ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 01/20/2014

ClinicalTrials.gov ID: NCT01075815

Study Identification

Unique Protocol ID:	700642-500
Brief Title:	A Clinical Trial to Determine the Effect of Lutropin Alfa on Embryo Quality and Implantation Rate in Advanced Reproductive Age
Official Title:	Exploratory Study to Determine the Effect of Lutropin Alfa on Embryo Quality and Their Implantation in Women of Advanced Reproductive Age
Secondary IDs:	2008-002281-55 [EudraCT Number]

Study Status

Record Verification:	January 2014
Overall Status:	Terminated
Study Start:	November 2008
Primary Completion:	October 2010 [Actual]
Study Completion:	October 2010 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	Sponsor
Collaborators:	Merck, S.L., Spain

Oversight

FDA Regulated?:	Yes
Applicable Trial?:	Section 801 Clinical Trial? No

	Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 08/05/2008 Board Name: Comité Etico Regional de la Comunidad de Madrid Board Affiliation: Consejería de Sanidad Phone: 91 5867128 Email:
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Spain: Agencia Española de Medicamentos y Productos Sanitarios

Study Description

Brief Summary: This is a multicentric, open, randomized, comparative trial aimed to assess the influence of recombinant luteinizing hormone (r-LH) supplementation during controlled ovarian stimulation (COS) in advanced reproductive age in terms of improved embryo competence which allows to transfer less embryos to avoid high grade multiple pregnancy without reducing the pregnancy rate.

Detailed Description: This study will be carried out by the Grupo de Interés de Salud Embrionaria (GISE) group (part of the Spanish Fertility Society) who uses strict criteria to select the embryos most suitable for successful transference.

OBJECTIVES

Primary objective:

- To determine the benefit of r-LH supplementation in COS prior to in-vitro fertilization (IVF)/intracytosolic sperm injection (ICSI) in advanced reproductive age, in terms of embryo competence to implant, as compared against no r-LH supplementation

Secondary objectives:

To evaluate the benefit of r-LH supplementation in COS, in terms of:

- follicular development
- length of the stimulation
- oocyte number and their maturity
- fertilization rate
- embryo number and quality
- gestational sacs
- abortion
- ongoing pregnancies
- local and systemic safety of r-LH administration

The study will consist of 2 groups randomized in 1:1 ratio and each subject would be followed up until the confirmation of her pregnancy status. Each subject will be administered gonadotropin releasing hormone (GnRH) agonist subcutaneously

daily from previous mid luteal phase to r-hCG administration as a standard practice to achieve down regulation. Each subject will also be administered recombinant follicle stimulating hormone (r-FSH) at a starting dose of 300 IU from S1 up to ovarian stimulation completion (r-hCG day) as a part of standard practice. In addition to the above concurrent therapies, one group will be administered experimental treatment (Luveris®) and the other group (control group) will not be administered any other drug (control treatment) during the stimulation period from stimulation start (S1) up to ovarian stimulation completion or stimulation cancellation respectively. Ovarian stimulation on an average takes 11 days and it is expected that stimulation period will not be extended beyond 15 days. A single injection of r-hCG will be administered intramuscularly or subcutaneously after the last injection of Luveris or r-FSH to achieve final follicular maturation. After, 34-36 hours of administration of r-hCG OPU will be done for oocyte retrieval and embryo transfer (ET) will be conducted within 5 days from OPU. Subjects will also be provided luteal support with natural progesterone and will be followed until delivery or miscarriage. Ultrasound and estradiol (E2) assessment of follicular growth will be conducted at various time points during the stimulation period with or without treatment adjustment.

Conditions

Conditions:	Infertility Ovulation Induction
Keywords:	Infertility Ovulation induction Luveris Controlled ovarian stimulation Reproductive technologies, assisted

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2
Intervention Model:	Parallel Assignment
Number of Arms:	2
Masking:	Open Label
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	76 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: rFSH + rhLH Recombinant human luteinizing hormone (rhLH,Luveris®) injection 150 IU subcutaneously daily along with rFSH 300 IU subcutaneously daily from S1 to S4 and then rFSH dose can be adjusted depending on the ovarian response till r-hCG administration day.	Drug: Recombinant human luteinizing hormone (rhLH) Other Names: • Luveris® • Lutropin alfa Drug: Recombinant follicle-stimulating hormone (rFSH)
Active Comparator: rFSH rFSH injection 300 IU subcutaneously daily from S1 to S4 and then dose can be adjusted depending on the ovarian response till r-hCG administration day.	Drug: Recombinant follicle-stimulating hormone (rFSH)

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 35 Years

Maximum Age:

Gender: Female

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Pre-menopausal female subject aged greater than (>) 35 years
- Subjects with baseline FSH serum level less than or equal to (<=) 10 IU/liter (l), LH and E2 levels within local normal range and plasma prolactin levels < 30 nanogram/milliliter (ng/ml)
- Subjects with regular spontaneous menstrual cycles of 25-35 days
- Subjects with infertility justifying IVF/ICSI-ET treatment
- Subjects programmed for COS with r-FSH under GnRH agonist protocol
- Sperm from current male partner suitable for IVF/ICSI according to local lab, unless sperm donor is foreseen
- Subjects with presence of both ovaries
- Subjects whose uterine cavity is able to sustain embryo implantation or pregnancy
- Subjects with normal papanicolaou test (PAP) smear within previous 3 years
- Subjects with body mass index (BMI) < 30 at stimulation start
- Subjects who receive confirmation of not being pregnant by a negative beta-hCG test (urine or blood) prior to starting r-FSH administration
- Subjects willing and able to comply with the protocol for the duration of the study
- Subjects who have given informed consent prior to any study-related procedure not part of normal medical care

Exclusion Criteria:

- Subjects or her male partners who are known to be human immunodeficiency virus, hepatitis B virus or hepatitis C virus positive
- Subjects with any clinically significant systemic disease; tumors of the hypothalamus and pituitary gland; ovarian, uterine or mammary cancer; hormonal abnormality and/or medical, biochemical, hematological condition which in the judgment of the investigator may interfere with gonadotropin treatment
- Subjects with more than 2 previous assisted reproductive technologies (ART) cycles
- Subjects in which previous cycles were cancelled due to poor response (< 3 antral follicles after 15 day of stimulation)
- Subjects with cryopreserved embryos from previous ART cycles
- Subjects with unexplained gynecological bleeding
- Subjects with polycystic ovaries, ovarian enlargement or cyst of unknown etiology
- Subjects known to have any contraindication to being pregnant and/or carrying pregnancy to term
- Subjects with known allergy to gonadotrophin preparations or any of the excipients
- Subjects known to have any active substance abuse or history of drug, medication or alcohol abuse in the past 5 years
- Subjects with previous entry into this study or simultaneous participation in another clinical drug trial
- Subjects who have refused to or inability to comply with the protocol

Contacts/Locations

Study Officials: Medical Responsible
Study Director
Merck, S.L., Spain, an affiliate of Merck KGaA, Darmstadt, Germany

Locations: Spain
FivMadrid, C/ Marqués de Urquijo, 26,
Madrid, Spain, 28008

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Pre-Assignment Details	One out of 76 randomized participants did not receive study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Overall Study

	rFSH + rhLH	rFSH
Started	40 [1]	35 [1]
Completed	30	31
Not Completed	10	4
Withdrawal before r-hCG administration	6	1
Withdrawal between rhCG-ovum pickup(OPU)	1	1
Withdrawal between OPU - embryo transfer	3	2

[1] Number of participants treated.

Baseline Characteristics

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.

	Description
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Baseline Measures

	rFSH + rhLH	rFSH	Total
Number of Participants	40	35	75
Age, Continuous [units: years] Mean (Standard Deviation)	37.2 (2.2)	37.3 (1.5)	37.2 (1.9)
Gender, Male/Female [units: participants]			
Female	40	35	75
Male	0	0	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Implantation Rate
Measure Description	Implantation rate was measured as the number of gestational sacs observed, divided by the number of embryos transferred.
Time Frame	Day 35-42 post ovum pick-up (OPU) (34-38 hours post recombinant human choriogonadotropin day {end of stimulation cycle}[approximately 28 days])
Safety Issue?	No

Analysis Population Description

Intention to treat (ITT) population included all randomized participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Implantation Rate [units: sacs per embryo] Mean (Standard Deviation)	0.2 (0.4)	0.2 (0.3)

Statistical Analysis 1 for Implantation Rate

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8762
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	0.0235
	Confidence Interval	(2-Sided) 95% -0.1546 to 0.1568
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Mean Number of Follicles Greater Than or Equal to 14 Millimeter (mm) on Recombinant Human Choriogonadotropin (r-hCG) Day
Measure Description	
Time Frame	r-hCG day (end of stimulation cycle [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Mean Number of Follicles Greater Than or Equal to 14 Millimeter (mm) on Recombinant Human Choriogonadotropin (r-hCG) Day [units: follicles] Mean (Standard Deviation)	7.7 (4.9)	8.7 (4.0)

Statistical Analysis 1 for Mean Number of Follicles Greater Than or Equal to 14 Millimeter (mm) on Recombinant Human Choriogonadotropin (r-hCG) Day

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3589
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Mean Number of Oocytes Retrieved

Measure Description	Mean number of oocytes retrieved per reporting group on the day of OPU (34-38 hours post r-hCG day (end of stimulation cycle [approximately 28 days]) was calculated. Oocyte retrieval is a technique used in in-vitro fertilization in order to remove oocytes from the ovary of the female, enabling fertilization outside the body.
Time Frame	34-38 hours post r-hCG day (end of stimulation cycle [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Mean Number of Oocytes Retrieved [units: oocytes] Mean (Standard Deviation)	5.9 (3.9)	7.7 (4.0)

Statistical Analysis 1 for Mean Number of Oocytes Retrieved

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0629
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]

	Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Number of Mature Oocytes Retrieved
Measure Description	Number of mature oocytes retrieved per reporting group on the day of OPU (34-38 hours post r-hCG day (end of stimulation cycle [approximately 28 days]) was calculated. Oocyte retrieval is a technique used in in-vitro fertilization in order to remove oocytes from the ovary of the female, enabling fertilization outside the body. The nuclear maturity was evaluated based on the presence of a germinal vesicle (GV) or whether oocytes were in metaphase I (Meta-I) or II (Meta-II) stage.
Time Frame	34-38 hours post r-hCG day (end of stimulation cycle [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Number of Mature Oocytes Retrieved [units: mature oocytes]	234	271

Statistical Analysis 1 for Number of Mature Oocytes Retrieved

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4728
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Number of Fertilized Oocytes (2 Pronuclei [PN])
Measure Description	Oocytes were fertilized using Intra-cytoplasmic Sperm Injection (ICSI) technique which is an in-vitro fertilization procedure in which a single sperm is injected directly into an egg under a microscope. The appearance of two 2PN is the first sign of successful fertilization as observed during in vitro fertilization, and is usually observed after ICSI. The zygote is then termed 2PN.
Time Frame	34-38 hours post r-hCG day (end of stimulation cycle [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Number of Fertilized Oocytes (2 Pronuclei [PN]) [units: 2PN oocytes]	128	136

Statistical Analysis 1 for Number of Fertilized Oocytes (2 Pronuclei [PN])

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0950
	Comments	[Not specified]
	Method	Fisher Exact
	Comments	[Not specified]

6. Secondary Outcome Measure:

Measure Title	Number and Quality of Embryos
Measure Description	Embryos were graded according to Spanish Association for the Study of Reproductive Biology (ASEBIR) criteria into different categories: (A) optimal quality with maximum capacity for implantation, (B) good quality with a high capacity for implantation, (C) regular with low possibility of implantation and (D) poor quality with very little possibility of implantation.
Time Frame	Day 2-3 post OPU (34-38 hours post r-hCG day {end of stimulation cycle}[approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. Here "N" represents the number of participants who had at least one fertilized oocyte.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	31	32
Number and Quality of Embryos [units: embyros]		
A + B (good quality)	69	65
C + D (poor quality)	56	73
Total embryos	125	138

7. Secondary Outcome Measure:

Measure Title	Number of Participants With Biochemical Pregnancies
Measure Description	Biochemical pregnancy was defined as a pregnancy diagnosed only by the detection of hCG in serum or urine and that does not develop into a clinical pregnancy.
Time Frame	2 months after OPU (34-38 hours post r-hCG day {end of stimulation cycle} [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Number of Participants With Biochemical Pregnancies [units: participants]	11	10

Statistical Analysis 1 for Number of Participants With Biochemical Pregnancies

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.9179
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Risk Ratio (RR)
	Estimated Value	0.9625
	Confidence Interval	(2-Sided) 95% 0.4655 to 1.9900
	Estimation Comments	[Not specified]

8. Secondary Outcome Measure:

Measure Title	Number of Participants With Clinical Pregnancies
Measure Description	Clinical pregnancy was defined as pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. It includes ectopic pregnancy.
Time Frame	2 months after OPU (34-38 hours post r-hCG day {end of stimulation cycle} [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Number of Participants With Clinical Pregnancies [units: participants]	10	10

Statistical Analysis 1 for Number of Participants With Clinical Pregnancies

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.7271
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]

Method of Estimation	Estimation Parameter	Risk Ratio (RR)
	Estimated Value	0.8750
	Confidence Interval	(2-Sided) 95% 0.4133 to 1.8524
	Estimation Comments	[Not specified]

9. Secondary Outcome Measure:

Measure Title	Total Dose of Recombinant Follicle Stimulating Hormone (r-FSH)
Measure Description	
Time Frame	2 months after OPU (34-38 hours post r-hCG day {end of stimulation cycle} [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Total Dose of Recombinant Follicle Stimulating Hormone (r-FSH) [units: IU] Mean (Standard Deviation)	2812.2 (719.4)	2970.3 (748.2)

Statistical Analysis 1 for Total Dose of Recombinant Follicle Stimulating Hormone (r-FSH)

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.3267
	Comments	[Not specified]

	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

10. Secondary Outcome Measure:

Measure Title	Estradiol (E2) Levels on r-hCG Day
Measure Description	
Time Frame	r-hCG day (end of stimulation cycle [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. Here "N" represents the number of participants with plasma E2 levels at r-hCG day.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	33	29
Estradiol (E2) Levels on r-hCG Day [units: picogram/milliter (pg/mL)] Mean (Standard Deviation)	1890.2 (1084.4)	1621 (827.8)

Statistical Analysis 1 for Estradiol (E2) Levels on r-hCG Day

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No

	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4164
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

11. Secondary Outcome Measure:

Measure Title	Number of Ovarian Stimulation Days
Measure Description	Ovarian stimulation included from first rFSH injection (S1) until day on which r-hCG was administered (r-hCG day). This period was divided into 2 parts: the first period in which 300 International Unit (IU) rFSH dose was constant and which covered from S1 to Day 4 of stimulation period (S4); the second period in which the rFSH dose could be adjusted depending on the ovarian response and which began on S4 and finished on the day on which the criteria for administration of r-hCG to induce the final follicular maturation were met.
Time Frame	S1 up to r-hCG day (end of stimulation cycle [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Number of Ovarian Stimulation Days [units: Days] Mean (Standard Deviation)	9.7 (2.1)	9.8 (1.9)

Statistical Analysis 1 for Number of Ovarian Stimulation Days

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5952
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

12. Secondary Outcome Measure:

Measure Title	Number of Recombinant Human Choriogonadotropin (r-hCG) Cycles Cancelled Due to Poor Response
Measure Description	Poor response was defined as 3 or less follicles of greater than or equal to 12 mm developing following at least 7 days of study treatment.
Time Frame	Up to 2 months after OPU (34-38 hours post r-hCG day {end of stimulation cycle} [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Number of Recombinant Human Choriogonadotropin (r-hCG) Cycles Cancelled Due to Poor Response [units: cycles]	4	1

13. Secondary Outcome Measure:

Measure Title	Total Number of Births
Measure Description	Total number of births per reporting group was calculated.
Time Frame	Up to 2 months after OPU (34-38 hours post r-hCG day {end of stimulation cycle} [approximately 28 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. Here "N" represents number of participants evaluated for this measure.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	34
Total Number of Births [units: births]	10	9

Statistical Analysis 1 for Total Number of Births

Statistical Analysis Overview	Comparison Groups	rFSH + rhLH, rFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.8852
	Comments	[Not specified]
	Method	Chi-squared
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Risk Ratio (RR)
	Estimated Value	0.9444
	Confidence Interval	(2-Sided) 95% 0.4347 to 2.0518
	Estimation Comments	[Not specified]

14. Secondary Outcome Measure:

Measure Title	Number of Participants With Adverse Events (AEs)
Measure Description	An AE was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship.
Time Frame	Baseline up to 2 months after OPU (34-38 hours post r-hCG day {end of stimulation cycle} [approximately 28 days])
Safety Issue?	Yes

Analysis Population Description

Safety population included all participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.

	Description
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Number of Participants With Adverse Events (AEs) [units: participants]	19	9

15. Secondary Outcome Measure:

Measure Title	Number of Participants With Ovarian Hyper Stimulation Syndrome (OHSS)
Measure Description	OHSS is a syndrome which can manifest with enlarged ovaries, advanced ascites with increased vascular permeability, pleural fluid accumulation, hemoconcentration, and increased blood clotting.
Time Frame	Baseline up to 2 months after OPU (34-38 hours post r-hCG day {end of stimulation cycle} [approximately 28 days])
Safety Issue?	Yes

Analysis Population Description

Safety population included all participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Number of Participants With Ovarian Hyper Stimulation Syndrome (OHSS)	1	0

	rFSH + rhLH	rFSH
[units: participants]		

16. Secondary Outcome Measure:

Measure Title	Number of Cycles Cancelled Due to Risk of Ovarian Hyper Stimulation Syndrome (OHSS)
Measure Description	OHSS is a syndrome which can manifest with enlarged ovaries, advanced ascites with increased vascular permeability, pleural fluid accumulation, hemoconcentration, and increased blood clotting.
Time Frame	Baseline up to 2 months after OPU (34-38 hours post r-hCG day {end of stimulation cycle} [approximately 28 days])
Safety Issue?	Yes

Analysis Population Description

Safety population included all participants who had received at least 1 dose of the study medication.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Measured Values

	rFSH + rhLH	rFSH
Number of Participants Analyzed	40	35
Number of Cycles Cancelled Due to Risk of Ovarian Hyper Stimulation Syndrome (OHSS) [units: cycles]	1	0

Reported Adverse Events

Time Frame	AEs are collected on an ongoing basis from day of written informed consent. All new AEs must be recorded until the post-treatment safety, on day 35-42 post-hCG administration. AEs are classified as pre-treatment, treatment-emergent and post-treatment.
Additional Description	Pre-Treatment:Medical conditions present at the initial study visit that did not worsen in severity or frequency during the study;Treatment-Emergent: If the onset date of the AE was on or after the first dose date of the study medication; Post-Treatment: If the onset date of the AE was post-hCG Days 35- 42 for participants who completed the study.

Reporting Groups

	Description
rFSH + rhLH	Recombinant human luteinizing hormone (rhLH, Luveris®) injection 150 International Units (IU) subcutaneously daily along with recombinant follicle-stimulating hormone (rFSH) 300 IU subcutaneously daily from Day 1 of stimulation period (S1) to Day 4 of stimulation period (S4) and then rFSH dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day.
rFSH	Recombinant follicle stimulating hormone (rFSH) injection 300 IU subcutaneously daily from S1 to S4 and then dose adjusted depending on the ovarian response till r-hCG administration day.

Serious Adverse Events

	rFSH + rhLH	rFSH
	Affected/At Risk (%)	Affected/At Risk (%)
Total	2/40 (5%)	1/35 (2.86%)
Congenital, familial and genetic disorders		
Trisomy 13 [A] *	0/40 (0%)	1/35 (2.86%)
Musculoskeletal and connective tissue disorders		
New born hip dysplasia [A] *	1/40 (2.5%)	0/35 (0%)
Skin and subcutaneous tissue disorders		
Cutaneous anginoma [A] *	1/40 (2.5%)	0/35 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 13.0

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 0%

	rFSH + rhLH	rFSH
	Affected/At Risk (%)	Affected/At Risk (%)
Total	17/40 (42.5%)	8/35 (22.86%)
Gastrointestinal disorders		
Abdominal pain [A] *	1/40 (2.5%)	0/35 (0%)
Bloating [A] *	2/40 (5%)	0/35 (0%)
Diarrhoea [A] *	1/40 (2.5%)	0/35 (0%)
Odynophagia [A] *	1/40 (2.5%)	0/35 (0%)
Retching [A] *	1/40 (2.5%)	0/35 (0%)
General disorders		
Erythema at the injection site [A] *	2/40 (5%)	0/35 (0%)
General malaise [A] *	1/40 (2.5%)	0/35 (0%)
Haematoma at the injection site [A] *	1/40 (2.5%)	0/35 (0%)
Inflammation [A] *	1/40 (2.5%)	1/35 (2.86%)
Inflammation at the injection site [A] *	1/40 (2.5%)	0/35 (0%)
Oedema [A] *	1/40 (2.5%)	0/35 (0%)
Pain [A] *	1/40 (2.5%)	2/35 (5.71%)
Pain at the injection site [A] *	5/40 (12.5%)	0/35 (0%)
Pruritus at the injection site [A] *	2/40 (5%)	0/35 (0%)
Reaction at the injection site [A] *	1/40 (2.5%)	0/35 (0%)
Swelling [A] *	0/40 (0%)	1/35 (2.86%)
Injury, poisoning and procedural complications		
Subcutaneous haematoma [A] *	2/40 (5%)	2/35 (5.71%)
Nervous system disorders		

	rFSH + rhLH	rFSH
	Affected/At Risk (%)	Affected/At Risk (%)
Burning sensation [A] *	1/40 (2.5%)	0/35 (0%)
Dizziness [A] *	1/40 (2.5%)	2/35 (5.71%)
Headache [A] *	4/40 (10%)	3/35 (8.57%)
Pregnancy, puerperium and perinatal conditions		
Premature birth [A] *	2/40 (5%)	1/35 (2.86%)
Psychiatric disorders		
Mood change [A] *	0/40 (0%)	1/35 (2.86%)
Reproductive system and breast disorders		
Dysmenorrhoea [A] *	0/40 (0%)	1/35 (2.86%)
Genital secretion [A] *	0/40 (0%)	1/35 (2.86%)
Ovarian hyperstimulation syndrome [A] *	1/40 (2.5%)	0/35 (0%)
Pelvic pain [A] *	1/40 (2.5%)	0/35 (0%)
Skin and subcutaneous tissue disorders		
Ecchymosis [A] *	3/40 (7.5%)	0/35 (0%)
Erythema [A] *	5/40 (12.5%)	0/35 (0%)
Pruritus [A] *	4/40 (10%)	1/35 (2.86%)
Vascular disorders		
Haematoma [A] *	4/40 (10%)	1/35 (2.86%)

* Indicates events were collected by non-systematic methods.
A Term from vocabulary, MedDRA 13.0

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

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