Clinical trial results:
A Randomised, Parallel Group, Assessor-Blind, Multicentre Study to Compare the Safety and Efficacy of Actavis rhFSH with Follitropin Alfa (GONAL-f®) in Stimulating Multiple Follicular Development in Women Participating in an Assisted Reproductive Technology Program

Summary

EudraCT number	2013-003788-67
Trial protocol	BE GB ES AT
Global end of trial date	08 November 2014

Results information

Result version number	v1 (current)
This version publication date	01 September 2018
First version publication date	01 September 2018

Trial information

Trial identification

Sponsor protocol code	FS1306

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Allergan plc
Sponsor organisation address	Clonshaugh Business & Technology Park, Coolock, Dublin, Ireland, D17 E400
Public contact	Clinical Trial Registry Team, Allergan plc, 001 877-277-8566, IR-CTRegistration@Allergan.com
Scientific contact	Therapeutic Area Head, Allergan plc, 001 862-261-7000, IR-CTRegistration@Allergan.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	08 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 November 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate equivalence between the numbers of oocytes retrieved after treatment with Actavis recombinant human follicle-stimulating hormone (rhFSH) or GONAL-f (follitropin alfa) in ovulatory participants in an assisted reproductive technology (ART) program.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 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	Belgium: 2
Worldwide total number of subjects	2
EEA total number of subjects	2

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)	2
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at one study site in Belgium.

Pre-assignment

Screening details:

Female participants, who were diagnosed with infertility, 18 to 35 years of age (inclusive) and were eligible for the Assisted Reproductive Technology (ART) program, were randomised in the study to one of two treatment arms: Actavis rhFSH or comparator GONAL-f. The study was terminated and no participants were enrolled in the GONAL-f arm.

Period 1

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

Arms

Arm title	Actavis rhFSH

Arm description:

During ART Cycle 1: once daily treatments with 150 International Units (IU) of Actavis rhFSH, subcutaneously for 5 days. Dose adjustment after 5 days up to maximum of 225 IU for a maximum of 19 days. If second ART cycle was needed: Actavis rhFSH dosing 150-225 IU once daily for 5 days and up to 300 IU up to 19 days. Starting on Day 5 of the Actavis rhFSH treatment until the day of human chorionic gonadotropin (hCG) injection daily injections of ganirelix acetate at a dose of 0.25 mg/0.5 mL. Single dose of 250 mcg recombinant hCG by injection once 3 or more follicles/cysts were ≥ 17 mm.

Arm type	Experimental
Investigational medicinal product name	Ganirelix acetate
Investigational medicinal product code	
Other name	Orgalutran®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Starting on Day 5 of the FSH treatment and continuing daily until the day of human chorionic gonadotropin (hCG) injection daily injections of ganirelix acetate at a dose of 0.25 mg/0.5 mL.

Investigational medicinal product name	Actavis rhFSH
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

During ART Cycle 1: once daily treatments with 150 IU dose subcutaneously for 5 days. Dose adjustment after 5 days up to maximum of 225 IU for a maximum of 19 days. If a second ART cycle was needed: 150-225 IU once daily for 5 days and up to 300 IU up to 19 days.

Investigational medicinal product name	Human chorionic gonadotropin (hCG)
Investigational medicinal product code	
Other name	Ovitrelle®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Single dose of 250 mcg recombinant hCG by injection.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: Investigator and data analyst were the blinded roles for this study.

Number of subjects in period 1	Actavis rhFSH
Started	2
Completed	0
Not completed	2
Early Termination of Study by Sponsor	1
Insufficient Therapeutic Response	1

Baseline characteristics

Reporting groups	
Reporting group title	Actavis rhFSH

Reporting group description:

During ART Cycle 1: once daily treatments with 150 International Units (IU) of Actavis rhFSH, subcutaneously for 5 days. Dose adjustment after 5 days up to maximum of 225 IU for a maximum of 19 days. If second ART cycle was needed: Actavis rhFSH dosing 150-225 IU once daily for 5 days and up to 300 IU up to 19 days. Starting on Day 5 of the Actavis rhFSH treatment until the day of human chorionic gonadotropin (hCG) injection daily injections of ganirelix acetate at a dose of 0.25 mg/0.5 mL. Single dose of 250 mcg recombinant hCG by injection once 3 or more follicles/cysts were ≥ 17 mm.

Reporting group values	Actavis rhFSH	Total	
Number of subjects	2	2	
Age Categorical Units: Subjects			
<=18 years	0	0	
Between 18 and 65 years	2	2	
>=65 years	0	0	
Sex: Female, Male Units: Subjects			
Female	2	2	
Male	0	0	

End points

End points reporting groups

Reporting group title	Actavis rhFSH

Reporting group description:

During ART Cycle 1: once daily treatments with 150 International Units (IU) of Actavis rhFSH, subcutaneously for 5 days. Dose adjustment after 5 days up to maximum of 225 IU for a maximum of 19 days. If second ART cycle was needed: Actavis rhFSH dosing 150-225 IU once daily for 5 days and up to 300 IU up to 19 days. Starting on Day 5 of the Actavis rhFSH treatment until the day of human chorionic gonadotropin (hCG) injection daily injections of ganirelix acetate at a dose of 0.25 mg/0.5 mL. Single dose of 250 mcg recombinant hCG by injection once 3 or more follicles/cysts were ≥ 17 mm.

Primary: Number of Oocytes Retrieved in the First Assisted Reproductive Technology (ART) Cycle

End point title	Number of Oocytes Retrieved in the First Assisted Reproductive Technology (ART) Cycle[1]

End point description:

The Modified Intent-to-Treat (MITT) population, all randomised participants who received at least 1 dose of GONAL-f or Actavis rhFSH, with data available for analysis.

End point type	Primary

End point timeframe:

Up to end of first ART cycle (up to approximately 15 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: No statistical analyses are reported for this Endpoint.

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: oocytes				
arithmetic mean (standard deviation)	()			

Notes:

[2] - Data not collected as participants discontinued study prior to oocyte retrieval.

Statistical analyses

No statistical analyses for this end point

Secondary: Pregnancy Rate

End point title	Pregnancy Rate

End point description:

Pregnancy rate was defined as percentage of participants with presence of at least one fetus with heart activity, at 10 weeks after embryo transfer. The per-protocol (PP) population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Up to end of first ART cycle (up to approximately 15 weeks)]

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[3]			
Units: percentage of participants				
number (not applicable)				

Notes:

[3] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Drug Dose Required During the ART Cycle

End point title	Total Drug Dose Required During the ART Cycle

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Up to end of first ART cycle (up to approximately 15 weeks)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[4]			
Units: International Units (IU)				
arithmetic mean (standard deviation)	()			

Notes:

[4] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days of Drug Stimulation During the ART Cycle

End point title	Number of Days of Drug Stimulation During the ART Cycle

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Up to end of first ART cycle (up to approximately 15 weeks)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[5]			
Units: days				
arithmetic mean (standard deviation)	()			

Notes:

[5] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Require an Increase of the Drug Dose

End point title	Percentage of Participants Who Require an Increase of the Drug Dose

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Up to end of first ART cycle (up to approximately 15 weeks)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[6]			
Units: percentage of participants				
number (not applicable)				

Notes:

[6] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Require a Decrease of the Drug Dose

End point title	Percentage of Participants Who Require a Decrease of the Drug Dose

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Up to end of first ART cycle (up to approximately 15 weeks)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[7]			
Units: percentage of participants				
number (not applicable)				

Notes:

[7] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Follicles/Cysts with Sizes ≥ 11 mm, ≥ 15 mm, or ≥ 17 mm

End point title	Number of Follicles/Cysts with Sizes ≥ 11 mm, ≥ 15 mm, or ≥ 17 mm

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Day 6, Day of human chorionic gonadotropin (hCG) administration (approximately Day 6-19)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[8]			
Units: follicles/cysts				
arithmetic mean (standard deviation)	()			

Notes:

[8] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Inhibin-B

End point title	Serum Concentration of Inhibin-B

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Pre-treatment on Day 1 and on day of hCG administration (approximately Day 6-19)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[9]			
Units: picograms per milliliter (pg/mL)				
arithmetic mean (standard deviation)	()			

Notes:

[9] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Estradiol (E2)

End point title	Serum Concentration of Estradiol (E2)

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Pre-treatment on Day 1 and on day of hCG administration (approximately Day 6-19)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[10]			
Units: pg/mL				
arithmetic mean (standard deviation)	()			

Notes:

[10] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Luteinizing Hormone (LH)

End point title	Serum Concentration of Luteinizing Hormone (LH)

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Pre-treatment on Day 1 and on day of hCG administration (approximately Day 6-19)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[11]			
Units: International Units per Liter (IU/L)				
arithmetic mean (standard deviation)	()			

Notes:

[11] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of FSH

End point title	Serum Concentration of FSH

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Pre-treatment on Day 1 and on day of hCG administration (approximately Day 6-19)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[12]			
Units: IU/L				
arithmetic mean (standard deviation)	()			

Notes:

[12] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Progesterone

End point title	Serum Concentration of Progesterone

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data

available for analysis.

End point type	Secondary

End point timeframe:

Pre-treatment on Day 1 and on day of hCG administration (approximately Day 6-19)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[13]			
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)	()			

Notes:

[13] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Fertilised Oocytes at 24 Hours after the Initiation of the in vitro Fertilisation (IVF) for Participants Who Are Not Choosing ICSI Procedure

End point title	Number of Fertilised Oocytes at 24 Hours after the Initiation of the in vitro Fertilisation (IVF) for Participants Who Are Not Choosing ICSI Procedure

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Up to end of first ART cycle (up to approximately 15 weeks)]

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[14]			
Units: fertilised oocytes				
arithmetic mean (standard deviation)	()			

Notes:

[14] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Metaphase II Oocytes after Oocyte Retrieval for Participants with ICSI Procedure

End point title	Number of Metaphase II Oocytes after Oocyte Retrieval for

	Participants with ICSI Procedure

End point description:

Metaphase II oocytes are defined as having extruded the first polar body and are in the resting phase of meiosis II. The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Up to end of first ART cycle (up to approximately 15 weeks)]

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[15]			
Units: metaphase II oocytes				
arithmetic mean (standard deviation)	()			

Notes:

[15] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Grade 1 and Grade 2 Embryos on Day 3 of Embryo Culture

End point title	Number of Grade 1 and Grade 2 Embryos on Day 3 of Embryo Culture

End point description:

The PP population, all participants in the MITT Population who, in the first ART cycle, completed the test or reference article treatment, had hCG injection, had oocyte retrieval, did not miss any ganirelix injections, did not have cycle cancellation, were without major protocol violation(s) and had data available for analysis.

End point type	Secondary

End point timeframe:

Up to end of first ART cycle (up to approximately 15 weeks)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[16]			
Units: embryos				
arithmetic mean (standard deviation)	()			

Notes:

[16] - No participants in the PP population as participants discontinued study prior to cycle completion.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Adverse Event (AEs)

End point title	Percentage of Participants with Adverse Event (AEs)

End point description:

Any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. In addition to novel events, an adverse event may be an exacerbation of a pre-existing medical condition that was present before the first test or reference article administration. Safety population included all participants who received at least one dose of study medication, with data available for analysis.

End point type	Secondary

End point timeframe:

From baseline to end of study (up to Day 10)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Ovarian Hyperstimulation Syndrome (OHSS)

End point title	Percentage of Participants with Ovarian Hyperstimulation Syndrome (OHSS)

End point description:

The safety population included all participants who received at least one dose of study medication, with data available for analysis.

End point type	Secondary

End point timeframe:

From baseline to end of study (up to Day 10)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with ART Cycle Cancellation Due to Safety Reasons

End point title	Percentage of Participants with ART Cycle Cancellation Due to Safety Reasons

End point description:

The safety population included all participants who received at least one dose of study medication, with data available for analysis.

End point type	Secondary

End point timeframe:

From baseline to end of study (up to Day 10)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: percentage of participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-FSH Antibodies

End point title	Percentage of Participants with Anti-FSH Antibodies

End point description:

The safety population included all participants who received at least one dose of study medication, with data available for analysis.

End point type	Secondary

End point timeframe:

From baseline to end of study (up to Day 10)

End point values	Actavis rhFSH			
Subject group type	Reporting group			
Number of subjects analysed	0[17]			
Units: percentage of participants				
number (not applicable)				

Notes:

[17] - Data not collected as study was terminated early.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From baseline to end of study (up to Day 10)

Adverse event reporting additional description:

Adverse Events are only reported for the Actavis rhFSH arm. No participants were enrolled in the GONAL-f arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	N/A

Reporting groups

Reporting group title	Actavis rhFSH

Reporting group description:

During ART Cycle 1: once daily treatments with 150 International Units (IU) of Actavis rhFSH subcutaneously for 5 days. Dose adjustment after 5 days up to maximum of 225 IU for a maximum of 19 days. If second ART cycle was needed: Actavis rhFSH dosing 150-225 IU once daily for 5 days and up to 300 IU up to 19 days. Starting on Day 5 of the Actavis rhFSH treatment until the day of human chorionic gonadotropin (hCG) injection daily injections of ganirelix acetate at a dose of 0.25 mg/0.5 mL. Single dose of 250 mcg recombinant hCG by injection once 3 or more follicles/cysts were ≥ 17 mm.

Serious adverse events	Actavis rhFSH		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Actavis rhFSH		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There are no Non-serious Adverse Events that occurred at a threshold of >=5% participants in any arm.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2013	Amendment 1: -Allowed higher initial and maximum FSH doses (225 and 300 IU respectively) for participants participating in the second ART cycle. -Adjusted the description of statistical analysis regarding primary efficacy endpoint and allowed the details of the statistical models to be discussed in SAP. -Added inquiries for infertility diagnosis, previous pregnancy/abortion history, and previous FSH exposure history in the Screening Visit 1. -Updated the Day 3 and Day 5 Embryo Assessment Criteria ased on the European Society of Human Reproductive and Embryology (ESHRE)'s most recent publication. -Combined and revised the Inclusion Criteria 4 and Exclusion Criteria 08 in the previous study protocol to redefine the 'adequate ovarian reserve' by both the serum FSH and AMH levels at Screening. -Redefined the Per-Protocol population as the second primary efficacy analysis population. -Added the summary of Phase 1 pharmacokinetic study (FS1203) results into the introduction section. -Removed the ferritin test from the clinical laboratory evaluations. -Changed the product name from Watson rhFSH to Actavis rhFSH throughout the document.
14 November 2013	Amendment 2: -Revised the Schedule of Events Tables (both first and second ART cycles) to list the study activities on the 'Day of Oocyte Retrieval/in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) Procedure' and 'Day 1 of Embryo Culture' in separate columns so that it will be congruent with the text of the study protocol and to clarify the start of 'Day 1 of Embryo Culture' -Revised the study procedures instructing sites to only record the size of each follicle/cyst ≥ 11 millimeters (mm) on FSH Treatment Day 1, Day 6, and the Day of hCG Injection.

04 March 2014	Amendment 3: -Removed the listing and description of doses and colors of five different strengths of auto-injectors. The healthcare providers will decide the dosing regimen for participants. -Revised the instruction for disposal of used auto-injectors. -Reduced the duration of allowable storage of auto-injectors at room temperature from up to 3 months to 7 days. -Adjusted the duration for the auto-injector to be placed at room temperature, if taken out of refrigerator (for warming up) before injection, from 10 minutes to 10-30 minutes. -Removed the information section for medical contact, devices manufacturer, and distributor. -Updated the corresponding protocol content to align with the revisions of the Instructions for Use for Actavis rhFSH Auto-Injectors. -Adjusted the starting time of adverse events assessment and documentation from the first test or reference article administration to the signing of informed consent. -Added the contact information for serious adverse event or medical emergency communication of the Medical Affairs of the Contract Research Organization. -Removed the specific timeslot of 'within 30 minutes' before test or reference article administration for blood sample collections. -Extended the ovarian hyperstimulation syndrome (OHSS) assessment, if needed, to at least 2 weeks after the hCG injection. -Added the description of study population of up to 60 subjects for second ART cycle. -Clarified the definition of ART cycle cancellation and related assessments for cycle cancellation. -Added description for the site personnel to remind participants to call the site if they experience any adverse events associated with the injection of rhFSH.
15 August 2014	Amendment 4: -Updated time windows and allow the sites more flexibility to accommodate participant's scheduling. -Clarification of study procedures. -Updated dosing of Crinone® Progesterone Gel 8%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 November 2014	Due to business decisions, the study was terminated early by the Sponsor.	-

Notes:

Limitations and caveats

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

Due to the early termination of the study, and with only 2 randomised participants in the study most analyses in this study could not be performed.

Notes: