ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 12/02/2013

ClinicalTrials.gov ID: NCT01071200

Study Identification

Unique Protocol ID:	IMP25289
Brief Title:	Study to Evaluate if the Addition of r-hLH (Luveris®) to FSH From Day 8 of Ovarian Stimulation is Able to Decrease Total FSH Dose and to Improve Cycle Outcome in Infertile Women Undergoing ART, Who Required High FSH Dose in a Previous Cycle (Luveris in ART)
Official Title:	A Phase III, Multicentric, Randomized, Open, Comparative Study to Evaluate if the Addition of Recombinant Human Luteinising Hormone [r-hLH (Luveris®)] to Follicle Stimulating Hormone (FSH) From Day 8 of Ovarian Stimulation is Able to Decrease Total FSH Dose and to Improve Cycle Outcome in Infertile Women Undergoing Assisted Reproduction Technology (ART), Who Required High FSH Dose in a Previous Cycle
Secondary IDs:	2004-002218-13 [EudraCT Number]

Study Status

Record Verification:	December 2013
Overall Status:	Terminated
Study Start:	March 2005
Primary Completion:	April 2009 [Actual]
Study Completion:	April 2009 [Actual]

Sponsor/Collaborators

Sponsor:	Merck KGaA
Responsible Party:	Sponsor
Collaborators:	Merck Serono S.P.A., Italy

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: 11/09/2004 Board Name: Ethic Committee Board Affiliation: EC of Azienda Ospedaliera Policlinico Sant'Orsola Malpighi - Università di Bologna Phone: +39 051 343934 Email:
Data Monitoring?:	
Plan to Share Data?:	
Oversight Authorities:	Italy: Ethics Committee

Study Description

Brief Summary:	The present study was designed to investigate, in hyporesponder subjects, that required in a previous assisted reproductive technologies (ART) cycle follicle stimulating hormone (FSH) >3500 International Unit (IU), the possibility to decrease through recombinant human luteinizing hormone (r-hLH) supplementation, the FSH amount per oocytes retrieved and in the mean time to improve the overall cycle outcome.
Detailed Description:	Recombinant human follicle stimulating hormone (r-hFSH), which totally lacks LH activity, is widely used to induce multiple follicle development in women under pituitary desensitization, in order to submit them to treatment with assisted reproduction techniques (ART). Clinical experience from hypogonadotropic-hypogonadic women suggests that while FSH alone is sufficient to induce follicle development, LH plays a significant part in final follicle maturation, estrogen synthesis and optimal endometrium growth. This was a phase III, multicentre, randomized, open-label comparative study to evaluate if the addition of r-hLH (Luveris) in a 2:1 ratio to FSH from day 8 of ovarian stimulation is able to decrease the total FSH dose and to improve cycle outcome in 250 infertile women undergoing ART, who required high FSH dose in a previous cycle (≥ 3500 IU). Subjects who have met all the inclusion criteria, achieved pituitary desensitization and started controlled ovarian hyperstimulation (COH) treatment with FSH, on stimulation day 8 (S8) received an identification number and will be allocated to one of the two following arms: Arm : FSH + r-hLH (2:1 ratio of FSH:r-hLH), Arm : FSH alone. Treatment with Luveris was commenced on day 8 (S8) and continued until injection of hCG or cancellation of the treatment cycle. Monitoring of stimulation, FSH dose escalation, criteria for injection of hCG, ovum pick up, embryo transfer and pregnancy confirmation took place according to standard management practice. The in-vitro fertilization (IVF) or intracytosolic sperm injection (ICSI) procedure, including luteal phase support, was performed according to each centres' normal procedures.

The subjects were followed up and the treatment outcome (menstruation or pregnancy) was recorded. The delivery outcome for any pregnant subjects was recorded in the Case Report Form (CRF).

Information on the delivery outcome for each pregnancy was collected. Information on adverse events was collected during the study period.

OBJECTIVES

The primary objective of the study was:

To determine whether the addition of r-hLH (Luveris) from day 8 of ovarian stimulation reduces the FSH dose needed to obtain/ retrieve each oocyte.

The secondary objectives of the study were:

- To determine whether the addition of Luveris to FSH at day 8 of ovarian stimulation improves cycle outcome based on secondary endpoints
- To determine the safety of Luveris in this indication

Conditions

Conditions:	Reproductive Techniques, Assisted
Keywords:	Reproductive Techniques, Assisted Recombinant human follicle stimulating hormone (r-hFSH) Recombinant leutinizing hormone (r-hLH)

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 3
Intervention Model:	Parallel Assignment
Number of Arms:	2
Masking:	Open Label
Allocation:	Randomized
Endpoint Classification:	Safety/Efficacy Study
Enrollment:	133 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: A Subjects treated with r-hFSH and r-hLH (2:1 ratio of r-hFSH:r-hLH)	Drug: Recombinant human Follicle Stimulating Hormone (r-hFSH) and Recombinant human Luteinizing Hormone (r-hLH) One r-hFSH and one r-hLH injection subcutaneously (s.c.) once daily during the treatment phase from Day 8 of stimulation until injection of human chorionic gonadotropin (hCG) or cancellation of the treatment cycle. Other Names: • r-hLH • r-hFSH
Active Comparator: B Subjects treated with r-hFSH alone	Drug: r-hFSH One r-hFSH injection s.c. once daily during the treatment phase from Day 8 of stimulation until injection of hCG or cancellation of the treatment cycle. Other Names: • r-hFSH

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age: 40 Years

Gender: Female

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Pre-menopausal infertile woman, aged 18 to 40 years inclusive, who wishes to conceive
- Regular, spontaneous menstrual cycle of 25-35 days
- Body mass index (BMI) ≤ 28
- FSH ≤ 10 IU/L (follicular phase, days 2-5)
- Prolactin (PRL) within the normal ranges
- Evidence of both ovaries by ultrasound scan
- Women undergoing IVF-Embryo Transfer (ET) or ICSI, down regulated with Gonadotropin releasing hormone analogues (GnRHa) (daily dose) under controlled ovarian hyperstimulation (COH) with FSH

- Washout > 90 days from last dose of clomiphene or gonadotrophin, before ongoing COH cycle
- Only one previous IVF-ET or ICSI cycle (in the last 9 months preceding the ongoing COH cycle) resulted in a hypo-response properly documented (from 6 to 12 oocytes with a total FSH dose ≥ 4000 IU)
- Negative pregnancy hCG test (urine or blood sample) before the ongoing COH cycles
- Willing and able to comply with the protocol for the duration of the study
- Written informed consent before applying any procedure related to the study protocol, which is not part of routine medical care, with the understanding that consent may be withdrawn by the subject at any time, without prejudice on their future medical care

Exclusion Criteria:

- Oligo/Anovulatory cycles (World Health Organization [WHO] I and II)
- Male partner azoospermia (assessed within the last 12 months)
- Follicular phase (day 2-5) FSH > 10 IU/L even if only once observed in the medical history
- Abnormal cervical cytology (assessed within the last 12 months)
- History of unexplained gynecologic hemorrhage
- Any contraindication to pregnancy
- Known allergy to gonadotrophin
- Any clinically important systemic disease (e.g. insulin-dependent diabetes mellitus, epilepsy, serious migraine, intermittent purpura, hepatic, renal or cardiovascular disease, serious corticoid-dependent asthma) which constitutes a contraindication to gonadotropin use
- Any medical condition which, according to the investigator's judgement, may affect the absorption, distribution, metabolism or excretion of the drug. In case of doubt, inclusion of the subject in question should be discussed with the Medical Responsible of Serono
- Known Human Immunodeficiency Virus (HIV) positivity
- Any substance abuse or history of drugs or alcohol abuse within the past 5 years
- Prior inclusion in the present study or simultaneous inclusion in a clinical study of another drug
- Refusal or inability to comply with the protocol

Contacts/Locations

Study Officials: Salvatore Longobardi
Study Director
Merck Serono S.p.A., Italy, an affiliate of Merck KGaA, Darmstadt, Germany

Locations: Italy
Merck Serono S.p.A.
Roma, Italy

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection s.c. administered according to investigator’s discretion till r-hCG administration day.

Overall Study

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Started	67	66
Completed	60	63
Not Completed	7	3
Lack of ovarian response	1	1
No fertilization	4	0
No oocytes retrieved	1	1
Ovarian Hyper Stimulation Syndrome	1	0
No viable embryos	0	1

Baseline Characteristics

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection s.c. administered according to investigator's discretion till r-hCG administration day.

Baseline Measures

	FSH + rhLH	Follicle-stimulating Hormone (FSH)	Total
Number of Participants	67	66	133
Age, Continuous [units: years] Mean (Standard Deviation)	35.6 (2.9)	35.0 (3.8)	35.3 (3.4)
Gender, Male/Female [units: participants]			
Female	67	66	133
Male	0	0	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Total Dose of Follicular Stimulating Hormone (FSH) for Retrieved Oocytes
Measure Description	
Time Frame	Baseline (Stimulation day 8 [S8]) until hCG day
Safety Issue?	No

Analysis Population Description

Modified intention-to-treat (mITT) population included all randomized participants who entered in the experimental phase at S8. Here "N" represents number of participants analyzed for this measure.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	64	64
Total Dose of Follicular Stimulating Hormone (FSH) for Retrieved Oocytes [units: IU] Mean (Standard Deviation)		
Baseline (S8)	904.6 (1068.1)	703.3 (924.5)
Baseline (S8) until hCG day	388.5 (631.3)	318.5 (534.0)

2. Secondary Outcome Measure:

Measure Title	Mean Total Follicle Stimulating Hormone (FSH) and Recombinant Human Luteinizing Hormone (r-hLH) Dose
Measure Description	
Time Frame	Baseline (S8) until hCG day
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	65
Mean Total Follicle Stimulating Hormone (FSH) and Recombinant Human Luteinizing Hormone (r-hLH) Dose [units: IU] Mean (Standard Deviation)		
Total FSH dose	1434.0 (678.1)	1595.0 (796.4)
Total r-hLH dose	575.9 (273.0)	0 (0)

3. Secondary Outcome Measure:

Measure Title	Mean Number of Ovarian Stimulation Days
Measure Description	
Time Frame	Baseline (S8) until hCG day
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	65
Mean Number of Ovarian Stimulation Days [units: Days] Mean (Full Range)	4.6 (2.0 to 10.0)	4.8 (1.0 to 9.0)

4. Secondary Outcome Measure:

Measure Title	Change From Baseline in Oestradiol (E2) Levels at Human Choriogonadotropin (hCG) Day
Measure Description	
Time Frame	Baseline (S8) and hCG day
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8. Here “N” represents number of participants analyzed and "n" represents the number of participants with plasma E2 levels at specified time points for respective treatment groups.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	59	59
Change From Baseline in Oestradiol (E2) Levels at Human Choriogonadotropin (hCG) Day [units: picogram/milliter (pg/mL)] Mean (Standard Deviation)		
Baseline (n = 59,59)	516.1 (353.6)	518.9 (334.2)
Change at hCG day (n = 40,47)	1391.6 (743.4)	1179.9 (746.5)

Statistical Analysis 1 for Change From Baseline in Oestradiol (E2) Levels at Human Choriogonadotropin (hCG) Day

Statistical Analysis Overview	Comparison Groups	FSH + rhLH, Follicle-stimulating Hormone (FSH)
	Comments	Change at hCG day : Wilcoxon two sample test was used to calculate p-value.

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.07
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	Mean Total Number of Retrieved Oocytes
Measure Description	Mean number of oocytes retrieved on the day of ovum pick up (OPU) was counted. 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	34-36 hours post-hCG (OPU)
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	65
Mean Total Number of Retrieved Oocytes [units: oocytes] Mean (Standard Deviation)	7.0 (4.6)	7.8 (3.9)

6. Secondary Outcome Measure:

Measure Title	Mean Number of Mature Oocytes (Metaphase II)
Measure Description	Mean number of metaphase II oocytes was counted for participants undergoing ovum pick up for IntraCytoplasmic Sperm Injection (ICSI). ICSI is a procedure in which a single spermatozoon is injected into the oocyte cytoplasm. Metaphase II stage of the oocyte was classified as the time at which the first polar body was observed microscopically. Metaphase II oocytes are a sub-group of the total number of oocytes.
Time Frame	34-36 hours post-hCG (OPU)
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8. Here "N" represents those participants undergoing ICSI whose oocytes were assessed for maturity (Metaphase II) using a microscope.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	59	62
Mean Number of Mature Oocytes (Metaphase II) [units: Metaphase II Oocytes] Mean (Standard Deviation)	5.1 (3.7)	5.7 (3.2)

7. Secondary Outcome Measure:

Measure Title	Fertilization Rate
Measure Description	Fertilization rate was measured as the ratio between number of fertilized oocytes and number of inseminated oocytes (maximum 3).
Time Frame	12-18 day post-hCG and/or Week 7
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	65
Fertilization Rate [units: ratio] Mean (Standard Deviation)	0.85 (0.29)	0.89 (0.20)

8. Secondary Outcome Measure:

Measure Title	Number of Obtained Embryos
Measure Description	Total number of obtained embryos with maximum 3 inseminated oocytes was calculated.
Time Frame	Day 3 post-hCG (Embryo transfer [ET])
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	65
Number of Obtained Embryos [units: embryos]	142	158

9. Secondary Outcome Measure:

Measure Title	Number of Transferred Embryos
Measure Description	Embryo transfer is the procedure in which one or more embryos are placed in the uterus or Fallopian tube.
Time Frame	Day 3 post-hCG (ET)
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	65
Number of Transferred Embryos [units: embryos]	60	63

10. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Pregnancy

Measure Description	
Time Frame	12-18 day post-hCG and/or Week 7
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	65
Percentage of Participants With Pregnancy [units: percentage of participants]	29.9	30.8

11. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Clinical Pregnancy
Measure Description	Clinical pregnancy is 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	12-18 day post-hCG and/or Week 7
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	65
Percentage of Participants With Clinical Pregnancy [units: percentage of participants]	23.9	18.5

12. Secondary Outcome Measure:

Measure Title	Percentage of Participants With Implantation
Measure Description	Implantation is the attachment and subsequent penetration by the zona-free blastocyst (usually in the endometrium) that starts five to seven days after fertilization.
Time Frame	12-18 day post-hCG and/or Week 7
Safety Issue?	No

Analysis Population Description

mITT population included all randomized participants who entered in the experimental phase at S8.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	65
Percentage of Participants With Implantation [units: percentage of participants]	13.38	11.39

13. Secondary Outcome Measure:

Measure Title	Number of Participants With Ovarian Hyper Stimulation Syndrome (OHSS)
Measure Description	OHSS is an exaggerated systemic response to ovarian stimulation characterized by a wide spectrum of clinical and laboratory manifestations. It is classified as mild, moderate or severe according to the degree of abdominal distention, ovarian enlargement and respiratory, haemodynamic and metabolic complications.
Time Frame	Baseline (S8) until 12-18 day post-hCG and/or Week 7
Safety Issue?	Yes

Analysis Population Description

Safety population included all the randomized participants who received at least one dose of the study drug.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	66
Number of Participants With Ovarian Hyper Stimulation Syndrome (OHSS) [units: participants]		
Mild OHSS	0	0
Moderate OHSS	1	0

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Severe OHSS	0	0

14. Secondary Outcome Measure:

Measure Title	Number of Cycles Cancelled Due to Risk of OHSS
Measure Description	OHSS is an exaggerated systemic response to ovarian stimulation characterized by a wide spectrum of clinical and laboratory manifestations. It is classified as mild, moderate or severe according to the degree of abdominal distention, ovarian enlargement and respiratory, haemodynamic and metabolic complications.
Time Frame	Baseline (S8) until 12-18 day post-hCG and/or Week 7
Safety Issue?	Yes

Analysis Population Description

Safety population included all the randomized participants who received at least one dose of the study drug.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Measured Values

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
Number of Participants Analyzed	67	66
Number of Cycles Cancelled Due to Risk of 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 12-18 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 12 - 18 for participants who completed the study.

Reporting Groups

	Description
FSH + rhLH	Follicle-stimulating hormone (FSH) injection administered according to investigator's discretion till Day 8 of stimulation period (S8) and treatment with recombinant human luteinizing hormone (rhLH, Luveris) injection 150 International Units (IU) subcutaneously (s.c.) daily was started from S8 until recombinant human choriogonadotropin (r-hCG) administration day. r-hLH was administered in a 2:1 ratio (FSH:r-hLH).
Follicle-stimulating Hormone (FSH)	FSH injection administered according to investigator's discretion till r-hCG administration day.

Serious Adverse Events

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
	Affected/At Risk (%)	Affected/At Risk (%)
Total	1/67 (1.49%)	2/66 (3.03%)
General disorders		
Cerclage [A] *	1/67 (1.49%)	0/66 (0%)
Left ectopic pregnancy [A] *	0/67 (0%)	1/66 (1.52%)
Renal colic [A] *	0/67 (0%)	1/66 (1.52%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA

Other Adverse Events

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

	FSH + rhLH	Follicle-stimulating Hormone (FSH)
	Affected/At Risk (%)	Affected/At Risk (%)
Total	2/67 (2.99%)	0/66 (0%)
General disorders		
Ovarian Hyper Stimulation Syndrome [A] *	1/67 (1.49%)	0/66 (0%)
Urticaria post intake of food (fish) [A] *	1/67 (1.49%)	0/66 (0%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA

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.

Results Point of Contact:

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