FERRING
PHARMACEUTICALS

Protocol (consolidated protocol incorporating amendment 03) Sites in South Korea, Taiwan and Vietnam

Title of trial: A randomised, controlled, assessor-blind, parallel groups, multicentre, Pan-Asian trial comparing the efficacy and safety of FE 999049 with follitropin alfa (GONAL-F) in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme
NCT number: NCT03296527
Sponsor trial code: 000145
Date: 27 September 2018

CLINICAL TRIAL PROTOCOL

A randomised, controlled, assessor-blind, parallel groups, multicentre, Pan-Asian trial comparing the efficacy and safety of FE 999049 with follitropin alfa (GONAL-F) in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme

Trial Code: 000145

US IND Number:	103,040
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:	3
Sponsor:	Ferring Pharmaceuticals A/S Global Clinical and Non-Clinical R&D Science and Medicine, Reproductive Health International PharmaScience Center Kay Fiskers Plads 11 2300 Copenhagen S Denmark Tel: (+45) 88 33 88 34
Version:	3.0 (consolidated protocol; changes introduced with amendment #03 version 1.0 and 2.0 implemented)
GCP Statement:	This trial will be performed in compliance with GCP

SYNOPSIS

TITLE OF TRIAL

A randomised, controlled, assessor-blind, parallel groups, multicentre, Pan-Asian trial comparing the efficacy and safety of FE 999049 with follitropin alfa (GONAL-F) in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme

SIGNATORY INVESTIGATOR

[redacted]

TRIAL SITES

A total of 15-30 trial sites in mainland China and other Asian countries, potentially Taiwan, South Korea and Vietnam.

PLANNED TRIAL PERIOD		**CLINICAL PHASE**
First patient first visit (FPFV):	Q2 2017	3
Last patient first visit (LPFV):	Q4 2018	
Last patient last visit (LPLV):	Q1 2019	
Post-trial follow-up completed:	Q1 2020	

BACKGROUND / RATIONALE

FE 999049 is a human recombinant follicle-stimulating hormone (rFSH) belonging to the pharmaceutical class of gonadotropins. It is intended for the following 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". FE 999049 will be delivered as a solution for injection for subcutaneous self-administration by an injection pen.

FE 999049 is expressed from a host cell line of human fetal retinal origin (PER.C6®). The PER.C6® cell line is well-characterised, and bio-testing of the master cell bank has demonstrated safety and consistency. FE 999049 is a glycoprotein which is composed of two non-covalently bound polypeptide chains, denoted alfa (α) and beta (β). The α-subunit contains 92 amino acid residues with 5 intrachain-disulphide bonds. The β-subunit contains 111 amino acid residues with 6 intrachain-disulphide bonds. Each subunit is N-glycosylated at two positions, and about 40% of the total mass is carbohydrates.

There are no commercially available rFSH products derived from human cell lines, but Ferring has recently submitted a Marketing Authorisation Application to the European Medicines Agency (EMA) for FE 999049 (October 2015) and received positive opinion from the Committee for Medicinal Products for Human Use (October 2016). Currently-approved rFSH products for the proposed indication, such as follitropin alfa (GONAL-F, Merck Serono) and follitropin beta (PUREGON, MSD), are derived from a Chinese hamster ovary (CHO) cell line. The amino acid sequence of FE 999049 is identical to the endogenous human FSH sequence and to that in existing CHO-derived rFSH products. Manufacturing from different cell systems leads to glycosylation heterogeneity between rFSH preparations. The glycosylation profile of recombinant proteins is dependent on the expressing cell line and the cell culture conditions. Differences in glycosylation

profile, sialic acid pattern and isoform profile, have been documented between FE 999049 and existing rFSH products from a CHO cell line. Comparison between the FE 999049 and the GONAL-F and PUREGON profiles indicate differences in acidity and carbohydrate side chains. As CHO cells lack enzymatic functions to construct more complex carbohydrate structures found in humans, the glycosylation profile of FE 999049 is more complex. In addition, RE 999049 contains both α2,3 and α2,6 sialylation patterns, while CHO-derived rFSH products exclusively carry 2,3 linked sialic acid; this difference further contributes to the observed differences in glycosylation profiles between FE 999049 and CHO-derived rFSH products.

Before the current trial, Ferring has completed four phase 1 trials, two phase 2 dose-response trials (one conducted in EU and one in Japan) and two phase 3 trials as part of the clinical development programme for FE 999049. A total of 1,927 subjects have been included in the completed clinical trials, of whom 1,112 subjects were exposed to FE 999049.

The two phase 2 trials were randomised, controlled, assessor-blind, multi-centre dose-response trials in which randomisation was stratified according to the subject's anti-Müllerian hormone (AMH) level at screening. In both trials, a statistically significant dose-response relationship for FE 999049 with respect to the number of oocytes retrieved was observed for the overall population and for each AMH strata. Furthermore, the dose-response profile observed in Japanese and European subjects was similar. An individualised FE 999049 dosing regimen based on subject's AMH level and body weight was designed by modelling and simulation and prospectively tested in the phase 3 trials.

During the phase 3 trials, 665 IVF/ICSI subjects were treated with FE 999049 in 1,012 treatment cycles. The two phase 3 trials supported the efficacy and safety of FE 999049 in the proposed indication. ESTHER-1 (trial 000004, Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World, ESTHER) was an efficacy trial designed to demonstrate non-inferiority of FE 999049 versus an approved recombinant FSH preparation with ongoing pregnancy rate and ongoing implantation rate as co-primary endpoints (as agreed with the EMA during Scientific Advice) and also to prospectively evaluate the outcome of the stratified medicine approach with the individualised FE 999049 dosing regimen based on the AMH level (measured by Elecsys® AMH Immunoassay, Roche Diagnostics) and body weight. ESTHER-2 (trial 000071) was a safety immunogenicity trial with up to two repeated treatment cycles in subjects who did not achieve an ongoing pregnancy in ESTHER-1. Both trials have been completed with respect to their intervention part.

The ESTHER-1 trial demonstrated non-inferiority of FE 999049 to GONAL-F for the two co-primary endpoints, ongoing pregnancy rate and ongoing implantation rate, for both the per-protocol (PP) and modified intention-to-treat (mITT) populations. Across treatment groups and analysis populations, the ongoing pregnancy rate was in the range 31-33% and the ongoing implantation rate in the range 35-37%.

The AMH dosing regimen for FE 999049 in controlled ovarian stimulation cycles led to a statistically significantly lower proportion of subjects with extreme ovarian response (<4 or ≥15 oocytes retrieved or <4 or ≥20 oocytes retrieved) compared to the GONAL-F group, when adjusted for AMH. Furthermore, the value of the individualised FE 999049 dosing regimen was reflected in statistically significant and clinically relevant reductions in ovarian hyperstimulation syndrome (OHSS) risk management compared to GONAL-F. Overall, the incidence of preventive interventions for early OHSS among subjects treated with FE 999049 was half of that observed with GONAL-F, which was a statistically significant reduction. The combined incidence of early

OHSS (all and those of moderate/severe grade) and/or preventive interventions for early OHSS was also statistically significantly reduced with FE 999049 in comparison to GONAL-F. Overall, there was a statistically significantly lower incidence of total OHSS and/or preventive interventions for early OHSS, and of total moderate/severe OHSS and/or preventive interventions for early OHSS with FE 999049 compared to GONAL-F.

A design similar to the phase 3 trial ESTHER-1 is being proposed for the present trial to be conducted in China and other Asian countries, with some modifications according to local practice. The primary objective of this trial is to demonstrate non-inferiority of FE 999049 compared with GONAL-F with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation.

OBJECTIVES

Primary Objective

- To demonstrate non-inferiority of FE 999049 compared with GONAL-F with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation

Secondary Objectives

- To compare the clinical benefits of FE 999049 in its dosing regimen to those of GONAL-F with respect to efficacy and safety
- To compare FE 999049 with GONAL-F with respect to ovarian response including follicular development and endocrine profile, as well as with respect to embryo development
- To assess the population pharmacokinetics of FE 999049
- To compare FE 999049 with GONAL-F with respect to treatment efficiency
- To compare FE 999049 with GONAL-F with respect to safety profile, including adverse events, routine safety laboratory parameters and local tolerability
- To evaluate the immunogenicity of FE 999049 after one treatment cycle
- To perform a health economic analysis comparing FE 999049 with GONAL-F

ENDPOINTS

Primary Endpoint

- Ongoing pregnancy rate (at least one intrauterine viable fetus 10-11 weeks after transfer)

Secondary Endpoints

- Positive βhCG rate (positive serum βhCG test 13-15 days after transfer)
- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer)
- Vital pregnancy rate (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer)
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of

embryos transferred)

- Ongoing implantation rate (number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of embryos transferred)
- Proportion of subjects with extreme ovarian responses, defined as <4, ≥15 or ≥20 oocytes retrieved
- Proportion of subjects with early OHSS (including OHSS of moderate/severe grade) and/or preventive interventions for early OHSS
- Proportion of subjects with cycle cancellation due to poor or excessive ovarian response or embryo transfer cancellation due to excessive ovarian response / OHSS risk
- Number and size of follicles on stimulation day 6 and end-of-stimulation
- Number of oocytes retrieved and proportion of subjects with <4, 4-7, 8-14, 15-19 and ≥20 oocytes retrieved
- Percentage of metaphase II oocytes (only applicable for those inseminated using ICSI), fertilisation rate as well as number and quality of embryos on day 3 after oocyte retrieval
- Circulating concentrations of LH, estradiol, progesterone, inhibin A and inhibin B on stimulation day 6 and end-of-stimulation
- Circulating concentrations of FSH on stimulation day 6, end-of-stimulation and oocyte retrieval as well as FSH population pharmacokinetic parameters
- Total gonadotropin dose and number of stimulation days
- Proportion of subjects with investigator-requested gonadotropin dose adjustments
- Frequency and intensity of adverse events
- Changes in circulating levels of clinical chemistry and haematology parameters and proportion of subjects with markedly abnormal changes
- Frequency and intensity of injection site reactions (redness, pain, itching, swelling and bruising) assessed by the subject during the stimulation period
- Proportion of subjects with treatment-induced anti-FSH antibodies, overall as well as with neutralising capacity
- Frequency and intensity of immune-related adverse events
- Proportion of subjects with cycle cancellations due to an adverse event, including immune-related adverse events, or due to technical malfunctions of the administration pen
- Proportion of subjects with late OHSS (including OHSS of moderate/severe grade)
- Rate of multi-fetal gestation, biochemical pregnancy, spontaneous abortion, ectopic pregnancy (with and without medical/surgical intervention) and vanishing twins
- Technical malfunctions of the administration pen

POST-TRIAL INFORMATION

- Live birth rate and 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, Pan-Asian non-inferiority trial comparing the efficacy and safety of two rFSH preparations, FE 999049 and follitropin alfa (GONAL-F), in first cycle subjects aged 20-40 years undergoing controlled ovarian stimulation for IVF/ICSI following a gonadotropin-releasing hormone (GnRH) antagonist protocol. The trial has been designed to demonstrate non-inferiority of FE 999049, a human cell line-derived rFSH preparation, versus an approved CHO-derived rFSH preparation, i.e. GONAL-F, with ongoing pregnancy rate as the primary endpoint. Secondary endpoints include pharmacokinetic profile of FE 999049, pharmacodynamic parameters of FSH action as well as efficacy and safety parameters related to controlled ovarian stimulation. The assessor-blind design ensures that the investigators and other assessors such as embryologists and central laboratory personnel are blinded to individual treatment allocation. The sponsor will break the blind when all subjects have completed the end-of-trial visit, in order to evaluate efficacy and safety up to the ongoing pregnancy visit.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. On day 2-3 of the menstrual cycle, subjects will be randomised in a 1:1 ratio to treatment with either FE 999049 or GONAL-F, and stimulation will be initiated. Randomisation will be stratified by centre and according to age (<35, 35-37 and 38-40 years). Subjects randomised to FE 999049 will have their individual dose determined on the basis of their AMH level at screening and their body weight at randomisation. The daily FE 999049 dose will be fixed throughout the stimulation period. For subjects with low AMH (<15 pmol/L) the daily FE 999049 dose is 12 µg, irrespective of body weight. For subjects with high AMH (≥15 pmol/L) the daily FE 999049 dose is on a continuous scale ranging from 0.19 to 0.10 µg/kg, i.e. dependent on actual AMH and body weight (*note*: the minimum and maximum allowed daily doses are 6 µg and 12 µg, respectively). Subjects can be treated with FE 999049 for a maximum of 20 days, and coasting is not allowed. For subjects randomised to GONAL-F, the dosing regimen is within labelling. The starting daily dose of GONAL-F is 150 IU and fixed for the first five stimulation days after which it may be adjusted by 75 IU per day based on the individual response. The maximum daily GONAL-F dose allowed is 450 IU. Subjects can be treated with GONAL-F for a maximum of 20 days, and coasting is not allowed.

During stimulation, subjects will be monitored by transvaginal ultrasound on stimulation day 1 and 6 and hereafter at least every second day. When the leading follicle reaches ≥15 mm, visits must be performed daily. To prevent a premature LH surge, a GnRH antagonist will be initiated on stimulation day 6 and continued throughout the stimulation period. Triggering of final follicular maturation will be done as soon as ≥3 follicles with a diameter ≥17 mm are observed. If there are <25 follicles with a diameter ≥12 mm, human chorionic gonadotropin (hCG) will be administered. If there are 25-35 follicles with a diameter ≥12 mm, a GnRH agonist can be administered or the cycle can be cancelled. In case of excessive follicular development, defined as >35 follicles with a diameter ≥12 mm, the cycle is to be cancelled. If it is judged by the investigator that ≥3 follicles with a diameter ≥17 mm cannot be reached, but 1 or 2 follicles with a diameter ≥17 mm are observed, the cycle may either be cancelled due to poor follicular development or triggering of final

follicular maturation is to be induced, as judged by the investigator.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation and the oocytes can be inseminated by IVF or ICSI. Rescue ICSI is not allowed. Fertilisation and embryo development will be assessed from oocyte retrieval to the day of transfer. For subjects who underwent triggering of final follicular maturation with hCG, transfer is performed on day 3 (embryo stage) after oocyte retrieval. Subjects <35 years at randomisation will have single embryo transfer if a good-quality embryo is available; otherwise, double embryo transfer will be performed (and single transfer if two embryos are not available). Subjects ≥35 years at randomisation will have double embryo transfer (and single transfer if two embryos are not available). Remaining embryos may be cryopreserved in accordance with local guidelines and/or regulations. For subjects who underwent triggering of final follicular maturation with GnRH agonist, no transfer will take place in the current fresh cycle and the embryos available will be cryopreserved on day 3, 5 or 6, according to local practice. All cryopreserved embryos can be used by the subject after completion of the trial, in accordance with local guidelines and/or regulations.

Vaginal progesterone will be provided for luteal phase support from the day of oocyte retrieval or the day after and at least until clinical pregnancy. Thereafter the investigator may decide to continue up to the ongoing pregnancy visit, according to local practice. Progesterone administration should not continue if menses, negative βhCG or pregnancy loss occurs. A serum βhCG test will be performed 13-15 days after transfer, clinical pregnancy will be confirmed by transvaginal ultrasound 5-6 weeks after transfer, and ongoing pregnancy will be confirmed by transvaginal or abdominal ultrasound 10-11 weeks after transfer.

Blood samples will be collected throughout the trial for the purpose of evaluating the endocrine profile, clinical chemistry and haematology parameters as well as anti-FSH antibodies. Endocrine parameters are assessed at screening, stimulation day 1, stimulation day 6 and end-of-stimulation, furthermore FSH is also assessed at oocyte retrieval. Clinical chemistry and haematology parameters are assessed at screening, stimulation day 1, end-of-stimulation and end-of-trial. Anti-FSH antibodies are collected at four occasions. The first blood sample is taken at the screening visit and is exclusively used as back-up samples for the anti-drug antibody assay development. The subsequent three samples are used for analysis of anti-FSH antibodies in the individual subjects in the trial, and are taken prior to dosing on stimulation day 1 and at two occasions post-dosing: 5-10 days after the last FE 999049 or GONAL-F dose (it may coincide with the transfer visit) and 19-28 days after the last FE 999049 or GONAL-F dose (it may coincide with the βhCG test visit). Subjects with a treatment-induced anti-FSH antibody response will be followed until the response has become negative or returned to the pre-dosing level, with a maximum follow-up period of one year.

Local tolerability of FE 999049 and GONAL-F following subcutaneous administration will be assessed by the subject three times daily: immediately, 30 minutes and 24 hours after each injection. The assessment of injection site reactions will be made throughout the stimulation period and recorded by the subjects in a diary.

Post-Trial Activities

Post-trial activities cover pregnancy and neonatal health follow-up. All subjects with an ongoing pregnancy will be followed till delivery to gather information on live birth rate. Furthermore, data will be gathered on neonatal health, including any congenital anomalies, at birth and at 4 weeks

after birth. These data will be reported separately.

NUMBER OF SUBJECTS

It is planned to randomise 1,000 subjects from 15-30 sites in mainland China and other Asian countries. Of the 1,000 subjects it is expected that 740 subjects will be recruited in China (i.e. possessing a Chinese identification card and having native Chinese parents) and the rest from other Asian countries, potentially Taiwan, South Korea and Vietnam. It is estimated that approximately 1,200 subjects should be screened to achieve 1,000 subjects eligible for randomisation.

CRITERIA FOR INCLUSION / EXCLUSION

This trial will include Asian women aged 20-40 years undergoing their first IVF/ICSI cycle. They have been diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or have partners diagnosed with male factor infertility, and are considered eligible for IVF or ICSI. The allowed body mass index (BMI) is 17.5-32.0 kg/m^2, thus including underweight, normal weight, overweight and obese subjects. The exclusion criteria incorporate the contraindications for the use of gonadotropins.

The complete list of inclusion and exclusion criteria is provided below.

Inclusion Criteria

1. Informed Consent Documents signed prior to screening evaluations.
2. In good physical and mental health in the judgement of the investigator.
3. Asian pre-menopausal females between the ages of 20 and 40 years. The subjects must be at least 20 years (including the 20th birthday) when they sign the informed consent and no more than 40 years (up to the day before the 41st birthday) at the time of randomisation.
4. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II (defined by the revised ASRM classification, 1996) or with partners diagnosed with male factor infertility, eligible for *in vitro* fertilisation (IVF) and/or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.
5. Infertility for at least one year before randomisation for subjects <35 years or for at least 6 months for subjects ≥35 years (not applicable in case of tubal or severe male factor infertility).
6. The trial cycle will be the subject's first controlled ovarian stimulation cycle for IVF/ICSI.
7. Regular menstrual cycles of 24-35 days (both inclusive), presumed to be ovulatory.
8. Hysterosalpingography, hysteroscopy, saline infusion sonography, or transvaginal ultrasound documenting a uterus consistent with expected normal function (e.g. no evidence of clinically interfering uterine fibroids defined as submucous or intramural fibroids larger than 3 cm in diameter, no polyps and no congenital structural abnormalities which are associated with a reduced chance of pregnancy) within 1 year prior to randomisation.
9. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. enlarged ovaries 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.

10. Early follicular phase (cycle day 2-4) serum levels of FSH between 1 and 15 IU/L (results obtained within 3 months prior to randomisation).
11. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests within 2 years prior to randomisation.
12. Body mass index (BMI) between 17.5 and 32.0 kg/m^2 (both inclusive) at screening.
13. Willing to accept transfer of 1-2 embryos.

Exclusion Criteria

1. Known endometriosis stage III-IV (defined by the revised ASRM classification, 1996).
2. One or more follicles ≥10 mm (including cysts) observed on the transvaginal ultrasound prior to randomisation on stimulation day 1 (puncture of cysts is allowed prior to randomisation).
3. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy (excl. ectopic pregnancy) and before week 24 of pregnancy).
4. Known abnormal karyotype of subject or of her partner / sperm donor, as applicable, depending on source of sperm used for insemination in this trial.
5. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
6. Known inherited or acquired thrombophilia disease.
7. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
8. Known porphyria.
9. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) with the exception of controlled thyroid function disease.
10. Known presence of anti-FSH antibodies (based on the information available in the subject's medical records; i.e. not based on the anti-FSH antibody analyses conducted in the trial).
11. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
12. Known moderate or severe impairment of renal or hepatic function.
13. Any abnormal finding of clinical chemistry, haematology or vital signs at screening which is clinically significant as judged by the investigator.
14. Currently breast-feeding.
15. Undiagnosed vaginal bleeding.
16. Known abnormal cervical cytology of clinical significance observed within three years prior to randomisation (unless the clinical significance has been resolved).
17. 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.

18. Pregnancy (negative urinary pregnancy tests must be documented at screening and prior to randomisation) or contraindication to pregnancy.
19. Known current active pelvic inflammatory disease.
20. Use of fertility modifiers during the last menstrual cycle before randomisation, including dehydroepiandrosterone (DHEA), metformin or cycle programming with oral contraceptives, progestogen or estrogen preparations.
21. Use of hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomisation.
22. Known history of chemotherapy (except for gestational conditions) or radiotherapy.
23. Current or past (1 year prior to randomisation) abuse of alcohol or drugs.
24. Current (last month) intake of more than 14 units of alcohol per week.
25. Current or past (3 months prior to randomisation) smoking habit of more than 10 cigarettes per day.
26. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
27. Previous participation in the trial.
28. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.

MEDICINAL PRODUCTS

Investigational Medicinal Products (IMPs)

IMP name	*Drug type*	*Active ingredient, route of administration and concentration*	*Daily dose*
FE 999049	rFSH	FE 999049 in solution for subcutaneous injection; 72 µg FSH in 2.16 mL	AMH <15 pmol/L: 12 µg. AMH ≥15 pmol/L: ranging from 0.19 to 0.10 µg/kg, i.e. depending on actual AMH. The minimum and maximum allowed doses are 6 µg per day and 12 µg per day, respectively. The dose is fixed throughout stimulation
GONAL-F	rFSH	Follitropin alfa in solution for subcutaneous injection; 900 IU (66 µg) FSH in 1.5 mL	Starting dose of 150 IU fixed for the first five stimulation days, followed by potential adjustments of 75 IU per day with a maximum dose of 450 IU per day

Concomitant Fertility Medication / Non-investigational Medicinal Products (NIMPs)

NIMP name	*Drug type*	*Active ingredient and route of administration*	*Dose*
CETROTIDE	GnRH antagonist	Cetrorelix acetate powder and solvent for solution for subcutaneous injection	0.25 mg, daily dose
OVITRELLE	hCG	Choriogonadotropin alfa in solution for subcutaneous injection	250 µg, single dose
GONAPEPTYL	GnRH agonist	Triptorelin acetate in solution for subcutaneous injection	0.2 mg, single dose
CRINONE	Progesterone	Progesterone gel for vaginal administration	90 mg, daily dose

DURATION OF TREATMENT

The maximum period of exposure to FE 999049 or GONAL-F is 20 days.

STATISTICAL METHODS

The primary objective of this trial is to demonstrate non-inferiority of FE 999049 compared with GONAL-F with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation. Ongoing pregnancy is defined as at least one intrauterine viable fetus 10-11 weeks after transfer. The non-inferiority limit for the difference between treatments (FE 999049 versus GONAL-F) is -10.0% (absolute) for the primary endpoint.

The trial is designed to have 90% power of achieving the primary objective for the overall trial population and to have 80% power in the Chinese population. Assuming an ongoing pregnancy rate of 32.2% in both treatment groups, a total of 918 subjects are needed in the PP analysis set. To account for major protocol deviations a total of 1,000 subjects should be randomised. To secure that consistency can be established between the results from the overall trial population and the Chinese trial population at least 740 subjects will be recruited in China. The remaining subjects will be recruited from other Asian countries.

Sample Size Monitoring

The overall ongoing pregnancy rate will be monitored in a blinded manner, as the number of subjects to be randomised may need to be increased beyond the planned 1,000, if the overall ongoing pregnancy rate observed in the trial is above the estimated 32.2% used for the sample size calculation. The expected maximum number of subjects to be randomised would then be approximately 1,144 (572 per treatment group), corresponding to an observed rate of 50%. Blinded monitoring of the assumptions underlying the sample size is recommended specifically for non-inferiority trials by Food and Drug Administration (FDA) and in general by EMA.

Primary Endpoint: Ongoing Pregnancy Rate

The non-inferiority hypothesis to be tested for the primary endpoint is

$$H_0: \pi_{FE} - \pi_{GF} \leq -10.0\% \text{ against the alternative } H_A: \pi_{FE} - \pi_{GF} > -10.0\%,$$

where π_{FE} and π_{GF} denote the ongoing pregnancy rate after treatment with FE 999049 and GONAL-F, respectively. Non-inferiority will be evaluated based on the overall trial population.

The null hypothesis (H_0) will be tested against the alternative (H_A) by constructing a two-sided 95% confidence interval for the difference in ongoing pregnancy rates. The primary analysis will be adjusted for the stratification factor (age group) by using the Mantel-Haenszel method to combine results across age groups. In brief, this corresponds to deriving a weighted average across age groups where the weight depends on the number of observations in each treatment group in each age stratum.

Evaluation of the Primary Objective

If the lower limit of the two-sided 95% confidence interval based on the overall population is greater than the non-inferiority limit (-10.0%) for both the full analysis set (FAS) and the PP analysis set, the null hypotheses will be rejected. In that case it will be claimed that FE 999049 is

non-inferior to GONAL-F with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation.

If the lower limit of the two-sided 95% confidence interval for the treatment difference based on the FAS not only lies above the non-inferiority limit (-10.0%) but also above zero then there is evidence of superiority in terms of statistical significance at the 5% level. The result based on the PP analysis set is not essential for the superiority claim but should lead to a comparable result for a robust interpretation.

A supportive evaluation of the subjects recruited in China will be conducted, and it is expected that the findings among the Chinese trial population will be consistent with the overall findings in the trial.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

α	alfa
AMH	anti-Müllerian hormone
ART	assisted reproductive technologies
ATC	Anatomical Therapeutic Chemical classification system
β	beta
βhCG	beta unit of human chorionic gonadotropin
BMI	body mass index
CBC	complete blood count
CHO	Chinese hamster ovary
CHEM-20	a blood test to measure the level of 20 different proteins, lipids and electrolytes
DHEA	dehydroepiandrosterone
e-CRF	electronic case report form
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
FPFV	first patient first visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	gonadotropin-releasing hormone
GPV	Global Pharmacovigilance Department
h	hour(s)
HBsAg	Hepatitis B Surface Antigen
hCG	human chorionic gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLT	high level term
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICH	International Conference on Harmonisation
ICMART	International Committee Monitoring Assisted Reproductive Technologies
ICMJE	International Committee of Medical Journal Editors
ICSI	intracytoplasmic sperm injection
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
ITT	intention-to-treat
IU	international units
IVF	*in vitro* fertilisation
L	litre
LH	luteinising hormone
LLOQ	lower limit of quantification
LPFV	last patient first visit

LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mEq	milliequivalent(s)
mg	milligram
mITT	modified intention-to-treat
MSR	minimum significant ratio
mL	millilitre
NCU	neonatal care unit
ng	nanogram
NIMP	non-investigational medicinal product
NICU	neonatal intensive care unit
OHSS	ovarian hyperstimulation syndrome
PER.C6®	host cell line of human fetal retinal origin
PGD	preimplantation genetic diagnosis
PGS	preimplantation genetic screening
pmol	picomol
PP	per-protocol
PT	preferred term
rFSH	recombinant follicle-stimulating hormone
rhCG	recombinant human chorionic gonadotropin
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries
SUSAR	suspected unexpected serious adverse reaction
TSH	thyroid-stimulating hormone
µg	microgram
ULOQ	upper limit of quantification
US	ultrasound
WHO	World Health Organization

AMH Unit Conversion Factors

1 pmol/L = 0.140 ng/mL
1 ng/mL = 7.143 pmol/L

Definition of Terms

Major congenital anomaly	A life threatening structural anomaly or one likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment.[1,2]
Minor congenital anomaly	Relatively frequent structural anomaly not likely to cause any medical or cosmetic problems.[1,2]

Medicinal Product Names

Product	*Trade name used in the protocol*	*Trade name in the participating countries*	*Company name used in the protocol*	*Company name in the participating countries*
Follitropin alfa	GONAL-F	GONAL-F (CH, KR, TW, VN)	Merck Serono	Merck Serono, Merck
Cetrorelix acetate	CETROTIDE	CETROTIDE (CH, KR, TW, VN)	Merck Serono	Merck Serono, Merck
Choriogonadotropin alfa	OVITRELLE (Trade name in EU where the product is sourced)	OVIDREL (CH, KR, TW) OVITRELLE (VN)	Merck Serono	Merck Serono, Merck
Triptorelin acetate	GONAPEPTYL (Trade name in EU where the product is sourced)	DECAPEPTYL (CH, KR, TW) FERTIPEPTIL (VN)	Ferring Pharmaceuticals	Ferring Pharmaceuticals
Progesterone	CRINONE	CRINONE (KR, TW, VN) Progesterone Sustained-release vaginal gel (CH)	Merck Serono	Merck Serono, Merck

CH: China; KR: South Korea; TW: Taiwan, VN: Vietnam

(Throughout this document, all trade names are written in capitals to comply with Ferring standard operating procedures)

1 INTRODUCTION

1.1 Background

FE 999049 is a human recombinant follicle-stimulating hormone (rFSH) belonging to the pharmaceutical class of gonadotropins. It is intended for the following 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". FE 999049 will be delivered as a solution for injection for subcutaneous self-administration by an injection pen.

FE 999049 is expressed from a host cell line of human fetal retinal origin (PER.C6®). The PER.C6® cell line is well-characterised, and bio-testing of the master cell bank has demonstrated safety and consistency. FE 999049 is a glycoprotein which is composed of two non-covalently bound polypeptide chains, denoted alfa (α) and beta (β). The α-subunit contains 92 amino acid residues with 5 intrachain-disulphide bonds. The β-subunit contains 111 amino acid residues with 6 intrachain-disulphide bonds. Each subunit is N-glycosylated at two positions, and about 40% of the total mass is carbohydrates.

There are no commercially available rFSH products derived from human cell lines, but Ferring has recently submitted a Marketing Authorisation Application to the European Medicines Agency (EMA) for FE 999049 (October 2015) and received positive opinion from the Committee for Medicinal Products for Human Use (October 2016). Currently-approved rFSH products for the proposed indication, such as follitropin alfa (GONAL-F, Merck Serono) and follitropin beta (PUREGON, MSD), are derived from a Chinese hamster ovary (CHO) cell line. The amino acid sequence of FE 999049 is identical to the endogenous human FSH sequence and to that in existing CHO-derived rFSH products. Manufacturing from different cell systems leads to glycosylation heterogeneity between rFSH preparations. The glycosylation profile of recombinant proteins is dependent on the expressing cell line and the cell culture conditions. Differences in glycosylation profile, sialic acid pattern and isoform profile, have been documented between FE 999049 and existing rFSH products from a CHO cell line. Comparison between the FE 999049 and the GONAL-F and PUREGON profiles indicate differences in acidity and carbohydrate side chains. As CHO cells lack enzymatic functions to construct more complex carbohydrate structures found in humans, the glycosylation profile of FE 999049 is more complex. In addition, FE 999049 contains both α2,3 and α2,6 sialylation patterns, while CHO-derived rFSH products exclusively carry 2,3 linked sialic acid; this difference further contributes to the observed differences in glycosylation profiles between FE 999049 and CHO-derived rFSH products.

Before the current trial, Ferring has completed four phase 1 trials, two phase 2 dose-response trials (one conducted in EU and one in Japan) and two phase 3 trials as part of the clinical development programme for FE 999049. A total of 1,927 subjects have been included in the completed clinical trials, of whom 1,112 subjects were exposed to FE 999049.

The two phase 2 trials were randomised, controlled, assessor-blind, multi-centre dose-response trials in which randomisation was stratified according to the subject's anti-Müllerian hormone (AMH) level at screening. In both trials, a statistically significant dose-response relationship for FE 999049 with respect to the number of oocytes retrieved was observed for the overall population and for each AMH strata. Furthermore, the dose-response profile observed in Japanese and European subjects was similar. An individualised FE 999049 dosing regimen based on subject's

AMH level and body weight was designed by modelling and simulation and prospectively tested in the phase 3 trials.

During the phase 3 trials, 665 IVF/ICSI subjects were treated with FE 999049 in 1,012 treatment cycles. The two phase 3 trials supported the efficacy and safety of FE 999049 in the proposed indication. ESTHER-1 (trial 000004, Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World, ESTHER) was an efficacy trial designed to demonstrate non-inferiority of FE 999049 versus an approved recombinant FSH preparation with ongoing pregnancy rate and ongoing implantation rate as co-primary endpoints (as agreed with the EMA during Scientific Advice) and also to prospectively evaluate the outcome of the stratified medicine approach with the individualised FE 999049 dosing regimen based on the AMH level (measured by Elecsys® AMH Immunoassay, Roche Diagnostics) and body weight. ESTHER-2 (trial 000071) was a safety immunogenicity trial with up to two repeated treatment cycles in subjects who did not achieve an ongoing pregnancy in ESTHER-1. Both trials have been completed with respect to their intervention part.

The ESTHER-1 trial demonstrated non-inferiority of FE 999049 to GONAL-F for the two co-primary endpoints, ongoing pregnancy rate and ongoing implantation rate, for both the per-protocol (PP) and modified intention-to-treat (mITT) populations. Across treatment groups and analysis populations, the ongoing pregnancy rate was in the range 31-33% and the ongoing implantation rate in the range 35-37%.

The AMH dosing regimen for FE 999049 in controlled ovarian stimulation cycles led to a statistically significantly lower proportion of subjects with extreme ovarian response (<4 or ≥15 oocytes retrieved or <4 or ≥20 oocytes retrieved) compared to the GONAL-F group, when adjusted for AMH. Furthermore, the value of the individualised FE 999049 dosing regimen was reflected in statistically significant and clinically relevant reductions in ovarian hyperstimulation syndrome (OHSS) risk management compared to GONAL-F. Overall, the incidence of preventive interventions for early OHSS among subjects treated with FE 999049 was half of that observed with GONAL-F, which was a statistically significant reduction. The combined incidence of early OHSS (all and those of moderate/severe grade) and/or preventive interventions for early OHSS was also statistically significantly reduced with FE 999049 in comparison to GONAL-F. Overall, there was a statistically significantly lower incidence of total OHSS and/or preventive interventions for early OHSS, and of total moderate/severe OHSS and/or preventive interventions for early OHSS with FE 999049 compared to GONAL-F.

A design similar to the phase 3 trial ESTHER-1 is being proposed for the present trial to be conducted in China and other Asian countries, with some modifications according to local practice. The primary objective of this trial is to demonstrate non-inferiority of FE 999049 compared with GONAL-F with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation.

For further information regarding FE 999049, please refer to the current edition of Investigator's Brochure.

1.2 Scientific Justification for Conducting the Trial

The present trial is a phase 3 trial designed to assess the efficacy and safety of the human-derived rFSH preparation FE 999049 in women undergoing controlled ovarian stimulation for the development of multiple follicles for ART. FE 999049 is the first rFSH preparation derived from a

human cell line. The dosing regimen for FE 999049 will be individualised for each woman based on her AMH level and body weight. The trial will support the registration of FE 999049 in China and other Asian countries.

1.3 Benefit / Risk Aspects

Benefits

The treatment cycle is 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 pregnancy. Subjects will be closely monitored, and they will have either the same or more frequent visits to the clinic compared to routine treatment, depending on local practice. In addition, the data obtained from the treatment cycle may provide useful information for optimising the ovarian response and for clinical planning of subsequent treatment cycles.

Risks

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

Gonadotropins

In this trial, controlled ovarian stimulation will be performed either with the individualised FE 999049 dosing regimen or with GONAL-F, a widely available recombinant FSH preparation used in line with its approved labelling. Both preparations will be administered subcutaneously.

To date, a total of 1,112 women have been exposed to FE 999049 in completed phase 1, 2 and 3 trials. The overall adverse event profile of the individualised FE 999049 dosing regimen appeared to be comparable to that of GONAL-F with the exception of fewer OHSS and/or preventive interventions with FE 999049. The most frequently reported adverse drug reactions during 1,012 treatment cycles with FE 999049 in the phase 3 programme were headache, pelvic discomfort, OHSS, pelvic pain, adnexa uteri pain, nausea and fatigue (all reported as common, i.e. 1% to < 10%). Uncommon adverse drug reactions reported with FE 999049 were diarrhoea, dizziness, mood swings, constipation, vomiting, abdominal discomfort, breast pain, breast tenderness, vaginal haemorrhage and somnolence. FE 999049 administered with the injection pen was well-tolerated with a low incidence of local injection site reactions. The severity of local injection site reactions was in general mild and comparable to that reported for GONAL-F administrated with the pre-filled pen.

The FE 999049 dosing regimen used in this trial is an individualised dosing regimen based on the subject's AMH and body weight. AMH is a well-established predictor of ovarian response to gonadotropin treatment and was confirmed to be the best endocrine marker of ovarian response to FE 999049 treatment in the phase 2 trial. The FE 999049 dosing is based on the Elecsys® AMH assay from Roche Diagnostics which displays better performance with less variability than other AMH assays.[3]

GONAL-F is a commercially available CHO-derived rFSH preparation with established safety and efficacy[4]. 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%)[4]. The GONAL-F dosing regimen used in this trial is in line with labelling recommendations.

Concerning well-known risks associated with the use of gonadotropin products for ovarian stimulation, subjects are closely monitored throughout the trial. 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. Early OHSS can potentially be prevented by withholding gonadotropins, withholding human chorionic gonadotropin (hCG) or administering gonadotropin-releasing hormone (GnRH) agonist for triggering of final follicular maturation. Very rare cases of serious allergic reactions have been reported after injection of gonadotropins. Concerning immunogenicity, the risk of treatment-induced anti-drug-antibodies for gonadotropin products is very low (estimated to be 0-2%[5,6,7,8,9,10,11]) and no safety or efficacy concern has been identified with regards to immunogenicity with FE 999049 or with the available rFSH preparations.

Procedures and Concomitant Fertility Medications

Subjects will undergo standard ART treatment procedures (e.g. transvaginal ultrasound, blood sampling, oocyte retrieval and transfer) and also receive concomitant fertility medication as part of the treatment cycle in 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 approved products and are considered generally well-tolerated. The most frequently reported adverse events with these concomitant medication products are similar to those reported for FSH preparations, such as headache, injection site reactions, pelvic pain, abdominal pain, abdominal distension and allergic reactions. Furthermore, the vaginal progesterone has been associated with vulvovaginal disorders and uterine spasms (at a frequency of 1-2%).

Pregnancy-related Events

A serious concern associated with ART cycles is the frequency of multiple pregnancies / births and the related neonatal health problems. To minimise the risk of multiple gestations, subjects will have transfer of 1 or 2 embryos of the highest quality available. 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 conceiving 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 indicate that participation in this trial is associated with a favourable benefit-risk ratio.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To demonstrate non-inferiority of FE 999049 compared with GONAL-F with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation

Secondary Objectives

- To compare the clinical benefits of FE 999049 in its dosing regimen to those of GONAL-F with respect to efficacy and safety
- To compare FE 999049 with GONAL-F with respect to ovarian response including follicular development and endocrine profile, as well as with respect to embryo development
- To assess the population pharmacokinetics of FE 999049
- To compare FE 999049 with GONAL-F with respect to treatment efficiency
- To compare FE 999049 with GONAL-F with respect to safety profile, including adverse events, routine safety laboratory parameters and local tolerability
- To evaluate the immunogenicity of FE 999049 after one treatment cycle
- To perform a health economic analysis comparing FE 999049 with GONAL-F

2.2 Endpoints

Primary Endpoint

- Ongoing pregnancy rate (at least one intrauterine viable fetus 10-11 weeks after transfer)

Secondary Endpoints

- Positive βhCG rate (positive serum βhCG test 13-15 days after transfer)
- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer)
- Vital pregnancy rate (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer)
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of embryos transferred)
- Ongoing implantation rate (number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of embryos transferred)
- Proportion of subjects with extreme ovarian responses, defined as <4, ≥15 or ≥20 oocytes retrieved

- Proportion of subjects with early OHSS (including OHSS of moderate/severe grade) and/or preventive interventions for early OHSS
- Proportion of subjects with cycle cancellation due to poor or excessive ovarian response or embryo transfer cancellation due to excessive ovarian response / OHSS risk
- Number and size of follicles on stimulation day 6 and end-of-stimulation
- Number of oocytes retrieved and proportion of subjects with <4, 4-7, 8-14, 15-19 and ≥20 oocytes retrieved
- Percentage of metaphase II oocytes (only applicable for those inseminated using ICSI), fertilisation rate as well as number and quality of embryos on day 3 after oocyte retrieval
- Circulating concentrations of LH, estradiol, progesterone, inhibin A and inhibin B on stimulation day 6 and end-of-stimulation
- Circulating concentrations of FSH on stimulation day 6, end-of-stimulation and oocyte retrieval as well as FSH population pharmacokinetic parameters
- Total gonadotropin dose and number of stimulation days
- Proportion of subjects with investigator-requested gonadotropin dose adjustments
- Frequency and intensity of adverse events
- Changes in circulating levels of clinical chemistry and haematology parameters and proportion of subjects with markedly abnormal changes
- Frequency and intensity of injection site reactions (redness, pain, itching, swelling and bruising) assessed by the subject during the stimulation period
- Proportion of subjects with treatment-induced anti-FSH antibodies, overall as well as with neutralising capacity
- Frequency and intensity of immune-related adverse events
- Proportion of subjects with cycle cancellations due to an adverse event, including immune-related adverse events, or due to technical malfunctions of the administration pen
- Proportion of subjects with late OHSS (including OHSS of moderate/severe grade)
- Rate of multi-fetal gestation, biochemical pregnancy, spontaneous abortion, ectopic pregnancy (with and without medical/surgical intervention) and vanishing twins
- Technical malfunctions of the administration pen

Post-trial Information

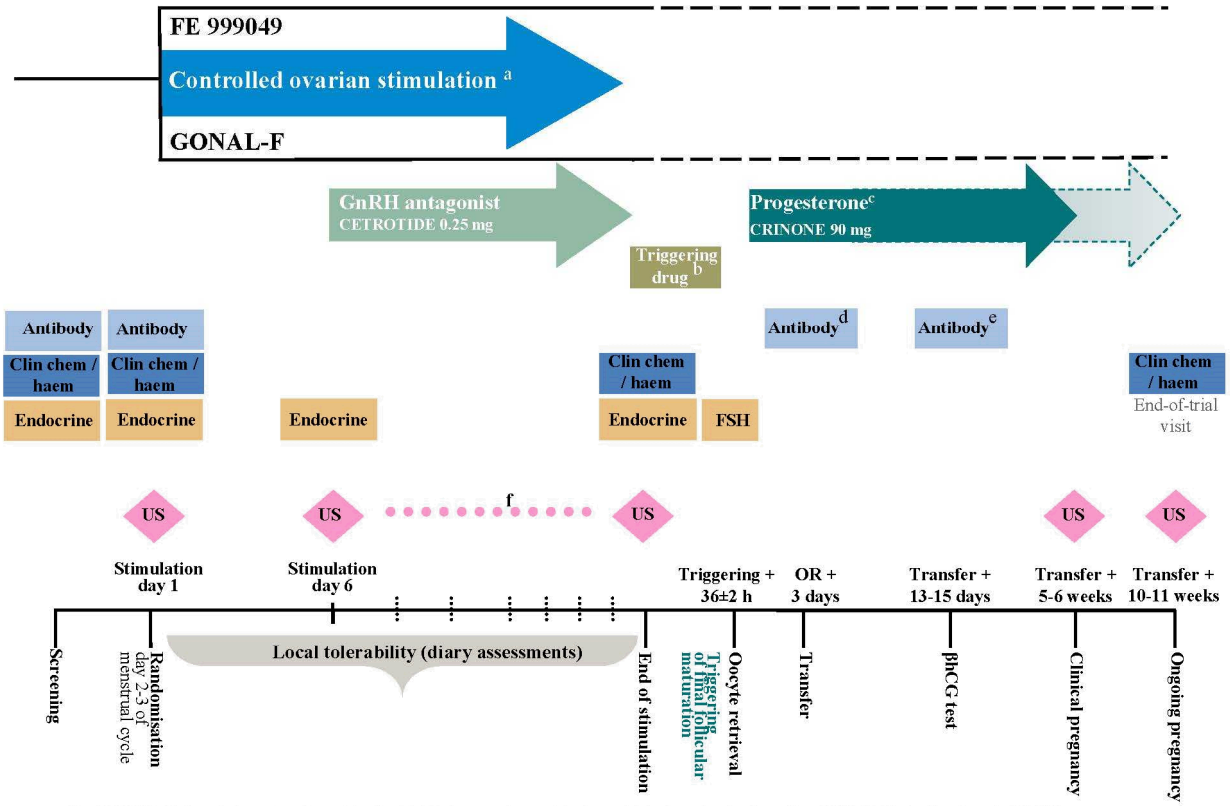
- Live birth rate and neonatal health, including minor/major congenital anomalies, at birth and at 4 weeks after birth

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.



a. The FE 999049 dose is based on the subject's AMH at screening and body weight at randomisation. The GONAL-F starting dose is 150 IU.
b. hCG (OVITRELLE 250 µg) or GnRH agonist (GONAPEPTYL 0.2 mg), depending on individual ovarian response.
c. Progesterone (CRINONE) administration will start on the day of oocyte retrieval or the day after and continue at least until clinical pregnancy, and maximal up to ongoing pregnancy.
d. 5-10 days after the last FE 999049 or GONAL-F dose (may coincide with the transfer visit).
e. 19-28 days after the last FE 999049 or GONAL-F dose (may coincide with the βhCG visit).
f. Stimulation day 1, 6 and hereafter at least every second day. When the leading follicle reaches ≥15 mm, visits will be scheduled daily.
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, Pan-Asian non-inferiority trial comparing the efficacy and safety of two rFSH preparations, FE 999049 and follitropin alfa (GONAL-F), in first cycle subjects aged 20-40 years undergoing controlled ovarian stimulation for IVF/ICSI following a GnRH antagonist protocol. The trial has been designed to demonstrate non-inferiority of FE 999049, a human cell line-derived rFSH preparation, versus an approved CHO-derived rFSH preparation, i.e. GONAL-F, with ongoing pregnancy rate as the primary endpoint. Secondary endpoints include pharmacokinetic profile of FE 999049, pharmacodynamic parameters of FSH action as well as efficacy and safety parameters related to controlled ovarian stimulation. The assessor-blind design ensures that the investigators and other assessors such as embryologists and central laboratory personnel are blinded to individual treatment allocation. The sponsor will break the blind when all subjects have completed the end-of-trial visit, in order to evaluate efficacy and safety up to the ongoing pregnancy visit.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. On day 2-3 of the menstrual cycle, subjects will be randomised in a 1:1 ratio to treatment with either FE 999049 or GONAL-F, and stimulation will be initiated. Randomisation will be stratified by centre and according to age (<35, 35-37 and 38-40 years). Subjects randomised to FE 999049 will have their individual dose determined on the basis of their AMH level at screening and their body weight at randomisation. The daily FE 999049 dose will be fixed throughout the stimulation period. For subjects with low AMH (<15 pmol/L) the daily FE 999049 dose is 12 µg, irrespective of body weight. For subjects with high AMH (≥15 pmol/L) the daily FE 999049 dose is on a continuous scale ranging from 0.19 to 0.10 µg/kg, i.e. dependent on actual AMH and body weight (*note*, the minimum and maximum allowed daily doses are 6 µg and 12 µg, respectively). Subjects can be treated with FE 999049 for a maximum of 20 days, and coasting is not allowed. For subjects randomised to GONAL-F, the dosing regimen is within labelling. The starting daily dose of GONAL-F is 150 IU and fixed for the first five stimulation days after which it may be adjusted by 75 IU per day based on the individual response. The maximum daily GONAL-F dose allowed is 450 IU. Subjects can be treated with GONAL-F for a maximum of 20 days, and coasting is not allowed.

During stimulation, subjects will be monitored by transvaginal ultrasound on stimulation day 1 and 6 and hereafter at least every second day. When the leading follicle reaches ≥15 mm, visits must be performed daily. To prevent a premature LH surge, a GnRH antagonist will be initiated on stimulation day 6 and continued throughout the stimulation period. Triggering of final follicular maturation will be done as soon as ≥3 follicles with a diameter ≥17 mm are observed. If there are <25 follicles with a diameter ≥12 mm, hCG will be administered. If there are 25-35 follicles with a diameter ≥12 mm, a GnRH agonist can be administered or the cycle can be cancelled. In case of excessive follicular development, defined as >35 follicles with a diameter ≥12 mm, the cycle is to be cancelled. If it is judged by the investigator that ≥3 follicles with a diameter ≥17 mm cannot be reached, but 1 or 2 follicles with a diameter ≥17 mm are observed, the cycle may either be cancelled due to poor follicular development or triggering of final follicular maturation is to be induced, as judged by the investigator.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation and the oocytes can be inseminated by IVF or ICSI. Rescue ICSI is not allowed. Fertilisation and embryo development will be assessed from oocyte retrieval to the day of transfer. For subjects who underwent triggering of final follicular maturation with hCG, transfer is performed on day 3 (embryo stage) after oocyte retrieval. Subjects <35 years at randomisation will have single embryo transfer if a good-quality embryo is available; otherwise, double embryo transfer will be performed (and single transfer if two embryos are not available). Subjects ≥35 years at randomisation will have double embryo transfer (and single transfer if two embryos are not available). Remaining embryos may be cryopreserved in accordance with local guidelines and/or regulations. For subjects who underwent triggering of final follicular maturation with GnRH agonist, no transfer will take place in the current fresh cycle and the embryos available will be cryopreserved on day 3, 5 or 6, according to local practice. All cryopreserved embryos can be used by the subject after completion of the trial, in accordance with local guidelines and/or regulations.

Vaginal progesterone will be provided for luteal phase support from the day of oocyte retrieval or the day after and at least until clinical pregnancy. Thereafter the investigator may decide to continue up to the ongoing pregnancy visit, according to local practice. Progesterone administration should not continue if menses, negative βhCG or pregnancy loss occurs. A serum βhCG test will be performed 13-15 days after transfer, clinical pregnancy will be confirmed by transvaginal ultrasound 5-6 weeks after transfer, and ongoing pregnancy will be confirmed by transvaginal or abdominal ultrasound 10-11 weeks after transfer.

Blood samples will be collected throughout the trial for the purpose of evaluating the endocrine profile, clinical chemistry and haematology parameters as well as anti-FSH antibodies. Endocrine parameters are assessed at screening, stimulation day 1, stimulation day 6 and end-of-stimulation, and furthermore FSH is also assessed at oocyte retrieval. Clinical chemistry and haematology parameters are assessed at screening, stimulation day 1, end-of-stimulation and end-of-trial. Anti-FSH antibodies are collected at four occasions. The first blood sample is taken at the screening visit and is exclusively used as back-up samples for the anti-drug antibody assay development. The subsequent three samples are used for analysis of anti-FSH antibodies in the individual subjects in the trial, and are taken prior to dosing on stimulation day 1 and at two occasions post-dosing: 5-10 days after the last FE 999049 or GONAL-F dose (it may coincide with the transfer visit) and 19-28 days after the last FE 999049 or GONAL-F dose (it may coincide with the βhCG test visit). Subjects with a treatment-induced anti-FSH antibody response will be followed until the response has become negative or returned to the pre-dosing level, with a maximum follow-up period of one year.

Local tolerability of FE 999049 and GONAL-F following subcutaneous administration will be assessed by the subject three times daily: immediately, 30 minutes and 24 hours after each injection. The assessment of injection site reactions will be made throughout the stimulation period and recorded by the subjects in a diary.

Post-Trial Activities

Post-trial activities cover pregnancy and neonatal health follow-up. All subjects with an ongoing pregnancy will be followed till delivery to gather information on live birth rate. Furthermore, data will be gathered on neonatal health, including any congenital anomalies, at birth and at 4 weeks after birth. These data will be reported separately.

3.1.3 Trial Schedule

First patient first visit (FPFV):	Q2 2017
Last patient first visit (LPFV):	Q4 2018
Last patient last visit (LPLV):	Q1 2019
Post-trial follow-up completed:	Q1 2020

3.2 Planned Number of Trial Sites and Subjects

It is planned to randomise 1,000 subjects from 15-30 sites in mainland China and other Asian countries. Of the 1,000 subjects it is expected that 740 subjects will be recruited in China (i.e. possessing a Chinese identification card and having native Chinese parents) and the rest from other Asian countries, potentially Taiwan, South Korea and Vietnam. It is estimated that approximately 1,200 subjects should be screened to achieve 1,000 subjects eligible for randomisation.

The assumptions underlying the sample size calculations will be monitored in a blinded manner (see sections 3.3, 9.1 and 9.10), and the number of randomised subjects may be adjusted up to a maximum of approximately 1,144 subjects, corresponding to an observed ongoing pregnancy rate of 50%.

3.3 Interim Analysis and Administrative Review

No interim analysis intended to compare treatment groups with respect to efficacy or safety is planned.

The overall ongoing pregnancy rate will be monitored in a blinded manner. This monitoring will be performed by the project statistician who will evaluate the overall ongoing pregnancy rate in relation to the assumptions underlying the sample size.

3.4 Data Monitoring Committee

No Data Monitoring Committee will be established for this trial.

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 demonstrate non-inferiority of FE 999049 compared with GONAL-F with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation.

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[12,13,14].

This is a randomised controlled trial using an approved gonadotropin preparation as active comparator. It is a parallel group design restricted to a single treatment cycle, as this design is preferred over a cross-over design in fertility trials. The trial will be open-label but 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, embryologists and central laboratory personnel. Similarly, Ferring staff will also remain blinded to individual subject treatment allocation during the conduct of the trial. The trial will be a multi-centre Pan-Asian trial. 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 trial is designed to demonstrate non-inferiority of FE 999049 versus GONAL-F with respect to ongoing pregnancy rate. The non-inferiority margin for the primary endpoint has been set at -10.0% (absolute) in line with other recent large randomised controlled trials in ART[15,16,17] and the power is 90% for the overall trial population and 80% power for the Chinese population. A non-inferiority margin of -8.0% (and a power of 80%) has been implemented in the pivotal phase 3 trial (ESTHER-1). However, the present phase 3 trial to be conducted in China and other Asian countries will not be a stand-alone trial but will be supported by the ESTHER-1 trial conducted in Europe and the Rest of World, arguing for a less strict non-inferiority limit in the present trial. Furthermore, narrowing the non-inferiority margin with 2% points (i.e. from -10.0% to -8.0%) would increase the sample size by 516 subjects but would only reduce the maximum allowed difference in the point estimates for the ongoing pregnancy rate for FE 999049 required to demonstrate non-inferiority versus the comparator, by 0.8% (further details are provided in section 9.1), which is not clinically relevant.

Subjects will undergo controlled ovarian stimulation with an individualised dosing regimen of FE 999049 based on the subject's AMH level and body weight, or with a labelling recommended dosing regimen of GONAL-F, following a GnRH antagonist protocol. The daily FE 999049 dose is fixed throughout the stimulation period in this trial. The daily GONAL-F dose is fixed for the first five stimulation days after which it may be adjusted by 75 IU per day based on the individual response, which is within the recommendations in the labelling. The selection of doses is described in detail in section 3.5.4. Monitoring of ovarian response by transvaginal ultrasound and blood sampling for assessment of several endocrine parameters will be performed regularly during stimulation.

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 and embryo development will be assessed from oocyte retrieval till the day of transfer, allowing evaluation of embryo development until cleavage stage. The duration of culture in this trial is adapted to clinical practice in Asia where transfer on day 3 after oocyte retrieval is the most common. In contrast, culture to blastocyst stage and transfer on day 5 after oocyte retrieval are incorporated in the phase 3 trial ESTHER-1, reflecting clinical practice in the participating countries in that trial.

The present protocol requires single or double embryo transfer on day 3 for all women, depending on age, with at least one good-quality embryo available. The scientific justification for incorporating these features is that it will ensure that the data obtained in this trial are in line with the current clinical directions taken for maintaining efficacy (i.e. ongoing pregnancy rates) and minimising risks (i.e. multiple pregnancies)[18,19,20]. The embryo transfer policy in this trial has been

adapted to clinical practice in Asia, and is not identical to the policy in the ESTHER-1 trial where single embryo (blastocyst) transfer is more strictly enforced.

Luteal phase support of the endometrium will be provided via vaginal progesterone. The progesterone product used in ESTHER-1 is not approved in all Asian countries and therefore another progesterone product which is approved in China and the other participating Asian countries will be used in the present trial. Furthermore, luteal phase support in this trial continues to at least the clinical pregnancy visit while it was stopped at the βhCG visit in ESTHER-1; this is a reflection of differences in local clinical practice.

Subjects who achieve a pregnancy will be followed till live birth to collect information on pregnancy outcome. In addition, neonatal health data will be gathered at birth and at 4 weeks after birth. These data will be reported separately.

3.5.2 Selection of Endpoints

The ultimate objective of fertility treatment is live birth. Ongoing pregnancy is considered an appropriate primary endpoint for efficacy trials, as ongoing pregnancy is the best predictor of live birth and it is definable within a time period in which other potential confounding factors are more easily controlled[14].

One of the secondary objectives is to compare the clinical benefits of FE 999049 in its dosing regimen to those of GONAL-F with respect to efficacy and safety. This objective is addressed by multiple endpoints to address it from several angles; i.e. proportion of subjects with extreme ovarian response, early OHSS (including moderate/severe grade), preventive interventions for early OHSS, cycle cancellations due to poor ovarian response development and cycle cancellation due to excessive ovarian response.

Additional secondary endpoints include pharmacodynamic parameters, such as ovarian response in terms of follicular development, endocrine profile and oocytes retrieved, and also oocyte / embryo quality. Follicular development and endocrine profile will be evaluated after the initial 5 days (i.e. before any potential dose adjustments in the GONAL-F group and before start of the GnRH antagonist) as well as at the end of stimulation. The endocrine profile consists of FSH, luteinising hormone (LH), estradiol, progesterone, inhibin A and inhibin B. Serum FSH levels will be used to assess the population pharmacokinetics associated with repeated dosing of FE 999049, which is also a secondary endpoint.

Clinical safety endpoints cover adverse events, early and late OHSS, preventive interventions for early OHSS, local tolerability, clinical chemistry and haematology parameters, immunogenicity and pregnancy-related events (i.e. multi-fetal gestations, biochemical pregnancies, spontaneous abortions, ectopic pregnancies and vanishing twins). Pre-defined local tolerability reactions, i.e. redness, pain, itching, swelling and bruising, will be assessed by the subjects on three occasions spanning from immediately after the subcutaneous injection till 24 hours after. Presence of anti-FSH antibodies will be evaluated 5-10 and 19-28 days after the last administration of FE 999049 or GONAL-F for assessment of a potential immunoglobulin M (IgM) response and a fully mounted immunoglobulin G (IgG) immune response, respectively[21,22,23]. Technical malfunction of the pens used for administration of the gonadotropin preparations will also be monitored.

Post-trial activities cover follow-up of ongoing pregnancies up to live birth. Neonatal health data at birth and at 4 weeks after birth will be gathered.

In conclusion, the list of primary and secondary endpoints is appropriate for an efficacy trial and furthermore includes items of special interest considering the profile of FE 999049 and specific recommendations from EMA.

3.5.3 Blinding

The two investigational medicinal products (IMPs) differ in presentation as FE 999049 is provided as a liquid in a cartridge to be administered via an injection pen whereas GONAL-F is provided as a liquid in a pre-filled pen. Furthermore, GONAL-F is manufactured by Merck Serono and bought commercially for use in this phase 3 trial. Therefore, a double-blind, double-dummy design is not feasible. The trial, however, is assessor-blind, ensuring unbiased evaluation by the investigators, embryologists and central laboratory personnel.

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 case report form (e-CRF). 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 75 IU per day as applicable if the subject is in the GONAL-F group, while no dose adjustments will be implemented if the subject is in the FE 999049 group. Requests for cycle cancellation due to inappropriate response or other medical reasons are followed, irrespective of treatment group.

The Ferring clinical trial team (i.e. data manager, statistician, trial manager, medical writer, pharmacovigilance manager and sponsor's responsible medical officer) will be blinded to treatment allocation until breaking of the blind. The blind will be broken when all subjects have completed the end-of-trial visit and the trial database is declared clean and locked.

3.5.4 Selection of Doses in the Trial

FE 999049

Modelling and simulation based on the efficacy and safety data obtained in the European phase 2 trial have been used to establish the overall dosing regimen for FE 999049 in the phase 3 trials. This is the same dosing regimen that was used in the phase 3 trial 000004 (ESTHER-1), where it has been shown to reduce the risk of extreme ovarian response, the risk of cycle cancellation due to excessive ovarian response, and the risk of early moderate/severe OHSS and/or prevention interventions for early OHSS, while obtaining a pregnancy rate that is non-inferior to GONAL-F.

AMH and body weight were found to influence the dose-response with regard to obtaining the aim of the model of the FE 999049 dosing regimen. The impact of body weight on ovarian response is clinically relevant for low dose levels of FE 999049, while the effect is only minor at dose levels of 12 µg and above. The individualised dosing regimen of FE 999049 in the present trial is described in detail in section 5.1.1 and is summarised as follows: For subjects with low AMH (<15 pmol/L) the daily FE 999049 dose is 12 µg, irrespective of body weight, and for subjects with high AMH (≥15 pmol/L) the daily FE 999049 dose is on a continuous scale ranging from 0.19 to 0.10 µg/kg, depending on the baseline AMH level. The minimum and maximum allowed daily doses are 6 µg and 12 µg, respectively.

GONAL-F

Subjects randomised to GONAL-F will be dosed according to the approved labelling. The starting dose of GONAL-F in this trial is 150 IU, which is the same starting dose as used in the ESTHER-1 trial. The European[4], Chinese[24], Taiwanese[25], South Korean[26] and Vietnamese[27] labelling's for GONAL-F state a starting dose of 150-225 IU, but provide no recommendation for when to use 150 IU and when to use 225 IU. In the absence of a recommendation from the manufacturer, the lowest effective dose has been selected as this would be a reasonable approach in clinical practice, especially as this trial will include subjects with no previous controlled ovarian stimulation for IVF/ICSI. This choice is also in line with the US labelling of GONAL-F[28] which recommends a starting dose of 150 IU in patients where the endogenous gonadotropin levels are not suppressed (such as the GnRH antagonist cycle, where prevention of premature LH surge is only initiated after 5 days of stimulation). The GONAL-F starting dose is fixed for the first five stimulation days after which it may be adjusted by 75 IU per day based on the individual response. For GONAL-F, the maximum daily dose allowed is 450 IU.

Concomitant Fertility Medication

The doses and overall treatment regimens for the GnRH antagonist, 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. The GnRH agonist is included as an option for triggering of final follicular maturation in subjects with 25-35 follicles with a diameter ≥12 mm, as this approach is associated with almost an elimination of the risk of early moderate/severe OHSS despite high ovarian response. The use of a GnRH agonist for triggering of final follicular maturation in a GnRH antagonist protocol is well-described in the literature and considered an acceptable alternative to cycle cancellation[29,30,31,32,33].

3.5.5 Selection of the Trial Population

This trial will include women undergoing their first IVF/ICSI cycle, as this group of subjects is considered the most appropriate population for a trial comparing the efficacy between gonadotropins and furthermore when using different dosing regimens. The subjects have been diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or have partners diagnosed with male factor infertility, and 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.

The exclusion criteria incorporate the contraindications for the use of gonadotropins.

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

3.5.6 Follow-up Procedures

Post-trial Activities

Post-trial activities cover pregnancy and neonatal health follow-up at birth and at 4 weeks after birth as described in section 7.4.1.

Safety Follow-up

As a safety precaution, subjects with treatment-induced anti-FSH antibody response will be followed until the response has become negative or returned to the pre-dosing level for at least 2 consecutive measurements with a maximum follow-up period of one year .The assessments will also be terminated if the subject commences a new treatment cycle with any gonadotropin preparation. Safety follow-up also includes follow-up on adverse events (with onset during the trial and classified as serious or related to IMP) until it is resolved or until the medical condition of the subject is stable.

Access to Therapy after End-of-trial

Concerning access to therapy after completion of the trial, FE 999049 is currently under clinical development and cannot be offered to subjects after participation in this clinical trial. However, several gonadotropin preparations are approved for controlled ovarian stimulation and are commercially available.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

Subjects must meet all of the criteria listed below to be eligible for participation in the trial.

1. Informed Consent Documents signed prior to screening evaluations.
2. In good physical and mental health in the judgement of the investigator.
3. Asian pre-menopausal females between the ages of 20 and 40 years. The subjects must be at least 20 years (including the 20th birthday) when they sign the informed consent and no more than 40 years (up to the day before the 41st birthday) at the time of randomisation.
4. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II (defined by the revised ASRM classification, 1996) or with partners diagnosed with male factor infertility, eligible for *in vitro* fertilisation (IVF) and/or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.
5. Infertility for at least one year before randomisation for subjects <35 years or for at least 6 months for subjects ≥35 years (not applicable in case of tubal or severe male factor infertility).
6. The trial cycle will be the subject's first controlled ovarian stimulation cycle for IVF/ICSI.
7. Regular menstrual cycles of 24-35 days (both inclusive), presumed to be ovulatory.
8. Hysterosalpingography, hysteroscopy, saline infusion sonography, or transvaginal ultrasound documenting a uterus consistent with expected normal function (e.g. no evidence of clinically interfering uterine fibroids defined as submucous or intramural fibroids larger than 3 cm in diameter, no polyps and no congenital structural abnormalities which are associated with a reduced chance of pregnancy) within 1 year prior to randomisation.
9. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. enlarged ovaries 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.
10. Early follicular phase (cycle day 2-4) serum levels of FSH between 1 and 15 IU/L (results obtained within 3 months prior to randomisation).
11. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests within 2 years prior to randomisation.
12. Body mass index (BMI) between 17.5 and 32.0 kg/m^2 (both inclusive) at screening.
13. Willing to accept transfer of 1-2 embryos.

4.1.2 Exclusion Criteria

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

1. Known endometriosis stage III-IV (defined by the revised ASRM classification, 1996).
2. One or more follicles ≥10 mm (including cysts) observed on the transvaginal ultrasound prior to randomisation on stimulation day 1 (puncture of cysts is allowed prior to randomisation).
3. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy (excl. ectopic pregnancy) and before week 24 of pregnancy).
4. Known abnormal karyotype of subject or of her partner / sperm donor, as applicable, depending on source of sperm used for insemination in this trial.
5. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
6. Known inherited or acquired thrombophilia disease.
7. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
8. Known porphyria.
9. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) with the exception of controlled thyroid function disease.
10. Known presence of anti-FSH antibodies (based on the information available in the subject's medical records; i.e. not based on the anti-FSH antibody analyses conducted in the trial).
11. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
12. Known moderate or severe impairment of renal or hepatic function.
13. Any abnormal finding of clinical chemistry, haematology or vital signs at screening which is clinically significant as judged by the investigator.
14. Currently breast-feeding.
15. Undiagnosed vaginal bleeding.
16. Known abnormal cervical cytology of clinical significance observed within three years prior to randomisation (unless the clinical significance has been resolved).
17. 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.
18. Pregnancy (negative urinary pregnancy tests must be documented at screening and prior to randomisation) or contraindication to pregnancy.
19. Known current active pelvic inflammatory disease.
20. Use of fertility modifiers during the last menstrual cycle before randomisation, including dehydroepiandrosterone (DHEA), metformin or cycle programming with oral contraceptives, progestogen or estrogen preparations.

21. Use of hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomisation.
22. Known history of chemotherapy (except for gestational conditions) or radiotherapy.
23. Current or past (1 year prior to randomisation) abuse of alcohol or drugs.
24. Current (last month) intake of more than 14 units of alcohol per week.
25. Current or past (3 months prior to randomisation) smoking habit of more than 10 cigarettes per day.
26. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
27. Previous participation in the trial.
28. 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 subject screening / enrolment log for all screened subjects must be maintained by the investigator.

4.2.2 Randomisation

On day 2-3 of the menstrual cycle, subjects will be randomised in a 1:1 ratio to treatment with either FE 999049 or GONAL-F, and stimulation will be initiated. Randomisation is performed centrally through the e-CRF and will be stratified according to age (<35, 35-37 and 38-40 years). 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. 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, metformin or cycle programming with oral contraceptives, progestogen or estrogen preparations, or hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomisation.

The subject must also not use metformin as ongoing treatment during the trial.

During the trial it is prohibited to administer any other fertility medications, than the ones provided as part of the trial regimen.

Dopamine agonist for preventive intervention of OHSS is not allowed.

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 Withdrawal Criteria

Withdrawal from Trial

The subjects have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the investigator should record the reason for the subject's withdrawal, if possible.

If, at the time of discontinuation, a dose of the IMP has already been administered, the subject must be advised to participate in the follow-up safety investigations, which will include all post-dosing antibody assessments and all procedures outlined in the end-of-trial visit.

The investigator also has the right to withdraw subjects. 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 e-CRF.

Withdrawal of Consent

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 Documents. 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 randomisation number.

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.

5 TREATMENTS

5.1 Investigational Medicinal Products (IMPs)

Subjects will be randomised to the following IMPs in a 1:1 ratio in the trial:

- FE 999049 manufactured by Ferring will be provided as a cartridge and an injection pen. One subcutaneous injection will be administered daily, starting on day 2-3 of the subject's menstrual cycle and continued throughout the stimulation period.
- GONAL-F (follitropin alfa for injection) manufactured by Merck Serono is provided as a pre-filled pen containing a liquid formulation for injection. One subcutaneous injection will be administered daily, starting on day 2-3 of the subject's menstrual cycle and continued throughout the stimulation period.

For information on warnings, precautions and treatment of overdose, please refer to the Investigator's Brochure for FE 999049 and the Prescribing Information for GONAL-F.

5.1.1 FE 999049 Dosing Regimen

Subjects randomised to FE 999049 will have their individual dose determined on the basis of their AMH level at screening and their body weight at randomisation. For subjects with low AMH (<15 pmol/L) the daily FE 999049 dose is 12 µg, irrespective of body weight. For subjects with high AMH (≥15 pmol/L) the daily FE 999049 dose is on a continuous scale ranging from 0.19 to 0.10 µg/kg, i.e. dependent on actual AMH and body weight. The minimum and maximum allowed daily doses are 6 µg and 12 µg, respectively.

The daily FE 999049 dose will be fixed throughout the stimulation period. Dosing will continue until the criterion for triggering of final follicular maturation has been met. Subjects can be treated with FE 999049 for a maximum of 20 days. Coasting is not allowed. Overdose and medication errors of IMP with and without clinical consequences will be tracked in the e-CRF and reviewed ongoing by Ferring GPV.

The complete FE 999049 dosing regimen is tabulated in detail in Table 5-1.

Table 5-1 FE 999049 Dosing Regimen

Treatment group	AMH concentration (pmol/L)	Daily dose fixed throughout stimulation	Minimum daily dose	Maximum daily dose
FE 999049	<15	12 µg		12 µg
	15-16	0.19 µg/kg	6 µg	12 µg
	17	0.18 µg/kg	6 µg	12 µg
	18	0.17 µg/kg	6 µg	12 µg
	19-20	0.16 µg/kg	6 µg	12 µg
	21-22	0.15 µg/kg	6 µg	12 µg
	23-24	0.14 µg/kg	6 µg	12 µg
	25-27	0.13 µg/kg	6 µg	12 µg
	28-32	0.12 µg/kg	6 µg	12 µg
	33-39	0.11 µg/kg	6 µg	12 µg
	≥40	0.10 µg/kg	6 µg	12 µg

AMH concentration will be rounded off to integers.
Subjects can be treated for a maximum of 20 days.

The FE 999049 preparation is administered as a single daily subcutaneous injection in the abdomen. The dose must not be split into two injections. To minimise local injection site reactions, it is advisable to change injection site regularly.

The first FE 999049 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 give the subject instructions for how to administer FE 999049.

Calculation of the FE 999049 Dose and Setting the Dose on the FE 999049 Pen

The subject's serum AMH concentration will be available from the blood sample taken at screening and analysed by a central laboratory using a qualified assay. The AMH concentration will be provided from the central laboratory directly to the e-CRF. The subject's body weight will be measured at randomisation using a calibrated scale and performed without shoes and overcoat. The body weight result will be entered into the e-CRF. The FE 999049 dosing algorithm has been programmed in the e-CRF, which calculates the FE 999049 dose based on the subject's AMH and body weight.

The FE 999049 injection pen has a dosing scale numbered from 0 to 24 µg. Each number is separated by two lines, each representing 0.33 µg. Thus, the pen can be set to supply doses rounded to the nearest 0.33 µg. Rounding off of the calculated dose may be needed, as in this example of a subject weighing 60.0 kg with an AMH level of 30 pmol/L for whom the calculated dose is 7.2 µg (0.12 µg/kg * 60.0 kg) which will then be rounded to 7.33 µg, i.e. 7 µg + 1 line on the pen. The minimum daily dose of 6 µg will be administered in cases like this example: a subject weighing 40.0 kg and with an AMH level of 40 pmol/L will have a calculated dose of 4.0 µg (0.10 µg/kg * 40.0 kg) which will then be rounded up to 6 µg. The e-CRF will provide the calculated dose in an output that matches the numbers and lines on the injection pen; i.e. any rounding off will be done automatically prior to providing the subject's calculated dose.

The trial medication delegate will be instructed and trained in the correct use of the pen, so that correct instructions can be provided to the subjects.

5.1.2 GONAL-F Dosing Regimen

For subjects randomised to GONAL-F, the dosing regimen is within labelling. The starting dose of GONAL-F is 150 IU per day and fixed for the first five stimulation days, after which it may be adjusted by 75 IU per day based on the individual response. The maximum daily GONAL-F dose allowed is 450 IU. Dosing will continue until the criterion for triggering of final follicular maturation has been met. Subjects can be treated with GONAL-F for a maximum of 20 days. Coasting is not allowed. Overdose and medication errors of IMP with and without clinical consequences will be tracked in the e-CRF and reviewed ongoing by Ferring GPV.

The GONAL-F dosing regimen is shown in detail in Table 5-2.

Table 5-2 GONAL-F Dosing Regimen

Treatment group	Starting dose stimulation day 1-5	Daily dose stimulation day 6 and onwards	Maximum daily dose
GONAL-F	150 IU	Adjustments of 75 IU per day allowed according to the individual response.	450 IU

Subjects can be treated for a maximum of 20 days.

The GONAL-F preparation is administered as a single daily subcutaneous injection in the abdomen. The dose must not be split into two injections. To minimise local injection site reactions, it is advisable to change injection site regularly.

The first GONAL-F 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 give the subject instructions for how to administer GONAL-F.

Setting the Dose on the GONAL-F Pen

The GONAL-F pen has a dosing scale applicable for the starting dose and subsequent potential dose adjustments.

The trial medication delegate will be instructed and trained in the correct use of the pen, so that correct instructions can be provided to the subjects.

5.2 Non-Investigational Medicinal Products (NIMPs)

As concomitant therapy in the controlled ovarian stimulation cycle, subjects will use the following non-investigational medicinal products (NIMPs) as illustrated in Table 5-3.

Table 5-3 Non-Investigational Medicinal Products (NIMPs)

NIMP	Trade name	Timing
GnRH antagonist	CETROTIDE	0.25 mg subcutaneous injection once daily, starting on stimulation day 6 and continued throughout the stimulation period.
hCG	OVITRELLE	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).
GnRH agonist	GONAPEPTYL	Two consecutive injections of 0.1 mg, i.e. a total of 0.2 mg, as soon as reaching the criterion for triggering of final follicular maturation with GnRH agonist (≥3 follicles with a diameter ≥17 mm and 25-35 follicles with a diameter ≥12 mm), unless the cycle is cancelled.
Progesterone	CRINONE	90 mg vaginal gel (8%) once daily, starting 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. (*Note*: not required for subjects who undergo triggering of final follicular maturation with GnRH agonist)

All NIMPs are used in line with the recommendations in the respective products' labelling for the indication of ART and/or standard clinical practice supported by literature.

5.3 Characteristics and Source of Supply

All medicinal products are provided by Ferring and will be handled according to the principles of Good Manufacturing Practice (GMP). Table 5-4 provides an overview of the presentation and manufacturer of each medicinal product.

Table 5-4 Characteristics and Source of Supply of Medicinal Products

IMP / NIMP	Presentation	Manufacturer
FE 999049 (rFSH)	FE 999049 is provided as a cartridge and an administration pen. Each cartridge contains a solution for injection delivering 72 µg FSH in 2.16 mL	Ferring Pharmaceuticals
GONAL-F (rFSH)	GONAL-F (follitropin alfa) is provided as a pre-filled pen containing a liquid formulation for injection. Each pen delivers 900 IU (66 µg) FSH in 1.5 mL	Merck Serono
CETROTIDE (GnRH antagonist)	CETROTIDE (cetrorelix acetate) is provided as powder and solvent for solution for injection. After reconstitution, 1 mL solvent contains 0.25 mg cetrorelix	Merck Serono
OVITRELLE (rhCG)	OVITRELLE (choriogonadotropin alfa) is provided as a pre-filled syringe (0.5 mL) for single use delivering 250 µg choriogonadotropin alfa	Merck Serono
GONAPEPTYL (GnRH agonist)	GONAPEPTYL (triptorelin acetate) is provided as a pre-filled syringe (1 mL) delivering 0.1 mg triptorelin acetate	Ferring Pharmaceuticals
CRINONE (progesterone)	CRINONE is provided as sustained-release vaginal gel 8% (90 mg) in prefilled applicators delivering 90 mg of progesterone	Merck Serono / Watson / Columbia / Actavis

5.4 Packaging and Labelling

Packaging and labelling of the medicinal products will be performed under the responsibility of the IMP department at Ferring in accordance with GMP and national regulatory requirements.

GONAL-F as well as all NIMPs are commercially available. No modification from the usual commercial state of GONAL-F will be made, except for trial-specific labelling. All medicinal products will be labelled with trial-specific labels, which contain a self-adhesive tear-off portion to be affixed to the drug label accountability form maintained at the trial site.

5.5 Conditions for Storage and Use

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

Deviations in storage temperature must be reported without delay and the medicinal products must not be used until further instructions from Ferring are received.

In case of technical malfunction of an administration pen, all relevant details (including time, date, a description of the malfunction and whether dosing was affected) of the incidence should be reported, the pen should be replaced and the treatment continued.

For information on warnings, precautions and treatment of overdose, please refer to the Investigator's Brochure for FE 999049 and the Product Information for GONAL-F as well as for OVITRELLE, GONAPEPTYL, CETROTIDE and CRINONE.

5.6 Blinding / Unblinding

5.6.1 Blinding

The trial is assessor-blind, and all investigators, embryologists and central laboratory personnel will be blinded to 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 e-CRF), 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.

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 75 IU per day as applicable if the subject is in the GONAL-F group, while no dose adjustments will be implemented if the subject is in the FE 999049 group. Requests for cycle cancellation due to inappropriate response or other medical reasons are followed, irrespective of treatment group.

The randomisation 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 e-CRF will not be accessible to assessors or the Ferring clinical trial team or laboratory personnel during the trial.

The Ferring clinical trial team (i.e. data manager, statistician, trial manager, medical writer, pharmacovigilance manager and sponsor's responsible medical officer) will be blinded to treatment allocation until breaking of the blind. The blind will be broken when the trial database is declared clean and locked.

5.6.2 Unblinding of Individual Subject Treatment

An emergency unblinding solution will be available to the investigator and designated persons at the sponsor. Breaking of the blind for individual subjects in emergency situations is only permitted in case of a suspected unexpected serious adverse reaction (SUSAR) or in case of an important adverse event where the knowledge of the IMP in question is required for therapeutic decisions for the management of the subject.

As far as the emergency permits, the need to break the blind will be agreed by the investigator and the sponsor. It should be recorded in the e-CRF that the code is broken, why, when and by whom. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding.

In case of accidental unblinding (e.g. the subject tells the investigator), the same documentation as for emergency unblinding must be obtained, i.e. why, when and by whom must be recorded in the e-CRF, and the event must also be recorded in the subject's medical record.

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 must be collected before the database is declared clean and locked.

5.7 Dispensing and Accountability, Return and Destruction

All handling of medicinal products (both IMP and NIMP) will be done by a trial medication delegate(s) at the site. The trial medication delegate will maintain subject dispensing logs, detailing the dates, quantities and batch numbers of dispensed and returned IMP and NIMP for each subject. The trial medication delegate will also manage the overall drug accountability at the site.

The monitor will verify drug accountability of IMP and NIMP throughout the trial and will document any discrepancies.

Concerning destruction, the trial medication delegate at the site must ensure destruction of dispensed IMP and NIMP in accordance with local legislation after drug accountability has been verified by the monitor and signed off by the trial medication delegate, while non-dispensed IMP and NIMP will be returned for destruction as instructed by the Ferring IMP Department.

5.8 Auxiliary Supplies

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

6 TRIAL PROCEDURES

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

Table 6-1 Trial Flow Chart – Subject Procedures

	Screening	Stimulation				Oocyte retrieval	Transfer	Pregnancy monitoring			End
		During stimulation			End-of-stimulation	OR	Transfer	βhCG	Clinical	Ongoing	End-of-trial
Timing	<90 days before randomisation	Day 1	Day 6	Day ≥7 to <20 [a]	End	36h ±2h after triggering	Day 3 after OR	13-15 days after transfer	5-6 weeks after transfer	10-11 weeks after transfer	[b]
Written informed consent	X										
Inclusion/exclusion criteria	X	X [c]									
Demographics	X										
Medical history	X										
Infertility history	X										
Menstrual history	X										
Reproductive history	X										
Smoking and alcohol habits	X										
Body weight and height	X	X [c],[d]									X [d]
Physical examination	X										X
Gynaecological examination	X										X
Pregnancy test	X	X [c]									
Ultrasound		X [c]	X	X	X				X	X	
Randomisation		X									
Vital signs	X	X [e]									X
Blood collection, clin chem / haem	X	X [e]			X						X
Blood collection, endocrine [f]	X	X [e]	X [g]		X [g]	X [h]					
Blood collection, antibodies [i]	X [j]	X [e]					X [k]	X [l]			X [l]
IMP dispensing		X	X [m]	X [m]							
NIMP dispensing			X [n]	X	X	X	X	X	X[o]		
Local tolerability (diary)		X	X	X	X						
Oocyte retrieval						X					
Embryo transfer							X				
βhCG test (local laboratory)								X			
Drug accountability			X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
End-of-trial form											X

a) Visits must be scheduled at least every second day; when the leading follicle reaches ≥15 mm visits must be scheduled daily.
b) End-of-trial assessments must be performed at the subject's last scheduled visit: at the earliest 19-28 days after the last IMP dose.
c) Performed before randomisation.
d) Only body weight.
e) Performed before the first IMP dose.
f) Endocrine parameters consist of a screening panel, a treatment panel, and FSH.
g) Performed at least 8 h after IMP administration.
h) FSH only.
i) All subjects with a treatment-induced antibody response must be followed until the response is negative or has returned to pre-dosing level, with a maximum follow-up period of one year.
j) Sample exclusively used as back-up samples for the anti-drug antibody assay development.
k) Blood sampling for antibody assessment must be done 5-10 days after the last IMP dose (this may coincide with the transfer visit; alternatively, a separate visit must be scheduled).
l) Blood sampling for antibody assessment must be done 19-28 days after the last IMP dose (this may coincide with the βhCG visit; alternatively, a separate visit must be scheduled).
m) The daily dose of FE 999049 is fixed throughout stimulation. The dose of GONAL-F is fixed for the first 5 days, after which it may be adjusted by 75 IU per day based on the individual response.
n) The trial medication delegate (or another qualified trial staff) should observe the general health of the subject, with emphasis on symptoms of an acute allergic reaction, for 30 min after the GnRH antagonist dosing.
o) Luteal phase support can be continued until the ongoing pregnancy visit, if applicable according to local practice. Progesterone administration should not continue if menses, negative βhCG or pregnancy loss occurs.
IMP: investigational medicinal product; NIMP: non-investigational medicinal product

6.1 Screening

Potential participants 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 (age, ethnicity, race)
- Collection of the following data:
  - Medical history (including any cysts)
  - Infertility history
  - Menstrual history
  - Reproductive history
  - Smoking and alcohol habits
- Body weight and height [*note*: these are used for calculation of BMI]
- Physical examination
- Vital signs
- Gynaecological examination
- Pregnancy test – must be negative
- Blood collection for central laboratory analysis of:
  - Clinical chemistry and haematology parameters [*note*: the results must be available before randomisation]
  - Endocrine parameters (screening panel: AMH, thyroid-stimulating hormone (TSH) and prolactin) [*note*: the results must be available prior to randomisation]
  - Anti-FSH antibodies [exclusively used as back-up samples for the anti-drug antibody assay development]
- Recording of use of any concomitant medication (within the last 3 months prior to signed informed consent for participation in the trial)
- 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 may proceed to the next visit, scheduled on day 2-3 of the menstrual cycle.

6.2 Stimulation

6.2.1 Stimulation Day 1

Subjects will attend the stimulation day 1 visit on day 2-3 of the menstrual cycle.

The following must take place prior to randomisation:

- Ensure that the subject is still eligible for participation in the trial
- Check those inclusion and exclusion criteria that were not possible during screening
- Body weight [*note*: this body weight result is used for dose calculation in the FE 999049 group and should be measured on a trial specific calibrated scale]
- Pregnancy test – must be negative
- 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.

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

- Randomisation, i.e. assignment to the lowest available subject number and thereby allocation to either FE 999049 or GONAL-F

The following must take place after randomisation but before administration of the first dose of IMP (FE 999049 or GONAL-F):

- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Blood collection for central laboratory analysis of:
  - Clinical chemistry and haematology parameters
  - Endocrine parameters (AMH and treatment panel: FSH, LH, estradiol, progesterone, inhibin A and inhibin B)
  - Anti-FSH antibodies

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]:

[a] Treatment can be initiated the same day. If puncture is not possible, randomisation may be postponed to the next menstrual cycles, assuming that the cyst will disappear and that the subject fulfils the inclusion criteria.

- If randomised to FE 999049; daily dose according to AMH level at screening and body weight at randomisation (see Table 5-1 for detailed instructions)
- If randomised to GONAL-F; starting dose for the first 5 days is fixed at 150 IU

- Hand out the diary to the subject. The subject must be instructed to assess and record local tolerability immediately, 30 min and 24 hours after each IMP administration throughout the entire stimulation period.

After the first administration of FE 999049 or GONAL-F, the subject must do the following:

- Assessment of local tolerability (recorded in a diary) – the first evaluation of local tolerability reactions at the injection site is done immediately after the subcutaneous injection of IMP, followed by the second evaluation 30 min after injection of IMP and the third evaluation 24 hours after injection of IMP (before the next day's injection of IMP).

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

- Take precautions in the event that the subject experiences an acute allergic reaction. 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 trial sites are requested to have facilities (i.e. medication, equipment and trained staff) and procedures in place for diagnosis and treatment of acute allergic reactions.
- Recording of use of any concomitant medication
- Recording of adverse events

The next visit must be scheduled for stimulation day 6.

6.2.2 Stimulation Day 6

The following must take place at stimulation day 6:

- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial triple-layer structure, endometrial echogenicity pattern, number and size of follicles)
- Blood collection for central laboratory analysis of:
  - endocrine parameters (treatment panel: FSH, LH, estradiol, progesterone, inhibin A and inhibin B) – the blood sample must be drawn at least 8 hours after the latest IMP administration
- Dispensing of IMP and potential dose adjustment
  - FE 999049: the daily dose is fixed throughout stimulation
  - GONAL-F: from stimulation day 6 and onwards, the daily dose may be adjusted by 75 IU per day based on the individual response
- Dispensing and administration of GnRH antagonist [the first administration of GnRH antagonist 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]
- Collection of local tolerability data (diary pages)

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

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

- In the first 30 min following the GnRH antagonist 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. *Note:* it is important that the subject does not mix up the injection sites for IMP and GnRH antagonist
- Instruct the subject to administer the GnRH antagonist at a daily dose of 0.25 mg throughout the stimulation period.

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.

6.2.3 Stimulation Days ≥7 to ≤20

These visits will 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 6.2.4):

- 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 antagonist, as applicable
- Collection of local tolerability data (diary pages)
- Drug accountability of IMP and GnRH antagonist
- Recording of use of any concomitant medication
- Recording of adverse events

6.2.4 End-of-stimulation

The end-of-stimulation visit takes 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 or GnRH agonist 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.

If the GnRH antagonist is administered in the morning it should also be administered on the day of triggering. If the GnRH antagonist is administered in the evening, no GnRH antagonist is to be given on the day of triggering.

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

Poor follicular development	Triggering criterion	Excessive follicular development
If it is judged by the investigator that ≥3 follicles with a diameter ≥17 mm cannot be reached, but 1 or 2 follicles with a diameter ≥17 mm are observed, the cycle may either be cancelled due to poor follicular development or triggering of final follicular maturation is to be induced, as judged by the investigator.	Criterion for triggering of final follicular maturation: • ≥3 follicles with a diameter ≥17 mm If <25 follicles with a diameter ≥12 mm are observed, hCG is administered.	In case of >35 follicles with a diameter ≥12 mm, the cycle is to be cancelled.
	If 25-35 follicles with a diameter ≥12 mm are observed, GnRH agonist can be administered; alternatively the cycle can be cancelled. Triggering drug must be administered the day the criterion is met.	If 25-35 follicles with a diameter ≥12 mm are observed, the cycle can be cancelled; alternatively GnRH agonist can be administered.

The investigator also has the option of cancelling the cycle for other relevant medical reasons, including adverse events and technical malfunctions of the administration pen.

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:
  - clinical chemistry and haematology parameters
  - endocrine parameters (treatment panel: FSH, LH, estradiol, progesterone, inhibin A and inhibin B) – the blood sample must be drawn at least 8 hours after the latest administration of IMP and GnRH antagonist
- Dispensing of hCG or GnRH agonist, as applicable
- Dispensing of GnRH antagonist
- Collection of local tolerability data (diary pages)
- Drug accountability of IMP and GnRH antagonist
- Recording of use of any concomitant medication

- Recording of adverse events

For subjects who receive a triggering drug, the next visit is the oocyte retrieval visit which must be scheduled 36h (±2h) after the administration of hCG or GnRH agonist.

For subjects with cycle cancellation, the next visit is the first post-dosing anti-FSH antibody blood sampling visit 5-10 days after the last FE 999049 or GONAL-F dose (section 6.5.2).

6.3 Oocyte Retrieval

Oocyte retrieval must take place 36h (±2h) after hCG or GnRH agonist administration. All oocytes from follicles with an estimated diameter ≥12 mm should 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 6.4.

The following must take place at the oocyte retrieval visit:

- Blood collection for central laboratory analysis of:
  - endocrine parameter (FSH only)
- Oocyte retrieval
- Dispensing of progesterone for luteal phase support – must be started on the day of oocyte retrieval or the day after and continued at least until clinical pregnancy [*note*: only applicable for subjects who underwent triggering of final follicular maturation with hCG and who had oocytes retrieved]
- Drug accountability of hCG or GnRH agonist, as applicable
- Collection of diary pages
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with oocytes retrieved following hCG administration, the next visit is the transfer visit 3 days after oocyte retrieval (section 6.5.1).

For subjects with oocytes retrieved following GnRH agonist administration, the oocytes will undergo the procedures described in section 6.4 and embryos will be cryopreserved on day 3, 5 or 6 after oocyte retrieval, according to local practice. The next visit for these subjects is the first post-dosing anti-FSH antibody assessment visit which must be scheduled 5-10 days after the last FE 999049 or GONAL-F dose (section 6.5.2).

For subjects with no oocytes retrieved, the next visit is the first post-dosing anti-FSH antibody assessment visit which must be scheduled 5-10 days after the last FE 999049 or GONAL-F dose (section 6.5.2).

6.4 Oocyte / Embryo Evaluation

The laboratory procedures regarding handling and evaluations 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.

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

	Day 0 (OR)	Day 1 after OR	Day 3 after OR
Oocyte retrieval (OR)	X		
Assessment of maturity stage (applicable for oocytes undergoing ICSI)	X		
Insemination by IVF or ICSI[b]	X		
Assessment of oocyte fertilisation		X	
Assessment of embryo quality			X
Transfer of 1 or 2 embryos of the highest quality available: – Subjects <35 years at randomisation: • single embryo transfer if a good-quality embryo is available • double embryo transfer if a good-quality embryo is not available (and if two embryos are available) – Subjects ≥35 years at randomisation: • double embryo transfer (if two embryos are available)			X
Cryopreservation of embryos, as applicable[c]			X[c]

Assisted hatching and pre-implantation genetic diagnosis (PGD) / pre-implantation genetic screening (PGS) are prohibited.

Day 0 (Oocyte Retrieval)

- Assessment of maturity stage (applicable for oocytes undergoing ICSI)
- Insemination at 0h using IVF or ICSI using ejaculated sperm (fresh or frozen) from partner or donor

Day 1 after Oocyte Retrieval

- Assessment of fertilisation (number of pronuclei)

[b] Rescue ICSI is not allowed.

[c] Cryopreservation of surplus embryos can be postponed to day 5 or 6, according to local practice.

Day 3 after Oocyte Retrieval

- Assessment of embryo quality:
  - Number of cells
  - Compaction status
  - 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
- Transfer of embryo (section 6.5)

Cryopreservation of surplus embryos should be performed on day 3 after oocyte retrieval. Cryopreservation can be postponed to day 5 or day 6 after oocyte retrieval, as applicable and according to local practice.

6.5 Transfer

6.5.1 Embryo Transfer

Transfer is performed on day 3 (embryo stage) after oocyte retrieval. The subject-related procedures are described below.

- Blood collection for central laboratory analysis of anti-FSH antibodies (first post-dosing assessment)
- Transfer of 1 or 2 embryo(s) of the highest quality available according to this policy:
  - Subjects <35 years at randomisation:
    - single embryo transfer if a good quality embryo is available
    - double embryo transfer if a good-quality embryo is not available (and single transfer if two embryos are not available).
  - Subjects ≥35 years at randomisation:
    - double embryo transfer (and single transfer if two embryos are not available).

  (note: transfer is only applicable for subjects who underwent triggering of final follicular maturation with hCG. Subjects who were administered GnRH agonist will not undergo transfer in the current fresh cycle).
- Dispensing of progesterone for luteal phase support
- Drug accountability of progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with embryo transfer, the next visit is the βhCG test visit which must be scheduled 13-15 days after transfer (section 6.6).

6.5.2 First Post-dosing Anti-FSH Antibody Assessment (5-10 Days after Last IMP Dose)

Subjects who have been exposed to FE 999049 or GONAL-F must have the first post-dosing anti-FSH antibody assessment performed 5-10 days after the last FE 999049 or GONAL-F dose. This may coincide with the transfer visit (section 6.5.1).

For subjects who do not attend the transfer visit, a separate visit must be scheduled, at which the following must take place:

- Blood collection for central laboratory analysis of anti-FSH antibodies
- Drug accountability of progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

6.6 βhCG Test

6.6.1 βhCG Test

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

The following must take place:

- Blood collection for local laboratory analysis of βhCG
- Blood collection for central laboratory analysis of anti-FSH antibodies (second post-dosing assessment)
- 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 blood sample for βhCG will be analysed by the local laboratory and evaluated according to the laboratory's reference ranges. In case of a borderline βhCG result, the test should be repeated. Subjects with a positive βhCG test must attend a clinical pregnancy visit 5-6 weeks after transfer (section 6.7). Subjects with a negative βhCG test must proceed to the end-of-trial assessments (section 6.9).

6.6.2 Second Post-dosing Anti-FSH Antibody Assessment (19-28 Days after Last IMP Dose)

Subjects who have been exposed to FE 999049 or GONAL-F must have the second post-dosing anti-FSH antibody assessment performed 19-28 days after the last FE 999049 or GONAL-F dose. This may coincide with the βhCG test visit (section 6.6.1).

For subjects who do not attend the βhCG test visit, a separate visit must be scheduled, at which the following must take place:

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

For subjects who do not attend the βhCG test visit, this second post-dosing anti-FSH antibody assessment may be done in connection with the end-of-trial visit (section 6.9).

6.7 Clinical Pregnancy

Subjects with a positive βhCG test must attend a visit 5-6 weeks after transfer.

The following must take place:

- Transvaginal ultrasound of uterus to assess any clinical pregnancy
- Drug accountability of progesterone
- Dispensing of progesterone for luteal phase support, if continued according to local practice
- 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. For subjects with a vital pregnancy, the next visit is the ongoing pregnancy visit 10-11 weeks after transfer (section 6.8). Subjects with no vital pregnancy must undergo end-of-trial assessments (section 6.9).

6.8 Ongoing Pregnancy

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

The following procedures / assessments must take place:

- Ultrasound (transvaginal or abdominal) of uterus to assess any intrauterine viable fetus
- Drug accountability of progesterone, if applicable
- 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.

6.9 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.

Due to the timing of the mandatory anti-FSH antibody assessments, the end-of-trial assessments can at the earliest be 19-28 days after the last FE 999049 or GONAL-F dose. This may coincide with the βhCG visit for subjects with a negative βhCG test.

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:

- Body weight
- Physical examination
- Gynaecological examination
- Vital signs
- Blood collection for central laboratory analysis of
  - clinical chemistry and haematology parameters
  - anti-FSH antibodies (second post-dosing assessment) [*note*: only applicable for subjects who have not already had a blood sample taken for the second post-dosing anti-FSH antibodies assessment as described in sections 6.6.1 and 6.6.2]
- Drug accountability, if applicable
- Recording of use of any concomitant medication
- Recording of adverse events
- Completion of end-of-trial form

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

6.10 Post-trial Activities

Pregnancy Follow-up

All subjects with an ongoing pregnancy will be followed till delivery to gather information on live birth rate. Furthermore, data will be gathered on neonatal health, including any congenital anomalies, at birth and at 4 weeks after birth as described in section 7.4.1.

7 TRIAL ASSESSMENTS

7.1 Assessment Related to Primary Endpoint

7.1.1 Ongoing Pregnancy

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 Assessments Related to Secondary Endpoints

7.2.1 βhCG Test

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

7.2.2 Clinical Pregnancy

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.[d,34] For intrauterine and ectopic pregnancies, the number of gestational sacs with fetal heart beat as well as without fetal heart beat will be recorded.

7.2.3 Vital Pregnancy

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.

7.2.4 Implantation

Implantation is determined based on the transvaginal ultrasound performed at the clinical pregnancy visit. Implantation rate will be defined as the number of gestational sacs 5-6 weeks after transfer divided by number of embryos transferred.

7.2.5 Ongoing Implantation

Ongoing implantation is determined based on the ultrasound performed at the ongoing pregnancy visit. Ongoing implantation rate will be defined as the number of intrauterine viable fetuses

[d] 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.

10-11 weeks after transfer divided by number of embryos transferred.

7.2.6 Extreme Ovarian Response

The number of oocytes retrieved will be counted at the oocyte retrieval visit. Extreme ovarian response will be defined as retrieval of <4, ≥15 or ≥20 oocytes.

7.2.7 Early OHSS (including OHSS of Moderate/Severe Grade) and/or Preventive Interventions for Early OHSS

Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation. Classification of grade is according to Golan's classification system (see section 8.3 for details) and all OHSS cases will be graded as mild, moderate or severe. Preventive interventions for early OHSS cover cycle cancellation due to excessive ovarian response or triggering of final follicular maturation with GnRH agonist.

7.2.8 Cycle Cancellation due to Poor or Excessive Ovarian Response or Embryo Transfer Cancellation due to Excessive Ovarian Response / OHSS Risk

The reason for each cycle cancellation will be recorded. Cycle cancellations related to inappropriate ovarian response will include poor and excessive follicular development. Cycle cancellation due to poor follicular development is implemented when the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached by stimulation day 20. Cycle cancellation due to excessive follicular development is implemented when >35 follicles with a diameter ≥12 mm are observed (can also be implemented if there are 25-35 follicles with a diameter ≥12 mm). The reason for each embryo transfer cancellation will be recorded. Transfer cancellation due to adverse events such as the Medical Dictionary for Regulatory Activities preferred terms (MedDRA PTs) "ovarian hyperfunction" and "ovarian hyperstimulation syndrome" and "high progesterone" in subjects with embryos available for transfer will be considered as transfer cancellations due to excessive response / OHSS risk.

7.2.9 Number and Size of Follicles during Stimulation

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. Data will be recorded separately for the right and left ovary.

7.2.10 Number and Distribution of Oocytes Retrieved

The number of oocytes retrieved will be recorded at the oocyte retrieval visit. The proportion of subjects with <4 oocytes (low response), 4-7 oocytes (moderate response), 8-14 oocytes (targeted response), 15-19 oocytes (hyperresponse) and ≥20 oocytes (severe hyperresponse) will be calculated.

7.2.11 Metaphase II Oocytes

Maturity stage will be assessed prior to insemination for oocytes that will undergo ICSI. Maturity

stage will be categorised as germinal vesicle, metaphase I, metaphase II, degenerated or other.

7.2.12 Fertilisation Rate

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

7.2.13 Number and Quality of Embryos on Day 3

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

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

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).

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).

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

A good quality embryo is defined as an embryo with ≥6 blastomeres and ≤20% fragmentation, without signs of multinucleation.

7.2.14 Circulating Levels of Endocrine Parameters

During treatment, the following panel of endocrine parameters will be evaluated (treatment panel): FSH, LH, estradiol, progesterone, inhibin A and inhibin B.

Blood samples will be drawn at stimulation day 1[e], stimulation day 6 and the end-of-stimulation visit. The sample on stimulation day 1 (baseline) will be collected prior to the first dose of FE 999049 or GONAL-F, and samples drawn at stimulation day 6 and the end-of-stimulation visit will be collected at least 8 hours after the previous FE 999049, GONAL-F or GnRH antagonist administration. The samples will be analysed at a central laboratory. The investigator will review and evaluate the laboratory results. The Laboratory Report will be signed and dated by the investigator.

7.2.15 FSH Population Pharmacokinetics

In addition to the sampling time points mentioned in section 7.2.14, blood samples will also be drawn at the oocyte retrieval visit for analysis of FSH.

Based on the serum FSH samples obtained during the trial, a population pharmacokinetic model will be developed to assess the pharmacokinetics of FE 999049 and confirm predictors for FSH

[e] AMH will also be included in the stimulation day 1 analyses.

concentration levels, such as body weight.

7.2.16 Total Gonadotropin Dose and Number of Stimulation Days

The start and end dates as well as daily dose of IMP will be recorded and used to calculate the total FE 999049 or GONAL-F dose administered and the number of stimulation days.

7.2.17 Gonadotropin Dose Adjustments

Investigator-requested decreases and increases of the gonadotropin dose will be captured during the stimulation period.

7.2.18 Adverse Events

Adverse events will be recorded from the signed informed consent for participation in the trial until the end-of-trial visit. For each adverse event the following parameters are recorded by the investigator on the Adverse Event Log: description of event, date and time of onset, intensity, causal relation to IMP, action taken to IMP, other actions taken, seriousness of the adverse event, date and time of outcome, and outcome. Furthermore, the pattern (e.g. the frequency, time of onset, intensity, seriousness and outcome) of the most frequent / relevant adverse events will be tabulated.

7.2.19 Clinical Chemistry and Haematology Parameters

The following clinical chemistry and haematology parameters will be analysed at a central laboratory:

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.

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, platelets.

Blood samples will be drawn at screening, on stimulation day 1, end-of-stimulation and end-of-trial. The samples from the screening visit will be used for safety and eligibility evaluation of the subject before randomisation. The sample at stimulation day 1 (baseline) must be drawn before the first FE 999049 or GONAL-F injection. The investigator will review the laboratory results and evaluate and document whether the abnormal results are non-clinically or clinically significant. The Laboratory Report will be signed and dated by the investigator.

7.2.20 Injection Site Reactions

Every day throughout the stimulation period, the subjects will assess the local tolerability of subcutaneous injections of FE 999049 or GONAL-F at three time points relative to the daily administration: immediately after the injection, 30 minutes after the injection and 24 hours after the injection. The following injection site reactions will be assessed: redness, pain, itching, swelling

and bruising. The presence and intensity of each injection site reaction will be rated as one of the following: none, mild, moderate or severe.

The subject will record the assessments in a diary and the diary data will subsequently be transcribed to the e-CRF.

7.2.21 Anti-FSH Antibodies

Blood samples for assessment of anti-FSH antibodies in the individual subjects in the trial will be drawn pre-dosing and post-dosing:

- Screening [*note*: this sample is exclusively used as back-up sample for the anti-drug antibody assay development]
- Stimulation day 1, prior to dosing (baseline; pre-dosing sample)
- 5-10 days after the last FE 999049 or GONAL-F dose
  This may coincide with the transfer visit. Subjects not reaching transfer must be called in for this extra visit.
- 19-28 days after the last FE 999049 or GONAL-F dose
  This may coincide with the βhCG visit. In case of discontinuation before the βhCG visit, this assessment should be done at the end-of-trial visit scheduled 19-28 days after the last FE 999049 or GONAL-F dose.

Ferring has developed the following assays for evaluating the immunogenicity of FE 999049 or GONAL-F:

Assay 1) A screening immunoassay, assessing the presence in serum of anti-FSH antibodies, using a parametric cut-point approach with a 5% false positive rate.

Assay 2) A confirmatory immunoassay, confirming or disconfirming the specificity of any positive results in assay 1), using a parametric cut-point approach with a 0.1% false positive rate.

Assay 3) A titre immunoassay determining the antibody response titre of any anti-FSH antibodies confirmed in assay 2).

Assay 4) A cell-based assay qualitatively assessing the neutralising capacity of any anti-FSH antibodies confirmed in assay 2), using a parametric cut-point approach with a 1% false positive rate.

Assay 5) A cell-based assay determining the neutralising antibody response titre of any positive result in assay 4).

Assay 6) A confirmatory assay based on native FSH, in order to assess cross-reactivity with native FSH of any anti-FSH antibodies confirmed to be specific towards exogenous FSH in assay 2), using a parametric cut-point approach with a 0.1% false positive rate.

In subjects with a negative pre-dosing sample, a treatment-induced anti-FSH antibody response will be defined as any post-dosing sample being positive in the confirmatory assay; Assay 2).

In subjects with a positive pre-dosing sample, a treatment-induced anti-FSH antibody response will be defined as a statistically determined fold increase in titres from the pre-dosing assessment to a post-dosing assessment.[f]

All positive samples in the confirmatory Assay 2) will be further characterised for titre, neutralising capacity (qualitatively and titre) and cross-reactivity. A subject is defined to have treatment-induced anti-FSH antibodies with neutralising capacity if the subject has a positive outcome of assay 4) after IMP administration compared to pre-dose.

The proportion of subjects with treatment-induced anti-FSH antibodies and the proportion of subjects with treatment-induced anti-FSH antibodies with neutralising capacity are secondary endpoints.

Subjects with a treatment-induced anti-FSH antibody response (both with and without neutralising capacity) will be followed until the response becomes negative or has returned to pre-dosing level. These subjects will be called in for monthly assessments for a period of 3 months after the last post-dosing anti-FSH antibody sampling. If required, further assessments will be made quarterly, i.e. 6, 9 and 12 months after the last post-dosing anti-FSH antibody sampling. The assessments will be terminated when two consecutive assessments are negative or indicate that the pre-dosing level has been reached, with a maximum follow-up period of one year. The assessments will also be terminated if the subject commences a new treatment cycle with a gonadotropin preparation.

7.2.22 Immune-related Adverse Events

All adverse events reported in the trial will be analysed to identify those that potentially are immune-related. To identify all possible cases, a broad-scope search on Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs), including ‘Hypersensitivity’, ‘Anaphylactic reactions’, ‘Angioedema’ and ‘Severe cutaneous adverse reactions’ will be considered. Moreover, to identify the potential cases manifested by non-specific symptoms and not covered by these SMQs, other MedDRA PTs like ‘Musculoskeletal pain’, ‘Asthenia’, ‘Pyrexia’, ‘Chills’, ‘Body temperature increased’, ‘Influenza like illness’, ‘Injection related reaction’, ‘Pre-syncope'’ and ‘Syncope’ will also be taken into account. Hypersensitivity reactions manifested by local symptoms will be identified using the MedDRA high level term (HLT) ‘injection site reactions’. The SMQs may include very specific as well as less specific terms; hence a narrow-scope search on these SMQs will be carried out to identify those cases that are highly likely to represent an immune-related aetiology.

7.2.23 Cycle Cancellations due to an Adverse Event, including Immune-related Adverse Events, or due to Technical Malfunctions of the Administration Pen

The reason for each cycle cancellation will be recorded. Among the options are adverse events, including immune-related adverse events, and technical malfunctions of the administration pen.

[f] The fold increase in titres will be determined by minimum significant ratio (MSR) experiments during assay validation. The clinical trial report will clearly state the MSR used in the data evaluation.

7.2.24 Late OHSS (including OHSS of Moderate/Severe Grade)

Late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation. Classification of grade is according to Golan's classification system (see section 8.3 for details) and all OHSS cases will be graded as mild, moderate or severe.

7.2.25 Multi-fetal Gestation, Biochemical Pregnancy, Spontaneous Abortion, Ectopic Pregnancy and Vanishing Twins

Data related to multi-fetal gestation defined as a pregnancy with more than one fetus will be recorded. Furthermore, data related to the occurrence of biochemical pregnancy, spontaneous abortion, ectopic pregnancy (with and without medical/surgical interventions) and vanishing twins will also be recorded.

7.2.26 Pen Malfunction

Incidences of technical malfunctions of the administration pen will be recorded.

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 race and nationality. Chinese subjects must possess a Chinese identification card and have native Chinese parents.

7.3.2 Medical History

Any relevant medical history 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 at the randomisation visit. This will also cover information about any previous treatment for infertility, including type of treatment and gonadotropin preparations used.

7.3.4 Menstrual History

Information about the menstrual history (average cycle length) will be obtained during the screening period.

7.3.5 Reproductive History

Information about the reproductive history will be obtained during the screening period. This will include number of clinical pregnancies, number of fetuses and outcome. Information on primary versus secondary infertility will be derived.

7.3.6 Smoking and Alcohol Habits

Information about smoking and alcohol habits will be obtained during the screening period. Smoking will be categorised as 0, 1-5 or 6-10 cigarettes per day. Alcohol will be categorised as 0, 1-7 or 8-14 units per week.

7.3.7 Body Weight and Height

Body weight will be measured at screening, stimulation day 1 and at end-of-trial. Body weight will be measured without shoes and overcoat and using a calibrated scale. The body weight at randomisation will be used for dose calculation in the FE 999049 group.

Height will only be measured at screening and will be used to calculate BMI.

7.3.8 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 on 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.

7.3.9 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 8 and 9 (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.

7.3.10 Endocrine Parameters at Screening

At screening, the following panel of endocrine parameters will be evaluated (screening panel): AMH, TSH and prolactin. The sample will be analysed at a central laboratory.

The results of the screening panel must be available prior to randomisation. The investigator will review and evaluate the laboratory results (with the exception of AMH, which will not be made available to the investigator). The Laboratory Report will be signed and dated by the investigator.

The AMH samples collected at screening may be used for correlation analysis of Elecsys® AMH immunoassay results determined at provincial local laboratories versus the central laboratory.

7.3.11 Vital Signs

Systolic and diastolic blood pressure as well as pulse will be measured at screening, stimulation day 1 and end-of-trial. All assessments of vital signs will be done while the subject is in supine position after resting for 3 minutes.

7.3.12 Ovarian Volume

As part of the transvaginal ultrasounds performed at stimulation day 1 and end-of-stimulation, the size – length, width and depth (recorded in mm) – of each ovary is measured and used for subsequent calculation of ovarian volume.

7.3.13 Endometrial Status

Transvaginal ultrasound of the uterus to assess the endometrial status will be conducted at all visits 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.

7.3.14 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.

7.3.15 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.

7.3.16 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 antagonist, hCG and GnRH agonist. Details on drug dispensing and accountability are provided in section 5.7.

7.3.17 End-of-trial Form

An end-of-trial form must be filled in at the subject's last visit, irrespective of whether the subject completes the trial or not. Completion / discontinuation status will be recorded, as well as date and reason for discontinuation in case the subject did not complete the trial.

7.4 Assessments Related to Post-trial Information

7.4.1 Pregnancy Follow-up

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, will be gathered. Further, 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 any other relevant medical conditions. These follow-up data can be obtained from the subject, unless medical judgement is required.

These data will be reported separately.

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 the biological samples (blood) in this trial. All biological samples will be analysed at central laboratories and will be maintained in storage after the end of the trial. Destruction will take place within 2 years after reporting of the trial or when methods /

results have been adequately validated. For all biological samples collected in the trial, it applies that analyses beyond those described in the protocol can only be performed after obtaining the required approvals. The processes related to handling of biological samples will be described in the informed consent documents, and biobank / data protection legislation including local legislation will be adhered to.

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 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 end-of-trial visit.

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 in each subject's e-CRF with information about:

- Adverse event
- Date and time of onset

- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome
- Outcome
- Seriousness

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

Adverse Event

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.[g]

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).

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.

[g] Exception: if an adverse event with onset before the first IMP administration (i.e. a pre-treatment adverse event) changes in intensity after the administration of the IMP, this must be recorded as two separate events. The initial adverse event should be recorded with outcome "not yet recovered" and the date and time of outcome is when the intensity changed. The second adverse event should be recorded with date and time of onset when the intensity changed.

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 activity.
Moderate:	Event sufficient to affect usual activity (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 with the IMP or the event recurs on rechallenge with the IMP.

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.

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 (medication schedule maintained or no action taken)
- 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.

Date and Time of Outcome

The date and time 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
- Not recovered
- Fatal

8.3 Adverse Events of Special Interest and/or Requiring Special Handling

8.3.1 Ovarian Hyperstimulation Syndrome (OHSS)

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[35] 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) Heaemoconcentration 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 must be reported as such. Note that 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.

In addition to early OHSS and late OHSS overall, emphasis will be placed on OHSS of moderate/severe grade.

Preventive Interventions of Early OHSS

Preventive interventions of early OHSS include the following:

- Cycle cancellation due to excessive ovarian response

- Triggering of final follicular maturation with GnRH agonist

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 the following (for moderate/severe OHSS):
  - Progesterone and estradiol
  - 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)
  - 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)
  - 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 Local Tolerability

Injection site reactions after administration of IMP (FE 999049 and GONAL-F) 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. Local tolerability of IMP constitutes a secondary endpoint and will be evaluated in detail based on the subjects' recordings in the diary.

Local tolerability reactions after administration of NIMP are to be reported as adverse events if they fulfil the definition of an adverse event.

8.3.3 Treatment-induced Anti-FSH Antibodies

Presence of treatment-induced anti-FSH antibodies is not to be reported as an adverse event. These data will be described as part of the secondary endpoints.

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.

8.3.6 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 post-trial follow-up will be defined as a late pregnancy loss.

8.3.7 Multiple Pregnancies

Multi-fetal gestations are not to be reported as adverse events. These data will be described as part of the secondary endpoints.

8.4 Serious Adverse Events

8.4.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined a serious adverse event if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is *per se* not an event, but an outcome.
is **life-threatening**	The term life-threatening refers to an adverse event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient **hospitalisation** or prolongation of existing hospitalisation	The term hospitalisation means that the subject was admitted to hospital or that existing hospitalisation was extended as a result of an event. Hospitalisation describes a period of **at least 24 hours**. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalisation. However, medical judgement must always be exercised and when in doubt the case should be considered serious (i.e. if case fulfils the criterion for a medically important event). Hospitalisations for administrative or social purposes do not constitute a serious adverse event. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
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 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 Post-trial Follow-up

The following untoward medical occurrences reported as part of the pregnancy outcome and neonatal health data collection will be recorded as serious adverse events. Data will be collected at birth and at 4 weeks after birth.

- Death of mother in connection with pregnancy or labour
- Death of neonate

- Stillbirth (≥ gestational age 24 weeks + 0 days, calculated from the day of transfer + 17 days[34])
- Neonate admitted to the NICU regardless of duration or NCU for more than 2 hours
- Congenital anomaly / birth defect
- Medically important event

In case of admission to NICU or NCU, the reason for admission must be reported as a serious adverse event, rather than just the act of hospitalisation.

Congenital anomalies will be coded by Ferring using both MedDRA and ICD-10 and classified as minor or major[h] in accordance with the EMA guideline[1].

8.4.2 Collection, Recording and Reporting of Serious Adverse Events

Serious Adverse Event Reporting by the Investigator

All serious adverse events must be reported **immediately** to Ferring Global Pharmacovigilance as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of a serious adverse event.

The investigator is responsible for submitting the completed Serious Adverse Event (SAE) Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the serious adverse event.

Serious Adverse Event (SAE) Report Form

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

Global Pharmacovigilance, Ferring Pharmaceuticals A/S
E-mail: safety.mailbox@ferring.com
Fax: [redacted]

Information to be Entered / Updated in the e-CRF

Completion of the Demographics, Adverse Event form, Medical History form and Concomitant Medication form 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 e-CRF for Ferring Global Pharmacovigilance to access the information.

[h] Major abnormalities: a life threatening structural anomaly or one likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment.
Minor anomalies: relatively frequent structural anomaly not likely to cause any medical or cosmetic problems.

Additional information relevant to the serious adverse event such as hospital records, results from investigations, e.g. laboratory parameters (that are not already uploaded in the e-CRF), invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring Global 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, such details such as subject's name, address, and hospital ID number should be concealed and instead subject number should be provided.

The investigator will supply Ferring and the ethics committee with any additional requested information such as results of post-mortem examinations and hospital records.

Expedited Reporting by Ferring

Ferring will report all adverse events that are **serious, unexpected and with a reasonable possible causality to the IMP** as judged by either the investigator or Ferring to the relevant parties within the stipulated timelines.

The expectedness is assessed by Ferring according to the current edition of the Investigator's Brochure for FE 999049 and the Product Information for GONAL-F.[4]

Serious adverse events will be considered reportable regardless of whether or not the IMP was used in accordance with the provisions in the protocol, Investigator's Brochure and labelling.

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 it is resolved or until the medical condition of the subject is stable.

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. If the event is 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 End-of-trial

If an investigator becomes aware of a serious adverse event after the end of the trial, and he/she assesses the serious adverse event to have a reasonable possible causality to the IMP (FE 999049 or GONAL-F) or a NIMP where Ferring is Marketing Authorisation Holder (i.e. GONAPEPTYL) the case will have to be reported to Ferring, regardless how long after the end of the trial this takes place.

8.5.3 Follow-up of Serious Adverse Events with Onset during the Post-Trial

For post-trial serious adverse events in neonates, where the neonate has not recovered at the 4-weeks follow-up assessment, the investigator must follow up until 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.

9 STATISTICAL METHODS

The Ferring Global Biometrics Department will be responsible for the statistical analyses of the primary and secondary endpoints. This section details the planned statistical analyses for the primary endpoint and outlines the planned statistical analyses for the secondary endpoints. All analyses and further descriptions of the statistical methodology for the primary and secondary endpoints will be included in the Statistical Analysis Plan (SAP) available before the first subject is randomised. A separate SAP will be prepared to cover the post-trial information.

The Ferring Health Economics & Outcome Research department will perform a health economic analysis of FE 999049 in comparison with GONAL-F utilising relevant data recorded in this trial. The details of this analysis will be described in a separate health economic analysis plan.

9.1 Determination of Sample Size

The primary objective of this trial is to demonstrate non-inferiority of FE 999049 compared with GONAL-F with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation. The non-inferiority limit for the difference between treatments (FE 999049 versus GONAL-F) is -10.0% (absolute) for the primary endpoint.

The trial is designed to have 90% power of achieving the primary objective for the overall trial population and 80% power in the Chinese population. The number of subjects needed to achieve 90% power depends on the assumptions regarding the ongoing pregnancy rate. The ongoing pregnancy rate is defined as the number of subjects with at least one intrauterine viable fetus 10-11 weeks after transfer divided by the number of randomised and exposed subjects.

Considerations for Choice of Non-inferiority Margin

Assuming that the ongoing pregnancy rate is 32.2% in both treatment groups, then the total number of subjects needed to achieve 90% power is governed by the choice of non-inferiority margin. In order to establish non-inferiority, the two-sided 95% confidence interval must lie entirely above the chosen non-inferiority margin. Therefore, the power of the test is directly related to the width of the two-sided 95% confidence interval. The width of this confidence interval is inversely related to the square root of the sample size, i.e. a quadrupling of the sample size will lead to a halving of the width of the confidence interval. In fact, increasing the sample size with 500 subjects from 100 to 600 reduces the width of the confidence band with 59%, while the impact of a similar increase in number of subjects from 1,000 to 1,500 only reduces the width of the confidence band with 18%.

The sample sizes for three different non-inferiority margins are shown in Table 9-1. As shown, changing the non-inferiority margin from -12.0% to -10.0% requires 280 additional subjects, while tightening the margin with an additional 2.0% requires 516 additional subjects. To further illustrate the difference between these three non-inferiority margins, the width of the two-sided 95% confidence intervals and the precision quantified as ±1 standard error are also included in Table 9-1. As can be seen, increasing the sample size from 918 to 1,434 subjects reduces the standard error with 0.6 percentage points (from 3.1% to 2.5%).

The relation between the choice of non-inferiority margin and the maximum allowed difference in ongoing pregnancy rates leading to non-inferiority can also be derived. Assuming the observed rate for the GONAL-F group is 32.2% the minimum observed rate in the FE 999049 group that still leads to non-inferiority is shown in Table 9-1. For example, if the non-inferiority margin is -10.0% and the observed ongoing pregnancy rate in the GONAL-F group is 32.2%, then non-inferiority will only be established if the observed ongoing pregnancy rate in the FE 999049 group is at least 28.2%, i.e. the observed ongoing pregnancy rates must not differ with more than 4.0 percentage points. Tightening the margin to -8.0%, (i.e. adding 516 subjects) will require a minimum ongoing pregnancy rate of 29.0% in the FE 999049 in order to claim non-inferiority, i.e. a maximum difference of 3.2 percentage points. Hence, increasing the sample size from 918 to 1,436 subjects reduces the maximum allowable observed difference between treatments by 0.8 percentage points (from 4.0% to 3.2%).

Taking the above into account a non-inferiority margin of -10.0% (absolute) seems appropriate since further tightening of the non-inferiority margin will lead to an increase in sample size with only limited impact on the precision of the estimate and the maximum difference in observed rates leading to non-inferiority.

Table 9-1 Implications of Choice on Non-inferiority Margin on Sample Size, Precision and Difference in Observed Rates

Non-inferiority margin (absolute)	**-12.0%**	**-10.0%**	**-8.0%**
Subjects needed to achieve 90% power in the PP population*	638	918	1434
Expected width of two-sided 95% confidence interval	14.5%	12.1%	9.7%
Expected precision of estimate (± 1 standard error)	± 3.7%	± 3.1%	± 2.5%
Minimum ongoing pregnancy rate with FE 999049 needed to claim non-inferiority if the observed rate with GONAL-F is 32.2%	27.3%	28.2%	29.0%
Maximum difference that can be observed (GONAL-F minus FE 999049) leading to non-inferiority if the observed rate with GONAL-F is 32.2%	4.9%	4.0%	3.2%

* Assuming 8% major protocol deviations

Considerations for Sample Size

Table 9-2 summarises the required sample size to obtain 80% and 90% power for various rates (assumed equal in the two treatment groups) and assuming a non-inferiority margin of -10.0% (absolute).

Since this is a non-inferiority trial, the full analysis set (FAS) and the per-protocol (PP) analyses are equally important, i.e. non-inferiority should be established for both analysis sets in order to have a robust conclusion[36,37]. Therefore, the expected proportion of subjects with major protocol deviations should be taken into account when setting the total sample size for the trial. The proportion of subjects with major protocol deviations is assumed to be at most 8%.

Table 9-2 Sample Size by Ongoing Pregnancy Rate for the PP Analysis Set

Ongoing pregnancy rate (Assumed equal in the two treatment groups)	Assuming 80% power and -10.0% (absolute) non-inferiority margin		Assuming 90% power and -10.0% (absolute) non-inferiority margin	
	Number of subjects		Number of subjects	
	Per group	Total	Per group	Total
	PP*	PP*	PP*	PP*
25%	295	590	395	790
30%	330	660	442	884
32.2%	343	686	459	918
35%	358	716	479	958
40%	377	754	505	1010
45%	389	778	521	1042
50%	393	786	526	1052

* Assuming 8% major protocol deviations

Based on an assumed ongoing pregnancy rate of 32.2 % observed in the PP population of the ESTHER 1 trial, N=918 subjects are required in the PP population to obtain a power of 90%. Anticipating at most 8% major protocol deviations this results in N=1000 subjects to be randomised. The power is reasonably robust against deviations from the ongoing pregnancy rate assumption of 32.2%: a 35% ongoing pregnancy rate would still result in a 88.9% power, while lower rates will only increase the power (e.g. 30% yields 91.1% power). Recruiting at least 740 subjects in China is expected to secure that consistency can be established between the results from the overall trial population and the Chinese trial population. In addition, to obtain approval in other Asian countries at least 260 subjects are needed. Thus a total sample size of 1,000 subjects will be recruited for this trial.

A sample size re-assessment is planned and will be done without breaking the blind and without inflating the type 1 error of the trial, in line with the current regulatory guidelines (see section 9.10). The expected maximum number of subjects to be randomised would then be approximately 1,144 (572 per treatment group), corresponding to an observed rate of 50%.

9.2 Subject Disposition

All screened subjects will be accounted for.

Screened subjects who discontinue from the trial prior to randomisation are regarded as screening failures.

Subject disposition with respect to analysis sets will be tabulated by treatment group overall, by age stratum and country for all randomised subjects. This table will include the number of completed and discontinued subjects including reason for discontinuation. Screening failures and their primary reason for screening failure will also be included. Screening failures will not otherwise be accounted for.

A separate table will summarise the subject disposition with respect to analysis sets by trial site overall and by age stratum.

Subject disposition with respect to analysis sets will be listed for all randomised subjects including information on trial completion and reason for discontinuation for non-completers. Subjects who discontinued from the trial will also be listed separately.

9.3 Protocol Deviations

Major protocol deviations, such as significant non-compliance or other serious unforeseen deviations deemed to invalidate the data and affect the conclusions of the trial, will lead to exclusion of data from the PP analysis set. Data will not be excluded from the PP analysis set in case of minor protocol deviations. The list of major protocol deviations include, but is not restricted to:

- Unblinding of assessor
- Treatment not in accordance with randomisation
- Non-compliance with IMP for two or more days
- Administration of hCG for triggering of final follicular maturation was not given despite the triggering criterion for hCG administration was met
- GnRH agonist criterion met but hCG used for triggering of final follicular maturation
- GnRH agonist criterion not met but GnRH agonist used for triggering of final follicular maturation
- Non-compliance with the number of embryos transferred

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 and affect the conclusions of the trial 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. Major protocol deviations will be tabulated and listed by subject for the FAS analysis set.

9.4 Analysis Sets

Intention-to-Treat (ITT) Analysis Set

The intention-to-treat (ITT) analysis set is defined as all randomised subjects. Subjects will be analysed according to randomised treatment.

Full Analysis Set (FAS)

The FAS is defined as all randomised and exposed subjects. Subjects will be analysed according to randomised treatment.

Per-Protocol (PP) Analysis Set

The PP analysis set is defined as all randomised and exposed subjects except those excluded as a result of major protocol deviations as described in section 9.3.

Safety Analysis Set

The safety analysis set is defined as all randomised and exposed subjects. Subjects will be analysed according to actual treatment received.

9.5 Trial Population

9.5.1 General Considerations

All relevant baseline data will be summarised in tables including both treatment groups and a total column. The purpose of these tabulations is to characterise the treatment groups and assess the degree of similarity achieved by the randomisation. Baseline data will not be compared using statistical tests. Unless otherwise noted, tabulations will be produced overall and by age stratum for both the FAS and the PP analysis set. Continuous variables will be presented with number of subjects, mean, standard deviation, median, inter-quartile range, minimum, and maximum. Categorical variables will be presented with number and percentage of subjects within each specific category.

Listings will be produced for the FAS.

Unless otherwise noted, missing data will not be imputed.

9.5.2 Trial Population Parameters

Demographics and other Baseline Characteristics

Demographics and other baseline characteristics (smoking and alcohol habits, body measurements, ultrasound parameters, vital signs, and endocrine parameters) obtained before first exposure to IMP will be listed by subject and tabulated.

Medical History

All medical history will be coded using MedDRA. The version of MedDRA will be documented. Medical history will be listed by subject and summarised for each medical item. This summary table will be produced overall (i.e. not by age stratum) for the FAS.

Infertility History, Menstrual History and Reproductive History

Infertility history, menstrual history and reproductive history will be listed by subject and presented in summary tables.

Physical Examination and Gynaecological Examination

Physical examination and gynaecological examination performed during screening will be summarised per category. These tables will be produced overall (i.e. not by age stratum) for the FAS.

Concomitant Medication

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List. Prior and concomitant medication will be summarised by ATC classification 1st level (alphabetically) and ATC classification 2nd level (in decreasing order of frequency). These medications will be tabulated separately for:

- Prior medication, i.e. medication taken exclusively prior to treatment (i.e. with stop date/time before date/time of 1st IMP administration)
- Concomitant medication, i.e. medication taken during the treatment period (i.e. medication that was not stopped before date/time of 1st IMP administration and not started after the end-of-trial visit)

These tables will be produced overall (i.e. not by age stratum) for the FAS.

If the timing of the dose of a concomitant medication cannot be established in relation to the administration of IMP, it will be considered as concomitant medication.

Concomitant medications will be listed by subject.

9.6 Treatment Compliance

Treatment non-compliance will be presented in listings as non-compliance is expected to be limited.

9.7 Endpoint Assessments

9.7.1 General Considerations

Primary and Secondary Endpoints

The results of the analyses of the primary endpoint (ongoing pregnancy rate) based on the overall trial population are essential for the non-inferiority claim. The results obtained for the Chinese trial population is considered supportive of the overall conclusion. If the results for the Chinese trial population are markedly different from those obtained based on the overall trial population the reasons for this difference will be examined. The secondary endpoints positive βhCG rate, clinical pregnancy rate, vital pregnancy rate, implantation rate and ongoing implantation rate are considered supportive of the primary endpoint. However, non-inferiority does not need to be established for these secondary endpoints.

The remainder of the secondary endpoints are intended to provide additional characterisation of the treatments.

Analysis and Presentation of Primary and Secondary Endpoints

Summary tables and treatment comparisons for the primary endpoint and supportive secondary endpoints will be presented overall, by age stratum and country for both the FAS and PP analysis sets. Treatment comparisons will be produced for the overall trial population and for the Chinese population. As applicable for the remaining secondary endpoints, summary tables and treatment comparisons may be presented overall and by age stratum for the FAS and PP analysis sets.

All tabulations will present the treatment groups and include a total column. Continuous variables will be presented with number of subjects, mean, standard deviation, median, inter-quartile range, minimum, and maximum. Categorical variables will be presented with number and percentage of subjects within each specific category.

All statistical tests will be performed using a two-sided test at a 5% significance level. Treatment differences will (where appropriate) be presented with 95% confidence intervals and p-values corresponding to the statistical test of the hypothesis of ‘equal effect’ against the alternative of ‘different effect’.

Visual displays will be produced as appropriate. All primary and secondary efficacy endpoints will be listed for the FAS.

Multiplicity

No adjustments for multiplicity are required since there is only one primary endpoint and non-inferiority has to be established for both the FAS and the PP analysis sets. In addition, the testing for superiority will be made in a sequential manner, only if non-inferiority is established. The evaluation of the subjects recruited in China will be regarded as supportive. Concerning the secondary endpoints no formal adjustment for multiplicity will be utilised.

Missing Data

Missing observations for the primary endpoint ongoing pregnancy rate will be imputed as 'negative' irrespective of the reason why data are not recorded.

Missing observations for the supportive secondary endpoints positive βhCG rate, clinical pregnancy rate and vital pregnancy rate will be imputed as 'negative' unless a positive result is observed at a later pregnancy assessment. For example, if the outcome of βhCG is missing but clinical pregnancy is positive then βhCG will be imputed as 'positive'.

For subjects with transfer but missing information on the number of viable fetuses 10-11 weeks after transfer, the number of viable fetuses will be imputed as zero irrespective of why data are not recorded. For subjects with transfer but missing information on the number of gestational sacs 5-6 weeks after transfer, the number of gestational sacs will be imputed as the number of viable fetuses at 10-11 weeks after transfer.

For adverse events, missing values will be treated as missing, except for causality, intensity and seriousness of adverse events, where a worst-case approach will be used.

Missing values will not be imputed for any of the other secondary endpoints.

9.7.2 Primary Endpoint

This trial has one primary endpoint: Ongoing pregnancy rate. The primary objective of this trial is to demonstrate non-inferiority of FE 999049 compared with GONAL-F with respect to the primary endpoint in women undergoing controlled ovarian stimulation. The non-inferiority limit for the difference between treatments (FE 999049 versus GONAL-F) is -10.0% (absolute).

The non-inferiority hypothesis to be tested for the primary endpoint is

$$H_0: \pi_{FE} - \pi_{GF} \leq -10.0\% \text{ against the alternative } H_A: \pi_{FE} - \pi_{GF} > -10.0\%,$$

where π_{FE} and π_{GF} denote the ongoing pregnancy rate after treatment with FE 999049 and GONAL-F, respectively. Non-inferiority will be evaluated based on the overall trial population.

The primary analyses will be adjusted for the stratification factor (age group) by using the Mantel-Haenszel method to combine results across age groups. In brief, this corresponds to deriving a weighted average across age groups where the weight depends on the number of observations in each treatment group in each age stratum.

For the primary endpoint the null hypothesis (H_0) will be tested against the alternative (H_A) by constructing a two-sided 95% confidence interval for the difference in ongoing pregnancy rates. If the lower-limit of the two-sided 95% confidence interval is greater than the non-inferiority limit (-10.0%) for both the FAS and the PP analysis set, the null hypothesis will be rejected. In that case it will be claimed that FE 999049 is non-inferior to GONAL-F with respect to ongoing pregnancy rate in women undergoing controlled ovarian stimulation.

If the lower-limit of the two-sided 95% confidence interval for the treatment difference based on the FAS not only lies above the non-inferiority limit (-10.0%) but also above zero then there is evidence of superiority in terms of statistical significance at the 5% level. In this case, the p-value from the test for superiority will be reported and it will be claimed that FE 999049 is superior to GONAL-F for the primary endpoint analysed. The result based on the PP analysis set is not essential for the superiority claim but should lead to a comparable result for a robust interpretation.

There is no need for a multiplicity adjustment when switching from non-inferiority to superiority since it is a simple sequential test procedure. This interpretation is in line with the Food and Drug Administration (FDA) draft guidance on "Non-inferiority Clinical Trials"[36] and EMA's "Points to consider on switching between superiority and non-inferiority"[38].

Due to the large sample size the two-sided 95% confidence intervals will be established based on the asymptotic normal distribution as follows

$$\frac{\sum w_i RD_i}{\sum w_i} \pm 1.96 \sqrt{\frac{\sum w_i^2 SE(RD_i)^2}{\left(\sum w_i\right)^2}},$$

where all sums are over the three strata (i.e. i = 1 to 3) and

$RD_i = \hat{\pi}_{FE,i} - \hat{\pi}_{GF,i}$ is the observed difference in rates within age stratum *i*

$SE(RD_i) = \sqrt{\frac{\hat{\pi}_{FE,i}(1-\hat{\pi}_{FE,i})}{n_{FE,i}} + \frac{\hat{\pi}_{GF,i}(1-\hat{\pi}_{GF,i})}{n_{GF,i}}}$ is the standard error of the observed difference in rates within age stratum *i*

$w_i = \frac{n_{FE,i} n_{GF,i}}{n_{FE,i} + n_{GF,i}}$ is the weight assigned to age stratum *i*

$\hat{\pi}_{FE,i}$ is the observed rate in age stratum *i* in the FE 999049 group

$\hat{\pi}_{GF,i}$ is the observed rate in age stratum *i* in the GONAL-F group

$n_{FE,i}$ is the number of observations in the FE 999049 group in age stratum *i*

$n_{GF,i}$ is the number of observations in the GONAL-F group in age stratum *i*

A supportive evaluation of the subjects recruited in China will be conducted, and it is expected that the findings among the Chinese trial population will be consistent with the overall findings in the trial. If the results based on the Chinese trial population are markedly different from those obtained based on the overall trial population the implications for the overall conclusion of the trial will be evaluated.

Additional Analyses, including Sensitivity Analysis

The primary analyses described above will be repeated restricted to subjects with oocytes retrieved and to subjects with embryo(s) transferred. Since the trial is not powered to establish non-inferiority for these subgroups, the outcomes of these analyses are considered supportive of the primary analysis.

Besides stratification by age group the randomisation is also stratified by trial site. However, as detailed above, the primary analysis will be based on all data pooled across sites assuming homogeneity of the risk differences across sites. This assumption will be tested using the approach described by Lipsitz et al. (1998).[39] If there is statistically significant heterogeneity across sites the implications for the interpretation of the primary result will be discussed.

To evaluate the robustness of the conclusions, the following factors potentially impacting ongoing pregnancy will be evaluated one by one:

- Insemination method
- Primary reason for infertility
- Primary infertility
- Smoking status

For each factor, subjects will be grouped according to the levels of the factor and the primary analysis will be repeated using this grouping. The outcomes of these analyses are considered supportive and should lead to similar results as the primary analysis to ensure robustness of the conclusion.

As described in Section 6.5.1, transfer of one or two embryo(s) is to be performed on day 3 after oocyte retrieval. The decision to transfer either one or two embryo(s) is based on the subject's age and the quality and availability of embryo(s) on the day of transfer. Since this decision is based on observations performed after randomisation it can be affected by the treatment allocation. It is therefore not planned to perform a formal statistical analysis of the ongoing pregnancy rate adjusting for number of embryos transferred. The rationale for not including these adjustments in the primary analysis is that such an adjustment may hide or exaggerate the differences between treatments.[40] Instead the ongoing pregnancy rate will be presented by number of embryos transferred. Further, a frequency table will be produced to compare the treatment groups with respect to number of embryos transferred.

9.7.3 Secondary Endpoints

For each secondary endpoint the analysis based on the FAS will be used to assess the statistical significance of differences between treatments. The analysis based on the PP analysis set will be considered supportive and should lead to a similar but not necessarily statistically significant result in order to have a robust interpretation.

Positive βhCG Rate

The positive βhCG rate is considered supportive of the primary endpoint and will therefore be analysed in a similar manner.

Clinical Pregnancy Rate

The clinical pregnancy rate is considered supportive of the primary endpoint and will therefore be analysed in a similar manner. For subjects with clinical pregnancy, the type of clinical pregnancy (intrauterine or ectopic) will be tabulated.

Vital Pregnancy Rate

The vital pregnancy rate is considered supportive of the primary endpoint and will therefore be analysed in a similar manner. For subjects with a vital pregnancy, the number of intrauterine gestational sacs with fetal heart beat and the number of fetuses with fetal heart beat will be tabulated.

Implantation Rate

For implantation rate, the experimental unit will be the transferred embryos, i.e. the analysis will compare the proportions of embryos transferred that results in gestational sacs 5-6 weeks after transfer.

Ongoing Implantation Rate

For ongoing implantation rate, the experimental unit will be the transferred embryos, i.e. the analysis will compare the proportions of embryos transferred that results in intrauterine viable fetuses 10-11 weeks after transfer.

Extreme Ovarian Response

The analyses of extreme ovarian response will be performed using the following definitions of extreme ovarian response: <4 oocytes retrieved, ≥15 oocytes retrieved, ≥20 oocytes retrieved, <4 or ≥15 oocytes retrieved and <4 or ≥20 oocytes retrieved. Subjects with cycle cancellation due to poor ovarian response will be included as <4 oocytes retrieved. Subjects with cycle cancellation due to excessive ovarian response will be included as ≥15 and ≥20 oocytes retrieved.

For each definition the proportion of subjects with extreme ovarian response will be tabulated. Treatment groups will be compared using a logistic regression model with treatment and age group as factors. The possibility of an interaction will be tested. The difference between treatments will be reported as an odds ratio including 95% confidence interval and p-value for test of no treatment difference. If the expected number of observations is less than five in any of the cells in the contingency table then Fisher's exact test within strata will be used as alternative.

Early OHSS (Including OHSS of Moderate/Severe Grade) and/or Preventive Interventions for Early OHSS

OHSS will for each treatment group be tabulated by classification (mild, moderate, severe) and grade (1, 2, 3, 4, 5). Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation. Note that this includes OHSS with onset before triggering and OHSS with onset during stimulation where triggering is not performed.

This endpoint will be tabulated and analysed in a similar manner as the proportion of subjects with extreme ovarian response. The analysis will be performed for the proportion of subjects with early OHSS, the proportion of subjects with early OHSS of moderate or severe grade, the proportion of subjects with preventive interventions for early OHSS, the proportion of subjects with early OHSS and/or preventive interventions for early OHSS, and the proportion of subjects with early OHSS of moderate or severe grade and/or preventive interventions for early OHSS.

Cycle Cancellation due to Poor or Excessive Ovarian Response or Embryo Transfer Cancellation due to Excessive Ovarian Response / OHSS Risk

This endpoint will be tabulated and analysed in a similar manner as the proportion of subjects with extreme ovarian response. The analysis will be performed for the following: the proportion of subjects with cycle cancellation due to poor ovarian response, the proportion of subjects with cycle cancellation due to excessive ovarian response, the proportion of subjects with cycle cancellation due to poor or excessive ovarian response, the proportion of subjects with embryo transfer cancellation due to excessive ovarian response / OHSS risk.

Number and Size of Follicles during Stimulation

The follicle cohort on stimulation day 6 and end-of-stimulation will be summarised by treatment on the follicle level (number of follicles 8-9 mm, 10-11 mm, 12-14 mm, 15-16 mm and ≥17 mm) and on the subject level (total number of follicles, size of largest follicle, average follicle size, average size of three largest follicles, and number of follicles ≥8 mm, ≥10 mm, ≥12 mm, ≥15 mm and ≥17 mm). Continuous data will be compared between treatment groups using the van Elteren test stratified for age-group. Ordinal data will be compared using the Cochran-Mantel-Haenszel test for ordinal data stratified for age-group. Within strata comparisons will be based on Wilcoxon's test.

Number and Size Distribution of Oocytes Retrieved

The number of oocytes retrieved will be tabulated including both summary statistics and a frequency table with subjects grouped according to number of oocytes retrieved [<4 (low response), 4-7 (moderate response), 8-14 (targeted response), 15-19 (hyperresponse) and ≥20 (severe hyperresponse)]. Subjects with cycle cancellation due to poor ovarian response will be included in the <4 oocytes group. Subjects with cycle cancellation due to excessive ovarian response will be included in the ≥20 oocytes group. Continuous data will be compared between treatment groups using the van Elteren test stratified for age-group. Ordinal data will be compared using the Cochran-Mantel-Haenszel test for ordinal data stratified for age-group. Within strata comparisons will be based on Wilcoxon's test.

Metaphase II Oocytes

Oocytes undergoing ICSI will have their maturity stage assessed prior to insemination. The percentage of MII oocytes to oocytes retrieved for subjects where all oocytes are inseminated using ICSI will be tabulated. Further, the number of MII oocytes per subject will be tabulated including both summary statistics and a frequency table. Continuous data will be compared between treatment groups using the van Elteren test stratified for age-group. Ordinal data will be compared using the Cochran-Mantel-Haenszel test for ordinal data stratified for age-group. Within strata comparisons will be based on Wilcoxon's test.

Fertilisation Rate

An oocyte is defined as fertilised if it is scored as 2 pronuclei on day 1 after oocyte retrieval. For subjects with oocytes retrieved, the rate of fertilised oocytes to oocytes retrieved (and also the rate of fertilised oocytes to metaphase II oocytes for those inseminated using ICSI) will be tabulated. Further, the number of fertilised oocytes per subject will be tabulated including both summary statistics and a frequency table. Continuous data will be compared between treatment groups using the van Elteren test stratified for age-group. Ordinal data will be compared using the Cochran-Mantel-Haenszel test for ordinal data stratified for age-group. Within strata comparisons will be based on Wilcoxon's test.

Number and Quality of Embryos on Day 3

The number of embryos on day 3 including a breakdown by selected quality parameters will be tabulated including both summary statistics and frequency tables. Further, for subjects with oocytes retrieved, the rate of embryos to oocytes retrieved will be summarised overall and by selected quality parameters. Continuous data will be compared between treatment groups using the van Elteren test stratified for age-group. Ordinal data will be compared using the Cochran-Mantel-Haenszel test for ordinal data stratified for age-group. Within strata comparisons will be based on Wilcoxon's test.

Circulating Levels of Endocrine Parameters

Blood samples drawn at stimulation days 1 and 6 and end-of-stimulation are analysed for FSH, LH, estradiol, progesterone, inhibin A and inhibin B. Furthermore, blood samples drawn at the oocyte retrieval visit are also analysed for FSH. Values below the lower limit of quantification (LLOQ) will be included as LLOQ/2. Values above the upper limit of quantification (ULOQ) will be included as ULOQ.

Each endocrine parameter and the change from baseline for post-baseline measurements will be tabulated for stimulation day 1 (baseline), stimulation day 6 and end-of-stimulation (and also the oocyte retrieval visit for FSH). For each parameter the change from baseline will be compared between treatment groups using an analysis of covariance model (ANCOVA). The ANCOVA will be fitted to the relative change from baseline in log-transformed measurements with treatment and age strata as fixed factors and the log-transformed baseline measurement as covariate. The estimated treatment difference with 95% confidence interval will be presented on the scale of measurement (i.e. back-transformed using base e) and accompanied by the p-value for test of no treatment difference.

FSH Population Pharmacokinetics

A population pharmacokinetic model describing FSH concentrations following repeated dosing of FE 999049 will be prepared under the responsibility of the Ferring Experimental Medicine Department.

The results will be reported separately.

Total Gonadotropin Dose and Number of Stimulation Days

The total gonadotropin dose and the number of stimulation days will be tabulated and compared between treatment groups. These endpoints will be compared between treatments using Wilcoxon's test.

Gonadotropin Dose Adjustments

Investigator-requested decreases and increases of the gonadotropin dose will be captured during the stimulation period. The requested dose change (decrease / increase / no change) on stimulation day 6 will be tabulated. Further, the number of dose increase requests and number of dose decrease requests per subject will be tabulated. Treatment groups will be compared using chi-square tests.

Adverse Events

Adverse Events – General

Adverse events will be coded using MedDRA. The version of MedDRA will be documented.

Adverse events are grouped according to start of IMP as follows:

- Pre-treatment adverse event, i.e. any adverse event occurring after signed informed consent and before start of IMP, or a pre-existing medical condition that worsens in intensity after signed informed consent but before start of IMP.
- Treatment-emergent adverse event, i.e. any adverse event occurring after start of IMP and before the end-of-trial visit, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of IMP and before the end-of-trial visit.

Treatment-emergent adverse events will be presented in summary tables and listings. Pre-treatment adverse events will be presented in a listing only.

A treatment-emergent adverse event overview table will be prepared including the number of subjects reporting an adverse event, the percentage of subjects with an adverse event, and the number of events reported, for the following categories: all adverse events, severe adverse events, adverse reactions, adverse events leading to discontinuation, serious adverse events and deaths. An adverse reaction is an adverse event judged by the investigator to be related to IMP with a reasonable possibility.

Treatment-emergent adverse events will be tabulated by system organ class (SOC) alphabetically and preferred term (PT) in decreasing order of frequency. The following will be presented: number of subjects reporting an adverse event, the percentage of subjects with an adverse event, and the number of events reported.

Summary tables will be produced for the following: all adverse events, adverse events by causality (reasonable possibility / no reasonable possibility), adverse events leading to death, adverse events by intensity (mild / moderate / severe), adverse reactions by intensity (mild / moderate / severe), serious adverse events, adverse events leading to discontinuation, adverse events with an incidence of ≥5% in any treatment group, and non-serious adverse events with an incidence of ≥5% in any treatment group.

Clinical Chemistry and Haematology Parameters

Safety laboratory variables will be grouped under “Haematology” and “Clinical Chemistry”.

The baseline is based on the blood sample drawn at stimulation day 1. Treatment-emergent laboratory data will be obtained at end-of-stimulation and end-of-trial.

The circulating levels of clinical chemistry and haematology parameters including change from baseline will be tabulated for each time-point for each laboratory variable.

Shift tables will be prepared to compare baseline values to the end-of-stimulation and end-of-trial values, using a categorisation of low, normal and high values at each visit. Low, normal and high will be defined according to the reference ranges provided by the central laboratory.

For each laboratory variable, a summary table will be prepared displaying the proportion of subjects who have at least one markedly abnormal value. The table will also include a break-down by classification of the baseline value. Markedly abnormal criteria for the safety laboratory variables will be specified in the SAP.

All laboratory values will be listed by subject number and time point. Values outside the reference range and markedly abnormal values will be flagged.

Injection Site Reactions

For each injection site reaction (redness, pain, itching, swelling and bruising), the number of events and number of subjects experiencing those events will be tabulated by time (immediately, 30 minutes, 24 hours), reaction and intensity (none, mild, moderate and severe).

Treatment-Induced Anti-FSH Antibodies

The proportion of subjects with treatment-induced anti-FSH antibodies as well as the proportion of subjects with treatment-induced anti-FSH antibodies with neutralising capacity will be tabulated. Furthermore, all assessments of anti-FSH antibodies will be listed for subjects with a positive results in assay 1).

Immune-related Adverse Events

Potential immune-related adverse events will be tabulated using the SMQs, PTs and HLTs mentioned in section 7.2.22.

Cycle Cancellations due to an Adverse Event, including Immune-related Adverse Events, or due to Technical Malfunctions of the Administration Pen

A summary table will be prepared showing the proportion of subjects with cycle cancellations including reason for cancellation.

Late OHSS (Including OHSS of Moderate/Severe Grade)

OHSS will for each treatment group be tabulated by classification (mild, moderate, severe) and grade (1, 2, 3, 4, 5). Late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation.

This endpoint will be tabulated and analysed in a similar manner as the proportion of subjects with early OHSS. The analysis will be performed for the proportion of subjects with late OHSS and the proportion of subjects with late OHSS of moderate or severe grade.

Multi-fetal Gestation, Biochemical Pregnancy, Spontaneous Abortion, Ectopic Pregnancy and Vanishing Twins

Frequency tables will be prepared for these endpoints.

Pen Malfunction

The frequency of technical malfunctions of the administration pen will be tabulated.

9.8 Additional Safety Evaluations

Physical Examination

Physical examination at end-of-trial compared to baseline will be summarised in shift tables and all subjects with any abnormal finding will be listed per subject. The list will include both baseline and end-of-trial assessment for comparison.

Gynaecological Examination

Gynaecological examination at end-of-trial compared to baseline will be summarised in shift tables and all subjects with any abnormal finding will be listed by subject. The list will include both baseline and end-of-trial assessment for comparison.

Changes in Body Weight

Body weight will be measured at screening, on stimulation day 1 (baseline) and at end-of-trial. The actual measurements and the change from baseline will be tabulated.

Vital Signs

Vital signs and their change from stimulation day 1 (baseline) to end-of-trial will be summarised. Shift tables will be prepared to compare the baseline values with the end-of-trial values using the categorisation of low, normal and high values. Low, normal and high values will be specified in the SAP. All vital signs values will be listed per subject. Values outside the reference range will be flagged.

9.9 Post-trial Activities

A separate SAP will be prepared to cover the post-trial information.

The number and percentage of subjects with live birth will be presented by treatment group. Subjects with no information on live birth will be defaulted to a negative response.

Neonatal health, including minor/major congenital anomalies, at birth and at 4 weeks after birth will be presented by treatment group.

9.10 Interim Analyses and Administrative Review

No interim analysis intended to compare treatment groups with respect to efficacy or safety is planned.

A blinded sample size reassessment will take place when data on the primary endpoint are available for 70% of the planned subjects or when 800 subjects are randomised, whichever comes first. The sample size reassessment will be done without breaking the blind and without inflating the type I error of the trial, in line with the current regulatory guidelines for non-inferiority trials by FDA[36] and in general by EMA.[37]

A restricted recalculation rule for the sample size reassessment will be used. Accordingly 1,000 subjects should be randomised to achieve sufficient power if the ongoing pregnancy rate is 32.2%. If the ongoing pregnancy rate is above the expected 32.2%, the sample size can be adjusted up to a maximum of 1,144 (572 per treatment group), corresponding to an ongoing pregnancy rate of 50%. If the rate is below the expected 32.2% the sample size will not be decreased below the planned 1,000 subjects.

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 enrolled, the investigator will indicate in the source documents that the subject participates in this trial, and will record at least the following information, if applicable:

- Existence of subject (initials, date of birth)
- Confirmation of participation in trial (trial ID, subject ID)
- Informed consent(s) (date and time of oral information, date and time of handing out Informed Consent Documents, date and time of obtaining written informed consent(s))
- Eligibility for participation in the trial (documenting all inclusion / exclusion criteria)
- Relevant medical history, infertility history, menstrual history and reproductive history
- Body weight measurements
- Visit dates
- Any assessment performed, i.e. vital signs, physical examination, TVU, etc.
- Dates of administration of IMP
- Dates and daily doses of NIMP
- 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
- Results of βhCG test and ultrasound at clinical and ongoing pregnancy visits

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

No specific protocol data can be recorded directly in the e-CRF without prior written or electronic record.

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, clinical chemistry and haematology parameters will be available at the central laboratory. Laboratory reports will be available at the sites.

10.2 e-CRF

An e-CRF system provided by an independent third-party contract research organisation, Target Health Inc., will be used for data capture. The system is validated and access at all levels to the system is granted / revoked following sponsor and vendor procedures, in accordance with regulatory requirements and system requirements.

Data should be entered into the system within a reasonable time after the subject has attended a visit or after the data become available, as applicable.

The investigator will approve / authorise the e-CRF entries for each subject, with the exception of the treatment allocation module which is un-accessible to the investigator to maintain the assessor-blinding, with an electronic signature which is equivalent to a handwritten signature.

The e-CRF system and the database will be hosted at Target Health Inc. 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 Target Health Inc. The pdf-files will be stored in an electronic format and will be provided to the investigator before access to the e-CRF is revoked.

Errors occurring in the e-CRF 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, Ferring. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation.

10.4 Provision of Additional Information

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

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of e-CRF 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. When the first subject is randomised at the trial site a monitoring visit will take place shortly afterwards. For this trial, the frequency of the monitoring visits is intended to be approximately every second week (it can be adjusted depending on recruitment rate).

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 assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki[41] and all other relevant regulations.

The subjects must be informed by the investigator and in the Informed Consent Documents 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 committees.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the e-CRF 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 Documents, 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 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 committee 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 monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented in the e-CRF. A log of protocol deviation reports will be available in the e-CRF. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and filed in the Trial Master File at the end of the trial.

12.3 Premature Trial Termination

Both the investigator (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this 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.

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 to the signatory investigator.

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 based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site trials must be reported in entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the criteria established by the International Committee of Medical Journal Editors (ICMJE).[42] 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 external contract research organisation or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

If the investigator wishes to independently publish / present any results from the trial, the draft manuscript / presentation must be submitted in writing to Ferring for comment prior to submission. Comments will be given within 4 weeks from receipt of the draft manuscript. This statement does not give Ferring any editorial rights over the content of a publication, other than to restrict the disclosure of Ferring's intellectual property. If the matter considered for publication is deemed patentable by Ferring, scientific publication will not be allowed until after a filed patent application is published. Under such conditions the publication will be modified or delayed at the investigator's discretion, to allow sufficient time for Ferring to seek patent protection of the invention.

13.3.2 Public Disclosure Policy

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. Thus, it is the responsibility of Ferring to register the trial in an appropriate registry, i.e. www.ClinicalTrials.gov a website maintained by the National Library of Medicine (NLM) at the U.S. National Institutes of Health (NIH). Trial registration may occur in other registries in accordance with local regulatory requirements. A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Ethics Committee

An ethics committee will review the protocol, any potential protocol amendments and potential advertisements used for recruitment. The ethics committee will review the Subject Information Sheet and the Informed Consent Form, their updates (if any), and any written materials given to the subjects. All ethics committee approvals relevant for the clinic must be available before a subject is exposed to any trial-related procedure, including screening tests for eligibility. A list of all ethics committees to which the protocol has been submitted and the name of the chairmen will be included in the Clinical Trial Report.

14.2 Regulatory Authorities Notification

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All national regulatory approvals must be available in the relevant country 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 main trial is defined as LPLV and the end of post-trial follow-up is defined as the last assessment performed in the pregnancy follow-up period.

End-of-trial notification will be reported according to local regulations.

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.

Upon completion of the trial Ferring shall send the results of the clinical trial to the national regulatory authorities and the concerned ethics committees, according to local regulation.

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, in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

14.5 Subject Information and Consent

Informed Consent Documents regarding Participation in the Trial – Subject

The investigator will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, 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 Documents (consisting of the Subject Information and the Informed Consent Form) must be signed and dated by the subject and 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.

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 her decision.

The subject will receive a copy of the Informed Consent Documents.

If new information becomes available that may be relevant to the trial subject's willingness to continue participation in the trial, a new Subject Information and Informed Consent Form will be forwarded to the ethics committee(s) (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 her source records and data. Data protection will be handled in compliance with national / local regulations.

Informed Consent Documents regarding Data Collection on the Neonate – Parental

For countries where a separate information and informed consent form is required to collect pregnancy outcome data on the neonate, 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 Documents 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 a copy of the Informed Consent Documents.

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.

14.6 Trial Participation Card

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

- That she is participating in a clinical trial
- That the trial involves controlled ovarian stimulation with recombinant FSH (either an FSH preparation under clinical development or an approved FSH product)
- The name and phone number of the investigator
- Ferring Pharmaceuticals A/S, Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark [*note*: this statement is only to be included on the Subject Information Card if required by local regulations]

The subject will be asked to return the Trial Participation Card at the end-of-trial visit.

Each subject's primary care physician will be notified of their participation in the trial by the investigator, if the subject agrees and if applicable.

14.7 Delivery Data Checklist

Subjects with a positive ongoing pregnancy will be provided with a checklist for pregnancy follow-up, where the subject will be reminded to report the following information to the investigator:

<u>At delivery:</u>

- Date of delivery
- Way of delivery (vaginal / vacuum extraction / forceps / caesarean section)
- Position of neonate (head / breech / transverse / other – please specify)
- Gender
- Birth weight (kg)
- Birth length (cm)
- Apgar score after 1, 5 and 10 minutes
- Admission to NICU/NCU (reason and duration)
- Neonatal death
- Malformation / congenital anomaly

4 weeks after delivery (any new information since birth):

- Admission to NICU/NCU (reason and duration)
- Neonatal death
- Malformation / congenital anomaly
- Any relevant medical condition

14.8 Compliance Reference Documents

The Declaration of Helsinki, the consolidated ICH-GCP and other national law(s) in the countries 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 will be as 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, 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, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 15 years 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 anonymous e-CRF data for Ferring. The investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Documents for at least 15 years 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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