe:

At approximately 34 to 38 hours after r-hCG administration

End point values	Pergoveris	GONAL-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	477		
Units: oocytes				
arithmetic mean (standard deviation)	3.3 (± 2.71)	3.6 (± 2.82)		

Statistical analyses

Statistical analysis title	Comparison between Pergoveris and Gonal f groups
Comparison groups	Pergoveris v GONAL-f

Number of subjects included in analysis	939
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Poisson Regression Model
Parameter estimate	Mean difference (net)
Point estimate	-0.235
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4741
upper limit	0.003

Secondary: Ongoing pregnancy rate

End point title	Ongoing pregnancy rate

End point description:

Ongoing pregnancy rate was defined as the percentage of subjects with a ultrasound confirmation of at least one viable fetus (positive fetal heart beat). Modified intent-to-treat (MITT) analysis set included all randomized subjects who received at least 1 dose of GONAL-f or Pergoveris and did not have spontaneous pregnancy or death at approximately 34-38 hours after rhCG administration.

End point type	Secondary

End point timeframe:

70 days after embryo transfer

End point values	Pergoveris	GONAL-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	477		
Units: percentage of subjects				
number (not applicable)	11	12.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Live birth rate

End point title	Live birth rate

End point description:

Live birth rate was defined as the percentage of subjects with at least one live-born neonate. MITT analysis set included all randomized subjects who received at least 1 dose of GONAL-f or Pergoveris and did not have spontaneous pregnancy or death at approximately 34-38 hours after rhCG administration.

End point type	Secondary

End point timeframe:

Approximately 180 days following ongoing pregnancy determination

End point values	Pergoveris	GONAL-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	477		
Units: percentage of subjects				
number (not applicable)	10.6	11.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Embryo implantation rate

End point title	Embryo implantation rate

End point description:

Embryo implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred per subject. MITT analysis set included all randomized subjects who received at least 1 dose of GONAL-f or Pergoveris and did not have spontaneous pregnancy or death at approximately 34-38 hours after rhCG administration. Number of subjects analysed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

2 to 3 days following oocyte retrieval

End point values	Pergoveris	GONAL-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	319	349		
Units: sacs/embryos/subject				
number (not applicable)	14.7	15.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical pregnancy rate

End point title	Clinical pregnancy rate

End point description:

Clinical pregnancy rate defined as the percentage of subjects with a ultrasound confirmation of a gestational sac, with or without fetal heart activity. MITT analysis set included all randomized subjects who received at least 1 dose of GONAL-f or Pergoveris and did not have spontaneous pregnancy or death at approximately 34-38 hours after rhCG administration.

End point type	Secondary

End point timeframe:

35-42 days post r-hCG administration

End point values	Pergoveris	GONAL-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	477		
Units: percentage of subjects				
number (not applicable)	14.1	16.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Biochemical pregnancy rate

End point title	Biochemical pregnancy rate

End point description:

Biochemical pregnancy rate was defined as the percentage of subjects with a positive beta-hCG result from the serum pregnancy test. MITT Analysis Set included all randomized subjects who received at least 1 dose of GONAL-f or Pergoveris and did not have spontaneous pregnancy or death at approximately 34-38 hours after rhCG administration.

End point type	Secondary

End point timeframe:

15 to 20 days post r-hCG administration.

End point values	Pergoveris	GONAL-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	462	477		
Units: percentage of subjects				
number (not applicable)	17.3	23.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 180 days after ongoing pregnancy (maximum up to 365 days)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	GONAL-f

Reporting group description:

GONAL-f (r-hFSH) was self-administered subcutaneously once daily at a starting dose of 300 IU after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 mm; 250 mcg of r-hCG was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments based on the subject's response per site standard clinical practice.

Reporting group title	Pergoveris

Reporting group description:

Pergoveris (follitropin alfa and lutropin alfa) was administered subcutaneously once daily with a starting dose of 300 IU rhFSH/150 IU rhLH after confirmation of down regulation up to 21 days. After follicle attained mean diameter of 17-18 mm; 250 mcg of r-hCG was administered once subcutaneously to trigger final follicular maturation as per site standard practice. The dose adjustment for r-hFSH was allowed in 75 IU increments while maintaining the 2:1 ratio of r hFSH to r-hLH in the Pergoveris group based on the subject's response per site standard clinical practice.

Serious adverse events	GONAL-f	Pergoveris	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 477 (3.56%)	8 / 462 (1.73%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Fallot's tetralogy			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trisomy 21			

subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	3 / 477 (0.63%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abortion spontaneous			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature labour			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foetal death			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (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	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Imminent abortion			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature baby			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature delivery			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Threatened labour			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (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 cyst			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst ruptured			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian haemorrhage			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ovarian rupture			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (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: 0 %

Non-serious adverse events	GONAL-f	Pergoveris	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	151 / 477 (31.66%)	111 / 462 (24.03%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	10 / 477 (2.10%)	19 / 462 (4.11%)	
occurrences (all)	13	23	
Flushing			
subjects affected / exposed	0 / 477 (0.00%)	3 / 462 (0.65%)	
occurrences (all)	0	3	
Circulatory collapse			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	2	
Hypertension			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	3	
Venous thrombosis			

subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	12 / 477 (2.52%)	6 / 462 (1.30%)	
occurrences (all)	12	16	
Abortion missed			
subjects affected / exposed	5 / 477 (1.05%)	5 / 462 (1.08%)	
occurrences (all)	5	5	
Abortion			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Foetal death			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	2	0	
Placenta praevia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Vomiting in pregnancy			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 477 (0.84%)	5 / 462 (1.08%)	
occurrences (all)	7	5	
Injection site erythema			
subjects affected / exposed	4 / 477 (0.84%)	4 / 462 (0.87%)	
occurrences (all)	8	6	
Asthenia			
subjects affected / exposed	1 / 477 (0.21%)	2 / 462 (0.43%)	
occurrences (all)	1	2	
Chest discomfort			

subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Gait disturbance			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Hyperthermia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Injection site haematoma			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Crying			
subjects affected / exposed	3 / 477 (0.63%)	2 / 462 (0.43%)	
occurrences (all)	3	2	
Food allergy			
subjects affected / exposed	0 / 477 (0.00%)	2 / 462 (0.43%)	
occurrences (all)	0	2	
Allergy to arthropod bite			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	

Hypersensitivity			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	6 / 477 (1.26%)	6 / 462 (1.30%)	
occurrences (all)	6	7	
Vaginal haemorrhage			
subjects affected / exposed	6 / 477 (1.26%)	2 / 462 (0.43%)	
occurrences (all)	6	2	
Breast tenderness			
subjects affected / exposed	2 / 477 (0.42%)	3 / 462 (0.65%)	
occurrences (all)	2	3	
Adnexa uteri pain			
subjects affected / exposed	1 / 477 (0.21%)	2 / 462 (0.43%)	
occurrences (all)	2	2	
Dyspareunia			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	3	0	
Menstruation irregular			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Metrorrhagia			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	2	0	
Ovarian cyst			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	2	0	
Uterine polyp			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Vulvovaginal dryness			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	3	0	
Vulvovaginal pruritus			

subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Breast mass			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Nipple disorder			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Premenstrual pain			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Vaginal inflammation			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal burning sensation			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Vulvovaginal discomfort			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Breast pain			
subjects affected / exposed	2 / 477 (0.42%)	2 / 462 (0.43%)	
occurrences (all)	2	4	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 477 (0.00%)	3 / 462 (0.65%)	
occurrences (all)	0	3	
Rhinorrhoea			
subjects affected / exposed	1 / 477 (0.21%)	2 / 462 (0.43%)	
occurrences (all)	1	2	
Cough			

subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	2	0	
Nasal congestion			
subjects affected / exposed	0 / 477 (0.00%)	2 / 462 (0.43%)	
occurrences (all)	0	4	
Dyspnoea exertional			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Nasal discomfort			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 477 (0.63%)	2 / 462 (0.43%)	
occurrences (all)	3	2	
Insomnia			
subjects affected / exposed	3 / 477 (0.63%)	2 / 462 (0.43%)	
occurrences (all)	3	5	
Mood swings			
subjects affected / exposed	1 / 477 (0.21%)	3 / 462 (0.65%)	
occurrences (all)	1	3	
Nervousness			
subjects affected / exposed	2 / 477 (0.42%)	2 / 462 (0.43%)	
occurrences (all)	2	2	
Agitation			
subjects affected / exposed	0 / 477 (0.00%)	2 / 462 (0.43%)	
occurrences (all)	0	2	
Depressive symptom			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Affective disorder			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	

Depressed mood			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Irritability			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Libido increased			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Tearfulness			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Investigations			
Body temperature increased			
subjects affected / exposed	4 / 477 (0.84%)	1 / 462 (0.22%)	
occurrences (all)	4	1	
Weight increased			
subjects affected / exposed	2 / 477 (0.42%)	1 / 462 (0.22%)	
occurrences (all)	3	1	
Menstruation normal			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Blood creatinine increased			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Blood urine present			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Nitrite urine present			

subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Urine ketone body			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	2 / 477 (0.42%)	1 / 462 (0.22%)	
occurrences (all)	2	1	
Overdose			
subjects affected / exposed	2 / 477 (0.42%)	1 / 462 (0.22%)	
occurrences (all)	2	1	
Procedural pain			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	2	0	
Animal bite			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 477 (0.00%)	2 / 462 (0.43%)	
occurrences (all)	0	2	
Tachycardia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	58 / 477 (12.16%)	46 / 462 (9.96%)	
occurrences (all)	80	60	
Dizziness			
subjects affected / exposed	8 / 477 (1.68%)	4 / 462 (0.87%)	
occurrences (all)	8	4	
Migraine			

subjects affected / exposed	2 / 477 (0.42%)	5 / 462 (1.08%)	
occurrences (all)	2	7	
Somnolence			
subjects affected / exposed	1 / 477 (0.21%)	3 / 462 (0.65%)	
occurrences (all)	2	3	
Paraesthesia			
subjects affected / exposed	2 / 477 (0.42%)	1 / 462 (0.22%)	
occurrences (all)	2	1	
Head discomfort			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Disturbance in attention			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Sciatica			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia of pregnancy			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Lymph node pain			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	

Lymphadenopathy			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 477 (0.00%)	2 / 462 (0.43%)	
occurrences (all)	0	2	
Ear swelling			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Tinnitus			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Photophobia			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	12 / 477 (2.52%)	15 / 462 (3.25%)	
occurrences (all)	12	20	
Abdominal pain			
subjects affected / exposed	13 / 477 (2.73%)	12 / 462 (2.60%)	
occurrences (all)	13	15	
Diarrhoea			
subjects affected / exposed	7 / 477 (1.47%)	4 / 462 (0.87%)	
occurrences (all)	8	4	
Abdominal pain lower			
subjects affected / exposed	5 / 477 (1.05%)	5 / 462 (1.08%)	
occurrences (all)	5	5	
Vomiting			

subjects affected / exposed	5 / 477 (1.05%)	4 / 462 (0.87%)	
occurrences (all)	5	5	
Abdominal discomfort			
subjects affected / exposed	3 / 477 (0.63%)	5 / 462 (1.08%)	
occurrences (all)	3	5	
Abdominal distension			
subjects affected / exposed	7 / 477 (1.47%)	1 / 462 (0.22%)	
occurrences (all)	9	1	
Constipation			
subjects affected / exposed	1 / 477 (0.21%)	2 / 462 (0.43%)	
occurrences (all)	1	2	
Toothache			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Abdominal rigidity			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Abdominal tenderness			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Anal fissure			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia oral			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	4 / 477 (0.84%)	0 / 462 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	2 / 477 (0.42%)	2 / 462 (0.43%)	
occurrences (all)	2	2	
Dermatitis allergic			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	

Hyperhidrosis			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	2	0	
Acne			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Dermatitis atopic			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Papule			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Pityriasis rosea			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Skin burning sensation			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Solar dermatitis			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 477 (0.42%)	1 / 462 (0.22%)	
occurrences (all)	2	1	
Leukocyturia			

subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Proteinuria			
subjects affected / exposed	1 / 477 (0.21%)	1 / 462 (0.22%)	
occurrences (all)	1	1	
Cystitis noninfective			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Urethral pain			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 477 (1.26%)	4 / 462 (0.87%)	
occurrences (all)	6	5	
Arthralgia			
subjects affected / exposed	3 / 477 (0.63%)	2 / 462 (0.43%)	
occurrences (all)	5	2	
Neck pain			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	2	0	
Muscle tightness			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			

subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 477 (0.42%)	4 / 462 (0.87%)	
occurrences (all)	2	4	
Urinary tract infection			
subjects affected / exposed	3 / 477 (0.63%)	2 / 462 (0.43%)	
occurrences (all)	3	2	
Vulvovaginal mycotic infection			
subjects affected / exposed	3 / 477 (0.63%)	1 / 462 (0.22%)	
occurrences (all)	3	1	
Cystitis			
subjects affected / exposed	3 / 477 (0.63%)	0 / 462 (0.00%)	
occurrences (all)	3	0	
Gastroenteritis			
subjects affected / exposed	2 / 477 (0.42%)	1 / 462 (0.22%)	
occurrences (all)	3	1	
Oral herpes			
subjects affected / exposed	2 / 477 (0.42%)	1 / 462 (0.22%)	
occurrences (all)	2	1	
Sinusitis bacterial			
subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	2	0	
Bacterial disease carrier			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	

Conjunctivitis			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Genital herpes			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Hordeolum			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Vaginal infection			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 477 (0.21%)	0 / 462 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Increased appetite			

subjects affected / exposed	2 / 477 (0.42%)	0 / 462 (0.00%)	
occurrences (all)	2	0	
Fluid retention			
subjects affected / exposed	0 / 477 (0.00%)	1 / 462 (0.22%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2014	The following changes were made in the amended protocol: - The patient population and inclusion criteria of the trial were aligned with the 2011 Consensus Meeting of the European Society of Human Reproduction and Embryology (ESHRE)- - Clarification was made on the emergency unblinding procedure. - Clarification was made on the pregnancy testing criteria and embryology assessments. - Clarification was made on the definitions of serious adverse event and last safety visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported