A phase III, randomized, controlled, single-blind, multicentre, parallel arm trial to assess the efficacy and safety of Pergoveris® (follitropin alfa and lutropin alfa) and GONAL-f® (follitropin alfa) for multifollicular development as part of an assisted reproductive technology treatment cycle in poor ovarian responders, as defined by the European Society of Human Reproduction and Embryology criteria

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The primary objective of the trial is to demonstrate superiority of Pergoveris® versus GONAL-f® in poorovarian response (POR) patients defined according to modified criteria set forth by the European Society of Human Reproduction and Embryology (...

Ethical review	Approved WMO
Status	Pending
Health condition type	Ovarian and fallopian tube disorders
Study type	Interventional

Summary

ID

NL-OMON40576

Source
ToetsingOnline

Brief title
ESPART (Evaluating the Efficacy and Safety of Pergoveris® in ART)

Condition

- Ovarian and fallopian tube disorders

Synonym
infertility, poor ovarian responders

Research involving
Human

Sponsors and support

Primary sponsor: Merck
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: GONAL-f, Pergoveris, Phase III, poor ovarian responders

Outcome measures

Primary outcome

The primary endpoint of the trial will be the total number of retrieved oocytes per subject. This endpoint reflects the clinical response to the stimulation and the subsequent success of infertility treatment in terms of onset of pregnancy. Oocyte retrieval takes place at Visit 12.

Secondary outcome

The secondary endpoints for the trial will be:

• Ongoing pregnancy rate defined as the percentage of subjects with a transvaginal US confirmation of at least one viable fetus (positive fetal heart beat) performed at Visit 16.

• Live birth rate defined as the percentage of subjects with at least 1 live born neonate (Visit 17).

• Embryo implantation rate defined as the number of gestational sacs divided by

the number of embryos transferred per subject. This is determined at Visit 15.

• Clinical pregnancy rate defined as the percentage of subjects with a transvaginal US confirmation of a gestational sac, with or without fetal heart activity performed at Visit 15.

• Biochemical pregnancy rate defined as a positive beta-human chorionic gonadotrophin (β-hCG) result from the serum pregnancy test performed at Visit 14.

Study description

Background summary

Follicle-stimulating hormone (FSH) is used for the stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ARTs), such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), gamete intra-fallopian transfer, and zygote intra-fallopian transfer. As noted in the GONAL-f® Summary of Product Characteristics (SmPC), the standard treatment for multifollicular development in ART involves the administration of 150-225 international units (IU) of recombinant human follicle stimulating hormone (follitropin alfa) (r-hFSH) daily for the first days of treatment. Treatment is continued until adequate follicular development has been achieved, with the dose being adjusted according to a patient's response, to usually not higher than 450 IU daily. In the general non-selected population, adequate follicular development is achieved, on average, by the tenth day of treatment (range: 5 to 20 days). A single injection of 250 µg recombinant human chorionic gonadotrophin (r-hCG) or 5,000 IU up to 10,000 IU urinary-human chorionic gonadotrophin (hCG) is administered 24 to 48 hours after the last GONAL-f® injection to induce final follicular maturation. Down-regulation with a GnRH agonist or antagonist is commonly used to suppress the endogenous LH surge and to control tonic levels of LH.

Study objective

The primary objective of the trial is to demonstrate superiority of Pergoveris® versus GONAL-f® in poor
ovarian response (POR) patients defined according to modified criteria set

forth by the European Society of Human Reproduction and Embryology (ESHRE).

Study design

This is a phase III, randomized, controlled, single-blind, multicenter, parallel-arm trial to assess the safety and efficacy of Pergoveris® and GONAL-f® for multifollicular development as part of an assisted reproductive technology (ART) treatment cycle in poor ovarian responders, as defined by the ESHRE criteria.

Following signature of informed consent, the screening period (Visit 1) will be performed within 6 weeks prior to the start of the trial cycle. Once subject eligibility is confirmed, the subject will be enrolled in the trial. Pituitary down-regulation (Visit 2) with a gonadotrophinreleasing hormone (GnRH) agonist (triptorelin acetate) will be self-administered daily in subjects with spontaneous menses after ovulation and in anovulatory or oligo-ovulatory subjects with induced menses. In the case of the former, the GnRH agonist should start on cycle day 20-21 after confirmed ovulation. In the case of induced menses, the GnRH agonist will be started on cycle day 3-4 of induced menses.
Confirmation of down-regulation (Visit 3) will be assessed after at least 14 days of triptorelin acetate treatment (Visit 3a) with a serum E2 level of <= 50 pg/mL. If down-regulation is not confirmed, treatment with triptorelin acetate is authorized for an additional 7 days (maximum of 21 days of total triptorelin acetate treatment during this portion of the treatment protocol), and if the E2 is <= 50 pg/mL, down-regulation is confirmed (Visit 3b). If E2 is > 50 pg/mL, the subject will be excluded from further treatment and the trial. Ovarian stimulation (Visit 4) will begin within 4 days after down-regulation has been achieved and will continue for up to 21 days (Visits 5 - 10). Patient response to ovarian stimulation will be monitored according to the center*s standard criteria. Triptorelin acetate administration will be continued in subjects with confirmation of down-regulation until r-hCG administration. A single injection of 250 µg recombinant human chorionic gonadotrophin (r-hCG) will be administered to trigger final follicular maturation (Visit 11). Oocyte retrieval (Visit 12) will be performed vaginally under ultrasound (US) monitoring approximately 34-38 hours after receiving r-hCG. Oocyte and embryo quality assessments will be performed according to the criteria provided by the sponsor. In vitro fertilization or intracytoplasmic sperm injection (ICSI) and embryo transfer (ET) will be performed according to each subject*s specific requirements and the center*s standard practice. Embryo transfer (Visit 13) will be scheduled between 2 to 3 days following oocyte retrieval unless country-specific regulations dictate other requirements, which will then be recorded in the patient case report form. The number of embryos transferred will be dictated by local regulations. No more than 3 embryos will be transferred.
Luteal phase support will begin 24-48 hours after oocyte retrieval and will continue in subjects with clinical pregnancy for at least 7 weeks unless

miscarriage occurs. Follow-up of all subjects will occur day 15 to 20 following r-hCG administration for a serum pregnancy test (biochemical pregnancy) (Visit 14).
Pregnancy outcome will be determined for all subjects with a positive serum pregnancy test. All subjects with a positive pregnancy test and who do not experience an early miscarriage will undergo vaginal US examination between 35 and 42 days post r-hCG administration to assess the number of fetal sacs with or without fetal heart activity (clinical pregnancy determination, Visit 15).
Ten weeks after ET, ongoing pregnancy (at least 1 viable fetus with positive heart activity, Visit 16) will be assessed via vaginal US examination in all subjects who do not experience a miscarriage after confirmation of a clinical pregnancy. The outcome of ongoing pregnancy will be determined approximately 6 months later (live birth determination, follow-up Visit 17). This pregnancy outcome/delivery data will be collected and recorded after the completion of the trial. A separate, all-inclusive addendum report of the pregnancy outcome delivery data will be a supplemental report to the Pergoveris® in POR ART Trial Report. Adverse events and ovarian hyper stimulation syndrome (OHSS)-related symptoms will be assessed throughout the trial to monitor safety. Safety will also be evaluated through physical examination, vital signs, urinalysis, and hematology and clinical chemistry assessments. Local tolerability, as assessed through injection site reactions included in the label, will be documented.

Intervention

The investigational medicinal product is Pergoveris®.
Pergoveris® will be self-administered daily subcutaneously (SC) by the subject.
The reference therapy is GONAL-f®. GONAL-f® will be self-administered daily SC by the
subject.

Study burden and risks

The majority of ART patients benefit from FSH-only ovarian stimulation. However, some patients exhibit POR to FSH, which manifests as reduced follicular response, resulting in a reduced number of retrieved oocytes and a decreased likelihood of obtaining multiple embryos for transfer. Poor ovarian responders may undergo multiple unsuccessful ART treatment cycles due to inadequate follicular response, repeated cycle cancellation, or lack of pregnancy.

The trial concept reflects current clinical practice, which has been verified during the feasibility assessment phase for this trial. Furthermore, reports in the literature have documented the existence of a group of patients in whom treatment with exogenous r-hFSH alone at starting doses of 225 IU and higher and with appropriate dose increases according to the patient*s response result in development and retrieval of few oocytes, resulting in low number of embryos

available for transfer. Such patients can be characterized by having a previous cycle with limited pre-ovulatory follicles or oocytes; and/or having an abnormal Ovarian reserve test; and/or being of advanced maternal age or according to the ESHRE criteria for POR. The conventional approach of increasing FSH dose to improve follicular response appears to be ineffective in these patients. Supplementation with LH (or LH activity-containing formulations, such as human menopausal gonadotropins) has been widely used and reported in the literature as beneficial due to the pharmacological action of LH.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The current trial will enroll poor ovarian responders as aligned with the 2011 Consensus

meeting of the ESHRE.
1. Subject must be a poor responder
Additional inclusion criteria are:
2. Female subjects, 18 to < 41 years of age (according to date of birth at time of informed consent) who are eligible for ovarian stimulation and ART treatment, including ICSI
3. Absence of anatomical abnormalities of the reproductive tract that would interfere with implantation or pregnancy
4. Absence of any medical condition in which pregnancy is contraindicated
5. Body mass index 18 to 30 kg/m2, inclusive
6. Motile, ejaculatory sperm must be available (donated and/or cryopreserved sperm is allowed). Intracytoplasmic sperm injection will be allowed during this trial.
7. Minimum of 1 month without treatment with either clomiphene citrate or gonadotrophins prior to screening

Exclusion criteria

1. Primary ovarian failure
2. Preimplantation genetic screening or diagnosis
3. Two episodes of POR after maximal stimulation
4. History or presence of tumors of the hypothalamus or pituitary gland
5. History or presence of ovarian enlargement or cyst of unknown etiology, or presence of an ovarian cyst > 25 mm on the day of randomization
6. Presence of endometriosis grade III - IV, confirmed or suspected
7. Presence of uni- or bilateral hydrosalpinx
8. Abnormal gynecological bleeding of undetermined origin
9. Contraindication to being pregnant and/or carrying a pregnancy to term
10. History or presence of ovarian, uterine or mammary cancer
11. Use of testicular or epididymal sperm

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	22-04-2014
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Crinone
Generic name:	Progesterone
Product type:	Medicine
Brand name:	GONAL-f
Generic name:	follitropin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pergoveris
Generic name:	follitropin/lutropin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-01-2014
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	10-04-2014
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO	

Date:	24-04-2014
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	06-05-2014
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-08-2014
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-003817-16-NL
ClinicalTrials.gov	NCT02047227
CCMO	NL46583.075.13