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Efficacy and Safety of Pergoveris in Assisted Reproductive Technology—ESPART: rationale and design of a randomised controlled trial in poor ovarian responders undergoing IVF/ICSI treatment

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ABSTRACT

Introduction: The results of a recent meta-analysis showed that adding recombinant human luteinising hormone (r-hLH) to recombinant human follicle-stimulating hormone (r-hFSH) for ovarian stimulation was beneficial in poor responders, resulting in a 30% relative increase in the clinical pregnancy rate compared with r-hFSH monotherapy. However, a limitation of the meta-analysis was that the included studies used heterogeneous definitions of poor ovarian response (POR). Furthermore, the use of r-hLH supplementation during ovarian stimulation is a topic of ongoing debate, and well-designed, adequately powered, multicentre, randomised controlled trials in this setting are warranted. Therefore, the objective of the ESPART trial is to explore the possible superiority of a fixed-dose combination of r-hFSH plus r-hLH over r-hFSH monotherapy in patients with POR, as per a definition aligned with the European Society of Human Reproduction and Embryology (ESHRE) Bologna criteria.

Methods and analysis: Phase III, randomised, single-blind, parallel-group trial in women undergoing *in vitro* fertilisation and/or intracytoplasmic sperm injection. Approximately 946 women aged 18–<41 years from 18 countries will be randomised (1:1) to receive a fixed-dose combination of r-hFSH plus r-hLH in a 2:1 ratio (Pergoveris) or r-hFSH monotherapy (GONAL-f). The primary end point is the total number of retrieved oocytes per participant. Secondary end points include: ongoing pregnancy rate, live birth rate, implantation rate, biochemical pregnancy rate and clinical pregnancy rate. Safety end points include: incidence and severity of ovarian hyperstimulation syndrome, and of adverse events and serious adverse events.

Ethics and dissemination: The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki, with the International Conference on Harmonisation–Good Clinical Practice guidelines and all applicable regulatory requirements. All participants will provide written informed consent prior to entry. The results of this study will be publically disseminated.

Trial registration numbers: ClinicalTrials.gov identifier: NCT02047227; EudraCT Number: 2013-003817-16; Clinical Trial Protocol Number: EMR200061-005 V.3.0, 15 April 2014.

Strengths and limitations of this study

- To the authors' knowledge, the ESPART study will be the largest randomised controlled trial (RCT) conducted in women with poor ovarian response (POR). Furthermore, it is the first phase III study with a superiority design to evaluate the possible advantage of the addition of recombinant human luteinising hormone to recombinant human follicle-stimulating hormone for controlled ovarian stimulation in this patient population.
- The ESPART study fulfils the criteria of a robust, well-designed RCT, which uses a definition of POR that is consistent with the Bologna criteria.
- Although the ESPART study will recruit women with POR, as aligned with the Bologna criteria, clinical heterogeneity will still exist within this population of women. This may be mitigated by the large sample size and the stratified randomisation of women to treatment according to age and study site.

INTRODUCTION

Data indicate that one in six couples worldwide will experience an infertility problem at least once during their reproductive years.[1] *In vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) are commonly employed methods of assisted reproductive

technology (ART) for the treatment of infertility. Outcome rates with these techniques are comparable; in Europe, in 2011, the mean rates of pregnancy per embryo transfer were 33.2% and 31.6%, following IVF and ICSI, respectively.[1]

Currently, two recombinant forms of human FSH (follitropin alfa and follitropin β) are commercially available for controlled ovarian stimulation.[2]

While a majority of patients treated with r-hFSH monotherapy for assisted reproduction will benefit from treatment, as many as 26% will exhibit a poor ovarian response (POR).[3] Although the ideal treatment protocol for patients with a poor response to ovarian stimulation is yet to be identified, there is evidence to suggest that supplementation of r-hFSH with recombinant human luteinising hormone (r-hLH) may be beneficial in this population of women. Hypothetically, this is attributed to the widespread use of protocols utilising r-hFSH (with no LH activity), accompanied by observations of substantially lower LH concentrations than those observed with previously used protocols and during the natural menstrual cycle.[4] Data from a recently conducted meta-analysis including a total of 43 studies and 6443 patients overall showed that the addition of r-hLH to r-hFSH was beneficial in poor responders to ovarian stimulation (14 studies, n=1179), resulting in a 30% relative increase in the clinical pregnancy rate, compared with r-hFSH monotherapy.[5] The supplementation of r-hFSH with r-hLH in poor responders also led to a significant increase in the number of oocytes retrieved and the ongoing pregnancy rate. Moreover, a non-significant increase in the live birth rate was observed.[5] Data from a meta-analysis performed prior to that of Lehert *et al* showed that in patients of advanced reproductive age (a population likely to comprise a larger proportion of poor responders), the addition of r-hLH to r-hFSH improved the implantation and clinical pregnancy rates, compared with r-hFSH monotherapy.[6]

Despite these findings, the use of r-hLH supplementation during controlled ovarian stimulation remains a topic of ongoing debate. The results of several earlier meta-analyses conducted in general ART populations indicate that supplementation with r-hLH offers no benefit in terms of clinically significant end points in IVF/ICSI cycles, including the number of oocytes retrieved, the number of mature oocytes and the rates of implantation, pregnancy, miscarriage and/or live births.[4 7–9] Reasons for this may include insufficient numbers of patients, which is in contrast to the large number of studies and patients analysed by Lehert *et al* in 2014. Given the conflicting data regarding the use of LH supplementation during controlled ovarian stimulation, particularly regarding the target population and optimal treatment agent, it is widely agreed that well-designed, adequately powered, multicentre, randomised controlled trials (RCTs) are warranted in this setting.[4 7–10] To this end, the Efficacy and Safety of Pergoveris in Assisted Reproductive Technology (ESPART) trial has been initiated. The objective of the ESPART trial is to explore the possible superiority of a fixed-dose combination of r-hFSH plus r-hLH in a 2:1 ratio over r-hFSH monotherapy in patients with a POR, as per a definition aligned with the European Society of Human Reproduction and Embryology (ESHRE) Bologna criteria.[11] The design of and rationale for the ESPART trial are described in the current report.

METHODS

Study design

ESPART is an ongoing phase III, multicentre, single-blind, parallel-group RCT (ClinicalTrials.gov identifier: NCT02047227; EudraCT Number: 2013-003817-16). The ESPART trial, which is being conducted at more than 90 sites in 18 European countries, has been specifically designed to compare the efficacy and safety of controlled ovarian stimulation with a fixed-dose combination of r-hFSH plus r-hLH in a 2:1 ratio with r-hFSH monotherapy for multifollicular development in poor ovarian responders, as per a definition aligned with the Bologna criteria. The study is being performed in accordance with the clinical trial protocol, with ethical principles that have their origin in the Declaration of Helsinki, with the International Conference on Harmonisation–Good Clinical Practice guidelines and all applicable regulatory requirements. All participants in the ESPART study will provide written informed consent prior to entry.

Study participants

In order to participate in the study, women will be required to meet the following inclusion criteria: age 18–<41 years; body mass index 18–30 kg/m^2; eligibility for controlled ovarian stimulation and ART treatment (including ICSI); anticipated and/or confirmed POR to stimulation, using criteria aligned with the 2011 ESHRE Bologna criteria,[11] that is, at least two of the following three features: advanced maternal age (40–41 years); a previous cycle with ≤3 oocytes retrieved with a conventional stimulation protocol; and/or an abnormal ovarian reserve test (ORT) characterised by an anti-Müllerian hormone level (AMH) greater than or equal to the lower limit of assay detection to 1.3 ng/mL (inclusive); access to motile, ejaculatory sperm (including donated and/or cryopreserved sperm); and no treatment with clomiphene citrate or gonadotropins for ≥1 month prior to screening. Specific exclusion criteria include: primary ovarian failure; preimplantation genetic screening or diagnosis; two episodes of POR after maximal stimulation; history or presence of tumours of the hypothalamus or pituitary gland; history or presence of ovarian enlargement or cysts of unknown aetiology; presence of an ovarian cyst >25 mm on the day of randomisation; presence of confirmed or suspected Grade III–IV endometriosis; presence of unilateral or bilateral hydrosalpinx; abnormal gynaecological bleeding of

undetermined origin; malformation of the sexual organs incompatible with pregnancy; contraindication to being pregnant and/or carrying a pregnancy to term; currently pregnant; presence of a clinically significant concurrent medical condition (eg, diabetes) that would compromise participant safety or interfere with the trial assessments; known infection with HIV or active hepatitis B or C virus (including in the male partner); history or presence of ovarian, uterine or mammary cancer; known allergy or hypersensitivity to human gonadotropin preparations or to compounds structurally similar to any of the other medications administered during the trial; substance abuse that would interfere with the trial conduct; use of testicular or epididymal sperm; and/or participation in another ART clinical trial within the preceding 30 days.

Study treatments and interventions

Patients in the ESPART study will be enrolled for a maximum duration of 365 days, involving 17 clinic visits. Following screening (visit 1), eligible patients will initiate pituitary downregulation (visit 2) with daily triptorelin acetate (Decapeptyl; Ferring Pharmaceuticals, Saint-Prex, Switzerland) at a dose of 0.1 mg; treatment will be self-administered via subcutaneous injection and will start on day 20–21 of a normal cycle or on cycle day 3–4 of progesterone-induced menses in anovulatory or oligo-ovulatory patients. Within 4 days of confirmation of pituitary downregulation (serum oestradiol level ≤50 pg/mL after ≥14 but ≤21 days of triptorelin acetate (visits 3a and 3b)) and following a negative pregnancy test, patients will be randomised (1:1) to receive controlled ovarian stimulation with either a fixed-dose combination of r-hFSH 300 IU plus r-hLH 150 IU (follitropin alfa and lutropin alfa in a 2:1 ratio; Pergoveris; EMD Serono, Inc, Rockland, Massachusetts, USA) or r-hFSH 300 IU monotherapy (follitropin alfa; GONAL-f; EMD Serono, Inc, Rockland, Massachusetts, USA) (visit 4). Both treatment regimens, which will be administered concomitantly with daily triptorelin acetate, will be delivered subcutaneously at approximately the same time each day; study participants will be instructed on how to self-administer treatment, with the first dose to be administered at the clinic under supervision. Patients will be seen every 2–3 days from stimulation day 5–21 (visits 5–10). During this time, adjustments in the dose of r-hFSH will be made if clinically required, as monitored by study investigators; adjustments (increases or decreases) will be allowed in 75 IU increments (with concomitant automatic adjustment of r-hLH in participants treated with combination treatment in order to maintain a r-hFSH:r-hLH ratio of 2:1). The maximum daily dose of r-hFSH shall not exceed 450 IU. When follicle(s) reach a mean diameter of 17–18 mm, patients will receive a single injection of recombinant human chorionic gonadotropin (r-hCG; choriogonadotropin alfa; Ovidrel/Ovitrelle, EMD Serono, Inc, Rockland, Massachusetts, USA) at a dose of 250 µg, to induce final follicular maturation (visit 11). Approximately 34–38 h later, oocytes will be retrieved vaginally under ultrasound monitoring (visit 12) and IVF or ICSI will be performed. Embryos (no more than three) will be transferred 2–3 days following oocyte retrieval (visit 13). The procedures used for IVF, ICSI and embryo transfer as well as the total number of embryos transferred will depend on the study site's standard practices and/or local and country-specific regulations. Support of the luteal phase will be achieved using intravaginal 8% progesterone gel (Crinone; Fleet Laboratories Ltd, Watford, UK); treatment will be self-administered on a once-daily basis using single-use prefilled applicators containing a progesterone dose of 90 mg. Treatment will start within 48 h after oocyte retrieval and will continue for ≥7 weeks (unless miscarriage occurs) in participants with a clinical pregnancy.

Participants will be discontinued from the trial in the following situations: a lack of pituitary downregulation within 21 days of triptorelin acetate treatment; a lack of an appropriate response to controlled ovarian stimulation (ie, no follicles ≥12 mm and endometrial thickness ≤4 mm after 8 days of treatment and/or a clinically significant decrease in oestradiol levels for two consecutive days/visits); and an excessive response to controlled ovarian stimulation (indicating a risk of ovarian hyperstimulation syndrome).

Randomisation (1:1) to r-hFSH plus r-hLH or r-hFSH monotherapy will be stratified by study site and participant age (<35 or ≥35 years). When a participant is eligible for randomisation, the unblinded personnel at each investigator's site will contact an interactive voice response system (Cenduit GmbH, Switzerland) and treatment will be assigned accordingly. As per the single-blind nature of the study, investigators and site personnel (eg, assessing physicians, ultrasonographers, embryologists, etc) will remain blinded to the treatment regimen patients are receiving; trial nurses or pharmacists will instruct participants on the correct preparation, handling and storage of all study treatments, including how to perform dose adjustments, if indicated. All study medications will be packaged in secondary containers and will be labelled specifically for the trial by a qualified packaging provider.

Study objectives and end points

The primary objective of the study is to demonstrate the superiority of a fixed-dose combination of r-hFSH plus r-hLH in a 2:1 ratio over r-hFSH monotherapy in patients with a POR, as per a definition aligned with the ESHRE Bologna criteria. The primary end point is the total number of retrieved oocytes per participant. Secondary end points are as follows: ongoing pregnancy rate (percentage of participants with an ultrasound confirmation of ≥1 viable fetus (ie, positive fetal heart beat) performed 10±1 weeks after embryo transfer (visit 16)); live birth rate (percentage of participants with ≥1 live born neonate (visit 17); embryo implantation rate

(number of gestational sacs divided by the number of embryos transferred per participant at 35–42 days post-r-hCG administration (visit 15)); biochemical pregnancy rate (positive β-hCG result from a serum pregnancy test performed 15–20 days post-r-hCG administration (visit 14)); and clinical pregnancy rate (percentage of participants with an ultrasound confirmation of a gestational sac with or without fetal heart activity performed (visit 15)). Safety end points include: incidence and severity of ovarian hyperstimulation syndrome (OHSS; defined as the number of cases of OHSS during the ovarian stimulation period and their severity as assessed by the investigator) (visits 4–16); incidence of adverse events and serious adverse events (as assessed throughout the course of the trial); and local tolerability, including expected injection site reactions (pain, erythaema, haematoma, swelling and/or irritation at the injection site).

Statistical methods

Overall, 852 participants are planned to be enrolled to detect a difference of one retrieved oocyte between the two treatment arms, with a common SD of 4.5. Allowing for a drop-out rate of 10%, the total number of patients randomised to treatment is expected to be approximately 940, assuming an overall two-sided significance level of 0.05 and 90% power to detect the stated difference. A total of 1365 participants are expected to be screened to achieve a sample size of approximately 940 randomised patients.

Primary and secondary end points will be assessed in the modified intention-to-treat (ITT) population. Participants who do not undergo the oocyte retrieval process at visit 12 for other reasons (eg, withdrawal of consent, lost to follow-up), will have their number of oocytes retrieved counted as '0' for the analysis of the primary end point. Safety end points will be assessed in the safety population, which will be defined as all randomised participants who receive ≥1 dose of r-hFSH plus r-hLH or r-hFSH.

Depending on the distribution of the data, the primary efficacy variable will be analysed using either an analysis of variance (ANOVA) model (if the data are normally distributed) or a Poisson regression model (if the data are not normally distributed). Both models will include terms for treatment arm, site (or country or region) and age category.

Summary descriptive statistics will be used for all quantitative variables (eg, number of participants, number of missing values/participants, mean, SD, minimum, maximum, median, first quartile and third quartile. The frequency and percentage of participants and/or events will be calculated for all qualitative variables).

DISCUSSION

It is widely anticipated that with continued changes in the demographics of childbirth, an increasing proportion of women undergoing fertility treatment will exhibit a poor response to ovarian stimulation. Identifying suitable interventions that will improve outcomes in such women has proved challenging, owing to a lack of clarity about the causes and mechanisms of a POR, and to limitations in studies that have sought to address this unmet clinical need; such limitations include small patient populations, the use of diverse end points, inherent biases and/or a lack of consensus regarding the definition of a POR.[11–13]

The ESPART trial is an ongoing phase III, multicentre RCT that has been designed to compare the efficacy and safety of controlled ovarian stimulation with a fixed-dose combination of r-hFSH plus r-hLH in a 2:1 ratio against r-hFSH monotherapy for multifollicular development in women with a POR, as per a definition aligned with the ESHRE Bologna criteria. For a variety of compelling reasons, the ESPART study is expected to generate meaningful results that will enhance the overall quality of research in the field of assisted reproduction, improve treatment choices and benefit patients. First, it is the first phase III study with a superiority design to evaluate the possible advantage of supplemental r-hLH for controlled ovarian stimulation in women with a POR. Second, it likely represents the largest trial of its kind in women with or at risk of a POR; indeed, to the best of the authors' knowledge, the ESPART trial will include more than double the number of patients included in any other RCT that has compared r-hFSH plus r-hLH with r-hFSH monotherapy for multifollicular development in women undergoing IVF and/or ICSI, including RCTs in women with a POR.[5] Lastly, it uses a POR definition that is aligned with the ESHRE Bologna criteria.[11]

The ESHRE Bologna criteria were published in 2011 in an attempt to standardise the definition of a POR in a simple and reproducible manner, and to generate more homogeneous populations in which new treatment strategies could be tested and subsequently compared.[11] Since becoming available, the ESHRE Bologna criteria have been used to define women with a POR in several studies.[14–18] According to the criteria, a POR is defined as the presence of at least two of the following three features: advanced maternal age (≥40 years) or any other risk factor for POR; a previous POR (≤3 oocytes with a conventional stimulation protocol); and/or an ORT (ie, antral follicle count <5–7 or an AMH level <0.5–1.1 ng/mL). Women can also be considered poor responders in the absence of advanced maternal age or an abnormal ORT if they have experienced two episodes of POR after maximal stimulation.

It should be stressed that the definition of a POR in the current study is aligned with, but not identical to, the definition of a POR according to the ESHRE Bologna criteria so as to reduce heterogeneity of the patient population. First, a subset of patients qualified for POR based on the existence of advanced maternal age will not include patients aged >41 years (inclusive). Second, the presence of any other risk factor for POR is

not an inclusion criterion in the ESPART study. Third, an abnormal ORT will be based on the results of an AMH level greater than or equal to the lower limit of assay detection to 1.3 ng/mL inclusive. Finally, women will not be included (and indeed will be specifically excluded) if they have two episodes of POR after maximal stimulation. Furthermore, subjective criteria such as antral follicle count cannot be appropriately controlled and lack the reproducibility of quantifiable measurements such as serum AMH.

Although the ESHRE Bologna criteria establish a concept of minimum qualifying criteria for a POR, clinical heterogeneity, particularly in terms of baseline characteristics and clinical prognosis, is still possible within this population of women[19] and, by definition, within women in the current study. The suggested selection of patients in ESPART is intended to reduce such heterogeneity, which will also be mitigated by the large sample size and the stratified randomisation of women to treatment by age and investigation site.

As has been previously described, the use of LH supplementation during IVF/ICSI in women undergoing controlled ovarian stimulation is widely debated in the literature.[4–10] In particular, the population of women in whom LH supplementation may be beneficial remains a matter of debate. In this regard, the results of the recent meta-analysis by Lehert *et al*[5] suggest that the addition of r-hLH to r-hFSH may be beneficial in women with a POR. In order to confirm the results of this meta-analysis with a well-controlled, randomised phase III trial, this ESPART study was designed to answer the question of whether the addition of LH to controlled ovarian stimulation with FSH results in better cycle outcomes. With this in mind, and in order to demonstrate the additional benefit of adding LH to FSH in controlled ovarian stimulation, the clear comparator for the study is r-FSH alone. Supplementation with r-hLH will be initiated on day 1 of stimulation, which is in contrast with other studies, which have initiated LH on stimulation days 6–8 in patients with a POR.[20–24] The administration of r-hLH from stimulation day 1 is considered appropriate given that LH plays a key role in gonadal function from the early and mid-follicular phases, through to oocyte maturation and follicular luteinisation, and due to the fact that the LH receptor is present in follicles as small as 6 mm.[25 26]

Finally, we should mention that the standard treatment for multifollicular development in general ART populations involves the administration of r-hFSH at a dose of 150–225 IU for the first days of treatment,[27] but the starting dose of r-hFSH in the ESPART study will be 300 IU; the higher starting dose of r-hFSH used in the current study is consistent with the current clinical practice of using increased doses of gonadotropins in women with a POR.[28]

The ESPART trial was initiated in January 2014. Based on previous analyses, it is anticipated that the study results will show that a fixed-dose combination of r-hFSH and r-hLH in a 2:1 ratio during controlled ovarian stimulation is superior to r-hFSH monotherapy in women with a POR. The clinical importance of the study is considered to be high, owing to the paucity of well-designed, adequately powered, multicentre RCTs that have investigated the efficacy and safety of supplemental r-hLH in women undergoing controlled ovarian stimulation. Furthermore, because the study uses a POR definition that is aligned with the Bologna criteria, it supports the aim of the ESHRE to create more homogeneous populations in which new treatment strategies for POR can be tested and subsequently compared.

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Competing interests JS is an employee of EMD Serono Research & Development Institute, Inc.

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Notes