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

Unique Protocol ID:	IMP 28364
Brief Title:	EXpression PRofile Endometrium Samples Study (EXPRESS)
Official Title:	Open Label Pilot Study on Gene Expression Profiling of the Endometrial Tissue in Patients Undergoing Assisted Reproductive Technology [ART: In Vitro Fertilization (IVF)/ Intracytoplasmic Sperm Injection (ICSI)] With GONAL-f®
Secondary IDs:	2007-003938-41 [EudraCT Number]

Study Status

Record Verification:	December 2013
Overall Status:	Terminated
Study Start:	August 2008
Primary Completion:	August 2010 [Actual]
Study Completion:	August 2010 [Actual]

Sponsor/Collaborators

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

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: 2007-07-08 Board Name: COMITE de PROTECTION DES PERSONNE ILE DE FRANCE II Board Affiliation: Université Paris Descartes Phone: +33142864134 Email: depret@necker.fr
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis)

Study Description

Brief Summary:

This is a Phase IV, pilot, open-label, national, multi-centric study planned to determine the gene expression profiles and histologic changes of the endometrial tissue before and after stimulation with Gonal-f®. Physicians are interested in identifying predictive genetic markers in assisted reproductive technologies (ART) in addition to the clinical predictive factors already known. Among those predictive factors, the state of the endometrium is considered as an important implantation determining factor for which pharmacogenomic research is of great interest.

The direct benefits of this study will be to know whether the endometrial gene expression profile is modified in response to stimulation treatment and have an impact or not on the endometrial tissue receptivity. The potential benefits of this study could be to assess the therapy optimization based on individual treatment response and gene expression profile compared to group treatment response in infertile women and prediction of response to therapy based on gene expression profiling before and after Gonal-f® stimulation in infertile women.

Detailed Description:

This is a pilot open-label, national, multi-centre, Phase IV trial. This trial will be conducted with outpatients. Once subject has met all eligibility criteria, she will be treated with Gonal-f® prefilled pen and will receive on a randomization basis the GnRH agonist or antagonist. The follicle stimulating hormone (FSH) stimulation will start on day 2 of the menstrual cycle with a pre-defined fixed dose of 150 IU per day until follicles are recruited and developed. Dose adjustment will be allowed strictly in case of risk of ovarian hyperstimulation syndrome (OHSS). Ovulation triggering will be performed using a single injection of 250 mcg Ovitrelle®.

Ultrasound scans (US) will be performed concomitantly with hormonal assessment at each visit. Ovulation will be triggered as soon as there are at least 3 follicles > 16 mm, and with E2 > 1 mcg/L if agonist used. Oocyte retrieval, in vitro fertilization (IVF) or intra-cytoplasmic sperm injection (ICSI) and blastocyst transfer will be performed as per centre's standard practice. Vaginal progesterone will be administered in the luteal phase for all subjects (600 milligram per day [mg/d]).

Hormonal assessment and endometrial biopsy will be performed on:

- Day Luteinizing Hormone+7 ("LH+7") of the previous spontaneous cycle
- Day of Oocyte Retrieval (OR) of the stimulated cycle
- Day "OR+5 or 6" (biopsy performed only in subjects that did not have blastocyst(s) transfer).

Gene expression profiling will be carried out on ribonucleic acid (RNA) from endometrial tissue. As the main objective of this trial is to determine the gene expression profiles of endometrial tissue before and after controlled ovarian stimulation with Gonal-f®, a minimum of 2 endometrial samples per subject will be collected, 1 at day LH+7 of spontaneous cycle and 1 after the stimulation, on the day of OR.

The subjects will be followed up until 15 days after the last injection of Investigational Medicinal Products (IMPs) for the safety assessment. For subjects who will have blastocyst implantation, the pregnancy outcomes will be recorded until 12 weeks of gestation if a pregnancy is ongoing up to that period.

OBJECTIVES

Primary objective:

- To determine the gene expression profile and histological changes of endometrial tissue before (at day LH + 7 of spontaneous cycle) and after stimulation with Gonal-f® (Day of OR: 36 +/- 2 hours post r-hCG administration) in Assisted Reproductive Technology (ART) [IVF/ICSI]

Secondary objectives:

- To correlate the gene expression profile of the endometrial tissue at Day LH + 7 of the spontaneous cycle with the blastocyst implantation rate in subjects undergoing ART with Gonal-f®
- To correlate the gene expression profile and histological changes in endometrial tissue before and after stimulation by Gonal-f® with the "down regulation" protocol used (agonist or antagonist) and fertilization mode, IVF/ICSI
- To correlate the gene expression profile and histological changes in endometrial tissue before and after stimulation by Gonal-f® according to the hormonal status of subjects
- To characterize the gene expression profile and histology of endometrial tissue after stimulation with Gonal-f in subjects without blastocyst during the theoretical window of implantation (OR + 5 or 6 days)
- To characterize the gene expression profile and histology of endometrial tissue of good and poor responders to stimulation with Gonal-f® on the Day of OR (response being based on the following criteria):

    a. Quantity of mature oocytes retrieved:

        - Poor responders: 5 mature oocytes or less
        - Good responders: more than 8 mature oocytes

    b. Quantity of Gonal-f® used

Conditions

Conditions: In Vitro Fertilization

Keywords: Infertility
Gonal-f
gene expression
Assisted Reproductive Technologies
Follitropin alfa
endometrium

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 4
Intervention Model:	Parallel Assignment
Number of Arms:	2
Masking:	Open Label
Allocation:	Randomized
Endpoint Classification:	Efficacy Study
Enrollment:	27 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Gonal-f® + Ovitrelle® + Long Agonist Protocol	Drug: Gonal -f® [r-hFSH] On Day 2 of the menstrual cycle, a pre-defined fixed dose of 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH) will be administered until follicles are recruited and developed. Other Names: • Gonal-f® • Follitropin Alfa Drug: Ovitrelle® [r-hCG alfa] Ovulation triggering will be performed using a single injection of 250 microgram (mcg) recombinant human chorionic gonadotropin (r-hCG) alfa as soon as follicles satisfy the criteria for follicular development, that is at least 3 follicles greater than (>) 16 millimeter (mm), and with estradiol (E2) > 1 microgram per liter (mcg/L) if gonadotropin releasing hormone (GnRH) agonist will be used. Other Names: • Ovitrelle® • Ovidrel® Drug: Gonadotropin-releasing hormone (GnRH) Agonist To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) GnRH agonist daily will be given after endometrial biopsy, 7 days after the peak day of luteinizing

Arms	Assigned Interventions
	hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Experimental: Gonal-f® + Ovitrelle® + Multi-dose Antagonist Protocol	Drug: Gonal -f® [r-hFSH] On Day 2 of the menstrual cycle, a pre-defined fixed dose of 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH) will be administered until follicles are recruited and developed. Other Names: • Gonal-f® • Follitropin Alfa Drug: Ovitrelle® [r-hCG alfa] Ovulation triggering will be performed using a single injection of 250 microgram (mcg) recombinant human chorionic gonadotropin (r-hCG) alfa as soon as follicles satisfy the criteria for follicular development, that is at least 3 follicles greater than (>) 16 millimeter (mm), and with estradiol (E2) > 1 microgram per liter (mcg/L) if gonadotropin releasing hormone (GnRH) agonist will be used. Other Names: • Ovitrelle® • Ovidrel® Drug: Gonadotropin-releasing hormone (GnRH) Antagonist To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily will be given from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	35 Years
Gender:	Female
Accepts Healthy Volunteers?:	No
Criteria:	Inclusion Criteria:

- Infertile female or infertile male. Infertile female means diverse infertility etiologies including tubal disease (excepting hydrosalpinx) and so called "unexplained infertility"
- Suitable for ART: IVF undergoing first or second attempt, ICSI undergoing first attempt
- 18-35 years old, body mass index (BMI) less than or equal to 27 kilogram per square meter (kg/m^2), non smoking
- Normal ovarian status (FSH less than or equal to 9.45 International Units per Liter [IU/L], E2 less than or equal to 40 picogram per milliliter [pg/mL], Anti-Mullerian Hormone [AMH] greater than or equal to 18 picomole/liter [pmol/L]; within normal laboratory range values, normal ovaries sonography and uterine echo doppler)
- No history of active genito-urinary infection
- Normal thyroid function (or adequate substitution for at least 3 months)
- Negative cervical papanicolaou test within the last 12 months prior to study entry
- No hormonal therapy, including gonadotropins and progesterone, for at least 2 months prior to the study
- In couple with female infertility, male partner with normal sperm or moderate oligoasthenospermia in semen analysis and negative semen culture less than 6 months at the study entry
- Willingness and ability to comply with the protocol for the duration of the study
- Written informed consent prior to any study related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to their future medical care

Exclusion Criteria:

- Subjects with ongoing pregnancy, any pregnancy within 3 months prior to study entry, or any contraindication to pregnancy or carrying pregnancy to term
- Subjects with uterine malformation, diethylstilbestrol syndrome, adenomyosis, synechia
- Subjects with history of previous OHSS
- Subjects with polycystic ovarian syndrome (PCOS) according to the revised Rotterdam Consensus 2003
- Subjects with extra-uterine pregnancy during the previous 3 months
- Subjects with recurrent miscarriages (early or late, more than 2)
- Subjects having known infection with human immunodeficiency virus (HIV), hepatitis B or C virus, for subject or partner
- Subjects with abnormal gynecological bleeding of undetermined origin
- Subjects with history of major thromboembolic disease
- Subjects with endometriosis
- Subjects with presence or history of malignant tumors and related treatment
- Subjects with clinically significant systemic disease or clinically significant abnormal hematology, chemistry, or urinalysis results at screening
- Subjects with known allergy or hypersensitivity to Gonal-f® or Ovitrelle®
- Subjects with any active substance abuse or history of drug, medication or alcohol abuse in the past 5 years
- Subjects who have participated within 3 months prior to study entry in another clinical trial

Contacts/Locations

Study Officials:

Locations: France
Research Site
Paris, France

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Pre-Assignment Details	A total of 27 participants were enrolled in the study, out of which 2 participants withdrew the consent and 1 participant was excluded since endometrial biopsy was not possible.

Reporting Groups

	Description
Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Participants received 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH, Gonal-f®) subcutaneously (sc) starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 microgram (mcg) recombinant human chorionic gonadotropin alfa (r-hCG alfa, Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles greater than [>] 16 millimeter [mm], and with estradiol [E2] >1 microgram per liter [mcg/L]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) gonadotropin-releasing hormone (GnRH) agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Participants received 150 IU per day of r-hFSH (Gonal-f®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm). To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily was started from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Overall Study

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
Started	13	11
Completed	10	11

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
Not Completed	3	0
Lack of ovarian response	1	0
No fertilization	1	0
No transfer	1	0

Baseline Characteristics

Reporting Groups

	Description
Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Participants received 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH, Gonal-f®) subcutaneously (sc) starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 microgram (mcg) recombinant human chorionic gonadotropin alfa (r-hCG alfa, Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles greater than [>] 16 millimeter [mm], and with estradiol [E2] >1 microgram per liter [mcg/L]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Participants received 150 IU per day of r-hFSH (Gonal-f®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm). To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily was started from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Baseline Measures

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Total
Number of Participants	13	11	24
Age, Continuous [units: years] Mean (Standard Deviation)	29.8 (4.2)	31.0 (4.4)	30.4 (4.3)
Gender, Male/Female [units: participants]			
Female	13	11	24
Male	0	0	0

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Gene Expression of the Endometrium Following 1 Cycle With Gonal-f®
Measure Description	A list of genes based on gene expression profiling carried out on ribonucleic acid (RNA) extracted from endometrial tissue. The expression of messenger ribonucleic acid (mRNA) in endometrial tissue was measured by using microarrays such as the Affymetrix® GeneChip HG-U133 plus 2.0 array or equivalent.
Time Frame	Day of Oocyte Retrieval (36 +/- 2 hours post r-hCG administration) after COS by Gonal-f®
Safety Issue?	No

Analysis Population Description

Data were not analyzed for both agonist and antagonist protocol as total, which was the primary objective, since gene expression of the endometrium could not be performed due to poor quality of biopsy samples and poor recruitment in the study.

Reporting Groups

	Description
Gonal-f® + Ovitrelle®	Participants received 150 IU per day of r-hFSH (Gonal-F®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm [for both long agonist and multi-dose antagonist protocol], and with E2>1 mcg/L [for long agonist protocol]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation, either 0.1 mg GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) in long agonist protocol or 0.25 mg GnRH antagonist daily was started from Day 6 of GONAL-f® stimulation treatment in multi-dose antagonist protocol, as per SmPC.

Measured Values

	Gonal-f® + Ovitrelle®
Number of Participants Analyzed	0

No data displayed because Outcome Measure has zero total participants analyzed.

2. Primary Outcome Measure:

Measure Title	Number of Participants With a Specific Histological Pattern of the Endometrium Following 1 Cycle With Gonal-f®
Measure Description	Participants with each histological pattern of endometrium were analyzed. Histological patterns included: Proliferative phase (described as the endometrial on the first two weeks after the menstruation [or before ovulation]), Early secretory phase (first step of the secretory phase, located at the Day 16-18 of the cycle) and Intermediate secretory phase (secretory phase located at the Day 20-22 of the cycle and describes endometrial closer to the implantation phase).

Time Frame	Day of Oocyte Retrieval (36 +/- 2 hours post r-hCG administration) after COS by Gonal-f®
Safety Issue?	No

Analysis Population Description

Intention-to-Treat (ITT) population: participants who received at least 1 dose of study drug. "N" (number of participants analyzed) signifies participants evaluable for this measure. Results for both agonist and antagonist protocol are presented as total since assessment of histological pattern for whole study population was the primary objective.

Reporting Groups

	Description
Gonal-f® + Ovitrelle®	Participants received 150 IU per day of r-hFSH (Gonal-F®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm [for both long agonist and multi-dose antagonist protocol], and with E2>1 mcg/L [for long agonist protocol]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation, either 0.1 mg GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) in long agonist protocol or 0.25 mg GnRH antagonist daily was started from Day 6 of GONAL-f® stimulation treatment in multi-dose antagonist protocol, as per SmPC.

Measured Values

	Gonal-f® + Ovitrelle®
Number of Participants Analyzed	23
Number of Participants With a Specific Histological Pattern of the Endometrium Following 1 Cycle With Gonal-f® [units: participants]	
Proliferative phase	2
Early secretory phase	15
Intermediate secretory phase	6

3. Secondary Outcome Measure:

Measure Title	Gene Expression of the Endometrium in Participants With or Without Blastocyst Transfer
Measure Description	A list of genes based on gene expression profiling carried out on RNA extracted from endometrial tissue. The expression of mRNA in endometrial tissue was measured by using microarrays such as the Affymetrix® GeneChip HG-U133 plus 2.0 array or equivalent.

Time Frame	Day of Oocyte Retrieval (36 +/- 2 hours post r-hCG administration) after COS by Gonal-f®
Safety Issue?	No

Analysis Population Description

Data were not analyzed because gene expression of the endometrium could not be performed due to poor quality of biopsy samples and poor recruitment in the study.

Reporting Groups

	Description
Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Participants received 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH, Gonal-f®) subcutaneously (sc) starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 microgram (mcg) recombinant human chorionic gonadotropin alfa (r-hCG alfa, Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles greater than [>] 16 millimeter [mm], and with estradiol [E2] >1 microgram per liter [mcg/L]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Participants received 150 IU per day of r-hFSH (Gonal-f®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm). To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily was started from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Measured Values

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

4. Secondary Outcome Measure:

Measure Title	Gene Expression of the Endometrium Following 1 Cycle With Gonal-f® in Participants Having Undergone Agonist or Antagonist Protocol
Measure Description	A list of genes based on gene expression profiling carried out on RNA extracted from endometrial tissue. The expression of mRNA in endometrial tissue was measured by using microarrays such as the Affymetrix® GeneChip HG-U133 plus 2.0 array or equivalent.
Time Frame	Day of Oocyte Retrieval (36 +/- 2 hours post r-hCG administration) after COS by Gonal-f®
Safety Issue?	No

Analysis Population Description

Data were not analyzed because gene expression of the endometrium could not be performed due to poor quality of biopsy samples and poor recruitment in the study.

Reporting Groups

	Description
Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Participants received 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH, Gonal-f®) subcutaneously (sc) starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 microgram (mcg) recombinant human chorionic gonadotropin alfa (r-hCG alfa, Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles greater than [>] 16 millimeter [mm], and with estradiol [E2] >1 microgram per liter [mcg/L]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Participants received 150 IU per day of r-hFSH (Gonal-f®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm). To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily was started from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Measured Values

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

5. Secondary Outcome Measure:

Measure Title	Number of Participants With a Specific Histological Pattern of the Endometrium Following 1 Cycle With Gonal-f® and Having Undergone Agonist or Antagonist Protocol
Measure Description	Participants with each histological pattern of endometrium were analyzed. Histological patterns included: Proliferative phase (described as the endometrial on the first two weeks after the menstruation [or before ovulation]), Early secretory phase (first step of the secretory phase, located at the Day 16-18 of the cycle), Intermediate secretory phase (secretory phase located at the Day 20-22 of the cycle and describes endometrial closer to the implantation phase).
Time Frame	Day of Oocyte Retrieval (36 +/- 2 hours post r-hCG administration) after COS by Gonal-f®
Safety Issue?	No

Analysis Population Description

ITT population included those participants who received at least one dose of study medication. Here "N" (number of participants analyzed) signifies those participants who were evaluable for this measure.

Reporting Groups

	Description
Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Participants received 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH, Gonal-f®) subcutaneously (sc) starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 microgram (mcg) recombinant human chorionic gonadotropin alfa (r-hCG alfa, Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles greater than [>] 16 millimeter [mm], and with estradiol [E2] >1 microgram per liter [mcg/L]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Participants received 150 IU per day of r-hFSH (Gonal-f®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm). To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily was started from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Measured Values

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
Number of Participants Analyzed	12	11
Number of Participants With a Specific Histological Pattern of the Endometrium Following 1 Cycle With Gonal-f® and Having Undergone Agonist or Antagonist Protocol [units: participants]		
Proliferative phase	1	1
Early secretory phase	8	7
Intermediate secretory phase	3	3

6. Secondary Outcome Measure:

Measure Title	Gene Expression in Participants Without Blastocyst Transfer

Measure Description	A list of genes based on gene expression profiling carried out on RNA extracted from endometrial tissue. The expression of mRNA in endometrial tissue was measured by using microarrays such as the Affymetrix® GeneChip HG-U133 plus 2.0 array or equivalent.
Time Frame	Day 5 or 6 (window of implantation) after Oocyte Retrieval
Safety Issue?	No

Analysis Population Description

Data were not analyzed because gene expression of the endometrium could not be performed due to poor quality of biopsy samples and poor recruitment in the study.

Reporting Groups

	Description
Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Participants received 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH, Gonal-f®) subcutaneously (sc) starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 microgram (mcg) recombinant human chorionic gonadotropin alfa (r-hCG alfa, Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles greater than [>] 16 millimeter [mm], and with estradiol [E2] >1 microgram per liter [mcg/L]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Participants received 150 IU per day of r-hFSH (Gonal-f®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm). To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily was started from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Measured Values

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

7. Secondary Outcome Measure:

Measure Title	Number of Participants With a Specific Histological Pattern of the Endometrium in Participants Without Blastocyst Transfer

Measure Description	Participants with each histological pattern of endometrium were analyzed. Histological patterns included: Proliferative phase (described as the endometrial on the first two weeks after the menstruation [or before ovulation]), Early secretory phase (first step of the secretory phase, located at the Day 16-18 of the cycle), Intermediate secretory phase (secretory phase located at the Day 20-22 of the cycle and describes endometrial closer to the implantation phase).
Time Frame	Day 5 or 6 (window of implantation) after Oocyte Retrieval
Safety Issue?	No

Analysis Population Description

ITT population: participants who received at least one dose of study medication. "N" (number of participants analyzed) signifies participants who were evaluable for this measure. Data were not analyzed for Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol) group because there were no participants without blastocyst transfer in this group.

Reporting Groups

	Description
Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Participants received 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH, Gonal-f®) subcutaneously (sc) starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 microgram (mcg) recombinant human chorionic gonadotropin alfa (r-hCG alfa, Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles greater than [>] 16 millimeter [mm], and with estradiol [E2] >1 microgram per liter [mcg/L]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Participants received 150 IU per day of r-hFSH (Gonal-f®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm). To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily was started from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Measured Values

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
Number of Participants Analyzed	2	0
Number of Participants With a Specific Histological Pattern of the Endometrium in Participants Without Blastocyst Transfer [units: participants]		
Proliferative phase	0	
Early secretory phase	0	

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
Intermediate secretory phase	2	

8. Secondary Outcome Measure:

Measure Title	Gene Expression in Participants With Good or Poor Response to Gonal-f®
Measure Description	A list of genes based on gene expression profiling carried out on RNA extracted from endometrial tissue. The expression of mRNA in endometrial tissue was measured by using microarrays such as the Affymetrix® GeneChip HG-U133 plus 2.0 array or equivalent. Participants with poor response: 5 mature oocytes or less; participants with good response: more than 8 mature oocytes.
Time Frame	Day of Oocyte Retrieval (36 +/- 2 hours post r-hCG administration) after COS by Gonal-f®
Safety Issue?	No

Analysis Population Description

Data were not analyzed because gene expression of the endometrium could not be performed due to poor quality of biopsy samples and poor recruitment in the study.

Reporting Groups

	Description
Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Participants received 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH, Gonal-f®) subcutaneously (sc) starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 microgram (mcg) recombinant human chorionic gonadotropin alfa (r-hCG alfa, Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles greater than [>] 16 millimeter [mm], and with estradiol [E2] >1 microgram per liter [mcg/L]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Participants received 150 IU per day of r-hFSH (Gonal-f®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm). To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily was started from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Measured Values

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

9. Secondary Outcome Measure:

Measure Title	Number of Participants With a Specific Histological Pattern of the Endometrium in Participants With Good or Poor Response to Gonal-f®
Measure Description	Participants with each histological pattern of endometrium were analyzed. Histological patterns included: Proliferative phase (described as the endometrial on the first two weeks after the menstruation [or before ovulation]), Early secretory phase (first step of the secretory phase, located at the Day 16-18 of the cycle), Intermediate secretory phase (secretory phase located at the Day 20-22 of the cycle and describes endometrial closer to the implantation phase). Participants with poor response: 5 mature oocytes or less; participants with good response: more than 8 mature oocytes.
Time Frame	Day of Oocyte Retrieval (36 +/- 2 hours post r-hCG administration) after COS by Gonal-f®
Safety Issue?	No

Analysis Population Description

Data for histological pattern of the endometrium in participants with good or poor response to Gonal-f were not summarized because the number of participants in each group with respect to ovarian response were too low.

Reporting Groups

	Description
Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Participants received 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH, Gonal-f®) subcutaneously (sc) starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 microgram (mcg) recombinant human chorionic gonadotropin alfa (r-hCG alfa, Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles greater than [>] 16 millimeter [mm], and with estradiol [E2] >1 microgram per liter [mcg/L]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Participants received 150 IU per day of r-hFSH (Gonal-f®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm). To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily was started from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Measured Values

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
Number of Participants Analyzed	0	0

No data displayed because Outcome Measure has zero total participants analyzed.

Reported Adverse Events

Time Frame	Up to 15 days after the last Investigational Medicinal Product (IMP) administration or early termination
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 emerge or worsen relative to baseline during a clinical study with an IMP, regardless of causal relationship and even if no IMP has been administered.

Reporting Groups

	Description
Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Participants received 150 International Units (IU) per day of recombinant human follicle stimulating hormone (r-hFSH, Gonal-f®) subcutaneously (sc) starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 microgram (mcg) recombinant human chorionic gonadotropin alfa (r-hCG alfa, Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles greater than [>] 16 millimeter [mm], and with estradiol [E2] >1 microgram per liter [mcg/L]). To prevent premature ovulation in participants undergoing a controlled ovarian stimulation (COS), 0.1 milligram (mg) GnRH agonist daily was started after endometrial biopsy, 7 days after the peak day of luteinizing hormone (Day LH + 7) as per summary of product characteristics (SmPC), in long agonist protocol.
Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)	Participants received 150 IU per day of r-hFSH (Gonal-f®) sc starting from Day 2 of menstrual cycle until follicles were recruited and developed. Ovulation triggering was performed with a single dose of 250 mcg r-hCG alfa (Ovitrelle®) sc, as soon as follicles satisfied the criteria for follicular development (at least 3 follicles >16 mm). To prevent premature ovulation in participants undergoing a COS, 0.25 mg GnRH antagonist daily was started from Day 6 of Gonal-f® stimulation treatment as per SmPC, in multi-dose antagonist protocol.

Serious Adverse Events

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
	Affected/At Risk (%)	Affected/At Risk (%)
Total	0/13 (0%)	0/11 (0%)

Other Adverse Events

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

	Gonal-f® + Ovitrelle® (Long Agonist Protocol)	Gonal-f® + Ovitrelle® (Multi-dose Antagonist Protocol)
	Affected/At Risk (%)	Affected/At Risk (%)
Total	2/13 (15.38%)	1/11 (9.09%)
Gastrointestinal disorders		
Abdominal pain [A] *	1/13 (7.69%)	0/11 (0%)
Reproductive system and breast disorders		
Ovarian hyperstimulation syndrome [A] *	1/13 (7.69%)	0/11 (0%)
Pelvic pain [A] *	0/13 (0%)	1/11 (9.09%)

* Indicates events were collected by non-systematic methods.

A Term from vocabulary, MedDRA 13.1

Limitations and Caveats

Gene expression of the endometrium could not be analyzed due to poor quality of biopsy samples (poor mRNA quality) and poor recruitment in the study.

More Information

Certain Agreements:

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

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

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