Clinical trial results:
A Multi-Centre, Two-Arm, Interventional, Phase IV Study to Evaluate Tailoring of Recombinant FSH Treatment in Subjects With Chronic Anovulation Using the Gonal-f® Prefilled Pen in Women Undergoing Ovulation Induction

Summary

EudraCT number	2012-003227-38
Trial protocol	GB IE
Global end of trial date	23 July 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	EMR700623_535

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01871532
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre 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	25 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to investigate tailoring of recombinant follicle stimulating hormone (rFSH) treatment in subjects with chronic anovulation using 2 low dose protocols, by determining the proportion of cycles with monofollicular development.

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	15 July 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	Ireland: 4
Country: Number of subjects enrolled	United Kingdom: 20
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 8 centres in Ireland and United Kingdom.

Pre-assignment

Screening details:

A total of 24 subjects were enrolled in the study. Out of 24 only 21 subjects completed the study; 2 subjects discontinued due to hyper-response and 1 subject as per investigator's decision.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Low Dose Gonal-f

Arm description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 International unit (IU) for Week 1, then dose was gradually increased by 12.5 IU for two weeks, with a final increase of 25 IU, up to maximum dose of 100 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

Arm type	Experimental
Investigational medicinal product name	Gonal-f
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Gonal-f at a starting dose of 50 IU was administered subcutaneously up to maximum dose of 125 IU.

Investigational medicinal product name	Human chorionic gonadotropin (hCG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Human chorionic gonadotropin (hCG) 250 microgram (mcg) was administered subcutaneously.

Arm title	Standard Low Dose Gonal-f

Arm description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 IU for Week 1, then dose was gradually increased by 12.5 IU for two weeks, up to maximum dose of 125 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

Arm type	Experimental
Investigational medicinal product name	Human chorionic gonadotropin (hCG)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Human chorionic gonadotropin (hCG) 250 mcg was administered subcutaneously.

Investigational medicinal product name	Gonal-f
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Gonal-f at a starting dose of 50 IU was administered subcutaneously up to maximum dose of 75 IU.

Number of subjects in period 1	Low Dose Gonal-f	Standard Low Dose Gonal-f
Started	12	12
Subjects received hCG treatment	11	9 [1]
Completed	11	10
Not completed	1	2
Consent withdrawn by subject	1	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone represent the subjects who received treatment and were less than the total subjects in the arm.

Baseline characteristics

Reporting groups	
Reporting group title	Low Dose Gonal-f

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 International unit (IU) for Week 1, then dose was gradually increased by 12.5 IU for two weeks, with a final increase of 25 IU, up to maximum dose of 100 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

Reporting group title	Standard Low Dose Gonal-f

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 IU for Week 1, then dose was gradually increased by 12.5 IU for two weeks, up to maximum dose of 125 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

Reporting group values	Low Dose Gonal-f	Standard Low Dose Gonal-f	Total
Number of subjects	12	12	24
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	30.8	29.5	
standard deviation	± 2.96	± 3.75	-
Gender, Male/Female Units: Subjects			
Female	12	12	24
Male	0	0	0

End points

End points reporting groups

Reporting group title	Low Dose Gonal-f

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 International unit (IU) for Week 1, then dose was gradually increased by 12.5 IU for two weeks, with a final increase of 25 IU, up to maximum dose of 100 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

Reporting group title	Standard Low Dose Gonal-f

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 IU for Week 1, then dose was gradually increased by 12.5 IU for two weeks, up to maximum dose of 125 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

Primary: Percentage of Cycles With Monofollicular Development

End point title	Percentage of Cycles With Monofollicular Development[1]

End point description:

The monofollicular development was defined as the number of cycles with monofollicular development only one Follicle greater than or equal to (>=) 17 millimeter (mm) and no other follicles >=14 mm following up to 4 weeks Gonal-f treatment.

End point type	Primary

End point timeframe:

Baseline up to 4 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Data not assessed since study was terminated early due to delay in providing additional drug.

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: percentage of cycles				
number (not applicable)				

Notes:

[2] - Data not assessed since study was terminated early due to delay in providing additional drug.

[3] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Cycles With Bifollicular Development

End point title	Percentage of Cycles With Bifollicular Development

End point description:

The bifollicular development was defined as the number of cycles with bifollicular development of only two follicles greater than or equal to 17 mm.

End point type	Secondary

End point timeframe:

Baseline up to 4 weeks

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: percentage of cycles				
number (not applicable)				

Notes:

[4] - Data not assessed since study was terminated early due to delay in providing additional drug.

[5] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Cycles with Multifollicular Development

End point title	Percentage of Cycles with Multifollicular Development

End point description:

The multifollicular development was defined as the number of cycles with multifollicular development of three or more follicles >= 14 millimetre.

End point type	Secondary

End point timeframe:

Baseline up to 4 weeks

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: percentage of cycles				
number (not applicable)				

Notes:

[6] - Data not assessed since study was terminated early due to delay in providing additional drug.

[7] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of ovulatory cycles

End point title	Percentage of ovulatory cycles

End point description:

Ovulation was defined as a serum progesterone (P4) level >= 10 nanogram per milliliter (ng/mL) or Clinical Pregnancy. Clinical pregnancy was defined as pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. It excludes ectopic pregnancy.

End point type	Secondary

End point timeframe:

Baseline up to 42 days post human chorionic gonadotrophin (hCG) administration

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: percentage of cycles				
number (not applicable)				

Notes:

[8] - Data not assessed since study was terminated early due to delay in providing additional drug.

[9] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Cycles Wherein Human Chorionic Gonadotropin (hCG) was not Administered

End point title	Percentage of Cycles Wherein Human Chorionic Gonadotropin (hCG) was not Administered

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 4 weeks

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: percentage of cycles				
number (not applicable)				

Notes:

[10] - Data not assessed since study was terminated early due to delay in providing additional drug.

[11] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Cycles Resulting in Clinical Pregnancy

End point title	Percentage of Cycles Resulting in Clinical Pregnancy

End point description:

Clinical pregnancy was defined as pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. It excludes ectopic pregnancy.

End point type	Secondary

End point timeframe:

35-42 days post hCG administration

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: percentage of cycles				
number (not applicable)				

Notes:

[12] - Data not assessed since study was terminated early due to delay in providing additional drug.

[13] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Multiple Pregnancy

End point title	Number of Multiple Pregnancy

End point description:

Multiple pregnancy is a pregnancy where more than one fetus develops simultaneously in the womb. There are two types of twinning—identical and fraternal. Identical twins represent the splitting of a single fertilized zygote (union of two gametes or male/female sex cells that produce a developing fetus) into two separate individuals.

End point type	Secondary

End point timeframe:

35-42 days post hCG administration

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: subjects				
number (not applicable)				

Notes:

[14] - Data not assessed since study was terminated early due to delay in providing additional drug.

[15] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Fetuses

End point title	Number of Fetuses

End point description:

End point type	Secondary

End point timeframe:

35-42 days post hCG administration

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[16]	0[17]		
Units: fetuses				
number (not applicable)				

Notes:

[16] - Data not assessed since study was terminated early due to delay in providing additional drug.

[17] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Miscarriages After Confirmation of Clinical Pregnancy

End point title	Number of Miscarriages After Confirmation of Clinical Pregnancy

End point description:

Miscarriages were calculated per clinical pregnancy, and clinical pregnancy was defined as pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or confirmed by clinical signs of pregnancy. It excludes ectopic pregnancy.

End point type	Secondary

End point timeframe:

35-42 days post hCG administration

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	0[19]		
Units: subjects				
number (not applicable)				

Notes:

[18] - Data not assessed since study was terminated early due to delay in providing additional drug.

[19] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Ovarian Hyper Stimulation Syndrome (OHSS)

End point title	Number of Subjects with Ovarian Hyper Stimulation Syndrome (OHSS)

End point description:

OHSS was defined as an exaggerated systemic response to ovarian stimulation characterized by a wide spectrum of clinical and laboratory manifestations, classified as mild, moderate or severe according to the degree of abdominal distention, ovarian enlargement and respiratory, hemodynamic and metabolic

complications. Safety population included all subjects who were randomised and received at least 1 Gonal-f injection. Here "99999" signifies data was not evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Up to 42 days post hCG administration

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: subjects				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Recombinant Follicle Stimulating Hormone (rFSH) Stimulation

End point title	Duration of Recombinant Follicle Stimulating Hormone (rFSH) Stimulation

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 4 weeks

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[20]	0[21]		
Units: days				
arithmetic mean (standard deviation)	()	()		

Notes:

[20] - Data not assessed since study was terminated early due to delay in providing additional drug.

[21] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose of Recombinant Follicle Stimulating Hormone (r-FSH) Administered per Cycle

End point title	Total Dose of Recombinant Follicle Stimulating Hormone (r-FSH) Administered per Cycle

End point description:

End point type	Secondary

End point timeframe:

Baseline up to 4 weeks

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[22]	0[23]		
Units: IU				
arithmetic mean (standard deviation)	()	()		

Notes:

[22] - Data not assessed since study was terminated early due to delay in providing additional drug.

[23] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Anti-Mullerian Hormone (AMH) levels at Week 4

End point title	Change From Baseline in Anti-Mullerian Hormone (AMH) levels at Week 4

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[24]	0[25]		
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)	()	()		

Notes:

[24] - Data not assessed since study was terminated early due to delay in providing additional drug.

[25] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Testosterone Levels

End point title	Testosterone Levels

End point description:

End point type	Secondary

End point timeframe:
Baseline

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[26]	0[27]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:
[26] - Data not assessed since study was terminated early due to delay in providing additional drug.
[27] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Sex Hormone Binding Globulin (SHBG) levels

End point title	Sex Hormone Binding Globulin (SHBG) levels

End point description:

End point type	Secondary

End point timeframe:
Baseline

End point values	Low Dose Gonal-f	Standard Low Dose Gonal-f		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[28]	0[29]		
Units: ng/mL				
arithmetic mean (standard deviation)	()	()		

Notes:
[28] - Data not assessed since study was terminated early due to delay in providing additional drug.
[29] - Data not assessed since study was terminated early due to delay in providing additional drug.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to 8 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Standard Low Dose Gonal-f

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 International Units (IU) for Week 1, then dose was gradually increased by 12.5 IU for two weeks, up to maximum dose of 125 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

Reporting group title	Low Dose Gonal-f

Reporting group description:

Gonal-f was administered subcutaneously daily at a starting dose of 50 International unit (IU) for Week 1, then dose was gradually increased by 12.5 IU for two weeks, with a final increase of 25 IU, up to maximum dose of 100 IU, until Week 4 for subjects with minimal response. After adequate follicular development was achieved, the subject was administration human chorionic gonadotropin (hCG) within 24-48 hours of last Gonal-f injection as per investigator discretion.

Serious adverse events	Standard Low Dose Gonal-f	Low Dose Gonal-f	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (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	Standard Low Dose Gonal-f	Low Dose Gonal-f	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	2 / 12 (16.67%)	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Dry Mouth			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Abdominal tenderness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Breast tenderness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

Vaginal discharge			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2013	• The number of subjects planned to be enrolled in the study was updated to 116, a total of 55 subjects were planned to be enrolled in each arm. • Inclusion Criterion was added to ensure only subjects with clinically significant abnormal serum levels of Prolactin (PRL) in the early follicular phase were excluded. This change was made to ensure subjects with abnormal but not clinically significant serum levels of PRL were able to participate in the study. • Inclusion Criteria 8 and 9 were updated to include laparoscopy as an acceptable method to assess normal uterine cavity and tube patency in addition to hysteroscopy, Hysterosalpingography (HSG), or ultrasound scan. This change was made to ensure that all methods by which tube patency may be assessed were included. • Amended the PP protocol population definition in order to clarify the analysis population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was terminated because of delays in sourcing replacement Investigational Medicinal Product (IMP) for the study due to manufacturing delays hence the outcome measure was not assessed.

Notes: