Sponsor name	Ferring Pharmaceuticals A/S
NCT Number	NCT06173869
Sponsor Trial ID	000413
Official Title of Study	A Randomised Trial Comparing the Ovarian Response of a Starting Dose of Either 10 µg or 15 µg Follitropin Delta (FE 999049) to a Starting Dose of Either 150 IU or 225 IU Follitropin Alfa (GONAL-F) in Conventional Regimens in China (COCO)
Document Date	19 October 2023

CLINICAL TRIAL PROTOCOL

A randomised, controlled, assessor-blind, parallel groups, multicentre trial comparing the ovarian response of a starting dose of either 10 µg or 15 µg follitropin delta (FE 999049) to a starting dose of either 150 IU or 225 IU follitropin alfa (GONAL-F) in conventional regimens in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme in China

Trial 000413

COCO

UTN Number:	U1111-1286-6882
Investigational Medicinal Product:	FE 999049, human recombinant follicle-stimulating hormone (rFSH), solution for subcutaneous injection
Indication:	Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle
Phase:	3b
Name and Address of Sponsor:	Ferring Pharmaceuticals A/S Amager Strandvej 405 2770 Kastrup, Denmark Tel: (+45) 88338834
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A randomised, controlled, assessor-blind, parallel groups, multicentre trial comparing the ovarian response of a starting dose of either 10 µg or 15 µg follitropin delta (FE 999049) to a starting dose of either 150 IU or 225 IU follitropin alfa (GONAL-F) in conventional regimens in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme in China

SIGNATORY INVESTIGATOR

Professor Yingpu Sun, 1st Affiliated Hospital of Zhengzhou University, No.1 Longhu Zhonghuan Road, Jinshui District, Zhengzhou, Henan, China

TRIAL SITES

Approximately 10-15 sites in China

CENTRAL LABORATORY

Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd, No. 338 Jialilue Road, Zhangjiang Hi-Tech Park, Shanghai, China

PLANNED TRIAL PERIOD		**CLINICAL PHASE**
First patient first visit (FPFV):	Q2 2024	3b
Last patient last visit (LPLV):	Q4 2025	
Pregnancy Follow-up:	Q2 2026	

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

Follitropin delta (FE 999049) is a novel human recombinant follicle-stimulating hormone (rFSH) derived from a human cell line (PER.C6®). It is intended for the development of multiple follicles during controlled ovarian stimulation in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle. The first Marketing Authorisation approval of FE 999049 (REKOVELLE) was obtained by the European Commission in December 2016. A Biological License Application was submitted to the National Medical Products Administration in China in December 2020 for approval of FE 999049 with a proposed dosing regimen based on each woman's serum anti-Müllerian hormone (AMH) concentration and her body weight.

As of 01 April 2023, a total of 14 clinical trials have been completed as part of the FE 999049 global development programme: five phase 1 trials, two phase 2 trials, and seven phase 3 trials. A

total of 4,878 subjects have been included in the completed clinical trials, of whom 3,269 subjects were exposed to FE 999049. Out of the seven phase 3 trials, trial 000145 has been conducted in China and included a total of 759 Chinese IVF or ICSI subjects, of whom 378 subjects were exposed to FE 999049. These subjects received an individual dose in accordance with their serum AMH concentration and body weight, with a maximum dose of 12 µg, and were treated with a gonadotropin-releasing hormone (GnRH) antagonist protocol.

In contrast to the current proposed dosing regimen for FE 999049 in China, approved rFSH preparations in China have a conventional dosing approach. Based on the current Chinese local clinical practice, Ferring intends to evaluate the use of FE 999049 in a conventional dosing approach i.e. a standard starting dose fixed for the initial days of stimulation, followed by the possibility for subsequent dose adjustments. The present trial will evaluate the efficacy and safety of FE 999049 in a conventional dosing approach in a long GnRH agonist protocol for pituitary downregulation, as this protocol is commonly used in Chinese clinical practice. The majority of clinical trial data with FE 999049 has been generated in the GnRH antagonist protocol, but the long GnRH agonist protocol is commonly used in Chinese clinical practice and therefore that downregulation protocol will be applied.

OBJECTIVES

Primary Objective

- To compare FE 999049 at a starting dose of either 10 µg or 15 µg to GONAL-F at a starting dose of either 150 IU or 225 IU in conventional regimens with respect to ovarian response in women undergoing controlled ovarian stimulation in a long GnRH agonist protocol

Secondary Objectives

- To compare the follicular development, endocrine profile and embryo development associated with conventional dosing of FE 999049 and GONAL-F
- To compare the treatment efficiency associated with conventional dosing of FE 999049 and GONAL-F
- To compare the safety profile associated with conventional dosing of FE 999049 and GONAL-F

ENDPOINTS

Primary Endpoint

- Number of oocytes retrieved

Secondary Endpoints

- Number of follicles (total and by size category) on stimulation day 6 and end-of-stimulation
- Serum concentrations of estradiol and progesterone on stimulation day 6 and end-of-stimulation
- Number of fertilised oocytes and fertilisation rate
- Number of embryos (total and by quality)
- Total gonadotropin dose and number of stimulation days
- Positive βhCG (positive serum βhCG test 13-15 days after transfer) rate
- Clinical pregnancy (at least one gestational sac 5-6 weeks after transfer) rate
- Vital pregnancy (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer) rate
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of embryos transferred)
- Ongoing pregnancy (at least one intrauterine viable fetus 10-11 weeks after transfer) rate
- Ongoing implantation rate (number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of embryos transferred)
- Early ovarian hyperstimulation syndrome (OHSS), late OHSS, and total OHSS (all overall and by grade)

Pregnancy Follow-up Endpoints

- Live birth rate
- Neonatal health, including minor/major congenital anomalies, at birth and at 4 weeks after birth

METHODOLOGY

This will be a randomised, controlled, assessor-blind, parallel groups, multicentre, non-inferiority trial comparing the ovarian response of FE 999049 and GONAL-F in conventional regimens, using a starting dose of either 10 µg or 15 µg FE 999049 or 150 IU or 225 IU GONAL-F, in women undergoing controlled ovarian stimulation for IVF or ICSI following treatment in a long GnRH agonist protocol. The trial has been designed to demonstrate non-inferiority of FE 999049

versus GONAL-F with the number of oocytes retrieved as the primary endpoint. Secondary endpoints include pharmacodynamic parameters of follicle-stimulating hormone (FSH) action as well as efficacy and safety parameters related to controlled ovarian stimulation. Treatment efficiency in terms of gonadotropin use and duration of stimulation will also be evaluated. The assessor-blind design ensures that the investigators and other assessors such as embryologists are blinded to individual treatment allocation. A trial medication delegate will be responsible for all trial medication related issues, both practically at the clinic and in interactions with the subject.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. A long GnRH agonist protocol will be used for pituitary downregulation; treatment with GnRH agonist (triptorelin acetate, DECAPEPTYL, Ferring), 0.1 mg/day, will be initiated in the mid-luteal phase (i.e. cycle day 21-24) of subject's menstrual cycle. A minimum of 10 days with GnRH agonist administration should be ensured prior to confirmation of downregulation, which is defined as fulfilling the following criteria: 1) menstrual bleeding, 2) shed endometrium with a thickness <5 mm observed by transvaginal ultrasound, and 3) no ovarian follicles ≥10 mm (including cysts that cannot be punctured prior to stimulation) observed by transvaginal ultrasound. In case achievement of downregulation is doubtful or it is deemed helpful, serum estradiol is to be measured (<50 pg/mL or 180 pmol/L; local laboratory). Once downregulation is confirmed, randomisation and start of stimulation must occur within 7 days. Treatment with GnRH agonist is to be continued after confirmation of downregulation and throughout the stimulation period. If the subject has not experienced menstrual bleeding at the first assessment of confirmation of downregulation, a urinary pregnancy test is to be performed. If the subject is not pregnant, treatment with GnRH agonist will be continued and subsequent visit(s) for confirmation of downregulation will be scheduled according to local practice. If downregulation is not achieved after 28 days, treatment with GnRH agonist will be stopped and the subject will be discontinued from the trial as a screening failure.

Randomisation will be stratified according to the investigator's assessment of an appropriate starting dose (10 µg FE 999049 / 150 IU GONAL-F or 15 µg FE 999049 / 225 IU GONAL-F). Randomisation to FE 999049 and GONAL-F will be in a 1:1 ratio within each stratum. Subjects randomised to FE 999049 will receive a daily starting dose of 10 µg or 15 µg which will be fixed for the first five stimulation days. Based on the subject's ovarian response, the dose may be increased or decreased by 5 µg, with dose adjustments implemented not more frequently than once every 2 days. The minimum FE 999049 dose is 5 µg and the maximum FE 999049 dose is 20 µg. Subjects randomised to GONAL-F will receive a daily starting dose of 150 IU or 225 IU which will be fixed for the first five stimulation days. Based on the subject's ovarian response, the dose may be increased or decreased by 75 IU, with dose adjustments implemented not more frequently than once every 2 days. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU. Subjects can be treated with rFSH for a maximum of 20 days, and coasting is not allowed.

During stimulation, subjects will be monitored by transvaginal ultrasound on stimulation days 1 and 6 and thereafter at least every second day. When the leading follicle reaches a diameter of

≥15 mm, transvaginal ultrasound will be performed daily. Triggering of final follicular maturation with 250 µg human chorionic gonadotropin (hCG) (OVIDREL, Merck Serono) will be done as soon as ≥3 follicles with a diameter ≥17 mm are observed (i.e. on the day or the day after). Triggering can also be done in case 1 or 2 follicles with a diameter ≥17 mm are observed and the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached, and that triggering is preferred instead of cycle cancellation. If there are <25 follicles with a diameter of ≥12 mm, 250 µg hCG will be administered. If there are ≥25 follicles with a diameter of ≥12 mm, the cycle is to be cancelled (i.e. hCG will be withheld and the subject will not undergo oocyte retrieval). In case of poor ovarian response, defined as the investigator judging that the triggering criterion cannot be reached by day 20, similarly the cycle is to be cancelled. In case of risk of ovarian hyperstimulation syndrome (OHSS) or any other safety concern by the investigator, the cycle is to be cancelled.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation. All oocytes from follicles with an estimated diameter ≥12 mm must be retrieved. The oocytes can be inseminated by IVF or ICSI. Fertilisation will be assessed on day 1 after oocyte retrieval. The number and quality of embryos will be assessed on day 3 after oocyte retrieval. The embryo quality assessment will consist of the following embryo morphology parameters: number of blastomeres, degree of fragmentation, blastomere uniformity and visual signs of multinucleation. A good-quality embryo is defined as an embryo with ≥6 blastomeres and ≤20% fragmentation without signs of multinucleation, or with cleavage stage classified as compacting / compacted.

For subjects who undergo triggering of final follicular maturation with hCG and have ≥20 oocytes retrieved, no transfer of embryos will take place. For subjects who undergo triggering of final follicular maturation with hCG and have <20 oocytes retrieved, transfer of 1 or 2 embryos will be performed on day 3 after oocyte retrieval. The decision to transfer either 1 or 2 embryos will be based on the subject's wishes and the investigator's recommendation and in accordance with local guidelines and/or regulations. The number and quality of transferred embryo(s) will be recorded. Available embryo(s) can be cryopreserved (either on day 3 after oocyte retrieval or after continued culture to blastocyst stage on day 5 or day 6 after oocyte retrieval) and used by the subject after completion of the trial, in accordance with local guidelines and/or regulations.

Luteal phase support with progesterone (CRINONE, Merck Serono or UTROGESTAN, Besins Healthcare) will be initiated on the day of oocyte retrieval or the day after and continued at least until clinical pregnancy (will be stopped earlier in case of menses, negative βhCG or pregnancy loss). Thereafter the investigator may decide to continue luteal phase support up until the ongoing pregnancy visit, according to local practice. A serum βhCG test will be performed 13-15 days after transfer (local laboratory). Clinical and vital pregnancy will be confirmed by transvaginal ultrasound 5-6 weeks (35-48 days) after transfer, and ongoing pregnancy will be confirmed by transvaginal or abdominal ultrasound 10-11 weeks (70-83 days) after transfer.

Blood samples will be collected throughout the trial for the purpose of evaluating the endocrine profile and clinical chemistry and haematology parameters. AMH, thyroid-stimulating hormone (TSH), and prolactin concentrations will be assessed at screening whereas estradiol and progesterone concentrations will be assessed on stimulation days 1 and 6 and at end-of-stimulation. Clinical chemistry and haematology parameters will be assessed at screening and at end-of-trial.

Symptoms of OHSS will be recorded, and all OHSS events will be graded according to Golan's classification system. Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation, and late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation.

If trial procedures and/or assessments are to be performed on Sundays, public holidays or outside the opening hours of the clinic, the procedures and/or assessments can be postponed to the upcoming weekday (maximum one day after original visit schedule).

All subjects with an ongoing pregnancy will be followed until delivery for collection of information on pregnancy outcome. Data on neonatal health, including any congenital anomalies, at birth and at 4 weeks after birth will be collected and reported separately.

NUMBER OF SUBJECTS

The total number of subjects to be randomised is approximately 300 (150 subjects to treatment with FE 999049 and 150 subjects to treatment with GONAL-F).

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

1. Signed and dated Informed Consent Form for participation in the trial, obtained before any trial-related procedures.
2. Signed and dated Informed Consent Form for data collection on the neonate, obtained before randomisation to treatment.
3. In good physical and mental health in the judgement of the investigator.
4. Chinese pre-menopausal female between the ages of 20 and 40 years; at least 20 years (including the 20th birthday) when signing the informed consent and no more than 40 years (up to the day before the 41st birthday) at the time of randomisation.
5. Eligible for ovarian stimulation with a dose equivalent to 150 IU GONAL-F or 225 IU GONAL-F, as judged by the investigator.
6. Body mass index (BMI) between 17.5 and 32.0 kg/m^2 (both inclusive) at screening.
7. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility, eligible for in vitro

fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.

8. Infertility for at least one year before randomisation for subjects <35 years or for at least 6 months for subjects ≥35 years (criteria not applicable in case of tubal or severe male factor infertility).
9. Regular menstrual cycles of 24-35 days (both inclusive), presumed to be ovulatory.
10. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. no endometrioma greater than 3 cm, and no enlarged ovaries or ovarian cyst not due to polycystic ovarian syndrome, which would contraindicate the use of gonadotropins) and normal adnexa (e.g. no hydrosalpinx) within 1 year prior to randomisation. Both ovaries must be accessible for oocyte retrieval.
11. Early follicular phase (cycle day 2-4) serum levels of follicle-stimulating hormone (FSH) between 1 and 15 IU/L (results obtained within 3 months prior to randomisation).
12. Serum anti-Müllerian hormone (AMH) concentration of ≤35 pmol/L at screening.
13. Confirmation of downregulation prior to randomisation, defined as fulfilling all of the following criteria:
    a. menstrual bleeding
    b. shed endometrium with a thickness <5 mm observed by transvaginal ultrasound
    c. no ovarian follicles ≥10 mm (including cysts that cannot be punctured prior to stimulation) observed by transvaginal ultrasound

Exclusion Criteria

1. Primary ovarian failure.
2. Known endometriosis stage III-IV (defined by the revised ASRM classification, 1996).
3. More than three previous controlled ovarian stimulation cycles initiated, regardless of outcome.
4. History of previous episode of OHSS, exuberant ovarian response to gonadotropins, or polycystic ovarian syndrome.
5. Known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) which can compromise participation in the trial with the exception of controlled thyroid function disease.
6. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
7. Fibroid tumours of the uterus incompatible with pregnancy.
8. Currently breast-feeding.

9. Undiagnosed vaginal bleeding.
10. Findings at the gynaecological examination at screening which preclude gonadotropin stimulation or are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
11. Pregnancy (negative urinary pregnancy tests must be documented at screening and before randomisation to treatment) or contraindication to pregnancy.
12. Use of fertility modifiers during the last menstrual cycle before randomisation, including dehydroepiandrosterone (DHEA) or cycle programming with oral contraceptives, progestogen or estrogen preparations.
13. Known inherited or acquired thrombophilia disease.
14. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
15. Known porphyria.
16. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
17. Previous participation in the trial.
18. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.

MEDICINAL PRODUCTS

Investigational Medicinal Products

Name / active ingredient	Pharmaceutical dosage form	Dosing
FE 999049 / Follitropin delta	Solution for subcutaneous injection	Daily starting dose of either 10 µg or 15 µg, initiated within 7 days after confirmation of downregulation and fixed for the first five stimulation days. Based on the subject's ovarian response, the dose may be increased or decreased by 5 µg, with dose adjustments implemented not more frequently than once every 2 days. The minimum FE 999049 dose is 5 µg and the maximum FE 999049 dose is 20 µg. Subjects can be treated for a maximum of 20 days.
GONAL-F / Follitropin alfa	Solution for subcutaneous injection	Daily starting dose of either 150 IU or 225 IU, initiated within 7 days after confirmation of downregulation and fixed for the first five stimulation days. Based on the subject's ovarian response, the dose may be increased or decreased by 75 IU, with dose adjustments implemented not more frequently than once every 2 days. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU. Subjects can be treated for a maximum of 20 days.

Concomitant Fertility Medication

Name / active ingredient	Pharmaceutical dosage form	Dosing
DECAPEPTYL / triptorelin acetate (GnRH agonist)	Solution for subcutaneous injection	0.1 mg, daily dose
OVIDREL / hCG	Solution for subcutaneous injection	250 µg, single dose
CRINONE / progesterone	Gel for vaginal administration	90 mg, daily dose
UTROGESTAN [a)] / progesterone	Capsule for vaginal administration	200 mg, three times daily dose

a) UTROGESTAN may be used as an alternative to CRINONE. All subjects included in the trial will be treated with the same progesterone product.

DURATION OF TREATMENT

Subjects can be treated with FE 999049 or GONAL-F for a maximum of 20 days.

STATISTICAL METHODS

Sample Size Justification

In a previous trial (000145) comparing individualised dosing of FE 999049 with GONAL-F in a GnRH antagonist protocol, the standard deviation for number of oocytes retrieved in subjects from China receiving a starting dose of 150 IU of GONAL-F was 7.5. Assuming the standard deviation in this trial to be 7.5, and assuming the treatments to be equally effective for the primary endpoint (number of oocytes retrieved), a sample size of 133 subjects per treatment group will give 90% power to demonstrate non-inferiority of FE 999049 vs. GONAL-F. This is based on a non-inferiority margin of -3.00 oocytes, a one-sided 2.5% significance level, and was calculated using the normal approximation. A total of 300 subjects will be randomised in the trial to ensure at least 90% power also for the analysis of the per-protocol analysis set.

Primary Analysis

The non-inferiority comparison will be performed both for the full analysis set (including all randomised and exposed subjects; analysed as randomised) and the per-protocol analysis set (excluding subjects with major protocol deviations; analysed as treated). The primary endpoint, number of oocytes retrieved, will be compared between FE 999049 and GONAL-F using a negative binomial model with treatment and dose level (10 µg/150 IU or 15 µg/225 IU) as factors. The absolute treatment difference in number of oocytes retrieved and the associated two-sided 95% confidence interval will be derived from the model estimates using the delta method. Non-inferiority will be considered confirmed if the lower limit of the 95% confidence interval for the difference between FE 999049 and GONAL-F is greater or equal than -3.00.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

AMH	anti-Müllerian hormone
ANCOVA	analysis of covariance
ART	assisted reproductive technologies
ATC	Anatomical Therapeutic Chemical Classification System
CBC	complete blood count
CDE	Center for Drug Evaluation
CRO	contract research organisation
DHEA	dehydroepiandrosterone
EDC	electronic data capture
ET	embryo transfer
FAS	full analysis set
FPFV	first patient first visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	gonadotropin-releasing hormone
hCG	human chorionic gonadotropin
ICD	International Classification of Diseases
ICH	International Council for Harmonisation
ICMART	International Committee Monitoring Assisted Reproductive Technologies
ICMJE	International Committee of Medical Journal Editors
ICSI	intracytoplasmic sperm injection
IMP	investigational medicinal product
IRT	interactive response technology
IVF	in vitro fertilisation
LH	luteinising hormone
LLOQ	lower limit of quantification
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	non-investigational medicinal product
NLM	National Library of Medicine
NMPA	National Medical Products Administration

OHSS	ovarian hyperstimulation syndrome
OR	oocyte retrieval
PP	per-protocol
PT	preferred term
rFSH	recombinant follicle-stimulating hormone
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected, unexpected serious adverse reaction
TSH	thyroid-stimulating hormone
US	ultrasound
ULOQ	upper limit of quantification
UTN	Universal Trial Number
WHO	World Health Organization

Company Names

Ferring will be used as abbreviation for Ferring Pharmaceuticals.

1 INTRODUCTION

1.1 Background

Follitropin delta (FE 999049) is a novel human recombinant follicle-stimulating hormone (rFSH) derived from a human cell line (PER.C6®). It is intended for the development of multiple follicles during controlled ovarian stimulation in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle. The first Marketing Authorisation approval of FE 999049 (REKOVELLE) was obtained by the European Commission in December 2016. A Biological License Application was submitted to the National Medical Products Administration in China in December 2020 for approval of FE 999049 with a proposed dosing regimen based on each woman's serum anti-Müllerian hormone (AMH) concentration and her body weight.

As of 01 April 2023, a total of 14 clinical trials have been completed as part of the FE 999049 global development programme: five phase 1 trials, two phase 2 trials, and seven phase 3 trials. A total of 4,878 subjects have been included in the completed clinical trials, of whom 3,269 subjects were exposed to FE 999049. Out of the seven phase 3 trials, trial 000145 has been conducted in China and included a total of 759 Chinese IVF or ICSI subjects, of whom 378 subjects were exposed to FE 999049. These subjects received an individualised dose in accordance with their serum AMH concentration and body weight, with a maximum dose of 12 µg, and were treated with a gonadotropin-releasing hormone (GnRH) antagonist protocol.[1] The majority of clinical trial data with FE 999049 has been generated with the GnRH antagonist protocol.

An essential part of ovarian stimulation involves concomitant treatment with GnRH analogues to prevent premature luteinisation and ovulation,[2] which can be achieved via two different approaches: pituitary desensitisation with prolonged daily administration of a GnRH agonist or instant blockade of the pituitary luteinising hormone (LH) secretion with a GnRH antagonist.[3,4,5] Both treatments are effective in preventing premature LH surges[4,6,7] and comparable in respect of clinical outcomes, such as number of oocytes retrieved and live birth rates.[5,8] Nonetheless GnRH analogues differ in their safety profile,[9,10] GnRH agonist treatment being associated with adverse drug reactions related to hypoestrogenism and with higher incidence of OHSS compared with GnRH antagonist treatment, especially in predicted normal to high responders.[5,8,11]

Differently from the algorithmic dosing of FE 999049, which is based on each subject's serum AMH concentration and body weight, the starting dose in conventional dosing of rFSH is commonly based on age, previous IVF outcomes, and markers of ovarian reserve such as antral follicle counts and circulating AMH, follicle-stimulating hormone (FSH), and estradiol concentrations.[12,13] A starting dose of 150 or 225 IU rFSH is applied in women with anticipated normal ovarian response, 150 IU being applied in women of younger age and expected to have a robust response, and 225 IU being applied in women of older age or in women expected to have a less robust response.[14,15] The dose is fixed for the initial days of stimulation, followed by the possibility for subsequent dose adjustments.[14,16]

Previous trials comparing efficacy and safety of a GnRH antagonist protocol with a long GnRH agonist protocol using rFSH derived from Chinese hamster ovary cell lines in conventional dosing have consistently indicated that the cohort of recruited follicles is slightly smaller with the GnRH antagonist protocol. A difference in oocytes of -1.0 (95% confidence interval [CI]: -1.8; -0.2) was observed in the largest randomised controlled trial[7] which is in agreement with the difference of -1.1 (95% CI: -1.5; -0.6) in a Cochrane review including data from 27 randomised controlled trials.[17]

A phase 3b trial (000304)[18] investigating efficacy and safety of FE 999049 with individualised dosing in subjects undergoing controlled ovarian stimulation for IVF or ICSI, following either a long GnRH agonist protocol or a GnRH antagonist protocol, showed a higher number of oocytes retrieved in the long GnRH agonist protocol compared with the GnRH antagonist protocol with a difference of 1.31 [95% CI: 0.22; 2.40]. The result is similar to those reported from previous trials with other gonadotropin preparations.[7,19]

The present trial will evaluate the efficacy and safety of FE 999049 in a conventional dosing regimen, i.e. a standard starting dose fixed for the initial days of stimulation, followed by the possibility for subsequent dose adjustments, in a long GnRH agonist protocol in Chinese women undergoing controlled ovarian stimulation for IVF or ICSI.

1.2 Scientific Justification for Conducting the Trial

The current proposed dosing regimen for FE 999049 in the submitted application in China is based on each woman's serum AMH concentration and her body weight and is a fixed-dose regimen with the daily dose maintained throughout the stimulation period. In contrast, approved rFSH preparations in China have a conventional dosing approach. Based on the current Chinese local clinical practice, Ferring intends to evaluate the use of FE 999049 in a conventional dosing approach i.e. a standard starting dose fixed for the initial days of stimulation, followed by the possibility for subsequent dose adjustments. The present trial will evaluate the efficacy and safety of FE 999049 in a conventional dosing approach in a long GnRH agonist protocol for pituitary downregulation, as this protocol is commonly used in Chinese clinical practice.

1.3 Benefit / Risk Aspects

Benefits

The fertility medication used for downregulation of pituitary hormones, controlled ovarian stimulation, triggering of final follicular maturation, and all trial-related procedures will be provided to the participating subjects free of charge, as Ferring compensates the investigational sites for their expenses. Subjects participating in this trial may benefit by achieving a pregnancy.

Risks

The risks associated with ART treatment, including the risks of controlled ovarian stimulation and clinical and laboratory procedures, are explained to the subjects as part of the counselling prior to starting treatment.

GnRH agonist protocol

GnRH agonist treatment is associated with adverse drug reactions related to hypoestrogenism, such as mild to severe hot flushes and vaginal dryness, ovarian cysts in the initial flare up part of the treatment, and with higher incidence of OHSS compared with the GnRH antagonist treatment, especially in predicted normal to high responders.[5,8,11] Given the increased risk of excessive response and OHSS with the GnRH agonist protocol, specific safety measures were implemented in this trial. Consequently, only subjects considered appropriate to receive a starting dose equivalent to 150 IU or 225 IU of GONAL-F and subjects with serum AMH concentrations of ≤35 pmol/l are to be included, and subjects at risk of excessive response, OHSS, or PCOS are to be excluded. In addition, cycle cancellation withholding hCG triggering is mandatory if ≥25 follicles of ≥12 mm are observed at end-of-stimulation and embryo transfer cancellation is mandatory if ≥20 oocytes are retrieved. Investigators are allowed to cancel the cycle and the embryo transfer if they evaluate that there is excessive ovarian response or increased risk of OHSS.

Gonadotropins

In this trial, controlled ovarian stimulation will be with one of two rFSH preparations: FE 999049 or GONAL-F. Both preparations will be administered subcutaneously.

The most frequently reported adverse drug reactions during treatment with FE 999049 are headache, pelvic discomfort, ovarian hyperstimulation syndrome (OHSS), pelvic pain, nausea, adnexa uteri pain and fatigue.[1] OHSS is an intrinsic risk of the ovarian stimulation. Known gastrointestinal symptoms associated with OHSS include abdominal pain, discomfort, and distension, nausea, vomiting, and diarrhoea. Ovarian torsion and thromboembolic events are known to be rare complications of ovarian stimulation treatment.

GONAL-F is a commercially available rFSH preparation with established safety and efficacy. The most frequent adverse events in relation to use of GONAL-F are as follows: headache, ovarian cysts and injection site reactions (all reported as very common, i.e. ≥10%) and abdominal pain, abdominal distension, abdominal discomfort, nausea, vomiting, diarrhoea and mild or moderate OHSS including associated symptomatology (all reported as common, i.e. 1% to <10%).[20] The GONAL-F dosing regimen used in this trial is in line with labelling recommendations.

The most serious risk associated with gonadotropin treatment is OHSS. OHSS manifests itself with increasing degrees of severity. Moderate / severe OHSS is associated with marked ovarian enlargement, fluid accumulation and other complications. In patients treated with a GnRH agonist protocol, early OHSS can be prevented by withholding gonadotropins or withholding human chorionic gonadotropin (hCG). Very rare cases of serious allergic reactions have been reported after injection of gonadotropins.

Trial Procedures and Concomitant Fertility Medications

Subjects will undergo standard ART treatment procedures (e.g. ovarian stimulation monitoring by transvaginal ultrasound and blood sampling, oocyte retrieval and transfer) and also receive standard concomitant fertility medication as part of this trial. The transvaginal ultrasound examinations may be associated with mild discomfort and a very rare risk of infection. The blood sampling might be associated with mild discomfort, bruising and a very rare risk of infection. The oocyte retrieval procedure is associated with discomfort and very rarely infections and bleeding. The transfer procedure is associated with mild discomfort and very rarely infections and mild bleeding. The concomitant fertility medications are generally well-tolerated. The most frequent adverse events are similar to those reported for gonadotropins, such as headache, injection site reactions, pelvic pain, abdominal pain, abdominal distension and allergic reactions. Furthermore, vaginal progesterone has been associated with vulvovaginal disorders and uterine spasms (at a frequency of 1-2%), and the GnRH agonist with vaginal bleeding/spotting (>10%). Ovarian cyst formation is also a recognised complication of GnRH agonist use.

Pregnancy-related Events

A serious concern associated with ART cycles is the frequency of multiple pregnancies / births and the related neonatal health problems. The number of embryos transferred will, for each subject, depend on the local regulations and clinical practice. Participation in this trial does not imply transfer of more embryos than what is judged appropriate by the subject, the investigator and local guidelines and/or regulations. The incidence of miscarriage and ectopic pregnancy is higher in women undergoing controlled ovarian stimulation than in women conceiving spontaneously, though the risk of ectopic pregnancy is mainly higher in patients with a history of tubal infertility. Furthermore, the prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions; this is thought to be due to differences in parental characteristics (e.g. maternal age and sperm characteristics) and multiple pregnancies.

Benefits / Risks

Participation in this trial is not expected to have a negative influence on the subject's likelihood of achieving an adequate ovarian response compared to normal clinical practice. Furthermore, participation does not imply extra risks for the subjects in comparison to routine controlled ovarian stimulation. In conclusion, the evaluation of benefits and risks indicates that participation in this trial is associated with a favourable benefit-risk ratio.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To compare FE 999049 at a starting dose of either 10 µg or 15 µg to GONAL-F at a starting dose of either 150 IU or 225 IU in conventional regimens with respect to ovarian response in women undergoing controlled ovarian stimulation in a long GnRH agonist protocol

Secondary Objectives

- To compare the follicular development, endocrine profile and embryo development associated with conventional dosing of FE 999049 and GONAL-F
- To compare the treatment efficiency associated with conventional dosing of FE 999049 and GONAL-F
- To compare the safety profile associated with conventional dosing of FE 999049 and GONAL-F

2.2 Endpoints

Primary Endpoint

- Number of oocytes retrieved

Secondary Endpoints

- Number of follicles (total and by size category) on stimulation day 6 and end-of-stimulation
- Serum concentrations of estradiol and progesterone on stimulation day 6 and end-of-stimulation
- Number of fertilised oocytes and fertilisation rate
- Number of embryos (total and by quality)
- Total gonadotropin dose and number of stimulation days
- Positive βhCG (positive serum βhCG test 13-15 days after transfer) rate
- Clinical pregnancy (at least one gestational sac 5-6 weeks after transfer) rate
- Vital pregnancy (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer) rate
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of embryos transferred)
- Ongoing pregnancy (at least one intrauterine viable fetus 10-11 weeks after transfer) rate
- Ongoing implantation rate (number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of embryos transferred)

- Early ovarian hyperstimulation syndrome (OHSS), late OHSS, and total OHSS (all overall and by grade)

Pregnancy Follow-up Endpoints

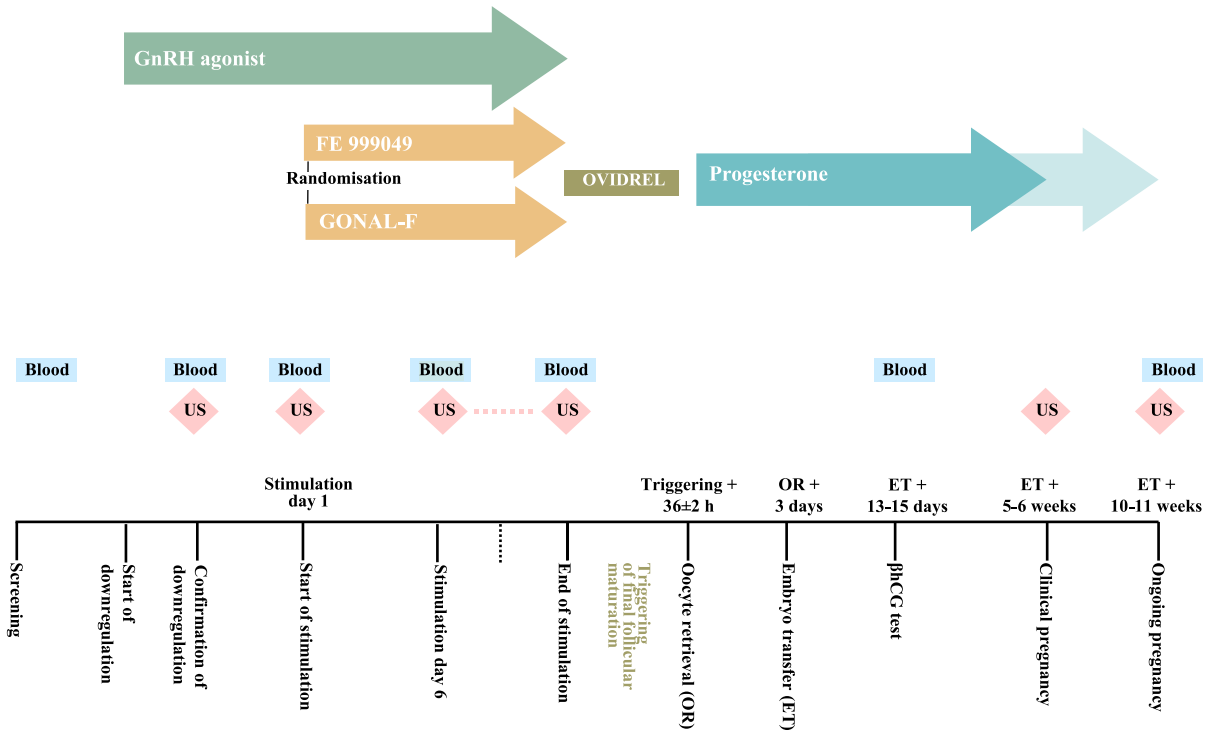
- Live birth rate
- Neonatal health, including minor/major congenital anomalies, at birth and at 4 weeks after birth

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

A diagram illustrating the trial period is shown in Figure 3-1.



Blood collection: For eligibility criteria, confirmation of downregulation (if applicable), endocrine profile and clinical chemistry and haematology parameters, and for βhCG test.
Ultrasound: For confirmation of downregulation and for monitoring during stimulation. Stimulation day 1 assessments may be combined with confirmation of downregulation assessments, if downregulation is confirmed. Monitoring will continue day 6 and thereafter at least every second day. When the leading follicle reaches a diameter of ≥15 mm, assessments will be performed daily.
Luteal phase support: Progesterone will be initiated on the day of oocyte retrieval or the day after and continued until clinical pregnancy (will be stopped earlier in case of menses, negative βhCG or pregnancy loss). The investigator may decide to continue luteal phase support up until the ongoing pregnancy visit, according to local practice.

ET: embryo transfer, GnRH: gonadotropin-releasing hormone, OR: oocyte retrieval; US: ultrasound

Figure 3-1 Trial Diagram – Trial Period

3.1.2 Overall Design and Control Methods

Trial Design

This will be a randomised, controlled, assessor-blind, parallel groups, multicentre, non-inferiority trial comparing the ovarian response of FE 999049 and GONAL-F in conventional regimens, using a starting dose of either 10 µg or 15 µg FE 999049 or 150 IU or 225 IU GONAL-F, in women undergoing controlled ovarian stimulation for IVF or ICSI following treatment in a long GnRH agonist protocol. The trial has been designed to demonstrate non-inferiority of FE 999049 versus GONAL-F with the number of oocytes retrieved as the primary endpoint. Secondary endpoints include pharmacodynamic parameters of FSH action as well as efficacy and safety parameters related to controlled ovarian stimulation. Treatment efficiency in terms of gonadotropin use and duration of stimulation will also be evaluated. The assessor-blind design ensures that the investigators and other assessors such as embryologists are blinded to individual treatment allocation. A trial medication delegate will be responsible for all trial medication related issues, both practically at the clinic and in interactions with the subject.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. A long GnRH agonist protocol will be used for pituitary downregulation; treatment with GnRH agonist (triptorelin acetate, DECAPEPTYL, Ferring), 0.1 mg/day, will be initiated in the mid-luteal phase (i.e. cycle day 21-24) of the subject's menstrual cycle. A minimum of 10 days with GnRH agonist administration should be ensured prior to confirmation of downregulation, which is defined as fulfilling the following criteria: 1) menstrual bleeding, 2) shed endometrium with a thickness <5 mm observed by transvaginal ultrasound, and 3) no ovarian follicles ≥10 mm (including cysts that cannot be punctured prior to stimulation) observed by transvaginal ultrasound. In case achievement of downregulation is doubtful or it is deemed helpful, serum estradiol is to be measured (<50 pg/mL or 180 pmol/L; local laboratory). Once downregulation is confirmed, randomisation and start of stimulation must occur within 7 days. Treatment with GnRH agonist is to be continued after confirmation of downregulation and throughout the stimulation period. If the subject has not experienced menstrual bleeding at the first assessment of confirmation of downregulation, a urinary pregnancy test is to be performed. If the subject is not pregnant, treatment with GnRH agonist will be continued and subsequent visit(s) for confirmation of downregulation will be scheduled according to local practice. If downregulation is not achieved after 28 days, treatment with GnRH agonist will be stopped and the subject will be discontinued from the trial as a screening failure.

Randomisation will be stratified according to the investigator's assessment of an appropriate starting dose (10 µg FE 999049 / 150 IU GONAL-F or 15 µg FE 999049 / 225 IU GONAL-F). Randomisation to FE 999049 and GONAL-F will be in a 1:1 ratio within each stratum. Subjects randomised to FE 999049 will receive a daily starting dose of 10 µg or 15 µg which will be fixed for the first five stimulation days. Based on the subject's ovarian response, the dose may be increased or decreased by 5 µg, with dose adjustments implemented not more frequently than once every 2 days. The minimum FE 999049 dose is 5 µg and the maximum FE 999049 dose is 20 µg. Subjects randomised to GONAL-F will receive a daily starting dose of 150 IU or 225 IU which will

be fixed for the first five stimulation days. Based on the subject's ovarian response, the dose may be increased or decreased by 75 IU, with dose adjustments implemented not more frequently than once every 2 days. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU. Subjects can be treated with rFSH for a maximum of 20 days, and coasting is not allowed.

During stimulation, subjects will be monitored by transvaginal ultrasound on stimulation days 1 and 6 and thereafter at least every second day. When the leading follicle reaches a diameter of ≥15 mm, transvaginal ultrasound will be performed daily. Triggering of final follicular maturation with 250 µg hCG (OVIDREL, Merck Serono) will be done as soon as ≥3 follicles with a diameter ≥17 mm are observed (i.e. on the day or the day after). Triggering can also be done in case 1 or 2 follicles with a diameter ≥17 mm are observed and the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached, and that triggering is preferred instead of cycle cancellation. If there are <25 follicles with a diameter of ≥12 mm, 250 µg hCG will be administered. If there are ≥25 follicles with a diameter of ≥12 mm, the cycle is to be cancelled (i.e. hCG will be withheld and the subject will not undergo oocyte retrieval). In case of poor ovarian response, defined as the investigator judging that the triggering criterion cannot be reached by day 20, similarly the cycle is to be cancelled. In case of risk of OHSS or any other safety concern by the investigator, the cycle is to be cancelled.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation. All oocytes from follicles with an estimated diameter ≥12 mm must be retrieved. The oocytes can be inseminated by IVF or ICSI. Fertilisation will be assessed on day 1 after oocyte retrieval. The number and quality of embryos will be assessed on day 3 after oocyte retrieval. The embryo quality assessment will consist of the following embryo morphology parameters: number of blastomeres, degree of fragmentation, blastomere uniformity and visual signs of multinucleation. A good-quality embryo is defined as an embryo with ≥6 blastomeres and ≤20% fragmentation without signs of multinucleation, or with cleavage stage classified as compacting / compacted.

For subjects who undergo triggering of final follicular maturation with hCG and have ≥20 oocytes retrieved, no transfer of embryos will take place. For subjects who undergo triggering of final follicular maturation with hCG and have <20 oocytes retrieved, transfer of 1 or 2 embryos will be performed on day 3 after oocyte retrieval. The decision to transfer either 1 or 2 embryos will be based on the subject's wishes and the investigator's recommendation and in accordance with local guidelines and/or regulations. The investigator has the option of cancelling the embryo transfer for medical reasons. The number and quality of transferred embryo(s) will be recorded. Available embryo(s) can be cryopreserved (either on day 3 after oocyte retrieval or after continued culture to blastocyst stage on day 5 or day 6 after oocyte retrieval) and used by the subject after completion of the trial, in accordance with local guidelines and/or regulations.

Luteal phase support with progesterone (CRINONE, Merck Serono or UTROGESTAN, Besins Healthcare) will be initiated on the day of oocyte retrieval or the day after and continued at least until clinical pregnancy (will be stopped earlier in case of menses, negative βhCG or pregnancy loss). Thereafter the investigator may decide to continue luteal phase support up until the ongoing pregnancy visit, according to local practice. A serum βhCG test will be performed 13-15 days after

transfer (local laboratory). Clinical and vital pregnancy will be confirmed by transvaginal ultrasound 5-6 weeks (35-48 days) after transfer, and ongoing pregnancy will be confirmed by transvaginal or abdominal ultrasound 10-11 weeks (70-83 days) after transfer.

Blood samples will be collected throughout the trial for the purpose of evaluating the endocrine profile and clinical chemistry and haematology parameters. AMH, thyroid-stimulating hormone (TSH), and prolactin concentrations will be assessed at screening, whereas estradiol and progesterone concentrations will be assessed on stimulation days 1 and 6 and at end-of-stimulation. Clinical chemistry and haematology parameters will be assessed at screening and at end-of-trial.

Symptoms of OHSS will be recorded, and all OHSS events will be graded according to Golan's classification system. Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation, and late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation.

If trial procedures and/or assessments are to be performed on Sundays, public holidays or outside the opening hours of the clinic, the procedures and/or assessments can be postponed to the upcoming weekday (maximum one day after original visit schedule).

All subjects with an ongoing pregnancy will be followed until delivery for collection of information on pregnancy outcome. Data on neonatal health, including any congenital anomalies, at birth and at 4 weeks after birth will be collected and reported separately.

3.1.3 Trial Schedule

First patient first visit (FPFV): Q2 2024
Last patient last visit (LPLV): Q4 2025
Pregnancy follow-up completed: Q2 2026

3.2 Planned Number of Trial Sites and Subjects

An approximate number of 300 subjects is planned for randomisation (150 subjects to treatment with FE 999049 and 150 subjects to treatment with GONAL-F) at 10-15 sites in China.

3.3 Interim Analysis

No interim analysis is planned.

3.4 Data Monitoring Committee

No Data Monitoring Committee will be established for this trial. During the trial, the Safety Management Team at the sponsor will evaluate blinded safety data on a regular basis.

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

The primary objective of the trial is to compare FE 999049 at a starting dose of either 10 µg or 15 µg to GONAL-F at a starting dose of either 150 IU or 225 IU in conventional regimens with respect to ovarian response in women undergoing controlled ovarian stimulation in a long GnRH agonist protocol. In China, approved rFSH preparations such as follitropin alfa (GONAL-F) and follitropin beta (PUREGON/FOLLISTIM) have a conventional dosing approach, i.e. fixed starting dose for initial days of stimulation followed by possibilities for subsequent dose adjustments. In contrast, the dosing regimen proposed in the submitted application for FE 999049 in China is based on each woman's serum AMH concentration and her body weight using a GnRH antagonist protocol. The dose selection is further discussed in Section 3.5.4.

A long GnRH agonist protocol is commonly used in Chinese clinical practice and therefore that downregulation protocol will be applied in the current trial. The majority of clinical trial data with FE 999049 has been generated in a GnRH antagonist protocol. Data from a phase 3b trial conducted in EU (Trial 000304), showed that number of oocytes retrieved after controlled ovarian stimulation using an individualised FE 999049 dosing regimen based on serum AMH concentrations and body weight of women, with serum AMH concentrations of ≤35 pmol/L, was higher with the long GnRH agonist protocol compared to the GnRH antagonist protocol, with a difference of 1.31 [95% CI: 0.22; 2.40]. The number of oocytes retrieved was influenced by age and serum AMH concentration, and the difference between the protocols was largest for younger patients and for patients with higher ovarian reserve. No differences in incidence of OHSS or in the overall safety profile were observed between the protocols. After controlled ovarian stimulation using the individualised FE 999049 dosing regimen, live birth rate and neonatal health follow-up data collected up to 4 weeks after birth were similar for the two protocols. For reassurance of neonatal health data after controlled ovarian stimulation using the conventional FE 999049 dosing regimen with the GnRH agonist protocol, neonatal health data will be collected up to 4 weeks after birth as follow-up to the current trial.

The current trial is randomised and controlled using an approved gonadotropin preparation as active comparator. It is a parallel group design restricted to a single treatment cycle. The trial will be assessor-blind. A double-blind design is not considered feasible for the present trial for various practical reasons, which are described in detail in Section 3.5.3. The assessor-blinding will ensure blinding and thereby unbiased evaluation by the investigators and other assessors such as embryologists. Similarly, Ferring staff will also remain blinded to individual subject treatment allocation during the conduct of the trial (delegated functions that need access to treatment allocation to fulfil their responsibilities are exempted). The trial will be multicentre. This set-up ensures that the required number of subjects can be recruited within a reasonable time and also has the advantage that it should facilitate subsequent generalisation of the results. The selected population, expected to be representative for patients undergoing controlled ovarian stimulation in IVF or ICSI cycles, is further discussed in Section 3.5.5.

This trial is designed to demonstrate non-inferiority of FE 999049 vs. GONAL-F with respect to the number of oocytes retrieved. The non-inferiority margin has been set to 3.00 oocytes, as this margin is regarded to be appropriate for demonstrating the efficacy of FE 999049 treatment in a conventional dosing regimen with a long GnRH agonist protocol. The margin of 3.00 oocytes is in line with the regulatory precedence in Europe for rFSH biosimilars,[21] and is also a common clinical standard for clinical trials in China demonstrating equivalence between rFSH drug and comparator, e.g. GONAL-F to obtain regulatory approval from the National Medical Products Administration (NMPA).[22,23,24] Furthermore, the mean number of oocytes retrieved with placebo (i.e. without stimulation) would be approximately 1, and the expected mean number of oocytes retrieved expected with GONAL-F (active control drug) will be approximately 10. Therefore, the efficacy difference between the active control and placebo would be approximately 9, implying that the M1 (defined in the regulatory guideline for clinical non-inferiority trials in China) [25] is considerably larger than 3.00. A successful non-inferiority result will therefore both ensure that the effect of FE 999049 is better than placebo and clinically equivalent to GONAL-F, according to regulatory precedence for rFSH biosimilars in Europe and China.[22,23,24,26,27] Selection of endpoints is further discussed in Section 3.5.2.

Strict criteria have been incorporated in the design of this comparative trial to properly assess the effect of the interventions on treatment outcome. In general, standardisation of criteria, timing of assessments, procedures and interventions have to a great extent been incorporated in the design of this trial to minimise variation.[28,29,30]

For safety reasons, only subjects with serum AMH concentrations of ≤35 pmol/L at screening are eligible for randomisation to treatment and treatment is limited by maximum doses of 20 µg FE 999049 and 300 IU GONAL-F for a maximum of 20 days. Additional safety measures include cycle cancellation for subjects with ≥25 follicles with a diameter ≥12 mm or for safety concerns, as judged by the investigator, and transfer cancellation for subjects with retrieval of ≥20 oocytes.

Oocytes will be inseminated by either IVF or ICSI reflecting the procedures used in the target population for the proposed indication. Embryos will be cultured for 3 days; oocyte fertilisation will be assessed on day 1 and number and quality of embryos will be assessed on day 3 after oocyte retrieval. The duration of culture in this trial is adapted to clinical practice in China where transfer on day 3 after oocyte retrieval is the most common.

To minimise the risk of multiple gestations, subjects will have transfer of 1 or 2 embryos of the highest quality available. The decision to transfer either 1 or 2 embryos on day 3 will be based on the subject's wishes and the investigator's recommendation and in accordance with local guidelines and/or regulations.

3.5.2 Selection of Endpoints

The present trial has been designed as a non-inferiority trial with number of oocytes retrieved as the primary endpoint reflecting the pharmacological effect of FSH on follicular development and growth. Known pharmacological effects of FSH are associated with risks of developing OHSS.

Oocytes retrieved is commonly used as primary endpoint for this kind of drugs. The set of secondary endpoints is considered appropriate for an efficacy trial and includes items of special interest related to controlled ovarian stimulation. Safety will be closely monitored and the frequency of OHSS (early, late, and total) is included.

3.5.3 Blinding

The two investigational medicinal products (IMPs) differ in presentation. GONAL-F is manufactured by Merck Serono and bought commercially for use in this phase 3b trial. A double-blind, double-dummy design is not considered feasible. The trial, however, is assessor-blind, ensuring unbiased evaluation by the investigators and other assessors such as embryologists.

One or more trial medication delegate(s) will be identified at each site. The trial medication delegate will be responsible for all trial medication related issues, both practically at the clinic and in interactions with the subject. To maintain the assessor-blinding, the trial medication delegate is not allowed to perform any assessments in the trial. Information on treatment allocation is only available to the trial medication delegate. The investigator does not have access to these modules in the electronic data capture (EDC) system. Thus, only the trial medication delegate at the site, the monitors and the participating subjects will know the treatment allocation once the subjects are randomised. Precaution will be taken to ensure that the treatment allocations are not available to the investigators or other assessors throughout the trial. Subjects will be clearly instructed to only discuss their treatment allocation with the trial medication delegate, and to not mention it to the investigator.

Drug accountability forms and other forms identifying treatment allocation are kept unavailable to the investigator. The subject will during the informed consent process be informed, both verbally and in writing, to not disclose her treatment allocation to the investigator. Trial staff is provided training in the importance of maintaining blinding, and trial medication delegates are also helped to set up systems at the clinic.

The trial medication delegate will dispense the trial medication to the subject (and may also do the actual administration at the clinic, if required). The investigator will, based on the follicular development, judge if dose adjustments are recommended and state his/her directions on a form developed for that purpose, which will be used to inform the trial medication delegate. Depending on whether the subject is being treated with FE 999049 or GONAL-F, the trial medication delegate will provide detailed instructions to the subject in line with the dosing regimen for each preparation as outlined in the protocol. In other words, if the investigator recommends a dose adjustment, the

trial medication delegate will implement a decrease or increase of 5 µg per day as applicable if the subject is in the FE 999049 group, or of 75 IU per day as applicable if the subject is in the GONAL-F group. Requests for cycle cancellation due to inappropriate response or other medical reasons are followed, irrespective of treatment group.

The Ferring clinical trial team will be blinded to treatment allocation until breaking of the blind. Delegated functions that need access to treatment allocation to fulfil their responsibilities are exempted. Details are provided in a trial-specific Blinding Plan.

3.5.4 Selection of Doses in the Trial

The proposed dosing regimen for FE 999049 in the submitted application in China is based on each woman's serum AMH concentration and her body weight, and is a fixed-dose regimen with the daily dose maintained throughout the stimulation period. Proposed maximum daily dose of FE 999049 is 12 µg for the first treatment cycle and 24 µg in subsequent treatment cycles. Approved starting doses of GONAL-F for ART in China, 150-225 IU fixed for the initial days of stimulation followed by the possibility for subsequent dose adjustments with a maximum daily dose of 450 IU, provided a reference point for evaluating the ovarian response observed with FE 999049.

Based on clinical trial data from more than 1,500 patients undergoing controlled ovarian stimulation with individualised FE 999049 dosing regimen in a GnRH antagonist protocol, it has been possible to establish the daily FE 999049 dose that provides a comparable ovarian response (i.e. number of oocytes retrieved and number of follicles ≥12 mm and serum estradiol at end-of-stimulation) as 150 IU/day GONAL-F.[31] These clinical trial data suggest that a daily dose of 10.0 [95% CI 9.2; 10.8] µg FE 999049 provides an ovarian response equal to that obtained with 150 IU GONAL-F. Applying this dose equivalence factor, it is extrapolated that 15 µg/day FE 999049 will provide an ovarian response comparable to that obtained with 225 IU/day GONAL-F. The dose equivalence factor between FE 999049 and GONAL-F was confirmed in 759 Chinese patients in Trial 000145, for whom 10.2 [95% CI: 9.3–11.2] µg FE 999049 provided an equal ovarian response to that obtained with 150 IU GONAL-F.[32]

The starting dose of 15 µg FE 999049 has not previously been evaluated in the Chinese population. In this population, subjects undergoing a first treatment cycle have been exposed to a maximum of 12 µg FE 999049 (Trial 000145). In other populations, subjects undergoing repeated treatment cycles have been exposed to a maximum of 24 µg FE 999049 without any safety concerns (Trial 000071).[1]

In the current trial, the choice of starting dose level (10 µg FE 999049 / 150 IU GONAL-F or 15 µg FE 999049 / 225 IU GONAL-F) is based on the investigator's clinical judgement. The distribution of starting doses in the trial population will thereby reflect the distribution of starting doses used in clinical practice. After the first 5 days with stimulation at a fixed dose, the dose may be increased or decreased based on the subject's ovarian response by 5 µg FE999049 or 75 IU GONAL-F which are considered doses of similar magnitude based on the extrapolation described above. Dose

adjustments may be implemented not more frequently than once every 2 days. This possibility for a gradual increase in dose and a maximum dose of 20 µg/day FE 999049 or 300 IU/day GONAL-F for a maximum duration of 20 days constitutes a safe approach for the subjects. The starting dose level of GONAL-F is in line with labelling recommendations.[20]

The doses of overall treatment regimens for the GnRH agonist, hCG, and progesterone products are in line with the recommendations in the respective products' labelling for the indication of ART and/or standard clinical practice.

3.5.5 Selection of Trial Population

This trial will include women who have been diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II, or have partners diagnosed with male factor infertility, and who are considered eligible for IVF or ICSI. The trial will include women up to 40 years of age and will thereby cover the patient age span in which most ART treatments are performed. The allowed body mass index (BMI) is 17.5-32.0 kg/m^2, thus including underweight, normal weight, overweight and obese subjects.

Because the ovarian stimulation treatment is to be performed using a GnRH agonist protocol, only patients with a serum AMH concentration of ≤35 pmol/L are to be included to avoid exposing patients with a high ovarian reserve to an increased risk of developing excessive response or OHSS.

The exclusion criteria incorporate the contraindications for the use of gonadotropins and other concomitant fertility medications used in the trial.

Altogether, the population selected for this trial would be expected to be representative for subjects undergoing controlled ovarian stimulation in IVF or ICSI cycles in China.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

Subjects must meet all of the criteria below to be eligible for participation on this trial.

1. Signed and dated Informed Consent Form for participation in the trial, obtained before any trial-related procedures.
2. Signed and dated Informed Consent Form for data collection on the neonate, obtained before randomisation to treatment.
3. In good physical and mental health in the judgement of the investigator.
4. Chinese pre-menopausal female between the ages of 20 and 40 years; at least 20 years (including the 20th birthday) when signing the informed consent and no more than 40 years (up to the day before the 41st birthday) at the time of randomisation.
5. Eligible for ovarian stimulation with a dose equivalent to 150 IU GONAL-F or 225 IU GONAL-F, as judged by the investigator.
6. Body mass index (BMI) between 17.5 and 32.0 kg/m^2 (both inclusive) at screening.
7. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility, eligible for in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.
8. Infertility for at least one year before randomisation for subjects <35 years or for at least 6 months for subjects ≥35 years (criteria not applicable in case of tubal or severe male factor infertility).
9. Regular menstrual cycles of 24-35 days (both inclusive), presumed to be ovulatory.
10. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. no endometrioma greater than 3 cm, and no enlarged ovaries or ovarian cyst not due to polycystic ovarian syndrome, which would contraindicate the use of gonadotropins) and normal adnexa (e.g. no hydrosalpinx) within 1 year prior to randomisation. Both ovaries must be accessible for oocyte retrieval.
11. Early follicular phase (cycle day 2-4) serum levels of follicle-stimulating hormone (FSH) between 1 and 15 IU/L (results obtained within 3 months prior to randomisation).
12. Serum anti-Müllerian hormone (AMH) concentration of ≤35 pmol/L at screening.
13. Confirmation of downregulation prior to randomisation, defined as fulfilling all of the following criteria:
    a. menstrual bleeding
    b. shed endometrium with a thickness <5 mm observed by transvaginal ultrasound
    c. no ovarian follicles ≥10 mm (including cysts that cannot be punctured prior to stimulation) observed by transvaginal ultrasound

4.1.2 Exclusion Criteria

Subjects meeting any of the criteria listed below will not be eligible for participation in this trial.

1. Primary ovarian failure.
2. Known endometriosis stage III-IV (defined by the revised ASRM classification, 1996).
3. More than three previous controlled ovarian stimulation cycles initiated, regardless of outcome.
4. History of previous episode of ovarian hyperstimulation syndrome (OHSS), exuberant ovarian response to gonadotropins, or polycystic ovarian syndrome.
5. Known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) which can compromise participation in the trial with the exception of controlled thyroid function disease.
6. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
7. Fibroid tumours of the uterus incompatible with pregnancy.
8. Currently breast-feeding.
9. Undiagnosed vaginal bleeding.
10. Findings at the gynaecological examination at screening which preclude gonadotropin stimulation or are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
11. Pregnancy (negative urinary pregnancy tests must be documented at screening and before randomisation to treatment) or contraindication to pregnancy.
12. Use of fertility modifiers during the last menstrual cycle before randomisation, including dehydroepiandrosterone (DHEA) or cycle programming with oral contraceptives, progestogen or estrogen preparations.
13. Known inherited or acquired thrombophilia disease.
14. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
15. Known porphyria.
16. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
17. Previous participation in the trial.
18. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

The participating subjects will be recruited among the patients attending the clinics included in the trial. Advertisements may be used if approved by the local ethics committee and regulatory authorities, as applicable according to local regulations.

A screening number is allocated to each subject who has given written informed consent to participate in the trial. A subject must always be assigned to the lowest available screening number at each site. A screening log of all screened subjects must be maintained by the investigator.

4.2.2 Randomisation

Once downregulation is confirmed, subjects will within 7 days be randomised in a 1:1 ratio to FE 999049 or GONAL-F and stimulation will be initiated. Randomisation will be stratified according to the investigator's assessment of an appropriate starting dose (10 µg FE 999049 / 150 IU GONAL-F or 15 µg FE 999049 / 225 IU GONAL-F). Randomisation is performed centrally through the interactive response technology (IRT) system. The randomisation number will be allocated to the subject together with the treatment allocation and starting dose. When a subject is randomised to the trial, she will always be assigned to the lowest available randomisation number within site and stratum. An independent statistician at the Ferring Global Biometrics Department will prepare a computer-generated randomisation list and randomisation is performed in blocks. Blocks will be maintained within trial sites, i.e. the randomisation will be stratified by trial site. The block size will only be revealed when the trial database is declared clean and locked. An overview of recruitment will be recorded on a subject identification code list for all randomised subjects kept by the investigator.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

The subjects must not have used fertility modifiers, including DHEA or cycle programming with oral contraceptives, progestogen or estrogen preparations during the last menstrual cycle before randomisation. Neither used any non-registered investigational drugs during the last 3 months prior to randomisation.

Use of any medication other than the trial medication provided for this trial should be avoided from the screening period until completion of the trial. Occasional use of over-the-counter medication or prescription drugs may be allowed at the discretion of the investigator.

Any concomitant therapies used during the trial or within 3 months prior to screening will be recorded in the source documents and in the EDC system, along with the main reason for their prescription/use.

4.3.2 Prohibited Therapy

It is prohibited to continue therapy outside the scope of the trial with medicinal products provided specifically for the trial.

4.4 Discontinuation Criteria

The subjects have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. The investigator should record the reason for the subject's withdrawal, if possible. The investigator also has the right to discontinue subjects due to safety concerns, including any adverse event indicating that continued participation endangers the safety of the subject, or due to significant non-compliance with trial procedures.

For any discontinuation, the investigator will obtain all the required details and document the date of the premature termination and the main reason in the EDC system.

If the subject withdraws her consent, no further data will be obtained. However, already obtained samples may be analysed. This will be described in the Informed Consent Form. The subject can request destruction of samples which would otherwise have been kept in storage.

4.5 Subject Replacement

A subject can only be assigned one screening number and one randomization number, i.e. a subject cannot be re-screened.

Subjects who discontinue prematurely from the trial after randomisation are not to be replaced, i.e. randomisation numbers are uniquely linked to each subject and cannot be re-used.

4.6 Trial Stopping Criteria

Occurrence of the following may warrant consideration of trial termination:

- Life-threatening serious adverse events with suspected causality to the IMP(s)

The internal Safety Management Team at the sponsor will review each occurrence and provide a recommendation as to whether to terminate the trial. The composition and responsibilities of the internal Safety Management Team are described in a separate charter.

For general trial stopping criteria related to the conduct of clinical trials see Section 12.3.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Products

Subjects will be randomised in a 1:1 ratio to FE 999049 : GONAL-F. Treatment with FE 999049 and GONAL-F is described in Table 5-1. GONAL-F is authorised in China, whereas authorisation of FE 999049 is pending in China.

Table 5-1 Investigational Medicinal Products and Dosing Regimens

Name / active ingredient	Pharmaceutical dosage form; strengths	Dosing
FE 999049 / Follitropin delta	Solution for subcutaneous injection; 12 µg / 0.36 mL, 36 µg / 1.08 mL, 72 µg / 2.16 mL	Daily starting dose of either 10 µg or 15 µg, initiated within 7 days after confirmation of downregulation and fixed for the first five stimulation days. Based on the subject's ovarian response, the dose may be increased or decreased by 5 µg, with dose adjustments implemented not more frequently than once every 2 days. The minimum FE 999049 dose is 5 µg and the maximum FE 999049 dose is 20 µg. Subjects can be treated for a maximum of 20 days.
GONAL-F / Follitropin alfa	Solution for subcutaneous injection; 150 IU / 0.25 ml, 300 IU / 0.5 ml, 450 IU / 0.75 mL, and 900 IU / 1.5 ml	Daily starting dose of either 150 IU or 225 IU, initiated within 7 days after confirmation of downregulation and fixed for the first five stimulation days. Based on the subject's ovarian response, the dose may be increased or decreased by 75 IU, with dose adjustments implemented not more frequently than once every 2 days. The minimum GONAL-F dose is 75 IU and the maximum GONAL-F dose is 300 IU. Subjects can be treated for a maximum of 20 days.

The first IMP injection will take place at the clinic and will be performed either by the trial medication delegate or the subject under supervision by the trial medication delegate. Subsequent injections can be done at home or at the clinic. The trial medication delegate will be instructed and trained in the correct use of the devices, so that correct instructions can be provided to the subjects.

Administration of IMP after reaching the triggering criterion or coasting are not allowed.

For information on warnings, precautions, and treatment of overdose, please refer to the Investigator's Brochure for FE 999049[1] and the Summary of Product Characteristics for GONAL-F.[20]

5.1.2 Non-Investigational Medicinal Products

As concomitant fertility medication during the trial, subjects will use non-investigational medicinal products (NIMPs) in Table 5-2. All NIMPs are authorised in China.

Table 5-2 Non-investigational Medicinal Products and Dosing Regimens

Name / active ingredient	Pharmaceutical dosage form; strengths	Dosing
DECAPEPTYL / triptorelin acetate (GnRH agonist)	Solution for subcutaneous injection; 01 mg / 1 mL	0.1 mg subcutaneous injection once daily, starting in the mid-luteal phase of the subject's menstrual cycle (i.e. day 21-24) and continued throughout the stimulation period.
OVIDREL / hCG	Solution for subcutaneous injection; 250 µg / 0.5 mL	A single 250 µg subcutaneous injection as soon as reaching the criterion for triggering of final follicular maturation with hCG (≥3 follicles with a diameter ≥17 mm and <25 follicles with a diameter ≥12 mm) [*Note:* triggering can also be done in case 1 or 2 follicles with a diameter ≥17 mm is observed and the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached, and that triggering is preferred instead of cycle cancellation].
CRINONE / progesterone	Gel for vaginal administration; 8%	90 mg vaginal gel once daily, initiated on the day of oocyte retrieval or the day after and continued at least until clinical pregnancy. Progesterone support will be terminated earlier in case of no transfer, menses, negative βhCG or pregnancy loss.
UTROGESTAN [a)] / progesterone	Capsule for vaginal administration; 200 mg	200 mg vaginal capsule three times daily, i.e. in the morning, at lunchtime and at bedtime, initiated on the day of oocyte retrieval or the day after and continued at least until clinical pregnancy. Progesterone support will be terminated earlier in case of no transfer, menses, negative βhCG or pregnancy loss.

a) UTROGESTAN, approved for ART treatment in China, may be used as an alternative to CRINONE in this trial. All subjects included in the trial will be treated with the same progesterone product.

For information on warnings, precautions, and treatment of overdose, please refer to the Summary of Product Characteristics for DECAPEPTYL[33], OVIDREL[34], CRINONE[35], and UTROGESTAN[36].

5.2 Characteristics and Source of Supply

All medicinal products will be provided by Ferring and handled according to the principles of Good Manufacturing Practice (GMP). Table 5-3 provides an overview of the presentation and manufacturer of each medicinal products.

Table 5-3 Characteristics and Source of Supply of Medicinal Products

Name	Presentation	Manufacturer
FE 999049	Pre-filled pen for multiple use delivering dose (in mg) as appropriate.	Ferring Pharmaceuticals
GONAL-F	Pre-filled pen for single use delivering dose (in IU) as appropriate.	Merck Serono
DECAPEPTYL	Pre-filled syringe for single use delivering 0.1 mg triptorelin acetate.	Ferring Pharmaceuticals
OVIDREL	Pre-filled pen for single use delivering 250 µg choriogonadotropin alfa.	Merck Serono
CRINONE	Sustained-release vaginal gel in prefilled applicators delivering 90 mg of progesterone.	Merck Serono
UTROGESTAN [a)]	Vaginal capsule delivering 200 mg progesterone.	Besins Healthcare

a) UTROGESTAN, approved for ART treatment in China, may be used as an alternative to CRINONE in this trial. All subjects included in the trial will be treated with the same progesterone product

5.3 Packaging and Labelling

Packaging and labelling of the medicinal products will be performed under the responsibility of the Clinical Trial Supply department at Ferring in accordance with GMP and national regulatory requirements. The IMPs will be packaged according to a kit number list. All medicinal products will be labelled with trial-specific labels containing a unique kit number to ensure traceability. The labels will include a self-adhesive tear-off, which is to be affixed to the dispensing records maintained at the trial site. Details on the packaging and labelling of each medicinal product are provided in the Trial Supply Manual.

5.4 Conditions for Storage and Use

A trial medication delegate will ensure that the medicinal products will be stored under appropriate conditions in a secure location with controlled access. The storage compartment shall be monitored regularly and the temperature shall be documented.

The storage conditions for the IMPs and NIMPs will be as described on the trial-specific or commercial box labels. Deviations in temperature must be reported to Ferring as instructed in the Trial Supply Manual.

5.5 Blinding / Unblinding

5.5.1 Blinding

The trial is assessor-blind, and investigators and other assessors such as embryologists are blinded to individual treatment allocation throughout the trial. The trial medication delegate at site (person responsible for IMP/NIMP), the trial coordinator at site (person entering data into the EDC system), the monitors, and the participating subjects will know the treatment allocation once the subjects are randomised. Precaution must be taken to ensure that the treatment allocations are not available to the investigators or other assessors throughout the trial. Subjects must be clearly instructed to only discuss their treatment allocation with the trial medication delegate, and to not mention it to the investigator or other assessors.

The trial medication delegate will dispense the trial medication to the subject (and may also do the actual administration at the clinic, if required). The investigator will, based on the follicular development, judge if dose adjustments are recommended and state his/her directions on a form developed for that purpose, which will be used to inform the trial medication delegate. Depending on whether the subject is being treated with FE 999049 or GONAL-F, the trial medication delegate will provide detailed instructions to the subject in line with the dosing regimen for each preparation as outlined in the protocol. In other words, if the investigator recommends a dose adjustment, the trial medication delegate will implement a decrease or increase of 5 µg of FE 999049 or 75 IU GONAL-F as applicable. Requests for cycle cancellation due to inappropriate response or other medical reasons are followed, irrespective of treatment group.

The randomisation list and the kit number list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is declared clean and locked. Likewise, the treatment allocation information in the EDC system will not be accessible to assessors or the Ferring clinical trial team (delegated functions that need access to treatment allocation to fulfil their responsibilities are exempted) or laboratory personnel during the trial.

5.5.2 Unblinding of Individual Subject Treatment

An emergency unblinding procedure will be available for the investigator and designated personnel at the sponsor through the IRT.

Emergency Unblinding by Investigator

It is the investigator's responsibility to decide whether it is medically necessary to know which IMP the subject receives, or has received, to ensure the subject's welfare and safety, and thereby the responsibility to break the blind for individual subjects in emergency situations resides with the investigator. Breaking of the blind for individual subjects in emergency situations could be required in case of important adverse events where the knowledge of the IMP in question is required for decisions related to the medical management of the subject.

The investigator who unblinds a treatment will use the IRT system and is required to enter a password before the treatment code can be broken. The IRT system records when, and by whom,

the code was broken. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided. The investigator should notify the ethics committees about the circumstances for unblinding in accordance with local requirements.

In case the IRT system cannot be accessed by the investigator, and hence the emergency unblinding cannot be performed within the IRT, a back-up procedure is in place.

In case of accidental unblinding (e.g. the subject tells the investigator), the same procedure as for emergency unblinding must be followed, i.e. the investigator/person who was accidentally unblinded will enter a password in the IRT system and must record the reason for unblinding. The IRT system records when, and by whom, the code was broken. In addition, the event must also be recorded in the subject's medical record.

Unblinding by Ferring

If Ferring needs to unblind a treatment, the IRT system will be used for unblinding. It is a requirement to enter a password before the treatment code can be broken. The IRT records when, and by whom, the code was broken. The code break will occur according to corporate operational procedures for unplanned unblinding of trial subjects. In case of suspected, unexpected serious adverse reactions (SUSARs), it may be necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the authorities and/or ethics committees. In that situation, every effort will be made to maintain blinding of sponsor personnel involved in data analysis and interpretation. Other personnel may be unblinded for SUSARs, including trial site staff as well as staff acting on behalf of Ferring.

Information on whether the blind has been broken for any subjects is available in the IRT system and must be collected before the database is declared clean and locked.

5.6 Treatment Compliance, Dispensing, and Accountability

Investigational medicinal products will be dispensed only to subjects who meet the eligibility criteria and are randomised to a treatment group in the trial. A trial medication delegate at the site will use an IRT system to assign and dispense IMP kits as per the randomisation performed within the IRT. The trial medication delegate(s) will also record the dates and quantities of the IMPs dispensed to and returned by each subject, as well as manage the overall drug accountability for each subject within the IRT.

In order to monitor compliance with IMP treatment, the subjects are to return boxes and used, partially used, or unused pens to the trial medication delegate. For compliance with NIMP treatment, boxes and unused pens, syringes, and applicators are to be returned to the trial medication delegate. Used or partially used NIMPs are to be discarded in safety containers. Compliance will be monitored by the trial medication delegate at the following visits: end-of-stimulation, oocyte retrieval, embryo transfer, βhCG test, clinical pregnancy, and at the day of end-of-trial assessments. The trial medication delegate will maintain subject dispensing logs, detailing the dates, quantities, and batch numbers of dispensed and returned medicinal products for each

subject in the IRT. The trial medication delegate will also manage the overall drug accountability at the site.

The monitor will verify the drug accountability during the trial.

IMP medication errors with and without clinical consequences will be tracked in the EDC system and reviewed on an ongoing basis by Ferring Global Pharmacovigilance.

5.7 Auxiliary Supplies

Ferring will be responsible for the supply of safety containers for collection of used pens, syringes, applicators, and needles.

5.8 Return and Destruction of Medicinal Products and Auxiliary Supplies

All used and unused (non-dispensed) IMPs/NIMPs will be disposed as instructed in the Trial Supply Manual, after drug accountability has been finalised.

6 TRIAL PROCEDURES

6.1 Trial Flow Chart

The flow of the trial procedures for subjects is shown in Table 6-1.

Table 6-1 Trial Flow Chart – Subject Procedures

	Screening	**Downregulation**		**Stimulation**				**Oocyte retrieval (OR)**	**Embryo transfer (ET)**	**βhCG test**	**Clinical pregnancy**	**Ongoing pregnancy**	**End**
	<90 days before random-isation	Initiation	Con-firmation [a)]	Day 1	Day 6	Day ≥7 to <20 [b)]	End	36 ± 2h after triggering	3 days after OR	13-15 days after ET	5-6 weeks (35-48 days) after ET	10-11 weeks (70-83 days) after ET	End-of-trial [c)]
Written informed consent	X												
Inclusion/exclusion criteria	X	X		X [d)]									
Demographics	X												
Medical history	X												
Infertility history	X												
Body weight, height	X												
Physical examination	X												X
Gynaecological examination	X												X
Urinary pregnancy test (local laboratory)	X	X	X [e)]	X [d)]									
Dispensing of IMP/NIMP, as applicable		X	X	X	X	X	X	X	X	X			
Downregulation (GnRH agonist administration)		X [f)] X											
Transvaginal ultrasound			X	X [d)]	X	X	X				X	X [g)]	
Blood collection, endocrine (central laboratory) [h)]	X			X	X		X						
Blood collection, clinical chemistry / haematology (central laboratory) [i)]	X												X
Blood collection, estradiol (local laboratory)			X [j)]										
Randomisation				X [k)]									
Controlled ovarian stimulation (IMP administration)				X X									

	Screening	**Downregulation**		**Stimulation**				**Oocyte retrieval (OR)**	**Embryo transfer (ET)**	**βhCG test**	**Clinical pregnancy**	**Ongoing pregnancy**	**End**
	<90 days before randomisation	Initiation	Confirmation [a)]	Day 1	Day 6	Day ≥7 to <20 [b)]	End	36 ± 2h after triggering	3 days after OR	13-15 days after ET	5-6 weeks (35-48 days) after ET	10-11 weeks (70-83 days) after ET	End-of-trial [c)]
Triggering of final follicular maturation (hCG administration)							X						
Oocyte retrieval								X					
Luteal phase support (progesterone administration)								X·····X [l)]					
Embryo transfer									X				
Blood collection, βhCG (local laboratory)										X			
Drug accountability							X	X	X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X

a) A minimum of 10 days with GnRH agonist administration should be ensured prior to confirmation of downregulation, which is defined as fulfilling the following criteria: 1) menstrual bleeding, 2) shed endometrium with a thickness <5 mm observed by transvaginal ultrasound, and 3) no ovarian follicles ≥10 mm (including cysts that cannot be punctured prior to stimulation) observed by transvaginal ultrasound. Subsequent visit(s) for confirmation of downregulation may be scheduled according to local practice. If downregulation is not achieved after 28 days, treatment with GnRH agonist will be stopped and the subject will be discontinued from the trial. If downregulation is confirmed, the subject may proceed to controlled ovarian stimulation and undergo the stimulation day 1 assessments on the same day.
b) Visits must be scheduled at least every second day; when the leading follicle reaches a diameter of ≥15 mm visits must be scheduled daily.
c) End-of-trial assessments must be performed at the subject's last scheduled visit (or alternatively at a separate end-of-trial visit within 7 days of the last scheduled trial visit). For subjects who undergo triggering of final follicular maturation, the end-of-trial visit must take place at least 9 days after triggering to cover the assessment of early OHSS (onset ≤9 days after triggering).
d) To be performed before randomisation to treatment.
e) If the subject has not experienced menstrual bleeding at the first assessment of confirmation of downregulation, a urinary pregnancy test is to be performed.
f) Subjects will start pituitary downregulation with GnRH agonist (triptorelin acetate, DECAPEPTYL) 0.1 mg/day subcutaneously in the mid-luteal phase (i.e. cycle day 21-24) of their menstrual cycle.
g) Abdominal or transvaginal ultrasound.
h) Screening: AMH, TSH, and prolactin; stimulation day 1 (before randomisation to treatment and administration of the first IMP dose), stimulation day 6 and end-of-stimulation: estradiol and progesterone.
i) CHEM-20 and CBC
j) In case achievement of downregulation is doubtful or it is deemed helpful, estradiol is to be measured (<50 pg/mL or 180 pmol/L).
k) Once downregulation is confirmed, randomisation and start of stimulation must occur within 7 days. Randomisation will be stratified according to the investigator's assessment of an appropriate starting dose (10 µg FE 999049 / 150 IU GONAL-F or 15 µg FE 999049 / 225 IU GONAL-F).
l) Luteal phase support with progesterone will be initiated on the day of oocyte retrieval or the day after and continued at least until clinical pregnancy (will be stopped earlier in case of menses, negative βhCG or pregnancy loss). Thereafter the investigator may decide to continue luteal phase support up until the ongoing pregnancy visit, according to local practice.

AMH: anti-Müllerian hormone, CBC: complete blood count, ET: embryo transfer, GnRH: gonadotropin-releasing hormone, hCG: human chorionic gonadotropin, IMP: investigational medicinal product, OHSS: ovarian hyperstimulation syndrome, OR: oocyte retrieval, TSH: thyroid-stimulating hormone

6.2 Screening

Potential subjects will be scheduled to come to the clinic for the screening assessments. Screening must be initiated within 90 days before stimulation day 1 (randomisation).

The following must take place during the screening period:

- Signed and dated written informed consent, obtained prior to any trial-related procedures
- Allocation of a screening number
- Check of inclusion and exclusion criteria (those which are possible to check at screening)
- Demographics (date of birth, ethnicity, race)
- Collection of the following data:
  - Relevant medical history (including any cysts)
  - Infertility history
- Body weight and height [*note*: the results will be used for calculation of BMI]
- Physical examination
- Gynaecological examination
- Urinary pregnancy test – must be negative
- Blood collection for central laboratory analysis of:
  - Endocrine parameters (screening panel: AMH, TSH, and prolactin) [*note*: the results must be available before randomisation]
  - Clinical chemistry and haematology parameters [*note*: the results must be available before randomisation]
- Recording of use of any concomitant medication within the last 3 months prior to signed informed consent for participation
- Recording of adverse events (from the date of signed informed consent for participation in the trial)

Subjects considered eligible for the trial based on the inclusion and exclusion criteria assessed at this time point will be provided a subject participation card and proceed to the next visit scheduled on day 21-24 of their menstrual cycle.

6.3 Downregulation

Subjects will attend the downregulation visit on day 21-24 of their menstrual cycle.

The following must take place prior to initiation of pituitary downregulation:

- Ensure that the subject is still eligible for participation in the trial
- Check those inclusion and exclusion criteria that were not possible during screening
- Urinary pregnancy test – must be negative
- Recording of use of any concomitant medication
- Recording of adverse events

Once the above has been completed, the following must be performed by the trial medication delegate:

- Dispensing and administration of GnRH agonist [the first administration of GnRH agonist takes place at the clinic and can be done by either the trial medication delegate or the subject under supervision by the trial medication delegate]

The GnRH agonist should preferably be administered at the same time each day during the downregulation period and the timing of the GnRH agonist administrations should be aligned with the IMP administrations during the stimulation period.

Finally, this must be done before the subject leaves the clinic:

- In the first 30 min following the GnRH agonist administration, the trial medication delegate (or another qualified trial staff) must observe the subject's general health with emphasis on symptoms of an acute allergic reaction.
- Instruct the subject to administer the GnRH agonist at a daily dose of 0.1 mg until the end-of-stimulation visit.

After the downregulation visit, the next visit must be scheduled to ensure a minimum of 10 days with GnRH agonist administration.

6.4 Confirmation of Downregulation

Subjects will attend a visit for confirmation of downregulation. The following criteria must be fulfilled before the subject can proceed to stimulation with FE 999049:

- The subject must have experienced menstrual bleeding
- The subject must have a shed endometrium <5 mm visible on transvaginal ultrasound
- The subject must not have any ovarian follicles ≥10 mm (including cysts that cannot be punctured prior to stimulation) visible on transvaginal ultrasound

In case the subject has not experienced withdrawal bleeding after 10 days, a urinary pregnancy test is to be performed. In case achievement of downregulation is doubtful or it is deemed helpful, blood collection for serum estradiol measurement (<50 pg/mL or 180 pmol/L; local laboratory) is to be performed. If the subject is not pregnant and downregulation is still not confirmed, treatment with GnRH agonist will be continued and stimulation will be postponed. Subsequent visit(s) for confirmation of downregulation may be scheduled according to local practice. If downregulation is not achieved after 28 days, treatment with GnRH agonist will be stopped and the subject will be discontinued from the trial as a screening failure. Dispensing of GnRH agonist is to be performed by the trial medication delegate, if applicable.

If the subject fulfills the criteria for downregulation, the ultrasound performed to confirm downregulation can be combined with the ultrasound assessments performed on stimulation day 1 (see Section 6.5.1).

If downregulation is confirmed, the subject may proceed to controlled ovarian stimulation and undergo the stimulation day 1 assessments on the same day as downregulation is confirmed. A new visit must be scheduled for stimulation day 1 if the subject does not proceed directly to the stimulation day 1 assessments [*note:* visit must occur within 7 days after downregulation is confirmed].

6.5 Stimulation

6.5.1 Stimulation Day 1

Stimulation day 1 visit takes place after downregulation is confirmed. The following must take place before randomisation to treatment:

- Ensure that the subject is still eligible for participation in the trial
- Check those inclusion and exclusion criteria that were not possible during screening
- Urine pregnancy test – must be negative
- Blood collection for central laboratory analysis of estradiol and progesterone
- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, ovarian volume, number and size of follicles). If a cyst ≥10 mm is observed (functional or not), it should be punctured before treatment is initiated.[a] If the cyst was present at the screening visit, it should have been recorded on the medical history form. If the cyst presented between screening and stimulation day 1, it should be recorded on the adverse event form.

[a] Treatment can be initiated the same day. If puncture is not possible, the subject is not to be considered eligible for participation in the trial.

If the subject fulfils all inclusion and exclusion criteria, she will proceed to:

- Assessment of appropriate starting dose level (i.e. 10 µg FE 999049 / 150 IU GONAL-F or 15 µg FE 999049 / 225 IU GONAL-F) and allocation to the corresponding stratum.
- Randomisation to treatment (i.e. FE 999049 or GONAL-F) and assignment to the lowest available subject number within site and stratum.

Once the above has been completed, the following must be performed by the trial medication delegate. Care must be taken to ensure blinding of the investigator and other assessors.

- Dispense IMP according to randomisation and instruct the subject on how to administer the IMP
- Administer the 1st dose of IMP according to randomisation [administration of IMP takes place at the clinic and can be done by either the trial medication delegate or the subject under supervision by the trial medication delegate]:
  - If randomised to FE 999049; starting dose for the first 5 days is fixed at 10 µg or 15 µg according to investigator's assessment
  - If randomised to GONAL-F; starting dose for the first 5 days is fixed at 150 IU or 225 IU according to investigator's assessment
- Dispensing of GnRH agonist, as applicable

The IMP should preferably be administered at the same time each day during the stimulation period and the timing of the IMP administrations should be aligned with the GnRH agonist administrations.

Finally, this must be done before the subject leaves the clinic:

- Recording of use of any concomitant medication
- Recording of adverse events
- In the first 30 min following the IMP administration, the trial medication delegate (or another qualified trial staff) must observe the subject's general health with emphasis on symptoms of an acute allergic reaction.

The next visit must be scheduled for stimulation day 6.

6.5.2 Stimulation Day 6

The following must take place at stimulation day 6:

- Blood collection for central laboratory analysis of estradiol and progesterone – the blood sample must be drawn at least 8 hours after the latest IMP administration
- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial triple-layer structure, endometrial echogenicity pattern, number and size of follicles)
- Recording of use of any concomitant medication
- Recording of adverse events

Once the above has been completed, the following must be performed by the trial medication delegate. Care must be taken to ensure blinding of the investigator and other assessors.

- Dispensing of IMP and potential dose adjustment; from stimulation day 6 and onwards the daily dose may be adjusted based on the individual response
  - FE 999049: the daily dose may be increased or decreased by 5 µg, with dose adjustments implemented not more frequently than once every 2 days
  - GONAL-F: the daily dose may be increased or decreased by 75 IU, with dose adjustments implemented not more frequently than once every 2 days
- Dispensing of GnRH agonist, as applicable

After the stimulation day 6 visit, the next visits must be scheduled at least every second day throughout the remaining stimulation period. When the leading follicle reaches ≥15 mm, visits must be performed daily.

6.5.3 Stimulation Days ≥7 to ≤20

These visits must take place at least every second day throughout the remaining stimulation period. When the leading follicle reaches ≥15 mm, visits must be performed daily. Coasting is not allowed. The maximum period of stimulation is 20 days.

The following must take place at all visits throughout the remainder of the stimulation period (with the exception of the end-of-stimulation visit, which is described in Section 6.5.4):

- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial triple-layer structure, endometrial echogenicity pattern, number and size of follicles)
- Dispensing of IMP, as applicable
- Dispensing of GnRH agonist, as applicable
- Recording of use of any concomitant medication
- Recording of adverse events

6.5.4 End-of-stimulation

The end-of-stimulation visit must take place when the subject reaches the criterion for triggering of final follicular maturation or any of the cycle cancellation criteria because of poor or excessive follicular development as specified in Table 6-2. Administration of hCG must take place as soon as reaching the criterion for triggering of final follicular maturation.

If triggering as soon as reaching the criterion would lead to oocyte retrieval or embryo transfer on a day the clinic is closed e.g. Sunday or a public holiday, stimulation may be continued for one additional day, meaning triggering is delayed for a maximum of one day.

Table 6-2 Triggering and Cycle Cancellation Criteria related to Follicular Development

Poor follicular development	Triggering criterion [a)]	Excessive follicular development
If it is judged by the investigator that the triggering criterion cannot be reached by day 20, the cycle is cancelled.	≥3 follicles with a diameter ≥17 mm. 1 or 2 follicles with a diameter ≥17 mm and investigator judgement that ≥3 follicles with a diameter ≥17 mm cannot be reached and triggering is preferred instead of cycle cancellation. <25 follicles with a diameter ≥12 mm.	If ≥25 follicles with a diameter ≥12 mm, the cycle is cancelled.

a) The investigator has the option of cancelling cycles due to safety concerns. Administration of triggering drug must be performed the day the criterion is met or the day after.

The following must take place at end-of-stimulation visit:

- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial triple-layer structure, endometrial echogenicity pattern, ovarian volume, number and size of follicles)
- Blood collection for central laboratory analysis of estradiol and progesterone – the blood sample must be drawn at least 8 hours after the latest administration of IMP and GnRH agonist
- Dispensing of hCG, as applicable
- Drug accountability of hCG and IMP
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with cycle cancellation, end-of-trial assessments (Section 6.12) must take place at end-of-stimulation visit or, alternatively, at a separate end-of-trial visit within 7 days of the end-of-stimulation visit. For subjects who receive the triggering drug, the next visit is the oocyte retrieval visit which must be scheduled 36h (±2h) after the administration of hCG.

6.6 Oocyte Retrieval

Oocyte retrieval must take place 36h (±2h) after triggering of final follicular maturation. All oocytes from follicles with an estimated diameter ≥12 mm must be retrieved. Below are listed the procedures related to the subjects attending the oocyte retrieval visit, while procedures related to the oocytes are described in Section 6.7.

The following must take place at the oocyte retrieval visit:

- Oocyte retrieval
- Dispensing of progesterone for luteal phase support – must start on the day of oocyte retrieval or the day after and continue at least until clinical pregnancy (will be stopped earlier in case of menses, negative βhCG or pregnancy loss and may continue up until the ongoing pregnancy visit)
- Drug accountability of hCG
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with no oocytes retrieved, end-of-trial assessments (Section 6.12) must take place at a visit scheduled at least 9 days after triggering, to cover the assessment of early OHSS (onset ≤9 days after triggering). For subjects with oocytes retrieved, the next visit is the embryo transfer visit 3 days after oocyte retrieval (Section 6.8).

6.7 Oocyte / Embryo Evaluation

The laboratory procedures regarding handling and evaluation of oocytes and embryos are described in a trial-specific manual. This section provides an overview of the procedures and assessments to be made from oocyte retrieval till transfer at the embryo stage. The flow of the trial procedures for oocytes is shown in Table 6-3. Assisted hatching and pre-implantation genetic diagnosis / pre-implantation genetic screening are prohibited.

Table 6-3 Trial Flow Chart – Oocyte / Embryo Procedures

	Day 0 (OR)	Day 1 after OR	Day 3 after OR
Oocyte retrieval (OR)	X		
Insemination by IVF or ICSI	X		
Assessment of oocyte fertilisation		X	
Assessment of embryo quality			X
Transfer, if applicable			X
Cryopreservation or continued culture, if applicable [a)]			X

a) Available embryo(s) not used for transfer may be cryopreserved (either on day 3 after oocyte retrieval or after continued culture to blastocyst stage on day 5 or day 6 after oocyte retrieval).

ICSI: intracytoplasmic sperm injection, IVF: in vitro fertilisation, OR: oocyte retrieval

Oocyte / embryo-related procedures on Day 0 (oocyte retrieval):

- Assessment of maturity stage (applicable for oocytes undergoing ICSI)
- Insemination using IVF or ICSI using ejaculated sperm (fresh or frozen) from partner or donor

Oocyte / embryo-related procedures on Day 1 after oocyte retrieval:

- Assessment of fertilisation (number of pronuclei)

Oocyte / embryo-related procedures on Day 3 after oocyte retrieval:

- Assessment of embryo quality:
  - Number of blastomeres
  - Degree of fragmentation (either 0%, 1-10%, 11-20%, 21-50% or >50% fragmentation, or totally fragmented (no blastomeres recognised))
  - Blastomere uniformity (equally or unequally)
  - Visual signs of multinucleation (yes/no)

  Good quality embryo is defined as an embryo with ≥6 blastomeres and ≤20% fragmentation, without signs of multinucleation, or with cleavage stage classified as compacting / compacted
- Transfer of 1 to 2 embryos (Section 6.8)

Available embryo(s) can be cryopreserved (either on day 3 after oocyte retrieval or after continued culture to blastocyst stage on day 5 or day 6 after oocyte retrieval) and used by the subject after completion of the trial, in accordance with local guidelines and/or regulations.

6.8 Embryo Transfer

For subjects eligible to transfer, the transfer is performed on day 3 (embryo stage) after oocyte retrieval.

Subject-related procedures for embryo transfer:

- Transfer of 1 or 2 embryo(s) of the highest quality available. The decision to transfer either 1 or 2 embryos will be based on the subject's wishes and the investigator's recommendation and in accordance with local guidelines and/or regulations.
- Dispensing of progesterone for luteal phase support, if applicable

The following assessments must take place:

- Drug accountability of progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects who undergo triggering of final follicular maturation with hCG and have ≥20 oocytes retrieved, no transfer of embryos will take place and end-of-trial assessments (Section 6.12) must take place at a separate end-of-trial visit scheduled at least 9 days after triggering. For subjects with embryo transfer, the next visit is the βhCG test visit which must be scheduled 13-15 days after transfer (Section 6.9).

6.9 βhCG test

Subjects who have undergone transfer must attend a visit 13-15 days after transfer.

The following procedures / assessments must take place:

- Blood collection for local laboratory analysis of βhCG
- Dispensing of progesterone for luteal phase support, if applicable
- Drug accountability of progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

The βhCG test will be evaluated according to the laboratory's reference ranges. In case of a borderline βhCG result, the test should be repeated.

For subjects with a negative βhCG test, end-of-trial assessments as specified in Section 6.12 must take place at βhCG test visit or, alternatively, at a separate end-of-trial visit within 7 days of the βhCG test visit. For subjects with a positive βhCG test, the next visit is the clinical pregnancy visit 5-6 weeks after transfer (Section 6.10).

6.10 Clinical Pregnancy

Subjects with a positive βhCG test must attend a visit 5-6 weeks (35-48 days) after transfer.

The following procedures / assessments must take place:

- Transvaginal ultrasound of uterus to assess any clinical pregnancy
- Drug accountability of progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

If at least one gestational sac (either intrauterine or ectopic) is observed, this confirms a clinical pregnancy. If at least one intrauterine gestational sac with fetal heart beat is observed, this confirms a vital pregnancy.

The investigator has the option of continuing luteal phase support up until the ongoing pregnancy visit, according to local practice.

For subjects with no vital pregnancy, end-of-trial assessments as specified in Section 6.12 must take place at the clinical pregnancy visit. For subjects with a vital pregnancy, the next visit is the ongoing pregnancy visit 10-11 weeks after transfer (Section 6.11).

6.11 Ongoing Pregnancy

If a vital pregnancy has been documented, the subject must attend a visit 10-11 weeks (70-83 days) after transfer.

The following procedures / assessments must take place:

- Ultrasound (transvaginal or abdominal) of uterus to assess any intrauterine viable fetus
- Recording of use of any concomitant medication
- Recording of adverse events

If at least one intrauterine viable fetus is identified, this confirms an ongoing pregnancy.

For subjects attending the ongoing pregnancy visit, end-of-trial assessments as specified in Section 6.12 must take place at this visit.

6.12 End-of-trial

If a subject attends the scheduled trial visits, the end-of-trial assessments should take place at the last scheduled trial visit, i.e. for subjects with a confirmed vital pregnancy, the ongoing pregnancy visit would be the last scheduled trial visit and thus the visit where the end-of-trial assessments

should be done. Alternatively, a separate end-of-trial visit within 7 days of the last scheduled trial visit may be scheduled.

The following procedures / assessments must take place at the end-of-trial visit, irrespective of whether the subject discontinues the trial prematurely or completes it:

- Physical examination
- Gynaecological examination
- Recording of use of any concomitant medication
- Recording of adverse events
- Blood collection for central laboratory analysis of:
  - Clinical chemistry and haematology parameters

These assessments serve to document the subject's physical health at the end of the trial.

6.13 Pregnancy Follow-up

If an ongoing pregnancy has been documented, the subject will be followed until delivery for documentation on live birth. Neonatal health data, including any congenital anomalies, at birth and at 4 weeks after birth will be collected as follow-up to the current trial (Section 7.4).

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Primary Endpoint - Number of Oocytes Retrieved

Number of oocytes retrieved will be recorded at oocyte retrieval visit.

7.2 Assessments Related to Secondary Endpoints

7.2.1 Number of Follicles

Transvaginal ultrasound will be performed at all visits during the stimulation period to count the number of follicles and measure the size of the follicles. The data will be recorded in accordance with an EDC completion guideline.

7.2.2 Serum Concentrations of Estradiol and Progesterone

Blood samples will be drawn at stimulation day 1, stimulation day 6, and at end-of-stimulation visit to evaluate estradiol and progesterone concentrations in serum. The sample on stimulation day 1 (baseline) will be collected prior to the first dose of FE 999049 or GONAL-F.

The analysis will be performed at a central laboratory. The investigator will review and evaluate the laboratory results. The laboratory report will be signed and dated by the investigator.

7.2.3 Number of Fertilised Oocytes and Fertilisation Rate

Number of pronuclei will be counted on day 1 after insemination and recorded as 0, 1, 2 or >2. Fertilised oocytes with 2 pronuclei will be regarded as correctly fertilised.

Fertilisation rate is defined as the number of correctly fertilised oocytes divided by the number of oocytes retrieved.

7.2.4 Number of Embryos

Each embryo will be evaluated on day 3 after oocyte retrieval. A quality evaluation will consist of assessment of cleavage stage and embryo morphology parameters (blastomere uniformity, degree of fragmentation and visual signs of multinucleation).

Cleavage stage will be defined by the number of blastomeres: 1, 2, 3, 4, 5, 6, 7, 8, …. It will also be possible to indicate the compaction status instead of number of blastomeres.

Blastomere uniformity will be classified as equally sized blastomeres or unequally sized blastomeres (largest blastomere >25% larger in average diameter compared to the smallest blastomere).

Degree of fragmentation will be classified as one of the following: 0%, 1-10%, 11-20%, 21-50% or >50% fragmentation, or totally fragmented (no blastomeres recognised).

Visual sign of multinucleation will be evaluated as yes or no.

7.2.5 Total Gonadotropin Dose and Number of Stimulation Days

Start and end dates, as well as daily dose of IMP will be recorded.

7.2.6 Positive βhCG Rate

A serum βhCG test will be performed 13-15 days after transfer. If the test is positive according to the local laboratory's reference ranges, this confirms a positive βhCG.

7.2.7 Clinical Pregnancy Rate

A transvaginal ultrasound of the uterus will be performed 5-6 weeks after transfer. Clinical pregnancy will be defined as at least one gestational sac, either intrauterine or ectopic. The inclusion of ectopic pregnancies and the lack of specification of heart beat in the definition of clinical pregnancy is in line with the current International Committee Monitoring Assisted Reproductive Technologies (ICMART) and World Health Organization (WHO) glossary on ART terminology.[b, 37] For intrauterine and ectopic pregnancies, the number of gestational sacs with fetal heart beat as well as without fetal heart beat will be recorded.

7.2.8 Vital Pregnancy Rate

A transvaginal ultrasound of the uterus will be performed 5-6 weeks after transfer. Vital pregnancy will be defined as at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer.

7.2.9 Implantation Rate

Implantation is determined based on the transvaginal ultrasound performed at the clinical pregnancy visit.

Implantation rate is defined as the number of gestational sacs 5-6 weeks after transfer divided by number of embryos transferred.

[b] ICMART and WHO glossary on ART terminology: Clinical pregnancy – a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. It includes ectopic pregnancy.

7.2.10 Ongoing Pregnancy Rate

A transvaginal or abdominal ultrasound of the uterus will be performed 10-11 weeks after transfer. Ongoing pregnancy will be defined as at least one intrauterine viable fetus. For ongoing pregnancies, the number of intrauterine viable fetuses will be recorded.

7.2.11 Ongoing Implantation Rate

Ongoing implantation is determined based on the ultrasound performed at the ongoing pregnancy visit.

Ongoing implantation rate is defined as number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of embryos transferred.

7.2.12 Early OHSS, Late OHSS, and Total OHSS

Classification of grade is according to Golan's classification system (Section 8.3.2) and all OHSS cases will be graded as mild, moderate or severe. Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation and late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation.

7.3 Other Assessments

7.3.1 Demographics

Demographic information will be obtained during the screening period, including date of birth and confirmation of the subject's ethnicity and race. Subjects must possess a Chinese identification card and have native Chinese parents.

7.3.2 Medical History

Any relevant medical history (including any cysts) will be recorded at screening. This includes diagnoses / symptoms and whether it is a past or ongoing occurrence.

7.3.3 Infertility History

Information about the reasons of infertility will be obtained during the screening period. Duration of infertility will be recorded before randomisation on stimulation day 1. This will also cover information about any previous treatment for infertility, including type of treatment and gonadotropin preparations used.

7.3.4 Body Weight and Height

Body weight and height will be measured at screening. Body weight will be measured without shoes and overcoat and using a calibrated scale. The measures will be used for calculation of body mass index (BMI).

7.3.5 Physical Examination

A complete physical examination will be performed at screening and end-of-trial. Information will be recorded for general appearance, central and peripheral nervous system, head and neck (including ears, eyes, nose, mouth and throat), respiratory system, cardiovascular system, gastrointestinal system, lymphatic system, urinary system, musculoskeletal system and skin.

At screening, each category will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant findings at screening must be reported in the Medical History Log.

At end-of-trial, potential changes from screening to end-of-trial will be evaluated for each category. In case of changes, these will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant changes from screening to end-of-trial must be recorded as adverse events.

7.3.6 Gynaecological Examination

A complete gynaecological examination will be performed at screening and end-of-trial. Information will be recorded for breast, external genitalia, vagina, cervix, uterus, ovaries and fallopian tubes.

At screening, each category will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant findings at screening must be reported as medical history or as reason for infertility on the Infertility History form, as applicable, and evaluated in accordance with inclusion criteria 7 (Section 4.1.1).

At end-of-trial, potential changes from screening to end-of-trial will be evaluated for each category. In case of changes, these will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant changes from screening to end-of-trial must be recorded as adverse events.

7.3.7 Serum Concentrations of AMH, TSH, and Prolactin

A blood sample will be drawn at screening to evaluate circulating AMH, TSH, and prolactin concentrations.

The analysis will be performed at a central laboratory. The investigator will review and evaluate the laboratory results. The laboratory report will be signed and dated by the investigator.

7.3.8 Clinical Chemistry and Haematology Parameters

Blood samples will be drawn at screening and end-of-trial to evaluate clinical chemistry and haematology parameters.

CHEM-20: alanine transaminase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, bilirubin direct, bilirubin total, blood urea nitrogen, calcium, chloride, cholesterol total, creatinine, gamma-glutamyl transpeptidase, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, and uric acid.

Complete Blood Count (CBC): red blood cells, red blood cell morphology, white blood cells, white blood cell morphology, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, and platelets.

The analysis will be performed at a central laboratory. The investigator will review the laboratory results, evaluate and document whether any abnormal results are non-clinically or clinically significant. The Laboratory Report will be signed and dated by the investigator.

7.3.9 Ovarian Volume

As part of the transvaginal ultrasounds performed at stimulation day 1 and end-of-stimulation, the size of each ovary will be measured. Length, width, and depth will be recorded in mm. The measures will be used for calculation of ovarian volume.

7.3.10 Endometrial Status

Transvaginal ultrasound of the uterus to assess the endometrial status will be conducted on stimulation days 1 and 6 and thereafter at least every second day during the stimulation period. The endometrial status assessments consist of the following parameters: endometrial thickness, endometrial triple-layer structure and endometrial echogenicity pattern [*note*: the latter two are not assessed on stimulation day 1].

Endometrial thickness (composed of both layers of the endometrium) will be measured in the sagittal view of the uterus from the proximal and distal interfaces between the echogenic endometrium and the hypoechoic inner layer of the myometrium. Care should be taken not to include the hypoechoic subendometrial halo and to account for the presence of any fluid in the uterine cavity (not to be included in the endometrial thickness value). Endometrial thickness will be recorded in mm.

Endometrial triple-layer structure will be recorded as observed or not.

Endometrial echogenicity pattern will be recorded as hypoechogenic, isoechogenic, hyperechogenic, or not possible to evaluate.

7.3.11 Embryo Transfer Procedure

Any difficulty or eventuality (e.g. greater resistance is met, the procedure is time-consuming, there is a need to change to a harder catheter, uterine sounding or cervical dilation is carried out, or there is blood in any part of the catheter) during the transfer procedure will be noted.

7.3.12 Concomitant Medication

The use of any concomitant medication within the last 3 months prior to informed consent for participation in the trial (except medication used in previous infertility treatment cycles) and throughout the trial will be recorded. Recording of concomitant medication will be performed at all visits. Any changes in concomitant medications or treatments must be recorded at each visit.

7.3.13 Drug Dispensing and Accountability

For all medicinal products, dates of administration and dose administered will be recorded. Furthermore, time of administration will also be recorded for IMP, GnRH agonist, and hCG. Details on drug dispensing and accountability are provided in Section 5.1.

7.4 Pregnancy Follow-up

7.4.1 Live Birth Rate

For subjects with an ongoing pregnancy, information on the pregnancy period, including any relevant interventions performed and incidence of second or third trimester losses, as well as the pregnancy outcome, e.g. live birth[c], will be collected.

7.4.2 Neonatal Health

Neonatal health data will be collected at birth and at 4 weeks after birth for all children born. At birth, the data collected will include gender, birth weight and length, way of delivery, position of neonate and Apgar score as well as information on any congenital anomalies and admission to neonatal intensive care unit (NICU) or neonatal care unit (NCU). At 4 weeks after birth, the data collected will include any congenital anomalies, hospitalisations, death of neonate and important medical events. These follow-up data can be obtained from the subject, unless medical judgement is required.

[c] Live birth: gestational age ≥24 weeks + 0 days, calculated from the day of day 3 embryo transfer + 17 days

7.5 Handling of Biological Samples

A trial-specific laboratory manual will be provided to the participating sites, describing in detail how to handle, store, and transport biological samples in this trial. For biological samples collected in the trial, analyses beyond those described in the protocol can only be performed after obtaining required approvals. The processes related to handling of biological samples will be described in the Informed Consent Forms and biobank / data protection legislation, including local legislation, will be adhered to.

Blood and urine samples collected for local laboratory analyses will be destroyed after the analysis. Blood samples collected for central laboratory analyses will be maintained in storage after the end of the trial. Destruction will take place within 2 years after reporting of the trial.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An adverse event is any untoward medical occurrence in a subject participating in a clinical trial. It includes:

- Any unfavourable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital sign or finding from physical or gynaecological examination assessed as clinically significant by the investigator [*note:* pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not adverse events but are recorded as medical history].
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.

All adverse events will be coded by Ferring Global Pharmacovigilance using Medical Dictionary for Regulatory Activities (MedDRA; the version effective at trial start).

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the last visit; the last scheduled visit or a separate end-of-trial visit scheduled within 7 days of the last scheduled visit or at least 9 days after the end-of-stimulation visit (applicable to subjects who undergo triggering of final follicular maturation).

The sources of adverse events cover:

- The subject's response to questions about her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit).
- Symptoms spontaneously reported by the subject.
- Investigations and examinations where the findings are assessed by the investigator to be clinically significant changes or abnormalities.
- Other information relating to the subject's health becoming known to the investigator (e.g. hospitalisation).

8.2.2 Recording of Adverse Events

The investigator must record all adverse events in the Adverse Event Log provided for each subject in the EDC system with information about:

- Adverse event description
- Date and time of onset (time can be omitted, if applicable) [*note:* if date of onset of an event is the same as the date of informed consent or date of IMP administration, time is important and should not be omitted]
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- End date and time (time can be omitted, if applicable)
- Outcome
- Seriousness

Each of the items in the Adverse Event Log is described in detail in the following sections.

Adverse Event Description

Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

If a subject suffers from the same adverse event more than once and the subject recovers in between the events, the adverse events should be recorded separately. If an adverse event changes in intensity, a worst-case approach should be used when recording the event, i.e. the highest intensity and the longest duration of the event.[d] If a subject suffers from a pre-existing medical condition that worsens in intensity after signed informed consent, it should be recorded as an adverse event [*Note*: a procedure is not an adverse event; the reason for conducting the procedure is, hospitalisation is not an adverse event; the reason for hospitalisation is, death is not an adverse event, but the cause of death is (an exception is sudden death of unknown cause, which is an adverse event)].

[d] Exception: if an adverse event with onset before the first IMP administration (i.e. a pre-treatment adverse event) worsens in intensity after IMP administration, this must be recorded as two separate events. The initial adverse event should be recorded with outcome “not recovered”, without recording end date and time. The second adverse event should be recorded with date and time of onset when the intensity changed.

Date and Time of Onset

The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the adverse event is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed.

Intensity

The intensity of an adverse event must be classified using the following 3-point scale:

Mild: Awareness of signs or symptoms, but no disruption of usual activities

Moderate: Disruption of usual activities (disturbing)

Severe: Inability to work or perform usual activities (unacceptable)

Causal Relationship to IMP

The possibility of whether the IMP caused the adverse event must be classified as one of the following:

Reasonable possibility:

There is evidence or argument to suggest a causal relationship between the IMP and the adverse event. The adverse event may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

Examples:

- Adverse events that are uncommon but are known to be strongly associated with IMP exposure.
- Adverse events that are not commonly associated with IMP exposure, but the event occurs in association with other factors strongly suggesting causation, such as a strong temporal association or the event recurs on rechallenge.

No reasonable possibility:

There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the adverse event.

Examples:

- Known consequences of the underlying disease or condition under investigation.
- Adverse events common in the trial population, which are also anticipated to occur with some frequency during the course of the trial, regardless of IMP exposure.

An adverse drug reaction is defined as an adverse event assessed to be causally related to the administration of IMP with a reasonable possibility.

Action Taken to IMP

The action taken to the IMP in response to an adverse event must be classified as one of the following:

- No change (applicable for when the IMP regimen is maintained as well as for adverse events occurring before first dose of IMP or after last dose of IMP as per protocol)
- Discontinued
- Interrupted
- Dose reduced
- Dose increased

Other Action Taken

Adverse events requiring therapy must be treated with recognised standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the adverse event, this medication should be entered in the Concomitant Medication Log.

End Date and Time

The date and time (time can be deleted/omitted, if applicable) the subject recovered or died.

Outcome

The outcome of an adverse event must be classified as one of the following:

- Recovered (fully recovered or the condition has returned to the level observed at initiation of trial treatment)
- Recovered with sequelae (resulted in persistent or significant disability/incapacity)
- Recovering (the event is improving)
- Not recovered
- Fatal

8.3 Other Significant Adverse Events

8.3.1 Adverse Events Leading to Discontinuation

Adverse events leading to discontinuation from the trial, discontinuation from treatment, or dose reduction not defined in the clinical trial protocol will be considered as other significant adverse events.

8.3.2 Adverse Event of Special Interest

8.3.2.1 Ovarian Hyperstimulation Syndrome

Symptoms and Classification

OHSS is an adverse event of special interest during controlled ovarian stimulation. Investigators will record OHSS symptoms and use these symptoms directly to grade (1, 2, 3, 4 or 5) each OHSS case into Golan's classification system[38] as shown in Table 8-1.

Table 8-1 Classification of Mild, Moderate and Severe OHSS (Golan's Classification System)

Mild OHSS	
Grade 1	Abdominal distension and discomfort
Grade 2	Features of grade 1 plus nausea/vomiting and/or diarrhoea. Ovaries enlarged to 5-12 cm.[a)]
Moderate OHSS	
Grade 3	Features of mild OHSS plus ultrasonic evidence of ascites.[b)]
Severe OHSS	
Grade 4	Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax (or breathing difficulties). Paracentesis due to OHSS symptoms. [c)]
Grade 5	All of the above plus change in blood volume, increased blood viscosity due to haemoconcentration, coagulation abnormalities, and diminished renal perfusion and function.[d)] Hospitalisation due to OHSS symptoms.

a) For each ovary, the size will be the average of the greatest diameter and its greatest perpendicular diameter. Ovarian enlargement will be based on the average size of the right and left ovaries. The sizes of both ovaries should be recorded.

b) For subjects with transvaginal evidence of ascites, the size of the fluid pockets in the pelvis (Douglas pouch, vesico-uterine pouch, etc) should be estimated by measuring the greatest diameter and its greatest perpendicular diameter and multiplying these two numbers (the unit will be cm^2). Peritoneal fluid is the total size of all fluid pockets in the pelvis.

c) In case of paracentesis, the volume of fluid drained should be measured.

d) Haemoconcentration is defined as haematocrit >45 %. Electrolyte disturbances is defined as hyponatremia (sodium <135 mEq/L) and/or hyperkalemia (potassium >5.0 mEq/L). Coagulation abnormalities are defined as presence of thromboembolic events, abnormal prothrombin time or abnormal activated partial thrombin time. Diminished renal perfusion is defined as creatinine >1.2 mg/dl. Oliguria is defined as urine output less than 500 mL / 24 hours. Anuria is defined as failure to produce urine. If applicable, actual volume of urine output will be recorded.

All cases of OHSS must be reported as adverse events. Those that fall under the category serious adverse events (SAEs) must be reported as such [*Note:* the classification 'mild OHSS', 'moderate OHSS' and 'severe OHSS' does not refer to the classification of an adverse event's intensity (also rated mild, moderate, or severe)].

Subject narratives will be prepared for all moderate and severe OHSS cases.

Concerning timing, early OHSS will be defined as OHSS with onset ≤9 days after triggering of final follicular maturation and late OHSS will be defined as OHSS with onset >9 days after triggering of final follicular maturation.

All OHSS cases will be monitored on an ongoing basis and discussed at centralised monitoring meetings, as described in the centralised monitoring plan.

Investigations to be Conducted in Subjects where OHSS Symptoms are Observed

The following investigations must be conducted when OHSS symptoms are first observed and repeated when there are clinically relevant changes in the OHSS presentation:

- Body weight and maximum abdominal circumference (for all OHSS)
- Vital signs (for all OHSS)
- Blood sample for central laboratory analysis of (for moderate/severe OHSS):
  - Estradiol and progesterone
  - CHEM-20 (alanine transaminase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, bilirubin direct, bilirubin total, blood urea nitrogen, calcium, chloride, cholesterol total, creatinine, gamma-glutamyl transpeptidase, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, uric acid)
  - CBC (red blood cells, red blood cell morphology, white blood cells, white blood cell morphology, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, platelets)
  - Coagulation parameters (prothrombin time, activated partial thrombin time)

Any treatments of OHSS, e.g. intravenous administration of volume expanders, paracentesis, use of low-molecular-weight heparin and intravenous administration of albumin, must be recorded as concomitant medication.

8.3.2.2 Pregnancy Losses

The following terminology should be used for reporting of pregnancy losses during the trial:

Biochemical pregnancy:	Positive βhCG test but no gestational sac is observed on later transvaginal ultrasound, or menstruation is reported
Spontaneous abortion:	Positive βhCG test but all intrauterine gestational sacs are without fetal heart beat as documented by ultrasound, or there are no viable fetuses observed by ultrasound
Vanishing twin:	Spontaneous disappearance of an intrauterine gestational sac with or without heart beat in a pregnancy where one viable fetus remains as documented by ultrasound

Ectopic pregnancy:	Extrauterine gestational sac with or without fetal heart beat as documented by ultrasound or surgery

Concerning timing, a pregnancy loss occurring before ongoing pregnancy (i.e. during 1st trimester) will be defined as an early pregnancy loss, while a pregnancy loss occurring after ongoing pregnancy (i.e. during 2nd or 3rd trimester) during the pregnancy follow-up will be defined as a late pregnancy loss.

8.3.3 Local Tolerability

Injection site reactions after administration of IMP are only to be reported as adverse events if they require active management, i.e. discontinuation of IMP, additional investigations or treatment of the injection site reaction.

8.3.4 Menstrual Bleeding

Menstrual bleeding is only to be reported as an adverse event in case it is excessive, painful, delayed or in any other way deviating from the subject's normal menstruation. Menstrual bleeding associated with lack of pregnancy will be reported as part of the efficacy evaluation.

8.3.5 Ovarian Torsion

Any case of ovarian torsion will be reported as an adverse event and it will be specified whether it is associated with any signs or symptoms of OHSS.

8.4 Serious Adverse Events

8.4.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined as a serious adverse event if it:	**Guidance**
results in **death**	-
is **life-threatening**	The subject was at immediate risk of death at the time of the event. The criterion does not refer to an event which might hypothetically have caused death if it were more severe.
requires **hospitalisation**	Hospitalisation is defined as requiring in-patient admission to hospital or as prolongation of existing hospitalisation as a result of an event.
results in persistent or significant **disability/incapacity**	Disability / incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgement by the investigator.
is a **congenital anomaly/birth defect**	Observed in any offspring of the subject conceived during treatment with the IMP.
is an **important medical event**	Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Serious Adverse Events during Pregnancy Follow-up

Pregnancy outcome will be collected for all subjects with an ongoing pregnancy, as a follow-up to the current trial. Furthermore, neonatal health data will be collected at birth (i.e. data reported on the day of birth [day 0] or the day after [day 1]) and at 4 weeks after birth (reported between day 2 and day 28 [both inclusive]).

The following untoward medical occurrences reported as part of the pregnancy follow-up will be recorded as SAEs:

- Death of mother in connection with pregnancy or labor
- Death of neonate
- Stillbirth[e]
- Neonate admitted to the neonatal intensive care unit (NICU) regardless of duration, or neonate admitted to the neonatal care unit (NCU) for more than 2 hours[f]

[e] Stillbirth: gestational age ≥24 weeks + 0 days, calculated from the day of day 3 embryo transfer + 17 days.

[f] Only classifies as SAE if NICU / NCU admission is due to medical reasons, i.e. NICU / NCU admission due to hospital protocol only does not classify as SAE.

- Congenital anomaly / birth defect
- Important medical event in the neonate

In case of admission to NICU or NCU, the reason for admission must be reported as an SAE, rather than just the act of hospitalisation.

Congenital anomalies are defined as abnormalities of body structure or function that are present at birth and are of prenatal origin. For some congenital anomalies (e.g. patent ductus arteriosus or undescended testes), the case definition may vary depending on gestational age at delivery, i.e. they may be considered physiological among preterm neonates. Nevertheless, all abnormalities of body structure or function – both minor and major, detected in fetuses/neonates, and all events in doubt, regardless of other confounding factors like preterm birth – are to be reported as SAEs with the seriousness criterion 'congenital anomaly' for the purpose of safety surveillance. Congenital anomalies will be coded by Ferring using both MedDRA and International Classification of Diseases (ICD) and classified as minor or major [Note*:* congenital post-mortem findings following a pregnancy loss should not be reported as SAEs].

8.4.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be communicated **immediately** to Ferring Pharmacovigilance as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE.

The investigator is responsible for providing the completed and signed SAE Report Form with the fullest possible details **within 5 calendar days** of his/her knowledge of the SAE. In case collected follow-up information leads to changes in the investigator causality assessment, the investigator must re-sign the SAE form.

The same timelines apply for both the SAE Report Form and any follow-up with additional information regarding the SAE, i.e. 24 hours within obtaining knowledge of the follow-up information and 5 calendar days for providing the fullest possible details.

Serious Adverse Event Report Form

The SAE Report Form is included in the EDC system and must be completed and submitted according to the instructions provided on the form. In case the EDC system cannot be accessed and hence the SAE Report Form cannot be filled in within the EDC system, a paper SAE Report Form should be used and sent to Ferring Pharmacovigilance using the contact details below.

Global Pharmacovigilance, Ferring Pharmaceuticals A/S
E-mail: Safety.Mailbox@ferring.com
Fax: (+45) 88 38 01 47

Completion of the Demographics, Adverse Event Log, Medical History Log and Concomitant Medication Log are mandatory for initial reports and for follow-up reports if any relevant changes have been made since the initial report. Data entries must have been made in the EDC system for Ferring Pharmacovigilance to access the information.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g. laboratory parameters (that are not already uploaded in the EDC system), invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring Pharmacovigilance using the contact details in the section above. In any case this information must be supplied by the investigator upon request from Ferring. On any copies provided, personal details such as subject's name, address, and hospital name should be concealed and instead subject number should be provided.

The investigator will supply Ferring and the ethics committees with any additional requested information.

Overdose and medication errors of IMP with and without clinical consequences will be tracked in the EDC and reviewed by Ferring Pharmacovigilance on an ongoing basis.

Expedited Reporting by Ferring

Ferring will report all adverse events according to local regulations.

8.5 Follow-up of Adverse Events and Serious Adverse Events

8.5.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, the investigator must follow-up on each adverse event until the subject's last visit. After the subject's last visit, the investigator must follow-up on any adverse event classified as serious or considered to have a reasonable possible causality to the IMP until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to Ferring. Follow-up should continue until the outcome of recovered, recovered with sequelae, or fatal, has been reached. If the event is considered stable or a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

8.5.2 Collection of Serious Adverse Events with Onset after Last Visit in the Trial

If an investigator becomes aware of an SAE after the subject's last visit, diagnosed either to the subject herself or to the fetus / neonate, and investigator assesses the SAE to have a reasonable possible causality to IMP (FE 999049 or GONAL-F) or NIMP where Ferring is Marketing Authorisation Holder (DECAPEPTYL), the case will have to be reported to Ferring (see

Section 8.4.2), regardless how long after the end of the trial this takes place.

8.5.3 Follow-up of Serious Adverse Events in Neonates

During the follow-up of neonatal health, any serious adverse event reported as not recovered at the 4-weeks follow-up assessment must be followed by the investigator until the SAE has resolved. If the SAE is a chronic condition or the medical condition of the neonate is stable, the investigator and Ferring may agree that further follow-up is not required.

8.6 Technical Complaints

A technical complaint can include but is not limited to problems with dose delivery, the packaging material (e.g. label text is not legible) or the physical appearance of a trial product (e.g. particles or discoloration).

If a technical complaint is identified, the investigator must assess whether it may be associated with an adverse event and/or a medication error. Technical complaints are reported in accordance with instructions in the Trial Supply Manual.

9 STATISTICAL METHODS

9.1 Determination of Sample Size

In a previous trial (000145) comparing individualised dosing of FE 999049 with GONAL-F in a GnRH antagonist protocol, the standard deviation for number of oocytes retrieved in subjects from China receiving a starting dose of 150 IU of GONAL-F was 7.5. Assuming the standard deviation in this trial to be 7.5, and assuming the treatments to be equally effective for the primary endpoint (number of oocytes retrieved), a sample size of 133 subjects per treatment group will give 90% power to demonstrate non-inferiority of FE 999049 vs. GONAL-F. This is based on a non-inferiority margin of 3.00 oocytes, a one-sided 2.5% significance level, and was calculated using the normal approximation. A total of 300 subjects will be randomised in the trial to ensure at least 90% power also for the analysis of the per-protocol analysis set.

9.2 Subject Disposition

All subjects screened should be accounted for with respect to allocation to analysis sets and trial completion.

9.3 Protocol Deviations

Major protocol deviations, such as significant non-compliance or other serious unforeseen deviations deemed to invalidate the data for the primary endpoint, will lead to exclusion of data from the per-protocol (PP) analysis set. Data will not be excluded from the PP analysis set in case of minor protocol deviations or protocol deviations not affecting the primary endpoint. The list of major protocol deviations includes, but is not limited to:

- Unblinding of assessor
- Non-compliance with IMP for two or more days
- The hCG for triggering of final follicular maturation was incorrectly administered, resulting in no oocytes retrieved

The rating of protocol deviations in ‘minor’ and ‘major’ will be decided by the Ferring clinical team on the basis of a blinded review of data before declaration of clean file and lock of database. If the blinded review identifies serious unforeseen deviations deemed to impact the primary endpoint, these will also be rated as major deviations.

The list of major protocol deviations will be detailed and documented in the clean file document prior to database release.

9.4 Analysis Sets

9.4.1 Full Analysis Set

The full analysis set (FAS) comprises all randomised and exposed subjects. Subjects will be analysed according to randomised treatment.

9.4.2 Per Protocol Analysis Set

The per-protocol (PP) analysis set comprises all randomised and exposed subjects except those excluded as a result of major protocol deviations as described in Section 9.3. Subjects will be analysed according to actual treatment received.

9.4.3 Safety Analysis Set

The safety analysis set comprises all treated subjects and is analysed according to the actual treatment received.

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

Demographics and other baseline characteristics will be summarised by treatment group.

9.5.2 Medical History

Medical history will be coded using MedDRA and will be summarised by System Organ Class (SOC) and Preferred Term (PT).

9.5.3 Concomitant Medication

Concomitant medication will be coded using the World Health Organisation Drug Reference List and will be summarised by Anatomical Therapeutic Chemical Classification System (ATC) classification 1st level (alphabetically) and ATC classification 2nd level.

9.5.4 Other Safety Evaluations

Physical and gynaecological examination findings will be summarised by treatment group.

9.6 Statistical Analysis

9.6.1 General Considerations

Non-inferiority comparison for the primary endpoint will be performed for both the FAS and the PP analysis set. Other efficacy analyses will be performed for the FAS only. All descriptions of safety data (including the secondary endpoint on OHSS) will be based on the safety analysis set.

Missing data will, in general, not be imputed. For subjects without oocyte retrieval, the number of oocytes, fertilised oocytes, and embryos will be regarded as zero. For pregnancy endpoints, lack of data will be interpreted as a negative pregnancy, unless a subsequent pregnancy endpoint is confirmed to be positive. Missing endocrine values of stimulation day 1 will, when used as covariate, be imputed by the mean of all non-missing values for this visit.

All statistical analyses will be detailed in a Statistical Analysis Plan which will be issued as a separate document and finalised before FPFV.

9.6.2 Primary Endpoint

The primary endpoint, number of oocytes retrieved, will be compared between FE 999049 and GONAL-F using a negative binomial model with treatment and dose level (10 µg/150 IU or 15 µg/225 IU) as factors. The absolute treatment difference in number of oocytes retrieved and the associated two-sided 95% confidence interval will be derived from the model estimates using the delta method. Non-inferiority will be considered confirmed if the lower limit of the 95% confidence interval for the difference between FE 999049 and GONAL-F is greater or equal than -3.00.

9.6.3 Secondary Endpoints

Number of Follicles

Total number of follicles, and number of follicles ≥10 mm, ≥12 mm, ≥15 mm and ≥17 mm, on stimulation day 6 and at end-of-stimulation will (in separate analyses) be compared between FE 999049 and GONAL-F using the same negative binomial regression model as used for the primary endpoint.

Serum Concentrations of Estradiol and Progesterone

Serum concentrations of estradiol and progesterone on stimulation day 6 and at end-of-stimulation will (in separate analyses) be compared between FE 999049 and GONAL-F using analysis of covariance (ANCOVA) models with treatment and dose level as factors and with the serum concentration on stimulation day 1 as a covariate. Multiplicative models will be used, i.e. the serum concentrations will be log-transformed before analysis. The results of the analyses will be back-transformed and presented as estimated geometric means and mean treatment ratios. Values below the lower limit of quantification (LLOQ) will be estimated with LLOQ/2. Potential values above the upper limit of quantification (ULOQ) will be included as ULOQ.

Number of Fertilised Oocytes and Fertilisation Rate

Number of Fertilised oocytes will be compared between FE 999049 and GONAL-F using the same negative binomial regression model as used for the primary endpoint. The fertilisation rate (number of fertilised oocytes/number of oocytes) will be described for subjects with at least one oocyte retrieved.

Number of Embryos

Number of embryos and good-quality embryos will be compared between FE 999049 and GONAL-F using the same negative binomial regression model as used for the primary endpoint.

Total Gonadotropin Dose and Number of Stimulation Days

Total gonadotropin dose will be summarized by treatment and dose level. Number of stimulation days will be compared between FE 999049 and GONAL-F using an analysis of variance model with treatment and dose level as factors.

Pregnancy Endpoints (Positive βhCG rate, Clinical Pregnancy Rate, Vital Pregnancy Rate, and Ongoing Pregnancy Rate)

Pregnancy endpoints will be compared between FE 999049 and GONAL-F using a logistic regression model with treatment and dose level as factors. The results in terms of odds for pregnancy will be converted into proportions, difference in proportions, and a 95% confidence interval for difference in proportions using the delta method.

Implantation Rate and Ongoing Implantation Rate

Implantation rates will be described separately for subjects with single and multiple embryo transfer.

Early OHSS, Late OHSS, and Total OHSS

Occurrences of early OHSS, late OHSS, and total OHSS will be evaluated using descriptive statistics.

9.7 Safety – Adverse Events

Adverse events will be coded using MedDRA. Treatment-emergent adverse events[g] will be summarised by System Organ Class (SOC) and Preferred Term (PT).

[g] A treatment-emergent adverse event is any adverse event occurring after start of IMP and until the last scheduled visit (or alternatively at a separate end-of-trial visit within 7 days of the last scheduled trial visit), or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of IMP and until the end-of-trial visit.

Adverse events and other safety assessments will be evaluated using descriptive statistics. For OHSS, see Section 9.6.3.

9.8 Pregnancy Follow-up

Live birth will be compared between FE 999049 and GONAL-F using the same method as for pregnancy endpoints. Follow-up data on neonatal health will be described. These data will be reported separately.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – ICH Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents – ICH Definition

Source documents are defined as original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

Trial-specific Source Data Requirements – Ferring

Source documents need to be preserved for the maximum period of time permitted by local requirements. For each subject included in the trial, the investigator will record and retain source documents containing at least the following information, if applicable:

- Existence of subject (name, date of birth)
- Confirmation of participation in trial (trial ID, subject ID)
- Informed consent (date and time of oral information, date and time of handing out informed consent forms, date and time of obtaining written informed consents)
- Eligibility for participation in the trial (documenting all inclusion / exclusion criteria)
- Relevant medical and infertility history
- Body weight and height measurements
- Visit dates
- Any assessment performed, e.g. physical examination
- Dates and daily doses of IMP
- Dates and daily doses of NIMPs
- Dates and daily doses of concomitant medication
- Date of oocyte retrieval and number of oocytes retrieved
- Date of transfer and number and quality of embryos transferred
- Dates and results of βhCG test and ultrasound at clinical and ongoing pregnancy visits

- Adverse events (description as well as start/stop date and time)
- OHSS symptoms, preventive intervention (i.e. cycle cancellation), investigations and treatments
- Reason for discontinuation
- Event of unblinding, including the reason for unblinding
- Pregnancy outcome, i.e. live birth or pregnancy loss, and neonatal health at birth and 4 weeks after birth

No specific protocol data can be recorded directly in the EDC system without prior written or electronic record. The source of the various data will be described in a source agreement signed by the investigator and retained in the site file.

If the trial sites use electronic subject record systems, the sponsor will decide if the electronic subject records qualify for the trial and document the decision. If the electronic subject records system does not qualify for the trial, it may be considered to utilise certified printouts of the data in the electronic subject records system for source data as an exception.

The source data for the endocrine parameters will be available at the central laboratory.

10.2 EDC

An EDC system provided by an independent third-party contract research organisation (CRO) will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Ferring and vendor procedures, in accordance with regulatory and system requirements.

Trial data should be entered into the EDC system in a timely manner after the subject has attended a visit or after the data become available, as applicable.

The investigator will, in a timely manner, approve/authorise the EDC entries for each subject with an electronic signature which is equivalent to a handwritten signature.

The EDC system and the database will be hosted at the independent third party CRO. After the trial database is declared clean and locked, a final copy of the database will be stored at Ferring. The investigator will also receive a copy of the trial site’s final and locked data (including audit trail, electronic signature and queries) as write-protected PDF-files produced by the independent third party CRO. The PDF-files will be stored in an electronic format and will be provided to the investigator before access to the EDC system is revoked.

Entry errors occurring in the EDC system will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

10.3 Data Management

A data management plan will be created under the responsibility of the Global Biometrics Department of Ferring. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection and validation.

The data management plan will include information about the intended use of computerised systems and a description of the electronic data flow.

10.4 Provision of Additional Information

On request, the investigator will provide Ferring with additional data relating to the trial, duly pseudonymised and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Monitoring

The monitor will contact and, periodically, visit the investigator at the trial site to ensure adherence to the protocol, International Council for Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of EDC entries compared to source data, verification of drug accountability and compliance to safety reporting instructions. The investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The investigator will co-operate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits. In addition to on-site monitoring visits, remote monitoring is also an option. Remote monitoring is conducted off-site and may include video conference, telephone contact, and remote review of trial systems.

When the first subject is randomised at the trial site, a monitoring visit will take place shortly afterwards (maximum 30 days after randomisation). For this trial, the frequency of monitoring visits per site will be every 2 to 6 weeks, determined by the sponsor through a risk-based approach depending on recruitment rate, observed data quality, and overall site performance. The source data verification process and definition of key variables to be monitored will be described in detail in the Monitoring Plan for the trial.

11.2 Audit and Inspection

The investigator will make all the trial-related source data and records available at any time to quality assurance auditor(s) mandated by Ferring, or to domestic/foreign regulatory inspectors or representatives from ethics committees who may audit / inspect the trial.

The main purposes of an audit or inspection are to evaluate trial conduct and compliance with the trial protocol, ICH-GCP, the applicable regulatory requirements, and standard operating procedures. The subjects must be informed by the investigator and in the Informed Consent Forms that authorised Ferring representatives and representatives from regulatory authorities and ethics committees may wish to inspect their medical records. During audits / inspections the auditors / inspectors may copy relevant parts of the medical records. No personal identification apart from the screening / randomisation number will appear on these copies.

The investigator should notify Ferring without any delay of any inspection by a regulatory authority or ethics committee.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the EDC system or any other documents submitted to Ferring, the subjects will not be identified by their names, but by an identification system, which consists of an assigned number in the trial.

Documents that are not for submission to Ferring, e.g. the confidential subject identification code and the signed Informed Consent Forms, will be maintained by the investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by Ferring, and agreed upon by the investigator and Ferring, if applicable, prior to its implementation. Amendments may be submitted for consideration to the approving ethics committees and regulatory authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial subjects may be implemented prior to ethics committees' approval or favourable opinion.

12.2 Deviations from the Protocol

Deviations from the protocol should not occur. If deviations occur, the investigator must inform the sponsor, and the implications of the deviation must be reviewed and discussed. All deviations must be documented, and a record of protocol deviations should be retained by the investigator and sponsor.

12.3 Premature Trial Termination

At any time, the investigator has the right to terminate his/her participation in the trial, and Ferring has the right to terminate the trial. Reasons include, but are not limited to, Ferring terminating the trial due to safety reasons, e.g. due to a safety signal for the IMP arising from any source. Safety signals can include, for example, occurrence of life-threatening SAEs with suspected causality to the IMP; emergence of unjustifiable risk and/or toxicity in the risk-benefit analysis, e.g. due to occurrence of adverse events with suspected causality to the IMP that are unknown to date in respect of their nature, severity, duration or frequency in relation to the current established safety profile; or availability of new scientific evidence pertaining to patient safety, such as new insights from other clinical trials.

Should termination become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, Ferring and the investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and ethics committees will be informed.

In addition, Ferring reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter subjects at an acceptable rate.

Finally, the trial may be terminated due to request of the regulatory authority(ies), e.g. as a consequence of inspection, in case the ethics committee(s) withdraw(s) their favourable opinion or in case of unavailability of product(s), e.g. due to withdrawal of the license to manufacture or of the permission to import.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring and submitted for comments and signature(s) to the signatory investigator(s). Furthermore, the data and information collected during the pregnancy follow-up will be reported in a clinical trial report addendum including live birth and neonatal health at birth and at 4 weeks.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial will be the exclusive property of Ferring. The investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to Ferring.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the investigator(s) offered authorship and Ferring. In a multi-site trial, any publication must acknowledge all sites, and the results must be reported in a responsible and coherent manner and results from individual site(s) must not be published in advance of the primary publication of the entire trial, and must include a reference to the primary publication.

In addition, the following requirements must be adhered to:

(i) a presentation or publication of the results must not take place until 18 months after locking of the trial database, unless a) the results of the trial have already been published by Ferring, or b) specific written permission for publication is obtained in advance from Ferring.

(ii) at least 60 days in advance of any publication or presentation (or submission hereof) related to the trial, a copy of the relevant publication or presentation must be furnished to Ferring for review and redaction of confidential information. At Ferring's request, investigator(s) must delay the publication or presentation for up to an additional 90 days to enable Ferring to file patent applications or other intellectual property protection.

(iii) Ferring must be identified as the sponsor of the trial in any publication and presentation (including professional meetings and symposia).

Authorship is granted based on the International Committee of Medical Journal Editors (ICMJE) criteria (see current official version: http://www.ICMJE.org).[39] The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the investigator's and Ferring's opinion will be fairly and sufficiently represented in the publication.

Any CRO or external laboratory involved in the conduct of this trial has no publication rights regarding this trial.

13.3.2 Public Disclosure Policy

The ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. It is the responsibility of Ferring to register the trial in an appropriate public registry, e.g. www.clinicaltrials.gov; a website maintained by the National Library of Medicine (NLM) at the United States National Institutes of Health. The trial will also be made publicly available at the Chinese clinical trials register at www.cde.org.cn in accordance with local regulatory requirements. Trial results will be made publicly available in accordance with applicable regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Independent Ethics Committee

An independent ethics committee will review the protocol and any amendments and advertisements used for recruitment. The ethics committee will also review the Informed Consent Forms (including any updates) and any written materials given to the subjects. A list of all ethics committees to which the protocol has been submitted and name of the committee chairperson will be included in the clinical trial report.

14.2 Regulatory Authority Notification

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. The regulatory approval must be available before a subject is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-trial and End-of-trial Notification

The end-of-trial is defined as the date of the last visit that the last subject undergoes in this trial (LPLV), i.e. for subjects with a confirmed vital pregnancy, the ongoing pregnancy visit would be the last scheduled trial visit. The end-of-trial date will be recorded in the clinical trials register platform at the Center for Drug Evaluation (CDE) website. At the end of the clinical trial, the sponsor shall notify the concerned ethics committees about the completion of the clinical trial. In addition, the GCP office at each site must be informed.

Pregnancy follow-up will cover the period from LPLV to the end of the 4-week follow-up of the neonates.

In the case of early termination, Ferring must notify the end of the trial to the national regulatory authorities and the concerned ethics committees immediately and at the latest within 15 days after the trial is halted, clearly explaining the reasons, and describe follow-up measures, if any, taken for safety reasons. In addition, the GCP office at each site must be informed.

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki[40], in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

14.5 Subject Information and Consent

Informed Consent for Participation in the Trial – Subject

The investigator (or the person delegated by the investigator) will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, sources of funding, any possible conflicts of interest, anticipated benefits, potential risks of the trial and the discomfort it may entail, post-trial provisions and any other aspects of the trial which are relevant to the subject's decision to participate. The trial subject must be given ample time to consider participation in the trial before the consent is obtained. The Informed Consent Form must be signed and dated by the subject and the investigator (or the person delegated by the investigator) who has provided information to the subject regarding the trial before the subject is exposed to any trial-related procedure, including screening tests for eligibility. Subjects must be given the option of being informed about the general outcome and the results of the trial.

The investigator (or the person delegated by the investigator) will explain that the subject is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for her further care and without the need to justify his/her decision.

The subject will receive a copy of the signed and dated Informed Consent Form before any trial-related procedure.

If new information becomes available that may be relevant to the trial subject's willingness to continue participation in the trial, a new Informed Consent Form may be issued. In such case, the new Informed Consent Form will be forwarded to the ethics committees (and regulatory authorities, if required). The trial subjects will be informed about this new information and re-consent will be obtained.

Each subject will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, ethics committee representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review his/her source records and data. Data protection will be handled in compliance with applicable regulations.

Informed Consent for Data Collection on the Neonate – Child-custody Holder

The investigator (or the person delegated by the investigator) will obtain a freely given written consent from the child-custody holders, i.e. the subject and the subject's partner in case of joint custody. The child-custody holders must be given ample time before the consent is obtained. The Informed Consent Form must be signed and dated by the child-custody holders and the investigator who has provided information to the child-custody holders. Written consent by the child-custody holders regarding collection of pregnancy outcome data on the neonate must be obtained before the subject is randomised and preferably at the time of obtaining written consent by the subject regarding participation in the trial.

The investigator will explain that the child-custody holders are completely free to refuse to consent to this data collection or to withdraw consent at any time, without any consequences and without the need to justify their decision.

The child-custody holders will receive copies of the signed and dated Informed Consent Forms before randomisation to treatment.

The child-custody holders will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, ethics committee representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review the neonate's source records and data. Data protection will be handled in compliance with national / local regulations.

Partner Privacy Notice

The privacy notice explains the possibility that the partner's personal information (such as name, infertility diagnosis, etc.) may be included in the subject's medical record.

The partner will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, ethics committee representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may have access to the partner's personal information (such as name, infertility diagnosis, etc.). Protection of personal data will be handled in accordance with national / local regulations. Ferring will not collect, use or store any of the partner's personal data. The partner privacy notice must be given to the partner before the subject is randomised.

14.6 Subject Participation Card

The subject will be provided with a Subject Participation Card bearing the following information:

- That she is participating in a clinical trial (including trial code).
- That the trial involves controlled ovarian stimulation with rFSH
- The name and phone number of the investigator and address of the trial site.
- The name, address, and phone number of Ferring contact (as required by local regulations).

The subject will be asked to keep the Subject Participation Card in her possession at all times during the trial. The card should be discarded after the trial participation.

14.7 Compliance Reference Documents

The Declaration of Helsinki, the consolidated ICH-GCP, and other national law(s) in the country where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor and the investigator are defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the country where the trial takes place. The investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, including being responsible for all trial-related medical decisions, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

Ferring is, as sponsor, responsible for ensuring appropriate general/product liability insurance and, as required in accordance with applicable laws and regulations, country-specific liability insurance coverage for claims made by a trial subject for injury arising from the subject's participation in the trial.

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records that enable the conduct of the trial at the site to be fully understood, and for maintaining a record of the location of their essential documents including source documents, in accordance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 15 years, or longer if so required by local law, after the completion or discontinuation of the trial, if no further instructions are given by Ferring.

The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and pseudonymous EDC data for Ferring. The investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Forms for at least 15 years, or longer if so required by local law, after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the investigator and Ferring. Should the investigator elect to assign the trial documents to another party, or move them to another location, Ferring must be notified. If the investigator retires and the documents can no longer be archived by the site, Ferring can arrange having the Investigator File archived at an external archive.

16.2 Trial Master File

Ferring will archive the Trial Master File in accordance with ICH-GCP and applicable regulatory requirements.

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