ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
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Study Identification

Unique Protocol ID:	27262
Brief Title:	A Phase II Study to Assess the Efficacy and Safety of Luveris® (Lutropin Alfa) in Mid Follicular Phase for Controlled Ovarian Stimulation (COS) in Advanced Reproductive Age
Official Title:	Lutropin Alfa (Luveris®) in Mid Follicular Phase for Controlled Ovarian Stimulation (COS) in Advanced Reproductive Age: Phase II Clinical Trial
Secondary IDs:	2006-005268-19 [EudraCT Number]

Study Status

Record Verification:	January 2014
Overall Status:	Terminated
Study Start:	November 2007
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?:	No

IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 21/11/2006 Board Name: CEIC del Centro Internacional de Medicina Avanzada Board Affiliation: Conselleria de Sanitat Phone: +34 93 552 27 00 Email:
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	Spain: Spanish Agency of Medicines

Study Description

Brief Summary:

Ovarian reserve is related to chronological age; 35 years of age is the accepted threshold for significant decline in assisted reproductive technologies (ART) success with scarce follicular recruitment and poor oocyte retrieval. New therapeutic schemes are sought to improve follicular response in ovarian ageing because of the increasing number of infertile women aged older than 35 years who are trying to get pregnant. The advent of gonadotropin releasing hormone analogue antagonist (GnRHant) offers new perspectives to address the issues related to advanced reproductive age since it prevents premature luteinizing hormone (LH) surges while not causing suppression in the early follicular phase. Gonadotropin releasing hormone analogue antagonists are administered in the latter stage of the ovarian stimulation to prevent LH surge by competitive blockade of gonadotropin releasing hormone (GnRH) receptors, thus producing a marked decrease in LH levels just when the interplay between follicle stimulating hormone (FSH) and LH becomes important to complete follicular development and oocyte competence. Some studies in the past have shown the potential of recombinant human LH (r-hLH) supplementation in women of advanced reproductive age to improve oocyte quality, but these studies are of small size and did not provide data on the physiological mechanism behind the benefit obtained.

This randomized, comparative, parallel controlled Phase II study will be conducted in infertile female subjects aged 35-42 years undergoing in-vitro fertilization (IVF)/intra cytoplasmic sperm injection (ICSI), to investigate whether the addition of r-hLH (when the lead follicle is greater than [>] 14 millimeter [mm] in size), to the standard protocol with recombinant human FSH (r-hFSH) under GnRHant, improves the number and quality of oocytes retrieved, implantation rate, and pregnancy rate, while assessing the hormonal milieu in the ovarian follicular fluid. Comparison will be performed against ovarian stimulation without addition of r-hLH, that is (i.e.) with r-hFSH under GnRHant alone.

Detailed Description:

Preclinical pharmacology studies have demonstrated that r-hLH has a LH/human chorionic gonadotropin (hCG) receptor affinity similar to pituitary human luteinizing hormone (p-hLH), and is biologically active in-vitro in stimulating steroidogenesis and in promoting oocyte germinal vesicle breakdown. Several clinical studies have investigated the usefulness of r-hLH supplementation in normal ovulatory women undergoing ART and in almost all of them sub-populations of subjects have been identified who will benefit, when r-hLH is added to FSH.

OBJECTIVES

Primary objectives:

- To determine the efficacy of adding r-hLH at mid-follicular phase compared to not adding r-hLH, in women of 35-42 years of age included in a COS with r-hFSH under treatment with a GnRHant for IVF/ICSI, assessed by the number and quality of the oocyte
- To determine the safety of using r-hLH combined with r-hFSH in a protocol with a GnRHant, including incidence of ovarian hyperstimulation syndrome (OHSS) and adverse events (AEs) as well as local tolerability

Secondary objectives:

- To complete the verification of efficacy with additional assessments such as follicular growth, oocyte fertilization, embryo quality and pregnancy rates
- To investigate the underlying mechanism of possible improvement in oocyte quality by means of determining hormone levels (LH, FSH, T, E2, and hCG) levels in follicular fluid

Tertiary objectives:

- This is a phase-II study that did not aim to carry out assessment of pharmacoeconomics or quality of life

All subjects will undergo treatment with r-hFSH at a daily dose of 300-450 IU by subcutaneous route starting on the stimulation Day 1 (S1) until r-hCG administration. Upon detection of a lead follicle > 14 mm in diameter, GnRHant 0.25 milligram (mg)/ day subcutaneous administration will be initiated and continued up to r-hCG administration day. Subjects will be then randomly allocated (at any time between S1 and GnRHant initiation day) either to additional treatment with r-hLH at a daily fixed dose of 150 IU or continue treatment with r-hFSH alone. Gonadotropin releasing hormone antagonist and combined treatment with r-hLH plus (+) r-hFSH or r-hFSH alone will be administered until at least one follicle > 18 mm in diameter and two additional follicles > 16 mm in diameter are present and E2 levels are commensurate with the number and size of follicles present. A single injection of 250-500 microgram of r-hCG, will be given to induce final follicular maturation within 36 hours of the last r-hLH and/or r-hFSH injections and on the same day of the last GnRHant morning administration. Oocytes will be retrieved 34-38 hours after r-hCG administration, assessed, and fertilized in-vitro by ICSI. Not more than 3 embryos will be replaced on day 2 or 3 after OPU. The luteal phase will be supported by a daily vaginal administration of natural progesterone, starting after OPU and continuing either up to menstruation or the pregnancy test or, if the subject is pregnant, for at least 30 days after laboratory evidence of pregnancy. Each subject will be followed-up and the treatment outcome (pregnancy or menstruation) will be recorded.

For all subjects who received r-hCG and do not menstruate, a blood sample will be collected for local determination of serum beta-hCG level between post-hCG days 15-20. If positive (beta-hCG > 10 International Unit/liter [IU/L]), it should be confirmed by performing a second test within one week later. An ultrasound scan (US) will be performed at post-hCG days 35-42 on all subjects who will become pregnant provided that no miscarriage has occurred. The number of fetal sacs and fetal heart activity will be recorded. Active follow-up of all pregnancies will be performed, including those subjects withdrawn from the study.

Conditions

Conditions: Infertility
Ovulation Induction

Keywords: Infertility
Ovulation induction
Luveris
Lutropin alfa
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:	93 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: r-hLH + r-hFSH	Drug: r-hLH + r-hFSH Recombinant human follicle stimulating hormone (r-hFSH) injection will be administered subcutaneously once daily from stimulation Day 1(S1) at a starting dose of 300-450 International Unit (IU) and then dose adjusted depending on the ovarian response till recombinant human choriogonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection will be administered subcutaneously once daily at a constant dose of 150 IU with flexible start, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. Other Names: • Luveris® • Lutropin alfa Drug: Recombinant Human Choriogonadotropin (r-hCG) The r-hCG will be administered as a single dose of 250-500 microgram (mcg) subcutaneously in the same day after the last dose of the GnRH antagonist. Other Names: • Ovitrelle®

Arms	Assigned Interventions
	Drug: GnRH antagonist The GnRH antagonist will be administered at a starting at a dose of 0.25 milligram (mg) subcutaneously daily in the morning when the ultrasound discovers a follicle of greater than or equal to (>=) 14 mm, and maintained until at least one follicle of >=18 mm and two additional follicles of >=16 mm with appropriate plasma estradiol levels for the number and size of the existing follicles. Other Names: • Cetrotide®
Active Comparator: r-hFSH	Drug: r-hFSH Recombinant human follicle stimulating hormone (r-hFSH) injection will be administered subcutaneously once daily from S1 at a starting dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Drug: Recombinant Human Choriogonadotropin (r-hCG) The r-hCG will be administered as a single dose of 250-500 microgram (mcg) subcutaneously in the same day after the last dose of the GnRH antagonist. Other Names: • Ovitrelle® Drug: GnRH antagonist The GnRH antagonist will be administered at a starting at a dose of 0.25 milligram (mg) subcutaneously daily in the morning when the ultrasound discovers a follicle of greater than or equal to (>=) 14 mm, and maintained until at least one follicle of >=18 mm and two additional follicles of >=16 mm with appropriate plasma estradiol levels for the number and size of the existing follicles. Other Names: • Cetrotide®

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 35 Years

Maximum Age: 42 Years

Gender: Female

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Premenopausal woman, aged 35 to 42 years wanting to become pregnant
- Subjects with FSH baseline plasma levels less than or equal to 10 IU/L (Day 2-5 of the cycle) and with LH and E2 levels within the normal limits of the local laboratory
- Subjects having regular spontaneous menstrual cycle lasting 25-35 days
- Subjects with infertility that is susceptible to treatment with IVF/ICSI
- Subjects to be included in a COS protocol with r-hFSH and GnRHant
- Subjects with partner's sperm suitable for IVF/ICSI according to local laboratory, unless sperm donor is to be used
- Subjects with both ovaries
- Subjects with uterine cavity capable of sustaining the implantation of embryo or carrying a pregnancy
- Subjects with normal pap smear (papanicolaou) 6 months prior to be included in the study (signature of informed consent)
- Subjects with body mass index (BMI) less than (<) 30 at the beginning of ovarian stimulation
- Subjects with confirmed absence of pregnancy with the beta-hCG test (urine or blood) before starting the administration of r-hFSH
- Subjects willing to adjust to the protocol for the entire duration of the study
- Subjects who have given informed consent prior to any study-related procedure that is not part of normal medical care

Exclusion Criteria:

- Subjects or her partner with known positivity for human immunodeficiency virus (HIV) or Hepatitis-B /Hepatitis-C virus (HBV/HCV)
- Subjects with any systemic illnesses of clinical significance, hypothalamus and pituitary tumors; cancer of ovaries, uterus or breast; hormonal anomalies and/or medical, biochemical, hematological illnesses that, according to the investigator, could interfere with the treatment with gonadotropins
- Subjects with more than 2 previous ART cycles
- Subjects who have cancelled two previous ART cycles
- Subjects with frozen embryos from previous ART cycles
- Subjects with non-specific gynecological bleeding
- Subjects with ovaries that are polycystic, increased in size or with cysts of unknown etiology
- Subjects with any contraindication for becoming pregnant and/or carrying pregnancy to term
- Subjects with known allergy to gonadotropin preparations or any of the excipients
- Subjects with drug dependence or history of drug or alcohol abuse in the previous 5 years
- Subjects who have previously entered into this study or simultaneous participation in another clinical drug trial with drugs
- Subjects who are unwilling to or not being able to adjust to the study protocol

Contacts/Locations

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

Locations: Spain
Instituto Marqués
Barcelona, Spain, 08034

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Overall Study

	r-hFSH + r-hLH	r-hFSH
Started	46	47
Completed	31	34

	r-hFSH + r-hLH	r-hFSH
Not Completed	15	13
Withdrawal before r-hCG administration	2	3
Withdrawal between rhCG-ovum pickup(OPU)	4	8
Withdrawal between OPU - embryo transfer	8	2
Randomized but not treated	1	0

Baseline Characteristics

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Baseline Measures

	r-hFSH + r-hLH	r-hFSH	Total
Number of Participants	45	47	92
Age, Continuous [units: years] Mean (Standard Deviation)	36.6 (2.6)	36.3 (3.0)	36.4 (2.8)
Gender, Male/Female [units: participants]			
Female	45	47	92

	r-hFSH + r-hLH	r-hFSH	Total
Male	0	0	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Number of Oocytes Retrieved
Measure Description	Number of oocytes retrieved per reporting group on the day of ovum pick-up (OPU) (34-38 hours post r-hCG day) was calculated. Oocyte retrieval is a technique used in in-vitro fertilization (IVF) in order to remove oocytes from the ovary of the female participant, enabling fertilization outside the body.
Time Frame	Ovum pick-up (OPU) day (34-38 hours post r-hCG day [end of stimulation cycle {approximately 9 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. "N" (number of participants analyzed) signifies those participants who underwent ovum pick up.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	39	36

	r-hFSH + r-hLH	r-hFSH
Number of Oocytes Retrieved [units: oocytes] Mean (Standard Deviation)	10 (3.8)	10 (5.2)

Statistical Analysis 1 for Number of Oocytes Retrieved

Statistical Analysis Overview	Comparison Groups	r-hFSH + r-hLH, r-hFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.5739
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

2. Primary 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) 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 is assessed based on the presence of a germinal vesicle (GV) or whether oocytes were in metaphase I (Meta-I) or II (Meta-II) stage or atretic.
Time Frame	OPU day (34-38 hours post r-hCG day [end of stimulation cycle {approximately 9 days}])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. "N" (number of participants analyzed) signifies those participants who underwent ovum pick up.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	39	36
Number of Mature Oocytes Retrieved [units: mature oocytes]		
Geminal vesicle (GV)	60	37
Meta-I	44	26
Meta-II	275	292
Atresic	10	4

3. Primary Outcome Measure:

Measure Title	Number of Participants With Ovarian Hyper Stimulation Syndrome (OHSS)
Measure Description	Ovarian Hyper Stimulation Syndrome (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	S1 to 1 month ± 1 week post r-hCG day (end of stimulation cycle [approximately 9 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
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	45	47
Number of Participants With Ovarian Hyper Stimulation Syndrome (OHSS) [units: participants]	0	0

4. Primary Outcome Measure:

Measure Title	Number of Cycles Cancelled Due to Risk of Ovarian Hyper Stimulation Syndrome (OHSS)
Measure Description	Ovarian Hyper Stimulation Syndrome (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	S1 to 1 month ± 1 week post r-hCG day (end of stimulation cycle [approximately 9 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
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	45	47
Number of Cycles Cancelled Due to Risk of Ovarian Hyper Stimulation Syndrome (OHSS) [units: cycles]	0	0

5. Primary Outcome Measure:

Measure Title	Number of Participants With Adverse Events (AEs)
Measure Description	An adverse event (AE) was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an Investigational Medicinal Product (IMP), regardless of causal relationship and even if no IMP has been administered.
Time Frame	S1 to 1 month ± 1 week post r-hCG day (end of stimulation cycle [approximately 9 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
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	45	47
Number of Participants With Adverse Events (AEs) [units: participants]	3	0

6. Secondary Outcome Measure:

Measure Title	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 9 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
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	45	47
Number of Follicles Greater Than or Equal to 14 Millimeter (mm) on Recombinant Human Choriogonadotropin (r-hCG) Day [units: follicles] Mean (Standard Deviation)	8.6 (3.9)	7.4 (3.9)

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

Statistical Analysis Overview	Comparison Groups	r-hFSH + r-hLH, r-hFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.1734
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

7. Secondary Outcome Measure:

Measure Title	Endometrial Thickness on Recombinant Human Choriogonadotropin (r-hCG) Day
Measure Description	Endometrial thickness measurement was performed on the day of r-hCG administration.
Time Frame	r-hCG day (end of stimulation cycle [approximately 9 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. "N" (number of participants analyzed) signifies those participants who were evaluable for this measure.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	42	44

	r-hFSH + r-hLH	r-hFSH
Endometrial Thickness on Recombinant Human Choriogonadotropin (r-hCG) Day [units: mm] Mean (Standard Deviation)	9.5 (2.1)	8.8 (2.2)

Statistical Analysis 1 for Endometrial Thickness on Recombinant Human Choriogonadotropin (r-hCG) Day

Statistical Analysis Overview	Comparison Groups	r-hFSH + r-hLH, r-hFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0642
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

8. 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 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	OPU day (34-38 hours post r-hCG day [end of stimulation cycle {approximately 9 days}])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. "N" (number of participants analyzed) signifies those participants who underwent ovum pick up.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	39	36
Number of Fertilized Oocytes (2 Pronuclei [PN]) [units: 2PN oocytes]	203	203

9. Secondary Outcome Measure:

Measure Title	Number of Fertilized Oocytes at Stage 2 Pronuclei (2PN) or Higher Than 2PN
Measure Description	Oocytes were fertilized using 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 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. Fertilized oocytes at stage higher then 2PN are those oocytes which consist more than 2 pronuclei like oocyte having 3 pronuclei termed as 3PN, oocyte having 4 pronuclei termed as 4PN.
Time Frame	Day 35-42 post r-hCG day (end of stimulation cycle [approximately 9 days])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. "N" (number of participants analyzed) signifies those participants who underwent ovum pick up.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	39	36
Number of Fertilized Oocytes at Stage 2 Pronuclei (2PN) or Higher Than 2PN [units: oocytes]	210	210

10. Secondary Outcome Measure:

Measure Title	Number and Quality of Embryos
Measure Description	Embryos were classified into 5 different grades (1 to 5) based on their capacity of implantation. Grade 1 embryos were those with best capacity of implantation and Grade 5 embryos were those with worst capacity of implantation.
Time Frame	Day 2-3 post OPU (34-38 hours post r-hCG day [end of stimulation cycle {approximately 9 days}])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. "N" (number of participants analyzed) signifies those participants who continued with follicular development.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	39	35
Number and Quality of Embryos [units: embryos]		
1	22	39
2	46	35
3	56	49
4	18	13
5	64	70

11. Secondary 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 multiplied by 100.
Time Frame	Day 35-42 post OPU (34-38 hours post r-hCG day {end of stimulation cycle [approximately 9 days]})

Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. "N" (number of participants analyzed) signifies those participants who were evaluable for this measure.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	31	34
Implantation Rate [units: percent sacs per embryo] Mean (Standard Deviation)	30 (30)	20 (30)

Statistical Analysis 1 for Implantation Rate

Statistical Analysis Overview	Comparison Groups	r-hFSH + r-hLH, r-hFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.4080
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

12. 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	Day 35-42 post r-hCG day (end of stimulation cycle [approximately 9 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
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	45	47

	r-hFSH + r-hLH	r-hFSH
Number of Participants With Clinical Pregnancies [units: participants]	14	12

13. Secondary Outcome Measure:

Measure Title	Number of Participants in Whom Recombinant Human Chorionic Gonadotropin (r-hCG) Was Not Administered 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	r-hCG day (end of stimulation cycle [approximately 9 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
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	45	47

	r-hFSH + r-hLH	r-hFSH
Number of Participants in Whom Recombinant Human Chorionic Gonadotropin (r-hCG) Was Not Administered Due to Poor Response [units: participants]	1	3

14. Secondary Outcome Measure:

Measure Title	Number of Ovarian Stimulation Days
Measure Description	Ovarian stimulation included from first r-hFSH injection (S1) until day on which r-hCG was administered (r-hCG day).
Time Frame	Day 1 of stimulation period (S1) up to r-hCG day (end of stimulation cycle [approximately 9 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
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	45	47

	r-hFSH + r-hLH	r-hFSH
Number of Ovarian Stimulation Days [units: days] Mean (Standard Deviation)	9.4 (1.3)	8.8 (1.5)

Statistical Analysis 1 for Number of Ovarian Stimulation Days

Statistical Analysis Overview	Comparison Groups	r-hFSH + r-hLH, r-hFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0648
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

15. Secondary Outcome Measure:

Measure Title	Total Dose of Recombinant Human Follicle Stimulating Hormone (r-hFSH)
Measure Description	
Time Frame	Day 1 of stimulation period (S1) up to r-hCG day (end of stimulation cycle [approximately 9 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
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	45	47
Total Dose of Recombinant Human Follicle Stimulating Hormone (r-hFSH) [units: IU] Mean (Standard Deviation)	2916.1 (555.9)	2861.7 (693.8)

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

Statistical Analysis Overview	Comparison Groups	r-hFSH + r-hLH, r-hFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.6799
	Comments	[Not specified]
	Method	ANOVA

	Comments	[Not specified]

16. Secondary Outcome Measure:

Measure Title	Estradiol (E2) Levels on r-hCG Day
Measure Description	
Time Frame	r-hCG day (end of stimulation cycle [approximately 9 days])
Safety Issue?	No

Analysis Population Description

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

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	40	43
Estradiol (E2) Levels on r-hCG Day [units: picogram/milliter (pg/mL)] Mean (Standard Deviation)	1813.9 (1063.6)	1362.9 (774.1)

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

Statistical Analysis Overview	Comparison Groups	r-hFSH + r-hLH, r-hFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0634
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]
	Comments	[Not specified]

17. Secondary Outcome Measure:

Measure Title	Follicular Levels of Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and Human Chorionic Gonadotropin (hCG) at Ovum Pick up (OPU)
Measure Description	
Time Frame	OPU day (34-38 hours post r-hCG day [end of stimulation cycle {approximately 9 days}])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. "N" (number of participants analyzed) signifies those participants who were evaluable for this measure.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

	Description
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	35	35
Follicular Levels of Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and Human Chorionic Gonadotropin (hCG) at Ovum Pick up (OPU) [units: milli international unit (mIU)/mL] Mean (Standard Deviation)		
LH levels at OPU	1.8 (0.9)	2.0 (0.9)
FSH levels at OPU	8.3 (3.0)	9.0 (3.7)
hCG levels at OPU	142.2 (72.7)	136.2 (65.8)

18. Secondary Outcome Measure:

Measure Title	Follicular Levels of Estradiol (E2) at Ovum Pick up (OPU)
Measure Description	
Time Frame	OPU day (34-38 hours post r-hCG day [end of stimulation cycle {approximately 9 days}])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. "N" (number of participants analyzed) signifies those participants who were evaluable for this measure.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	35	35
Follicular Levels of Estradiol (E2) at Ovum Pick up (OPU) [units: pg/mL] Mean (Standard Deviation)	454508.0 (189835.8)	349605.3 (203895.8)

Statistical Analysis 1 for Follicular Levels of Estradiol (E2) at Ovum Pick up (OPU)

Statistical Analysis Overview	Comparison Groups	r-hFSH + r-hLH, r-hFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.0166
	Comments	[Not specified]
	Method	Other [Wilcoxon two sample test]

	Comments	[Not specified]

19. Secondary Outcome Measure:

Measure Title	Follicular Levels of Testosterone (T) at Ovum Pick up (OPU)
Measure Description	
Time Frame	OPU day (34-38 hours post r-hCG day [end of stimulation cycle {approximately 9 days}])
Safety Issue?	No

Analysis Population Description

ITT population included all randomized participants who had received at least 1 dose of the study medication. N" (number of participants analyzed) signifies those participants who were evaluable for this measure.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Measured Values

	r-hFSH + r-hLH	r-hFSH
Number of Participants Analyzed	35	35
Follicular Levels of Testosterone (T) at Ovum Pick up (OPU) [units: nanogram/milliliter (ng/mL)] Mean (Standard Deviation)	5.9 (1.5)	6.0 (1.8)

Statistical Analysis 1 for Follicular Levels of Testosterone (T) at Ovum Pick up (OPU)

Statistical Analysis Overview	Comparison Groups	r-hFSH + r-hLH, r-hFSH
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.8812
	Comments	[Not specified]
	Method	ANOVA
	Comments	[Not specified]

Reported Adverse Events

Time Frame	S1 up to 1 month ± 1 week post r-hCG day (end of stimulation cycle [approximately 9 days])
Additional Description	An adverse event (AE) was defined as any untoward medical occurrence in the form of signs, symptoms, abnormal laboratory findings, or diseases that emerges or worsens relative to baseline during a clinical study with an Investigational Medicinal Product (IMP), regardless of causal relationship and even if no IMP has been administered.

Reporting Groups

	Description
r-hFSH + r-hLH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from Day 1 of stimulation period (S1) at a starting dose of 300-450 international units (IU) and then dose adjusted depending on the ovarian response till recombinant human chorionic gonadotropin (r-hCG) administration day. Recombinant human luteinizing hormone (r-hLH, Luveris®, Lutropin alfa) injection administered subcutaneously once daily at a constant dose of 150 IU in the afternoon and gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 milligram (mg)/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 millimeter [mm] in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

	Description
r-hFSH	Recombinant human follicle stimulating hormone (r-hFSH) injection administered subcutaneously once daily from S1 at a staring dose of 300-450 IU and then dose adjusted depending on the ovarian response till r-hCG administration day. Gonadotropin releasing hormone (GnRH) antagonists injection administered subcutaneously once daily at a dose of 0.25 mg/day in the morning, depending on the follicular growth (when the lead follicle is greater than 14 mm in size), along with r-hFSH treatment as a separate injection till r-hCG administration day. On r-hCG day 250-500 microgram of r-hCG was administered subcutaneously once.

Serious Adverse Events

	r-hFSH + r-hLH	r-hFSH
	Affected/At Risk (%)	Affected/At Risk (%)
Total	2/45 (4.44%)	0/47 (0%)
Pregnancy, puerperium and perinatal conditions		
Ectopic pregnancy *	2/45 (4.44%)	0/47 (0%)

* Indicates events were collected by non-systematic methods.

Other Adverse Events

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

	r-hFSH + r-hLH	r-hFSH
	Affected/At Risk (%)	Affected/At Risk (%)
Total	1/45 (2.22%)	0/47 (0%)
Gastrointestinal disorders		
Vomiting *	1/45 (2.22%)	0/47 (0%)

* Indicates events were collected by non-systematic methods.

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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