

Protocol

Title of trial:

A Randomised, Controlled, Assessor-blind, Parallel Groups, Multicentre Trial Assessing the Efficacy and Safety of FE 999049 in Controlled Ovarian Stimulation in Japanese Women Undergoing an Assisted Reproductive Technology Programme

NCT number:

NCT03228680

Sponsor trial code:

000273

Date:

16 Mar 2018

CLINICAL TRIAL PROTOCOL

A randomised, controlled, assessor-blind, parallel groups, multicentre trial assessing the efficacy and safety of FE 999049 in controlled ovarian stimulation in Japanese women undergoing an assisted reproductive technology programme

Trial Code 000273

| | |
|---|--|
| IND Number: | 103,040 |
| Investigational Medicinal Product: | FE 999049, human recombinant follicle-stimulating hormone, 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 |
| Global Sponsor: | Ferring Pharmaceuticals A/S Global Clinical R&D Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark |
| Local Sponsor: | Ferring Pharmaceuticals Co., Ltd. Toranomon 2-chome Tower, 2-3-17 Toranomon, Minato-ku, Tokyo 105-0001, Japan |
| Version | 2.0 (Consolidated protocol; changes introduced with amendment #01 implemented) |
| GCP Statement: | This trial will be performed in compliance with GCP. |


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SYNOPSIS

TITLE OF TRIAL

A randomised, controlled, assessor-blind, parallel groups, multicentre trial assessing the efficacy and safety of FE 999049 in controlled ovarian stimulation in Japanese women undergoing an assisted reproductive technology programme

SIGNATORY INVESTIGATOR

 Department of Obstetrics and Gynaecology
Saitama Medical University, Faculty of Medicine

TRIAL SITES

Approximately 15-20 sites in Japan

PLANNED TRIAL PERIOD

First patient first visit (FPFV): Estimated Q3 2017
Last patient last visit (LPLV) / end-of-trial: Estimated Q1 2019
Pregnancy follow-up completed: Estimated Q4 2019

CLINICAL PHASE

3

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

FE 999049 is a human recombinant follicle-stimulating hormone (rFSH) developed by Ferring Pharmaceuticals. FE 999049 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”. Ferring has received Marketing Authorisation approval from the European Commission for FE 999049 (December 2016).

FE 999049 is derived from a human cell line (PER.C6[®]). This is in contrast to other currently-approved rFSH products for the proposed indication, such as follitropin alfa (GONAL-F, Merck Serono Co., Ltd.) and follitropin beta (FOLLISTIM, MSD K.K.), which 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 FOLLISTIM 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 α 2,3 and α 2,6 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.

The clinical translation of the differential glycosylation profile of FE 999049 has been reflected in clinical trials. Thus, daily multiple-dose administration of identical IU doses of FE 999049 and a CHO-derived rFSH product as determined in the rat in vivo Steelman-Pohley bioassay did not provide comparable pharmacokinetics (PK) and pharmacodynamics (PD), with the differential glycosylation profile of FE 999049 being considered the most likely cause for this finding. Consequently, it was considered that the rat in vivo Steelman Pohley bioassay might not fully reflect the potency of FE 999049 in humans, as supported by biotransformation studies in mice and rats and that using the protein content (μ g) in combination with a consistent drug substance quality profile would be more appropriate for expressing doses of FE 999049 than the bioactivity (international units (IU)). Therefore, FE 999049 is dosed by mass (μ g) rather than in IU.

A phase 1 trial conducted in healthy female Japanese volunteers demonstrated a linear, dose-response relationship of FE 999049 with respect to exposure. Furthermore, comparisons between Japanese and Caucasian women indicated similar PK profile with respect to C_{max} , AUC, t_{max} and $t_{1/2}$.

Two randomised, controlled, assessor-blind, parallel groups, multi-centre phase 2 anti-Müllerian hormone (AMH)-stratified trials were conducted in IVF/ICSI patients, one in overseas IVF/ICSI patients and one in Japanese IVF/ICSI patients with the purpose of determining the dose-response relationship of FE 999049 and the number of oocytes retrieved. 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 randomisation stratum (low AMH stratum: 5.0-14.9 pmol/L, high AMH stratum: 15.0-44.9 pmol/L). Furthermore, the observed dose-response profile was similar in the overseas trial and in the Japanese trial.

The development of FE 999049 has prospectively incorporated the use of a biomarker of ovarian response to gonadotropins (AMH) to identify patients at higher risk of reduced efficacy or increased safety concern, enabling stratification according to the patients' potential to respond to FE 999049. Furthermore, body weight has been shown to influence the exposure to FE 999049. Therefore, the posology of FE 999049 is individualised for each patient based on her body weight and serum AMH to obtain an ovarian response with favourable safety/efficacy profile. The outcome is a fixed-dose regimen supporting individualised ovarian stimulation with safe and efficient use of FE 999049 founded on current scientific knowledge and prospectively confirmed data.

The efficacy and safety of the FE 999049 individualised dosing regimen based on the woman's serum AMH and body weight has been confirmed in a large phase 3 trial, ESTHER-1 (Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World), conducted in 11 countries overseas including Europe, North America and Latin America. The ESTHER-1 trial was conducted in 1,326 IVF/ICSI patients who were randomised 1:1 to controlled ovarian stimulation with one of the following treatments: 1) FE 999049 in its individualised dosing regimen with the daily dose fixed throughout stimulation, or 2) an approved CHO-derived rFSH product (follitropin alfa, GONAL-F) at a standard starting dose of 150 IU/day followed by dose adjustments based on the subject's follicular response during stimulation. FE 999049 in its individualised dosing regimen was demonstrated to be non-inferior to follitropin alfa with respect to ongoing pregnancy rate (30.7% versus 31.6%) and ongoing implantation rate (35.2% versus 35.8%). For the overall population, there was no statistically significant difference between treatment groups in terms of number of oocytes retrieved, with an average of 10.0 for FE 999049 and 10.4 for follitropin alfa. Nevertheless, the individualised FE 999049 dosing regimen in comparison to follitropin alfa led to statistically significantly more oocytes retrieved among patients with AMH <15 pmol/L (population at risk of hyporesponse) with an average of 8.0 versus 7.0 and statistically significantly fewer oocytes among patients with AMH ≥15 pmol/L (population at risk of hyperresponse) with an average of 11.6 versus 13.3. The immediate clinical relevance of this shift in ovarian response with FE 999049 therapy was realised as statistically significantly fewer patients with extreme ovarian response compared to follitropin alfa, i.e. <4 oocytes among patients with AMH <15 pmol/L (12% versus 18%) and ≥15 or ≥20 oocytes among patients with AMH ≥15 pmol/L (28% versus 35%, and 10% versus 16%). The percentage of patients with an appropriate ovarian response, defined for FE 999049 as 8-14 oocytes, was reached by statistically significantly more patients treated with FE 999049 compared to follitropin alfa, i.e. 43% versus 38%, despite implementation of dose adjustments during stimulation for 37% of the patients in the follitropin alfa group in contrast to the fixed-dose individualised dosing regimen for FE 999049. A statistically significantly lower total gonadotropin dose in the FE 999049 group compared to the CHO-derived rFSH product group was observed with an average of 90 µg and 104 µg, respectively. From a safety perspective, the individualised dosing regimen of FE 999049 was associated with a statistically significant reduction in the proportion of subjects with early ovarian hyperstimulation syndrome (OHSS) and/or preventive interventions for early OHSS in comparison to the standard regimen of CHO-derived rFSH product, with an incidence of 4.7% in the FE 999049 group and 6.2% in the follitropin alfa group.

In Japan, the only rFSH preparation approved for the pursued indication is follitropin beta (FOLLISTIM).

The present trial aims to establish non-inferiority of FE 999049 versus FOLLISTIM with respect to number of oocytes retrieved and will document the efficacy and safety of FE 999049 in Japanese IVF/ICSI patients.

OBJECTIVES

Primary Objective

- To demonstrate non-inferiority of FE 999049 compared to FOLLISTIM with respect to number of oocytes retrieved in Japanese IVF/ICSI patients undergoing controlled ovarian stimulation

Secondary Objectives

- To compare FE 999049 with FOLLISTIM with respect to achieving pregnancy
- To compare FE 999049 with FOLLISTIM with respect to ovarian response and endocrine profile
- To compare FE 999049 with FOLLISTIM with respect to oocyte fertilisation and number and quality of embryos/blastocysts
- To compare FE 999049 with FOLLISTIM with respect to the frequency of OHSS and/or preventive interventions for early OHSS
- To compare FE 999049 with FOLLISTIM with respect to safety profile, including adverse events, routine safety laboratory parameters and local tolerability
- To compare FE 999049 with FOLLISTIM with respect to gonadotropin use

ENDPOINTS

Primary Endpoint

- Number of oocytes retrieved

Important Secondary Endpoint

- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer)

Secondary Endpoints

- Positive β hCG rate (positive serum β hCG test 13-15 days 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 blastocysts transferred)
- Proportion of subjects with cycle cancellation due to poor or excessive ovarian response or blastocyst transfer cancellation due to excessive ovarian response / OHSS risk
- Proportion of subjects with <4, 4-7, 8-14, 15-19 and ≥ 20 oocytes retrieved
- Proportion of subjects with extreme ovarian responses, defined as <4, ≥ 15 or ≥ 20 oocytes retrieved

- Proportion of subjects with preventive interventions for early OHSS
- Proportion of subjects with early OHSS (including OHSS of moderate/severe grade) and/or preventive interventions for early OHSS
- Proportion of subjects with late OHSS (including OHSS of moderate/severe grade)
- Proportion of subjects with OHSS (early and/or late) and/or preventive interventions for early OHSS
- Number and size of follicles on stimulation day 6 and end-of-stimulation
- Fertilisation rate as well as number and quality of embryos on day 3 and blastocysts on day 5 after oocyte retrieval
- Circulating concentrations of FSH, LH, estradiol, progesterone, inhibin A and inhibin B on stimulation day 6 and end-of-stimulation
- Total gonadotropin dose and number of stimulation days
- 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
- Technical malfunctions of the administration pens

Pregnancy Follow-up Information

- Ongoing pregnancy rate (at least one intrauterine viable fetus 10-11 weeks after transfer) and live birth rate
- Neonatal health at birth and at 4 weeks after birth

Note: Ferring intends to submit the Japanese New Drug Application (J-NDA) following completion of the main part of the trial (i.e. up to the clinical pregnancy visit), and to include the pregnancy follow-up data available at that time in the J-NDA. The pregnancy follow-up data can be submitted after completion.

METHODOLOGY

This will be a randomised, assessor-blind, controlled, parallel groups, multicentre trial assessing the efficacy and safety of FE 999049 in its individualised dosing regimen when used in first cycle Japanese patients 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 versus an rFSH product approved in Japan,

i.e. FOLLISTIM, with respect to number of oocytes retrieved.

Subjects will be screened within 60 days prior to start of stimulation 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 controlled ovarian stimulation with FE 999049 or FOLLISTIM. Randomisation will be stratified by centre and according to AMH levels at screening (<15 pmol/L and ≥ 15 pmol/L). Subjects randomised to FE 999049 will have their individual FE 999049 dose determined on the basis of their AMH level at screening and their body weight at start of stimulation. The daily FE 999049 dose will be fixed throughout the stimulation period. For subjects with AMH <15 pmol/L, the daily FE 999049 dose is 12 μg , irrespective of body weight. For subjects with AMH ≥ 15 pmol/L the daily FE 999049 dose is on a continuous scale ranging from 0.19 to 0.10 $\mu\text{g}/\text{kg}$, i.e. dependent on actual AMH and body weight. The minimum allowed daily FE 999049 dose is 6 μg and the maximum allowed daily FE 999049 dose is 12 μg . Subjects can be treated with FE 999049 for a maximum of 20 days, and coasting is not allowed. For subjects randomised to FOLLISTIM, the dosing regimen is within labelling. The starting dose of FOLLISTIM is 150 IU and fixed for the first five stimulation days after which it may be adjusted by 75 IU based on the individual response. The maximum daily FOLLISTIM dose allowed is 375 IU. Subjects can be treated with FOLLISTIM 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 3 follicles of ≥ 15 mm are observed, visits must be performed daily. To prevent a premature luteinising hormone (LH) surge, a GnRH antagonist will be initiated on stimulation day 6 at a daily dose of 0.25 mg and continued throughout the stimulation period. Triggering of final follicular maturation will be done with 5,000 IU urinary human chorionic gonadotropin (hCG) on the day when ≥ 3 follicles with a diameter ≥ 17 mm are observed. In case of excessive follicular development, defined as ≥ 25 follicles with a diameter ≥ 12 mm, the cycle should be cancelled (*note*: in case of 25-35 follicles with a diameter ≥ 12 mm, a GnRH agonist may be administered as triggering for final follicular maturation). In case of poor follicular development, defined as the investigator judging that ≥ 3 follicles with a diameter ≥ 17 mm cannot be reached by day 20, the cycle is to be cancelled.

Oocyte retrieval will take place 36h (± 2 h) after triggering of final follicular maturation and the oocytes can be inseminated by IVF or ICSI. Fertilisation and embryo development will be assessed from oocyte retrieval to the day of transfer. One blastocyst of the best quality available will be transferred on day 5 after oocyte retrieval while remaining blastocysts may be cryopreserved. For subjects who underwent triggering of final follicular maturation with GnRH agonist, no transfer will take place and blastocysts may instead be cryopreserved on day 5. All cryopreserved blastocysts can be used by the subject after completion of the trial, in accordance with the declaration by Japan Society of Obstetrics and Gynaecology (JSOG).

Vaginal progesterone tablets (LUTINUS, Ferring Pharmaceuticals) 100 mg three times daily will be

provided for luteal phase support from the day after oocyte retrieval until the day of the clinical pregnancy visit. Luteal phase support will only be provided to subjects planned to undergo transfer and can be terminated earlier in case of no transfer or a negative β hCG test. A β hCG test is performed 13-15 days after transfer followed by a transvaginal ultrasound 5-6 weeks after transfer to assess clinical and vital pregnancy. Subjects experiencing a full menstrual bleeding following transfer must have the β hCG test performed 7-15 days after transfer. The β hCG test is mandatory for all subjects who undergo transfer, irrespective of bleeding.

Blood samples will be collected during the trial for the purpose of evaluating the endocrine profile as well as clinical chemistry and haematology parameters. Endocrine parameters are measured at screening, stimulation day 1, stimulation day 6 and end-of-stimulation. Clinical chemistry and haematology parameters are assessed at screening, end-of-stimulation and end-of-trial. Local tolerability of FE 999049 following subcutaneous administration will be assessed by the subjects three times daily: immediately, 30 minutes and 24 hours after the injection. The assessment of injection site reactions will be made throughout the stimulation period and recorded by the subjects in a diary.

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

Pregnancy Follow-up

As obligatory follow-up, pregnancy progress and outcome data will be gathered for subjects with a vital pregnancy. Data will be collected on ongoing pregnancy (10-11 weeks after transfer) and pregnancy outcome as well as neonatal health at birth and at 4 weeks after birth. The pregnancy follow-up does not include any interventions but only data collection. The pregnancy follow-up data will be based on reports obtained from the subject's gynaecologist / obstetrician and the subject's Maternal and Child Health Handbook. The data will be retrieved by the trial site, either via the subject's gynaecologist / obstetrician, the subject herself, or other sources, as applicable.

Ferring intends to submit the J-NDA following completion of the main part of the trial (i.e. up to the clinical pregnancy visit), and to include the pregnancy follow-up data available at that time in the J-NDA. The pregnancy follow-up data can be submitted after completion.

NUMBER OF SUBJECTS

Approximately 328 subjects will be randomised in a 1:1 ratio to FE 999049 and FOLLISTIM.

CRITERIA FOR INCLUSION / EXCLUSION

Women eligible for IVF and/or ICSI treatment, undergoing their first IVF/ICSI cycle and diagnosed

with tubal infertility, unexplained infertility, infertility related to endometriosis stage I/II or with partners diagnosed with male factor infertility, will be included in this trial. Subjects will be 20-40 years of age, with a body mass index (BMI) of 17.5-32.0 kg/m².

Women with endometriosis stage III/IV, history of recurrent miscarriage or with contraindications to controlled ovarian stimulation with gonadotropins will be excluded from participation in this trial.

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

Inclusion Criteria

1. Informed Consent Documents signed prior to any trial-related procedures.
2. In good physical and mental health.
3. Japanese 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 Documents 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 American Society for Reproductive Medicine (ASRM) classification) or with partners diagnosed with male factor infertility, eligible for in vitro fertilisation (IVF) and/or intracytoplasmic sperm injection (ICSI) treatment using ejaculated sperm from male partner.
5. Infertility for at least 1 year before randomisation (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 screening. This also includes women who have been diagnosed with any of the above medical conditions but have had them surgically corrected within 1 year prior to screening.
9. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. no endometrioma greater than 3 cm or enlarged ovaries which would contraindicate the use of gonadotropins) and fallopian tubes and surrounding tissue without evidence of significant abnormality (e.g. no hydrosalpinx) within 1 year prior to screening. 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 screening).
11. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests within 1 year prior to screening.
12. Body mass index (BMI) between 17.5 and 32.0 kg/m² (both inclusive) at screening.
13. Willing to accept transfer of one blastocyst.

Exclusion Criteria

1. Known endometriosis stage III-IV (defined by the revised ASRM classification).
2. One or more follicles >10 mm (including cysts) observed on the transvaginal ultrasound prior to start of stimulation on stimulation day 1 (puncture of cysts prior randomisation is allowed).
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. In case the sperm production is severely impaired (concentration <1 million/mL), normal karyotype, including no Y-chromosome microdeletion, must be documented.
5. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
6. Known porphyria.
7. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
8. Known inherited or acquired thrombophilia disease.
9. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) which can compromise participation in the trial with the exception of controlled thyroid function disease.
10. Known presence of anti-FSH antibodies (based on the information available in the subject's medical records).
11. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
12. Any abnormal finding of clinical chemistry, haematology or vital signs at screening, which is judged clinically relevant by the investigator.
13. Known moderate or severe impairment of renal or hepatic function.
14. Currently breast-feeding.
15. Undiagnosed vaginal bleeding.
16. Known abnormal cervical cytology of clinical significance observed within 3 years prior to screening (unless the clinical significance has been resolved).
17. Findings from the laboratory analyses at screening which preclude gonadotropin stimulation.
18. Findings at the gynaecological examination at screening which preclude gonadotropin stimulation.
19. Findings at the gynaecological examination at screening which are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
20. Pregnancy (must be confirmed by negative urinary pregnancy tests at screening and prior to randomisation) or contraindication to pregnancy.
21. Known current active pelvic inflammatory disease.

22. Use of hormonal preparations (except for thyroid medication) or fertility modifiers during the last menstrual cycle before randomisation, including dehydroepiandrosterone (DHEA), metformin and cycle programming with oral contraceptives, progestogen or estrogen preparations.
23. Known history of chemotherapy (except for gestational conditions) or radiotherapy.
24. Current or past (1 year prior to randomisation) abuse of alcohol or drugs, and/or 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 drug substance or excipients in the medicinal products used in the trial.
27. Hypersensitivity to any drug substance or excipients in a GnRH or any GnRH analogue / derivative.
28. Previous participation in the trial.
29. Current participation in another trial, including follow-up period.
30. Use of any non-registered investigational drugs during the last 3 months prior to screening.

MEDICINAL PRODUCTS

Investigational Medicinal Products (IMPs)

| <i>Name</i> | <i>Drug type</i> | <i>Active ingredient, route of administration and concentration</i> | <i>Daily dose</i> |
|-------------|------------------|---|--|
| FE 999049 | rFSH | FE 999049 (follitropin delta) in solution for subcutaneous injection; 72 µg / 2.16 mL Pre-filled pen | 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 Dose is fixed throughout stimulation Minimum dose is 6 µg/day Maximum dose is 12 µg/day |
| FOLLISTIM | rFSH | Follitropin beta in solution for subcutaneous injection; 900 IU / 1.08 mL Cartridge and pen | Starting dose of 150 IU fixed for the first five stimulation days, followed by potential adjustments of 75 IU Minimum dose is 75 IU/day Maximum dose is 375 IU/day |

Concomitant Fertility Medication

| <i>Name</i> | <i>Drug type</i> | <i>Active ingredient and route of administration</i> | <i>Dose</i> |
|-------------|------------------|---|-----------------------|
| GANIREST | GnRH antagonist | Ganirelix pre-filled syringe for subcutaneous injection | 0.25 mg, daily dose |
| hCG FUJI | hCG | Choriogonadotropin for intramuscular injection | 5,000 IU, single dose |
| LUTINUS | Progesterone | Progesterone tablets for vaginal administration | 3 x 100 mg daily |

Note: In case of triggering of final follicular maturation with a GnRH agonist, a GnRH agonist nasal spray such as SUPRECUR (Sanofi / Mochida Pharmaceuticals Co., Ltd) or NASANYL (Pfizer) can be used according to local availability and at a dose according to site-specific procedures, e.g., a single dose of 300 µg SUPRECUR or 400 µg NASANYL.

STATISTICAL METHODS

Sample Size Calculation

The primary objective of this trial is to demonstrate non-inferiority of FE 999049 compared with FOLLISTIM with respect to number of oocytes retrieved in Japanese IVF/ICSI patients undergoing controlled ovarian stimulation. The non-inferiority margin for the difference between treatments (FE 999049 versus FOLLISTIM) is -3.0 oocytes. The standard deviation for the primary endpoint is estimated to 8.1 oocytes based on historical data with FOLLISTIM.

The sample size is determined to obtain 90% power to achieve the primary objective for the per-protocol (PP) analysis set for a 1:1 randomisation ratio between FE 999049 and FOLLISTIM and a one-sided t-test at a 2.5% significance level. Assuming the two treatments to be equally effective and a standard deviation of 8.1 oocytes, a sample size of 155 randomised subjects per treatment group would give 90% power. The proportion of subjects with major protocol deviations is assumed to be at most 5% and hence 328 randomised subjects are needed to provide 155 subjects/group in the PP analysis set.

Primary Statistical Analysis

The primary endpoint 'number of oocytes retrieved' will be analysed using an analysis of variance model with treatment and AMH stratum as fixed factors. The 2-sided 95% confidence limits for the mean treatment differences (FE 999049 - FOLLISTIM) will be calculated based on the fitted model for the full analysis set (FAS). Non-inferiority of FE 999049 compared with FOLLISTIM will be established if the 95% confidence interval lies entirely above -3.0 (the non-inferiority margin) for the FAS.

The hypotheses to be tested is:

$$H_0: OR_{FE\ 999049} - OR_{FOLLISTIM} \leq -3.0$$

$$H_1: OR_{FE\ 999049} - OR_{FOLLISTIM} > -3.0$$

where $OR_{FE\ 999049}$ and $OR_{FOLLISTIM}$ denote the number of oocytes retrieved with respective treatment.

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APPENDIX 2 Contact List

ATTACHMENT I Agreement on the Protocol

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

| | |
|------------------|---|
| AMH | anti-Müllerian hormone |
| ANCOVA | analysis of covariance |
| ART | assisted reproductive technologies |
| ASRM | American Society for Reproductive Medicine |
| ATC | Anatomical Therapeutic Chemical classification system |
| AUC | area under the curve |
| βhCG | beta unit of human chorionic gonadotropin |
| BMI | body mass index |
| CBC | complete blood count |
| CHO | Chinese hamster ovary |
| C _{max} | maximum concentration |
| DHEA | dehydroepiandrosterone |
| EC | Ethics Committee |
| eCRF | electronic case report form |
| EMA | European Medicines Agency |
| FAS | full analysis set |
| FPFV | first patient first visit |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GCU | growing care unit |
| GMP | Good Manufacturing Practice |
| GnRH | gonadotropin-releasing hormone |
| h | hour(s) |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| ICD-10 | International Statistical Classification of Diseases and Related Health Problems, 10 th revision |
| ICH | International Conference on Harmonisation |
| ICMART | International Committee Monitoring Assisted Reproductive Technologies |
| ICMJE | International Committee of Medical Journal Editors |

| | |
|---------------------|---|
| ICSI | intracytoplasmic sperm injection |
| IMP | investigational medicinal product |
| IND | investigational new drug |
| IRB | Institutional Review Board |
| ITT | intention-to-treat |
| IU | international units |
| IVF | in vitro fertilisation |
| J-GCP | Japanese Good Clinical Practice |
| J-NDA | Japanese New Drug Application |
| JSOG | Japan Society of Obstetrics and Gynaecology |
| L | Litre |
| LH | luteinising hormone |
| LLOQ | lower limit of quantification |
| LPLV | last patient last visit |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mL | millilitre |
| NCU | neonatal care unit |
| NICU | neonatal intensive care unit |
| NIMP | non-investigational medicinal product |
| OHSS | ovarian hyperstimulation syndrome |
| OR | oocyte retrieval |
| PER.C6 [®] | name of cell line of human fetal retinal origin |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| pmol | picomol |
| PP | per-protocol |
| PT | preferred term |
| rFSH | recombinant follicle-stimulating hormone |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reaction |
| t _½ | elimination/terminal half-life |
| t _{max} | time to C _{max} |
| TSH | thyroid-stimulating hormone |

µg microgram
ULOQ upper limit of quantification
WHO World Health Organization

AMH Unit Conversion Factors

1 pmol/L = 0.140 ng/mL

1 ng/mL = 7.143 pmol/L

1 INTRODUCTION

1.1 Background

FE 999049 is a human recombinant follicle-stimulating hormone (rFSH) developed by Ferring Pharmaceuticals. FE 999049 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”. Ferring has received Marketing Authorisation approval from the European Commission for FE 999049 (December 2016).

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 alpha (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.

FE 999049 is derived from a human cell line. This is in contrast to other currently-approved rFSH products for the proposed indication, such as follitropin alfa (GONAL-F, Merck Serono Co., Ltd) and follitropin beta (FOLLISTIM, MSD K.K.), which 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 FOLLISTIM 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 α 2,3 and α 2,6 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.

The clinical translation of the differential glycosylation profile of FE 999049 has been reflected in clinical trials. Thus, daily multiple-dose administration of identical international unit (IU) doses of FE 999049 and a CHO-derived rFSH product as determined in the rat in vivo Steelman-Pohley bioassay did not provide comparable pharmacokinetics (PK) and pharmacodynamics (PD), with the differential glycosylation profile of FE 999049 being considered the most likely cause for this finding. Consequently, it was considered that the rat in vivo Steelman Pohley bioassay might not fully reflect the potency of FE 999049 in humans, as supported by biotransformation studies in mice and rats and that using the protein content (μ g) in combination with a consistent drug

substance quality profile would be more appropriate for expressing doses of FE 999049 than the bioactivity (IU). Therefore, FE 999049 is dosed by mass (μg) rather than in IU.

A phase 1 trial (CS03) conducted in healthy female Japanese volunteers demonstrated a linear, dose-response relationship of FE 999049 with respect to exposure. Furthermore, comparisons between Japanese and Caucasian women indicated similar PK profile with respect to C_{max} , AUC, t_{max} and $t_{1/2}$.¹

Two randomised, controlled, assessor-blind, parallel groups, multi-centre phase 2 anti-Müllerian hormone (AMH)-stratified trials were conducted in IVF/ICSI patients, one in Europe (000009)² and one in Japan (000124)³, with the purpose of determining the dose-response relationship of FE 999049 and the number of oocytes retrieved. In both trials, randomisation was stratified according to AMH levels at screening; low AMH (5.0-14.9 pmol/L) or high AMH (15.0-44.9 pmol/L).^a

In the European dose-response phase 2 trial (000009), five doses of FE 999049 ranging from 5.2 $\mu\text{g}/\text{day}$ to 12.1 $\mu\text{g}/\text{day}$ were investigated and a reference group of an approved rFSH product (GONAL-F, 150 IU/day) was also included. In the Japanese dose-response phase 2 trial (000124), three doses of FE 999049 (6 $\mu\text{g}/\text{day}$, 9 $\mu\text{g}/\text{day}$ and 12 $\mu\text{g}/\text{day}$) were investigated and a standard therapy of the approved rFSH product (FOLLISTIM, 150 IU/day) was also included. At present, follitropin beta (FOLLISTIM) is the only medicinal product approved in Japan for controlled ovarian stimulation in IVF/ICSI cycles. In the European and the Japanese phase 2 trials, the daily dose was fixed throughout the stimulation period. 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 randomisation stratum. Acceptable pregnancy rates were achieved with all FE 999049 doses. Furthermore, the observed FE 999049 dose-response profile was similar in the European trial and in the Japanese trial.

The development of FE 999049 has prospectively incorporated the use of a biomarker of ovarian response to gonadotropins (AMH) to identify patients at higher risk of reduced efficacy or increased safety concern, enabling stratification according to the patients' potential to respond to FE 999049. Furthermore, body weight has been shown to influence the exposure to FE 999049. Therefore, the posology of FE 999049 is individualised for each patient based on her body weight and serum AMH to obtain an ovarian response with favourable safety/efficacy profile. The outcome is a fixed-dose regimen supporting individualised ovarian stimulation with safe and efficient use of FE 999049 founded on current scientific knowledge and prospectively confirmed data.

The efficacy and safety of the FE 999049 individualised dosing regimen based on the woman's serum AMH and body weight has been confirmed in a large phase 3 trial, ESTHER-1 (Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World)⁴, conducted in 11 countries overseas including Europe, North America and Latin America. The ESTHER-1 trial was

^a See conversion factor between the AMH units pmol/L and ng/mL on page 21.

conducted in 1,326 IVF/ICSI patients who were randomised 1:1 to controlled ovarian stimulation with one of the following treatments: 1) FE 999049 in its individualised dosing regimen with the daily dose fixed throughout stimulation, or 2) an approved CHO-derived rFSH product (follitropin alfa, GONAL-F) at a standard starting dose of 150 IU/day followed by dose adjustments based on the subject's follicular response during stimulation. FE 999049 in its individualised dosing regimen was demonstrated to be non-inferior to follitropin alfa with respect to ongoing pregnancy rate (30.7% versus 31.6%) and ongoing implantation rate (35.2% versus 35.8%). For the overall population, there was no statistically significant difference between treatment groups in terms of number of oocytes retrieved, with an average of 10.0 for FE 999049 and 10.4 for follitropin alfa. Nevertheless, the individualised FE 999049 dosing regimen in comparison to follitropin alfa led to statistically significantly more oocytes retrieved among patients with AMH <15 pmol/L (population at risk of hyporesponse) with an average of 8.0 versus 7.0 and statistically significantly fewer oocytes among patients with AMH ≥15 pmol/L (population at risk of hyperresponse) with an average of 11.6 versus 13.3. The immediate clinical relevance of this shift in ovarian response with FE 999049 therapy was realised as statistically significantly fewer patients with extreme ovarian response compared to follitropin alfa, i.e. <4 oocytes among patients with AMH <15 pmol/L (12% versus 18%) and ≥15 or ≥20 oocytes among patients with AMH ≥15 pmol/L (28% versus 35%, and 10% versus 16%). The percentage of patients with an appropriate ovarian response, defined for FE 999049 as 8-14 oocytes, was reached by statistically significantly more patients treated with FE 999049 compared to follitropin alfa, i.e. 43% versus 38%, despite implementation of dose adjustments during stimulation for 37% of the patients in the follitropin alfa group in contrast to the fixed-dose individualised dosing regimen for FE 999049. A statistically significantly lower total gonadotropin dose in the FE 999049 group compared to the CHO-derived rFSH product group was observed with an average of 90 µg and 104 µg, respectively.

The most serious risk associated with gonadotropin treatment is ovarian hyperstimulation syndrome (OHSS). Overall in the phase 3 trials overseas, OHSS and/or preventive interventions of early OHSS occurred in 4.4% of the FE 999049 cycles and 6.5% of the follitropin alfa cycles. Moderate/severe OHSS and/or preventive interventions for early OHSS were observed at an incidence of 3.3% and 5.6% of the treatment cycles with FE 999049 and follitropin alfa, respectively.

Previous studies have reported OHSS rates in Japanese patients between 5% and 28.3%.^{5,6,7} In the FE 999049 phase 2 trial in Japan, the incidence of early moderate/severe OHSS was 19.5% for subjects in the FOLLISTIM group. Despite the variation in the OHSS incidence reporting, the high OHSS incidence in Japanese IVF/ICSI patients illustrates a clear need in Japan for a treatment option with a safer OHSS profile. Based on more than 1,300 cycles in the ESTHER-1 phase 3 trial, the individualised dosing regimen of FE 999049 was associated with a statistically significant reduction in the proportion of subjects with early OHSS and/or preventive interventions for early OHSS in comparison to the standard regimen of CHO-derived rFSH product, with an incidence of 4.7% in the FE 999049 group and 6.2% in the follitropin alfa group. For further information regarding FE 999049, please refer to the Investigator's Brochure.⁸

The present trial aims to establish non-inferiority of FE 999049 versus FOLLISTIM with respect to number of oocytes retrieved and will document the efficacy and safety of FE 999049 in Japanese IVF/ICSI patients.

1.2 Scientific Justification for Conducting the Trial

As part of the global development programme for FE 999049, the purpose of the present trial is to establish non-inferiority of FE 999049 versus FOLLISTIM with respect to number of oocytes retrieved and to document the efficacy and safety of FE 999049 in Japanese IVF/ICSI patients.

1.3 Benefit / Risk Aspects

Benefits

Patients participating in this trial may benefit by achieving a pregnancy because of the treatment cycle and/or by obtaining blastocysts to be cryopreserved for later use in cryopreserved cycles. Subjects in this trial 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. Finally, Ferring bears the expenses for the treatment cycle.

Risks

The risks associated with ART treatment, including the risk of 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 with one of two rFSH preparations: FE 999049 or FOLLISTIM, a widely available recombinant FSH preparation, used according to its approved labelling. Both preparations will be administered subcutaneously.

As part of the development programme for FE 999049, a total of 1,927 subjects have to date been included in four phase 1 trials, two phase 2 trials (one conducted in EU and one in Japan) and the overseas phase 3 programme. Of these, 1,112 subjects were exposed to FE 999049 in a range from a single dose up to exposure in three consecutive stimulation cycles. During the phase 3 trials, 665 IVF/ICSI subjects were treated with FE 999049 in 1,012 treatment cycles. 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 for early OHSS 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 administered with the pre-filled pen.

FOLLISTIM is a commercially available CHO-derived rFSH product with established safety and efficacy.⁷ The most frequent adverse drug reactions in relation to use of FOLLISTIM are as follows: OHSS, headache, abdominal pain and injection site pain (all reported between 0.5% to ≤5%).⁷ The FOLLISTIM dosing regimen used in this trial is in line with labelling recommendations.

In the phase 2 trial in Japan, the adverse drug reactions most commonly reported (≥1%) by subjects exposed to FE 999049 were OHSS, ovarian enlargement, high progesterone and ascites. Injection site reactions following FE 999049 administration were recorded with very low incidences, with no apparent differences across dose levels and similar to that observed with FOLLISTIM.

OHSS

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. The incidence of early OHSS can be minimised by withholding gonadotropins, withholding human chorionic gonadotropin (hCG) or administering gonadotropin-releasing hormone (GnRH) agonist for triggering of final follicular maturation.

Immunogenicity

Concerning immunogenicity, the risk of treatment-induced anti-drug-antibodies for gonadotropin products has previously been reported as very low (estimated to be 0-2%).^{9,10,11,12,13} In the Japanese phase 2 trial (000124), the incidence of treatment-induced anti-FSH antibodies was 0.8% (1/117) in subjects treated with FE 999049. The titre was below the limit of quantification, and the anti-FSH antibodies were not of neutralising capacity. In the overseas phase 3 trial ESTHER-1, the incidence of treatment-induced anti-FSH antibodies was 1.05% (7/665) in the FE 999049 group. None of the anti-FSH antibodies were of neutralising capacity. A phase 3 trial overseas (ESTHER-2) was designed to evaluate the immunogenicity in patients undergoing up to two repeated treatment cycles, and was conducted in women who had failed to achieve an ongoing pregnancy in ESTHER-1. The trial consisted of two treatment cycles, cycle 2 and cycle 3, where women who failed to achieve an ongoing pregnancy in cycle 2 could be offered to start cycle 3. A total of 513 patients were included in cycle 2 and 188 patients in cycle 3. After repeated treatment with FE 999049, the incidence of anti-FSH antibodies was 0.8% (2/252) in cycle 2 and 1.1% (1/95) in cycle 3, indicating

no increase in anti-FSH antibodies during repeated exposure to FE 999049.¹⁴ Furthermore, these incidences were similar to those observed for the comparator (GONAL-F). All treatment-induced anti-FSH antibody samples in cycle 2 and 3 had titres below the limit of quantification. In addition, no treatment-induced anti-FSH antibodies in FE 999049 patients were of neutralising capacity (0% in all cycles).¹⁴

In conclusion, repeated treatment with FE 999049 in patients with pre-existing or treatment-induced anti-FSH antibodies did not increase the antibody titre, was not associated with decreased ovarian response, and did not induce immune-related adverse events. Also, the treatment-induced anti-FSH responses were shown to be transient in nature. Thus, no safety or efficacy concern has been identified with regards to immunogenicity with FE 999049.

Procedures and Concomitant Fertility Medications

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

Pregnancy-related Events

Oocytes will be inseminated using IVF or ICSI and subsequently cultured to day 5 (blastocyst stage) after oocyte retrieval. Although the frequency of cancellation of transfer is higher when culturing to blastocyst stage compared to culturing only to cleavage stage¹⁵, the pregnancy rates per started cycle are at least as good with blastocyst transfer as with cleavage embryo transfer¹⁵ and may even be higher.¹⁶ 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, single blastocyst transfer is mandatory. 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 to FOLLISTIM with respect to number of oocytes retrieved in Japanese IVF/ICSI patients undergoing controlled ovarian stimulation

Secondary Objectives

- To compare FE 999049 with FOLLISTIM with respect to achieving pregnancy
- To compare FE 999049 with FOLLISTIM with respect to ovarian response and endocrine profile
- To compare FE 999049 with FOLLISTIM with respect to oocyte fertilisation and number and quality of embryos/blastocysts
- To compare FE 999049 with FOLLISTIM with respect to the frequency of OHSS and/or preventive interventions for early OHSS
- To compare FE 999049 with FOLLISTIM with respect to safety profile, including adverse events, routine safety laboratory parameters and local tolerability
- To compare FE 999049 with FOLLISTIM with respect to gonadotropin use

2.2 Endpoints

Primary Endpoint

- Number of oocytes retrieved

Important Secondary Endpoint

- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer)

Secondary Endpoints

- Positive β hCG rate (positive serum β hCG test 13-15 days 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 blastocysts transferred)
- Proportion of subjects with cycle cancellation due to poor or excessive ovarian response or blastocyst transfer cancellation due to excessive ovarian response / OHSS risk

- Proportion of subjects with <4, 4-7, 8-14, 15-19 and ≥ 20 oocytes retrieved
- Proportion of subjects with extreme ovarian responses, defined as <4, ≥ 15 or ≥ 20 oocytes retrieved
- Proportion of subjects with preventive interventions for early OHSS
- Proportion of subjects with early OHSS (including OHSS of moderate/severe grade) and/or preventive interventions for early OHSS
- Proportion of subjects with late OHSS (including OHSS of moderate/severe grade)
- Proportion of subjects with OHSS (early and/or late) and/or preventive interventions for early OHSS
- Number and size of follicles on stimulation day 6 and end-of-stimulation
- Fertilisation rate as well as number and quality of embryos on day 3 and blastocysts on day 5 after oocyte retrieval
- Circulating concentrations of FSH, LH, estradiol, progesterone, inhibin A and inhibin B on stimulation day 6 and end-of-stimulation
- Total gonadotropin dose and number of stimulation days
- 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
- Technical malfunctions of the administration pens

Pregnancy Follow-up Information

- Ongoing pregnancy rate (at least one intrauterine viable fetus 10-11 weeks after transfer) and live birth rate
- Neonatal health at birth and at 4 weeks after birth

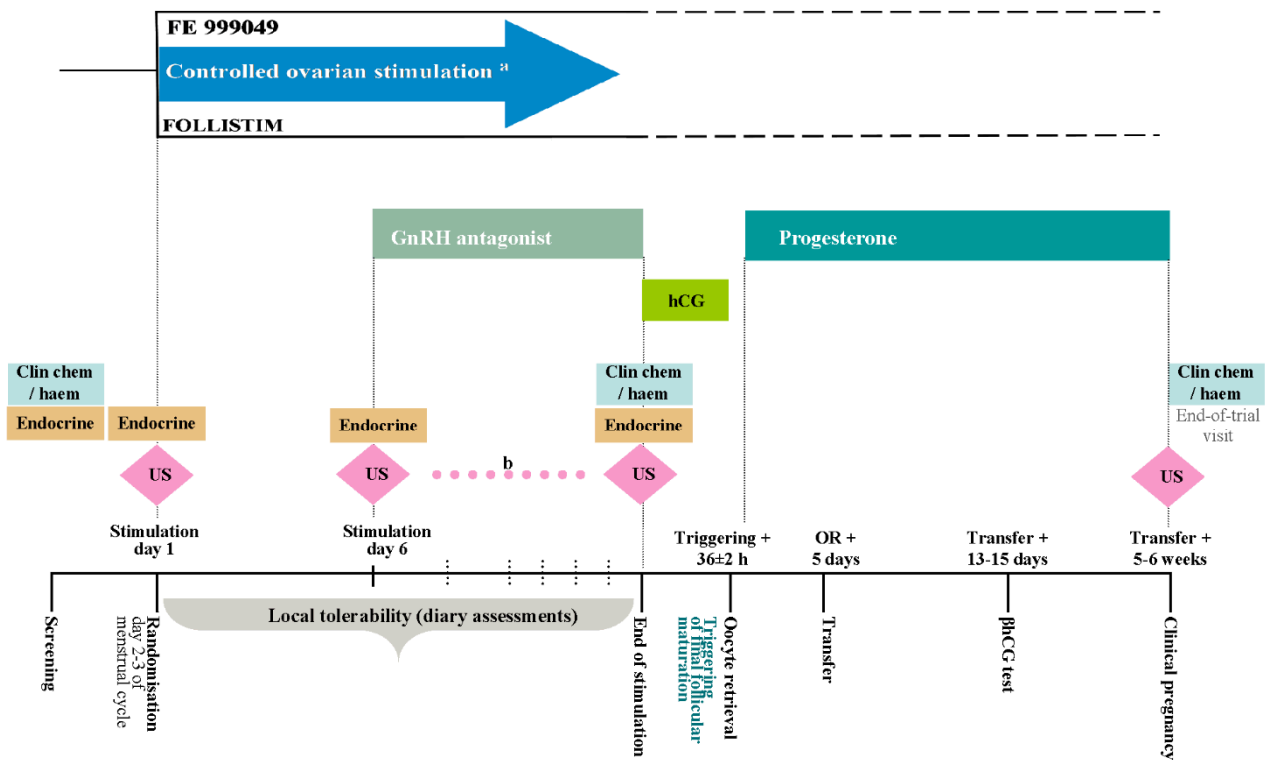
Note: Ferring intends to submit the Japanese New Drug Application (J-NDA) following completion of the main part of the trial (i.e. up to the clinical pregnancy visit), and to include the pregnancy follow-up data available at that time in the J-NDA. The pregnancy follow-up data can be submitted after completion.

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 FOLLISTIM starting dose is 150 IU.

^b Stimulation day 1 and 6 and hereafter at least every second day. When 3 follicles of ≥ 15 mm are observed, visits must be scheduled daily.

OR: Oocyte retrieval, US: Ultrasound

Figure 3-1 Trial Diagram – Trial Period

As obligatory follow-up, pregnancy progress and outcome data will be gathered for subjects with a vital pregnancy. Data will be collected on ongoing pregnancy (10-11 weeks after transfer) and pregnancy outcome as well as neonatal health at birth and at 4 weeks after birth. The pregnancy follow-up does not include any interventions but only data collection. The pregnancy follow-up data will be based on reports obtained from the subject's gynaecologist / obstetrician and the subject's Maternal and Child Health Handbook. The data will be retrieved by the trial site, either via the subject's gynaecologist / obstetrician, the subject herself, or other sources, as applicable.

Ferring intends to submit the J-NDA following completion of the main part of the trial (i.e. up to the clinical pregnancy visit), and to include the pregnancy follow-up data available at that time in the J-NDA. The pregnancy follow-up data can be submitted after completion.

3.1.2 Overall Design and Control Methods

Trial Design

This will be a randomised, assessor-blind, controlled, parallel groups, multicentre trial assessing the efficacy and safety of FE 999049 in its individualised dosing regimen when used in first cycle Japanese patients 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 versus an rFSH product approved in Japan, i.e. FOLLISTIM, with respect to number of oocytes retrieved.

Subjects will be screened within 60 days prior to start of stimulation 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 controlled ovarian stimulation with FE 999049 or FOLLISTIM. Randomisation will be stratified by centre and according to AMH levels at screening (<15 pmol/L and ≥ 15 pmol/L). Subjects randomised to FE 999049 will have their individual FE 999049 dose determined on the basis of their AMH level at screening and their body weight at start of stimulation. The daily FE 999049 dose will be fixed throughout the stimulation period. For subjects with AMH <15 pmol/L, the daily FE 999049 dose is 12 μ g, irrespective of body weight. For subjects with AMH ≥ 15 pmol/L the daily FE 999049 dose is on a continuous scale ranging from 0.19 to 0.10 μ g/kg, i.e. dependent on actual AMH and body weight. The minimum allowed daily FE 999049 dose is 6 μ g and the maximum allowed daily FE 999049 dose is 12 μ g. Subjects can be treated with FE 999049 for a maximum of 20 days, and coasting is not allowed. For subjects randomised to FOLLISTIM, the dosing regimen is within labelling. The starting dose of FOLLISTIM is 150 IU and fixed for the first five stimulation days after which it may be adjusted by 75 IU based on the individual response. The maximum daily FOLLISTIM dose allowed is 375 IU. Subjects can be treated with FOLLISTIM 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 3 follicles of ≥ 15 mm are observed, visits must be performed daily. To prevent a premature luteinising hormone (LH) surge, a GnRH antagonist will be initiated on stimulation day 6 at a daily dose of 0.25 mg and continued throughout the stimulation period. Triggering of final follicular maturation will be done with 5,000 IU urinary hCG on the day when ≥ 3 follicles with a diameter ≥ 17 mm are observed. In case of excessive follicular development, defined as ≥ 25 follicles with a diameter ≥ 12 mm, the cycle should be cancelled (*note*: in case of 25-35 follicles with a diameter ≥ 12 mm, a GnRH agonist may be administered as triggering for final follicular maturation). In case of poor follicular development, defined as the investigator judging that ≥ 3 follicles with a diameter ≥ 17 mm cannot be reached by day 20, the cycle is to be cancelled.

Oocyte retrieval will take place 36h (\pm 2h) after triggering of final follicular maturation and the oocytes can be inseminated by IVF or ICSI. Fertilisation and embryo development will be assessed

from oocyte retrieval to the day of transfer. One blastocyst of the best quality available will be transferred on day 5 after oocyte retrieval while remaining blastocysts may be cryopreserved. For subjects who underwent triggering of final follicular maturation with GnRH agonist, no transfer will take place and blastocysts may instead be cryopreserved on day 5. All cryopreserved blastocysts can be used by the subject after completion of the trial, in accordance with the declaration by Japan Society of Obstetrics and Gynaecology (JSOG).

Vaginal progesterone tablets (LUTINUS, Ferring Pharmaceuticals) 100 mg three times daily will be provided for luteal phase support from the day after oocyte retrieval until the day of the clinical pregnancy visit. Luteal phase support will only be provided to subjects planned to undergo transfer and can be terminated earlier in case of no transfer or a negative β hCG test. A β hCG test is performed 13-15 days after transfer followed by a transvaginal ultrasound 5-6 weeks after transfer to assess clinical and vital pregnancy. Subjects experiencing a full menstrual bleeding following transfer must have the β hCG test performed 7-15 days after transfer. The β hCG test is mandatory for all subjects who undergo transfer, irrespective of bleeding.

Blood samples will be collected during the trial for the purpose of evaluating the endocrine profile as well as clinical chemistry and haematology parameters. Endocrine parameters are measured at screening, stimulation day 1, stimulation day 6 and end-of-stimulation. Clinical chemistry and haematology parameters are assessed at screening, end-of-stimulation and end-of-trial. Local tolerability of FE 999049 following subcutaneous administration will be assessed by the subjects three times daily: immediately, 30 minutes and 24 hours after the injection. The assessment of injection site reactions will be made throughout the stimulation period and recorded by the subjects in a diary.

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

Pregnancy Follow-up

As obligatory follow-up, pregnancy progress and outcome data will be gathered for subjects with a vital pregnancy. Data will be collected on ongoing pregnancy (10-11 weeks after transfer) and pregnancy outcome as well as neonatal health at birth and at 4 weeks after birth. The pregnancy follow-up does not include any interventions but only data collection. The pregnancy follow-up data will be based on reports obtained from the subject's gynaecologist / obstetrician and the subject's Maternal and Child Health Handbook. The data will be retrieved by the trial site, either via the subject's gynaecologist / obstetrician, the subject herself, or other sources, as applicable.

Ferring intends to submit the J-NDA following completion of the main part of the trial (i.e. up to the clinical pregnancy visit), and to include the pregnancy follow-up data available at that time in

the J-NDA. The pregnancy follow-up data can be submitted after completion.

3.1.3 Trial Schedule

The estimated timelines for the trial are listed below.

| | |
|--|-------------------|
| First patient first visit (FPFV): | Estimated Q3 2017 |
| Last patient last visit (LPLV) / end-of-trial: | Estimated Q1 2019 |
| Pregnancy follow-up completed: | Estimated Q4 2019 |

3.2 Planned Number of Trial Sites and Subjects

It is planned to randomise approximately 328 subjects from approximately 15-20 sites in Japan.

3.3 Interim Analysis

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

3.4 Data Monitoring Committee (DMC)

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 FOLLISTIM with respect to number of oocytes retrieved in Japanese IVF/ICSI patients undergoing controlled ovarian stimulation.

Strict criteria have been incorporated in the design of this comparative efficacy 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.^{17,18,19}

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, the Ferring clinical trial team will also remain blinded to individual subject treatment

allocation during the conduct of the trial. The trial will be a multi-centre 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 FOLLISTIM with respect to number of oocytes retrieved. The non-inferiority margin for the primary endpoint has been set at -3.0 oocytes, based on considerations to clinical relevance and overseas regulatory precedence. The non-inferiority margin for the primary endpoint has been reviewed and agreed at the follow-up meeting for the Pharmaceuticals and Medical Devices Agency (PMDA) post-phase 2 trial consultation in December 2016.

Subjects will undergo controlled ovarian stimulation with an individualised dosing regimen of FE 999049 based on considerations of the subject's AMH level and body weight, or with a labelling recommended dosing regimen of FOLLISTIM, following a GnRH antagonist protocol. 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 5 days and embryo development will be assessed from oocyte retrieval till the day of transfer, allowing evaluation of embryo development until blastocyst stage. One blastocyst of the best quality available will be transferred on day 5 after oocyte retrieval while remaining blastocysts may be cryopreserved.

Subjects who achieve vital 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.

3.5.2 Selection of Endpoints

The present trial has been designed as a non-inferiority trial with number of oocytes retrieved as the primary endpoint. This parameter provides a direct measure of the main pharmacological action of gonadotropin preparations. The number of oocytes retrieved is considered an appropriate marker of ovarian response and thereby of the pharmacodynamics of an FSH preparation. The number of oocytes retrieved has also been used as the primary endpoint in the Japanese dose-response trial (000124). This primary endpoint is in accordance with the PMDA scientific advice (agreed upon during consultation post-phase 2 trial). In addition, per PMDA recommendation, clinical pregnancy rate is an important secondary endpoint.

One of the secondary objectives is to compare the clinical benefits of FE 999049 in its dosing regimen to those of FOLLISTIM with respect to efficacy and safety. This objective is investigated by multiple endpoints to address it from several angles; i.e. the feasibility of pregnancy, 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 and cycle cancellations due to excessive ovarian response.

Additional secondary endpoints include pharmacodynamic parameters, such as ovarian response in terms of follicular development, endocrine profile and also oocyte / embryo / blastocyst quality. Follicular development and endocrine profile will be evaluated after the initial 5 days as well as at the end of stimulation. The endocrine profile consists of FSH, LH, estradiol, progesterone, inhibin A and inhibin B.

Clinical safety endpoints cover adverse events, early and late OHSS, preventive interventions for early OHSS, local tolerability, clinical chemistry and haematology parameters. Pre-defined injection site reactions, i.e. redness, pain, itching, swelling and bruising, will be assessed by the subjects at three occasions (after each injection) spanning from immediately after the subcutaneous injection till 24 hours after. Technical malfunction of the pens used for administration of the gonadotropin preparations will also be monitored.

As obligatory follow-up, pregnancy progress and outcome data will be gathered for subjects with a vital pregnancy. Neonatal health data will be gathered to provide additional safety information. The follow-up extends till 4 weeks after birth.

3.5.3 Blinding

The FE 999049 and FOLLISTIM administration pens have different appearances. A double-blind design would require the patient to come to the clinic every day during the stimulation phase (an average of 9 days) to have the gonadotropin administered by a trial medication delegate. During the injections as well as the time immediately before and after, the patient would have to be blind-folded in order to not see the FE 999049 or FOLLISTIM pen. Furthermore, in clinical practice patients will perform self-administration of the FSH preparation, therefore a double-blind design would not reflect routine practice and it is considered to be unacceptable for the patients and not in accordance with medical practice of self-administration. The trial, however, is assessor-blind, ensuring unbiased evaluation by the investigators, embryologists and central laboratory personnel. Only the trial medication delegate personnel (persons responsible for investigational medicinal products (IMPs) / non-investigational medicinal products (NIMPs)), the monitors and the participating subjects will know the treatment allocation once the subjects are randomised. This assessor-blinded design has been reviewed and agreed with PMDA during consultation post-phase 2 trial.

The present 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, the monitors and the participating subjects will know the treatment allocation once the subjects are randomised. 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 person entering data into the electronic case report form (eCRF)). The investigator does not have access to these modules in the eCRF. 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 not to discuss their treatment allocation with 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 with training in the importance of maintaining blinding, and trial medication delegates are also helped to set up systems at the clinic.

The Ferring clinical trial team (i.e. data manager, statistician, trial manager, medical writer, pharmacovigilance manager and 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.

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 (000009) have been used to identify the overall dosing regimen for FE 999049. The objective of the FE 999049 dosing regimen is to obtain an appropriate ovarian response of 8-14 oocytes in most subjects, to minimise the proportion of subjects with <4 oocytes due to risk of unavailability of blastocysts for transfer, and to minimise the proportion of subjects with 15 oocytes or more as well as 20 oocytes or more due to the risk of early moderate/severe OHSS.

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 proposed individualised dosing regimen of FE 999049 is described in detail in section 5.1 and is summarised as follows: for subjects with AMH <15 pmol/L the daily FE 999049 dose is 12 µg, irrespective of body weight, and for subjects with 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 safety and efficacy of this dosing regimen has been confirmed in a phase 3 trial overseas (ESTHER-1). The phase 2 trial in Japan (000124) showed a similar dose-response for the Japanese population, which was corroborated by modelling and simulation of the efficacy data obtained in the Japanese phase 2 trial.

The dosing regimen of FE 999049 in this trial will be the same as the dosing regimen that was evaluated in the overseas phase 3 trial. However, a minimum daily dose of 6 µg FE 999049 is established to account for the lower body weight in the Japanese population and the maximum allowed daily FE 999049 dose is 12 µg. Thus, the daily dose of FE 999049 will be in the span from 6 µg to 12 µg. This dose range was evaluated in the Japanese phase 2 trial.

The FE 999049 dosing regimen has been reviewed and agreed at the PMDA post-phase 2 trial consultation on 27 June 2016. The present trial aims to confirm the efficacy and safety of the proposed dosing regimen in the Japanese population.

FOLLISTIM

Subjects randomised to FOLLISTIM will be dosed according to the approved labelling in Japan. The starting dose of FOLLISTIM in this trial is 150 IU. The labelling for FOLLISTIM states a starting dose of 150-225 IU, but provides 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 the efficacy trial will include patients with no previous controlled ovarian stimulation for IVF/ICSI. This approach was also adopted in the phase 3 trial overseas (ESTHER-1). The FOLLISTIM starting dose is fixed for the first five stimulation days after which it may be adjusted by 75 IU based on the individual response. For FOLLISTIM, the minimum daily dose allowed is 75 IU and the maximum daily dose allowed is 375 IU.

Concomitant Fertility Medication

The doses and overall treatment regimens for the GnRH antagonist (GANIREST), hCG (hCG FUJI) and progesterone (LUTINUS) 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 (used according to local availability and at a dose according to site-specific procedures, e.g., a single dose of 300 µg SUPRECUR or 400 µg NASANYL) 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 a reduced 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.^{20,21,22,23,24}

3.5.5 Selection of the Trial Population

The trial population is representative of patients undergoing IVF/ICSI treatment. The subjects are women diagnosed with tubal infertility, unexplained infertility, infertility related to endometriosis stage I/II or with partners diagnosed with male factor infertility, eligible for IVF and/or ICSI

treatment. Classification of endometriosis is based on the revised American Society for Reproductive Medicine (ASRM) classification.²⁵ Women with a history of recurrent miscarriage or with contraindications to controlled ovarian stimulation with gonadotropins will be excluded from participation in this trial.

For the purpose of this trial, subjects within the age group 20-40 years are considered suitable as increasing female age is associated with lower AMH and consequently fewer oocytes as well as a reduction in oocyte/embryo quality.²⁶ In this trial, oocytes will be cultured to blastocyst stage to gather as much information as possible on embryo development and single transfer has been implemented to facilitate interpretation of the pregnancy data.

The allowed body mass index (BMI) is within 17.5-32.0 kg/m² (both inclusive). This broad range in BMI will facilitate the subsequent recommendation of doses in underweight, normal weight, overweight and obese patients.

The exclusion criteria incorporate the contraindications for the use of gonadotropins and the concomitant fertility medication.

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

Pregnancy Follow-up

As obligatory follow-up, pregnancy progress and outcome data will be gathered for subjects with a vital pregnancy. Data will be collected on ongoing pregnancy (10-11 weeks after transfer) and pregnancy outcome as well as neonatal health at birth and at 4 weeks after birth. The pregnancy follow-up does not include any interventions but only data collection.

Access to Therapy after End-of-Trial

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

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 any trial-related procedures.
2. In good physical and mental health.
3. Japanese 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 Documents 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 American Society for Reproductive Medicine (ASRM) classification) or with partners diagnosed with male factor infertility, eligible for in vitro fertilisation (IVF) and/or intracytoplasmic sperm injection (ICSI) treatment using ejaculated sperm from male partner.
5. Infertility for at least 1 year before randomisation (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 screening. This also includes women who have been diagnosed with any of the above medical conditions but have had them surgically corrected within 1 year prior to screening.
9. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. no endometrioma greater than 3 cm or enlarged ovaries which would contraindicate the use of gonadotropins) and fallopian tubes and surrounding tissue without evidence of significant abnormality (e.g. no hydrosalpinx) within 1 year prior to screening. 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 screening).
11. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests within 1 year prior to screening.
12. Body mass index (BMI) between 17.5 and 32.0 kg/m² (both inclusive) at screening.
13. Willing to accept transfer of one blastocyst.

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 classification²⁵).
2. One or more follicles >10 mm (including cysts) observed on the transvaginal ultrasound prior to start of stimulation on stimulation day 1 (puncture of cysts prior randomisation is allowed).
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. In case the sperm production is severely impaired (concentration <1 million/mL), normal karyotype, including no Y-chromosome microdeletion, must be documented.
5. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
6. Known porphyria.
7. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
8. Known inherited or acquired thrombophilia disease.
9. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) which can compromise participation in the trial with the exception of controlled thyroid function disease.
10. Known presence of anti-FSH antibodies (based on the information available in the subject's medical records).
11. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
12. Any abnormal finding of clinical chemistry, haematology or vital signs at screening, which is judged clinically relevant by the investigator.
13. Known moderate or severe impairment of renal or hepatic function.
14. Currently breast-feeding.
15. Undiagnosed vaginal bleeding.
16. Known abnormal cervical cytology of clinical significance observed within 3 years prior to screening (unless the clinical significance has been resolved).
17. Findings from the laboratory analyses at screening which preclude gonadotropin stimulation.
18. Findings at the gynaecological examination at screening which preclude gonadotropin stimulation.
19. Findings at the gynaecological examination at screening which are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
20. Pregnancy (must be confirmed by negative urinary pregnancy tests at screening and prior to randomisation) or contraindication to pregnancy.
21. Known current active pelvic inflammatory disease.

22. Use of hormonal preparations (except for thyroid medication) or fertility modifiers during the last menstrual cycle before randomisation, including dehydroepiandrosterone (DHEA), metformin and cycle programming with oral contraceptives, progestogen or estrogen preparations.
23. Known history of chemotherapy (except for gestational conditions) or radiotherapy.
24. Current or past (1 year prior to randomisation) abuse of alcohol or drugs, and/or 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 drug substance or excipients in the medicinal products used in the trial.
27. Hypersensitivity to any drug substance or excipients in a GnRH or any GnRH analogue / derivative.
28. Previous participation in the trial.
29. Current participation in another trial, including follow-up period.
30. Use of any non-registered investigational drugs during the last 3 months prior to screening.

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 Institutional Review Board (IRB) / Ethics Committees (ECs) 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 FOLLISTIM, and stimulation will be initiated. Randomisation is performed centrally through the eCRF and will be stratified according to AMH levels at screening (<15 pmol/L and ≥ 15 pmol/L) and centre. 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

Prohibited Therapy before and during the Trial

The subjects must not have used hormonal preparations (except for thyroid medication) or fertility modifiers, including DHEA, metformin and cycle programming with oral contraceptives, progestogen or estrogen preparations from the start of the last menstrual cycle before randomisation until the end of the trial.

It is prohibited to administer other gonadotropins than FE 999049 or FOLLISTIM and concomitant fertility medication provided as part of the trial regimen.

Prohibited Therapy after the Trial

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. 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 eCRF.

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)

On day 2-3 of the menstrual cycle, subjects will be randomised in a 1:1 ratio to treatment with either FE 999049 or FOLLISTIM, and controlled ovarian stimulation will be initiated.

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 AMH <15 pmol/L the daily FE 999049 dose is 12 µg, irrespective of body weight. For subjects with 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 daily FE 999049 dose will be fixed throughout the stimulation period. The minimum allowed daily FE 999049 dose is 6 µg. The maximum allowed daily FE 999049 dose is 12 µg. 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.

The continuous part of the FE 999049 dosing regimen is illustrated in Figure 5-1, and the complete FE 999049 dosing regimen is tabulated in detail in Table 5-1.

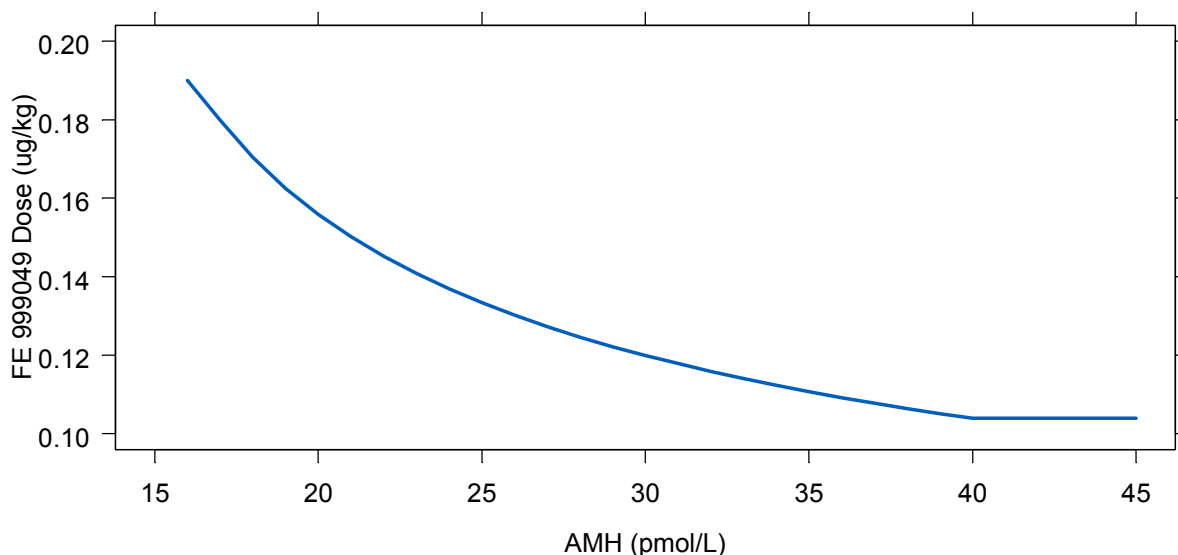


Figure 5-1 FE 999049 Dosing Regimen

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 Pre-Filled Pen

The subject's serum AMH concentration will be available from the blood sample taken at screening and analysed by a central laboratory using Elecsys® AMH assay from Roche Diagnostics. The AMH concentration will be provided from the central laboratory directly to the eCRF. 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 eCRF. The FE 999049 dosing algorithm has been programmed in the eCRF, which calculates the FE 999049 dose based on the subject's AMH and body weight.

The FE 999049 pre-filled injection pen is intended for subcutaneous administration of FE 999049. It is a non-sterile needle-based disposable device with integrated non-replaceable 3 mL cartridge containing the liquid FE 999049 drug product. Each cartridge holds multiple doses, the size of which are adjustable by the user. It is possible to set doses from 0.33 µg to 20.0 µg in increments of

0.33 µg. The FE 999049 pre-filled injection pen has a dosing scale numbered from 0 to 20 µg. Each number is separated by two lines, each line representing 0.33 µg.

The pre-filled injection pen can be set to deliver 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 75.0 kg with an AMH level of 35 pmol/L for whom the calculated dose is 8.25 µg ($0.11 \mu\text{g}/\text{kg} * 75.0 \text{ kg}$), which will then be rounded to 8.33 µg, i.e. 8 µg + 1 line on the pen. The eCRF will provide the calculated dose in an output that matches the numbers and lines on the pre-filled 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 pre-filled injection pen, so that correct instructions can be provided to the subject.

5.1.2 FOLLISTIM Dosing Regimen

For subjects randomised to FOLLISTIM, the dosing regimen is within labelling. The starting dose of FOLLISTIM is 150 IU and fixed for the first five stimulation days, after which it may be adjusted by 75 IU based on the individual response. The maximum daily FOLLISTIM dose allowed is 375 IU. Dosing will continue until the criterion for triggering of final follicular maturation has been met. Subjects can be treated with FOLLISTIM for a maximum of 20 days. Coasting is not allowed.

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

Table 5-2 FOLLISTIM Dosing Regimen

| Treatment group | Starting dose stimulation day 1-5 | Daily dose stimulation day 6 and onwards | Minimum daily dose | Maximum daily dose |
|-----------------|-----------------------------------|--|--------------------|--------------------|
| FOLLISTIM | 150 IU | Adjustments of 75 IU allowed according to the individual response. | 75 IU | 375 IU |

Subjects can be treated for a maximum of 20 days.

The FOLLISTIM 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 FOLLISTIM 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 FOLLISTIM.

5.2 Non-investigational Medicinal Products (NIMPs)

The following medicinal products will be used as concomitant fertility therapy in the controlled ovarian stimulation cycle:

- GnRH antagonist (GANIREST): 0.25 mg subcutaneous injection once daily starting on stimulation day 6 and continued throughout the stimulation period, although for a maximum of 15 days. GANIREST and FE 999049 / FOLLISTIM should be administered approximately at the same time. However, the preparations should not be mixed and different injection sites are to be used.
- hCG (hCG FUJI): 5,000 IU as a single intramuscular injection on the day of reaching the criterion for triggering of final follicular maturation with hCG.
- Vaginal progesterone (LUTINUS): 100 mg vaginal tablets three times daily, starting on the day after oocyte retrieval and continued until the day of the clinical pregnancy visit (5-6 weeks after transfer) unless progesterone support is terminated earlier in case of no transfer, menses, negative β hCG or pregnancy loss. Thus, the maximum duration of vaginal progesterone use within the trial is approximately 6-7 weeks.

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 5-3 provides an overview of the presentation and manufacturer of each medicinal product.

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

| Medicinal Product | Presentation | Manufacturer |
|-----------------------------------|---|-------------------------|
| FE 999049 (rFSH) | FE 999049 is provided as a pre-filled injection pen containing 72 µg/ 2.16 mL FE 999049. | Ferring Pharmaceuticals |
| FOLLISTIM (rFSH) | FOLLISTIM (follitropin beta) is provided as a cartridge and an administration pen. Each cartridge contains a solution for injection delivering 900 IU FSH in 1.08 mL. | MSD K.K. |
| GANIREST (GnRH antagonist) | GANIREST (ganirelix acetate) is provided as a pre-filled syringe. The syringe contains a solution for injection delivering 0.25 mg of ganirelix in 0.5 mL. | MSD K.K. |
| hCG FUJI (hCG) | hCG FUJI is provided as an ampoule and a diluent. An ampoule contains 5,000 IU of hCG. | Fuji Pharma |
| LUTINUS (vaginal progesterone) | LUTINUS is provided as tablets to be administered vaginally, each containing 100 mg of progesterone. | Ferring Pharmaceuticals |

5.4 Packaging and Labelling

Packaging and labelling of the medicinal products will be done under the responsibility of Ferring Pharmaceuticals in accordance with GMP and national regulatory requirements. Details on the packaging of each medicinal product are provided in Table 5-4.

Table 5-4 Packaging of Medicinal Products

| Medicinal Product | Packaging |
|-----------------------------------|--|
| FE 999049 (rFSH) | FE 999049 is provided in boxes containing 1 pre-filled pen. Single use disposable needles are packed separately in a commercial box containing 70 needles labelled with a trial-specific label. Pen and boxes will be labelled with trial-specific labels. |
| FOLLISTIM (rFSH) | FOLLISTIM is provided in commercial boxes containing 1 cartridge for multiple use. The commercial box of cartridge will be packed in a box with a trial-specific label. Pen for administration of FOLLISTIM is provided separately in a commercial box containing 1 pen. The commercial box of pen will be labelled with a trial-specific label. |
| GANIREST (GnRH antagonist) | GANIREST is provided in commercial boxes containing 1 prefilled syringe. The commercial box will be labelled with a trial-specific label. |
| hCG FUJI (hCG) | hCG FUJI is provided in commercial boxes containing 10 ampoules and diluents. The commercial box will be labelled with a trial-specific label. |
| LUTINUS (vaginal progesterone) | LUTINUS is provided in boxes containing 21 vaginal applicators (without any printings) and 21 vaginal tablets individually wrapped in a sealed foil pouch. The box will be labelled with a trial-specific label. |

FOLLISTIM, GnRH antagonist (GANIREST), hCG (hCG FUJI) and progesterone (LUTINUS) are commercially available in Japan and will be purchased centrally. No modification from the usual commercial state will be made of FOLLISTIM, GANIREST, hCG FUJI and LUTINUS except for trial-specific labelling. A leaflet specific for Japan will be distributed together with each medicinal product.

5.5 Conditions for Storage and Use

The investigator will ensure that the medicinal products are stored in appropriate conditions in a secure location with controlled access. The storage compartment will be monitored regularly and the temperature values will 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. Conditions for storage of the medicinal products before and after dispensing to the subjects are listed in Table 5-5.

Table 5-5 Conditions for Storage of Medicinal Products

| Medicinal Product | Before dispensing to subject | After dispensing to subject |
|-----------------------------------|---|---|
| FE 999049 (rFSH) | Store refrigerated at 2-8 °C. Do not freeze. Store in original package to protect from light. | Store at 2-30°C for up to 28 days. Do not freeze. Store in original package to protect from light. |
| FOLLISTIM (rFSH) | Store in refrigerator at 2-8 °C. Do not freeze. Store in original package to protect from light. | Store at 2-25 °C. Do not freeze. Store in original package to protect from light. |
| GANIREST (GnRH antagonist) | Store at 1-30 °C. Do not freeze. Store in original package to protect from light. | Store at 1-30 °C. Do not freeze. Store in original package to protect from light. |
| hCG FUJI (hCG) | Store at 1-15 °C. Do not freeze. Store in original package to protect from light. | <i>Generally this medicinal product will not be dispensed to subjects, but if dispensing to subjects is required, the conditions for storage are:</i> Store at 1-15 °C. Do not freeze. Store in original package to protect from light. |
| LUTINUS (vaginal progesterone) | Store at 1-30 °C. Do not freeze. Store in original package to protect from light. | Store at 1-30 °C. Do not freeze. Store in original package to protect from light. |

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 to the effective versions of the commercial product information for FOLLISTIM, GANIREST, hCG FUJI and LUTINUS.

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 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 FOLLISTIM, 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/day as applicable if the subject is in the FOLLISTIM 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 eCRF 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 procedure will be available for the investigator and designated personnel at the sponsor through the eCRF. It is the investigator's responsibility to decide whether it is medically necessary to know the investigational product the subject receives (i.e., unblinding) to ensure the subject's welfare and safety.

Breaking of the blind for individual subjects in emergency situations could be required in case of suspected unexpected serious adverse reactions (SUSARs) or in case of other important adverse events when 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. Where the event requires immediate unblinding by the investigator, the sponsor must be informed of the unblinding as soon as possible and provided with the rationale for unblinding.

The investigator who unblinds a treatment will use the eCRF and is required to enter a password and must record the reason for unblinding before the treatment code can be broken. The eCRF records when, and by whom, the code was broken. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided.

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

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

Information on whether the blind has been broken for any subjects is available in the eCRF and must be collected before the database is declared clean and is released to the trial statistician.

In case the eCRF cannot be accessed by the investigator, and hence the emergency unblinding cannot be performed within the eCRF system, the investigator should contact Ferring Global Pharmacovigilance using the contact details below:

Global Pharmacovigilance, Ferring Pharmaceuticals A/S

Tel: [REDACTED]

In case Ferring Global Pharmacovigilance cannot access the eCRF, a backup procedure involving the eCRF vendor is in place.

5.7 Dispensing and Accountability, Return and Destruction

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

The monitor will verify drug accountability of medicinal products throughout the trial and will document any discrepancies.

Concerning destruction, the trial medication delegate at the site must ensure destruction of dispensed/used medicinal products in accordance with local legislation after drug accountability have been verified by the monitor.

Non-dispensed / unused medicinal products will be returned for destruction as instructed by Ferring after drug accountability have been verified by the monitor.

5.8 Auxiliary Supplies

Ferring will supply safety containers for the collection of used 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 / cryopreservation | |
| Timing | <60 days before randomisation | Day 1 | Day 6 | Day ≥7 to <20 ^{a)} | End | 36h ±2h after triggering | 5 days after OR | 13-15 days after transfer | 5-6 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 | | | | | | | | | |
| Body measurements | X | X ^{c)} | | | | | | | | X |
| Physical examination | X | | | | | | | | | X |
| Gynaecological examination | X | | | | | | | | | X |
| Urinary pregnancy test | X | X ^{c)} | | | | | | | | |
| Blood collection, clin chem / haem | X | | | | X | | | | | X |
| Blood collection, endocrine | X ^{e)} | X ^{d) e)} | X ^{f)} | | X ^{f)} | | | | | |
| Ultrasound (ovaries and/or uterus) | | X ^{c)} | X | X | X | | | | X | |
| Vital signs | | X ^{d)} | | | | | | | | X |
| Randomisation | | X | | | | | | | | |
| FE 999049 or FOLLISTIM dispensing | | X ^{g)} | X ^{g)} | X ^{g)} | | | | | | |
| Local tolerability (diary) | | X | X | X | X | X | | | | |
| Concomitant fertility medication dispensing | | | X | X | X | X | X | X | | |
| Oocyte retrieval | | | | | | X | | | | |
| Transfer / cryopreservation | | | | | | | X | | | |
| βhCG test | | | | | | | | X ^{h)} | | |
| Drug accountability | | | X | X | X | X | X | X | X | X |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X |
| Adverse events | 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 3 follicles of ≥15 mm are observed visits must be scheduled daily.

b) End-of-trial assessments must be performed at the subject's last scheduled visit.

c) Performed before randomisation.

d) Performed before the first FE 999049 or FOLLISTIM dose.

e) Including AMH analysis

f) Must be drawn at least 8h after the previous administration of FE 999049 or FOLLISTIM and GnRH antagonist, as applicable.

g) If dispensing of FE 999049 or FOLLISTIM in special cases is not possible during stimulation, as an exception all FE 999049 or FOLLISTIM can be dispensed on stimulation day 1.

h) Subjects experiencing a full menstrual bleeding following transfer must have the βhCG test performed 7-15 days after transfer.

AMH: anti-Müllerian hormone; OR: oocyte retrieval.

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

6.1 Screening

Potential participants will be scheduled to come to the clinic for the screening assessments. Screening must be initiated within 60 days prior 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
 - Infertility history
 - Menstrual history
 - Reproductive history
- Body measurements (body weight, height) [*note*: these are used for calculation of BMI]
- Physical examination
- Gynaecological examination
- Urinary pregnancy test – must be negative
- Blood collection for central laboratory analysis of
 - Endocrine parameters: AMH, thyroid-stimulating hormone (TSH) and prolactin [*note*: the results must be available prior to randomisation]
 - Clinical chemistry and haematology parameters [*note*: the results must be available prior to randomisation]
- 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 measurements (body weight [*note*: this body weight result is used for dose calculation in the FE 999049 group])
- Urinary pregnancy test – must be negative
- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial echogenicity pattern, ovarian volume, number and size of follicles)

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 FOLLISTIM

The following must take place after randomisation but before administration of the first dose of FE 999049 or FOLLISTIM:

- Vital signs
- Blood collection for central laboratory analysis of endocrine parameters

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 FE 999049 or FOLLISTIM according to randomisation and instruct the subject on how to administer FE 999049 or FOLLISTIM, including that all subsequent FE 999049 or FOLLISTIM administrations are preferably to be done in the evening
- Administer the 1st dose of IMP according to randomisation [administration of IMP takes place at the clinic and can be done by either the trial medication delegate or the subject under supervision by the trial medication delegate]:
 - If randomised to FE 999049; daily dose is calculated by the eCRF according to AMH level at screening and body weight at randomisation (see Table 5-1 on page 45 for detailed instructions)
 - If randomised to FOLLISTIM; 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 injection of FE 999049 or FOLLISTIM throughout the entire stimulation period

After the first administration of FE 999049 or FOLLISTIM, the subject must do the following:

- Assessment of local tolerability (recorded in a diary) – the first evaluation of injection site reactions is done immediately after the subcutaneous injection of FE 999049 or FOLLISTIM, followed by the second evaluation 30 min after injection of FE 999049 or FOLLISTIM and the third evaluation 24 hours after injection of FE 999049 or FOLLISTIM (before the next day's injection of FE 999049 or FOLLISTIM)

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 administration of FE 999049 or FOLLISTIM, 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:

- Blood collection for central laboratory analysis of endocrine parameters – the blood sample must be drawn at least 8 hours after the latest FE 999049 or FOLLISTIM administration
- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial echogenicity pattern, number and size of follicles)
- Dispensing of FE 999049 or FOLLISTIM
[Note: If dispensing of FE 999049 or FOLLISTIM in special cases is not possible during stimulation, as an exception all FE 999049 or FOLLISTIM can be dispensed on stimulation day 1]
- 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]
- Drug accountability of FE 999049 or FOLLISTIM
- Collection of diary pages
- 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
- 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.

6.2.3 Stimulation Days ≥ 7 to ≤ 20

These visits will take place at least every second day throughout the remaining stimulation period. When 3 follicles of ≥ 15 mm are observed, visits must be scheduled daily. The maximum period of stimulation is 20 days.

The following must take place at all visits throughout the remainder of the stimulation period with exception of the end-of-stimulation visit (section 6.2.4):

- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial echogenicity pattern, number and size of follicles)
- Dispensing of FE 999049 or FOLLISTIM, as applicable
[Note: If dispensing of FE 999049 or FOLLISTIM in special cases is not possible during the stimulation period, as an exception all FE 999049 or FOLLISTIM can be dispensed on stimulation day 1]
- Dispensing of GnRH antagonist, as applicable
- Drug accountability of FE 999049 or FOLLISTIM and GnRH antagonist
- Collection of diary pages
- Recording of use of any concomitant medication
- Recording of adverse events

6.2.4 End-of-Stimulation

The end-of-stimulation visit takes place on the day when the subject reaches the criterion for triggering of final follicular maturation or any of the cycle cancellation criteria because of poor or excessive ovarian response.

| Poor ovarian response | Triggering criterion | Excessive ovarian response |
|---|--|--|
| If it is judged by the investigator that ≥ 3 follicles with a diameter ≥ 17 mm cannot be reached by stimulation day 20, the cycle is to be cancelled. | Criterion for triggering of final follicular maturation: <ul style="list-style-type: none"> ≥ 3 follicles with a diameter ≥ 17 mm hCG ^{a)} must be administered the day the triggering criterion is met. | In case of ≥ 25 follicles ≥ 12 mm, the cycle should be cancelled. <i>(note: in case of 25-35 follicles with a diameter ≥ 12 mm, GnRH agonist may be administered) ^{b)}</i> |

- a) hCG FUJI 5,000 IU as a single intramuscular injection will be administered on the day of reaching the criterion for triggering of final follicular maturation with hCG. In case it is not possible for the subject to attend a visit at the clinic for the intramuscular injection (typically occurring late in the evening), it will be accepted to implement site-specific routines for ensuring administration of hCG FUJI 5,000 IU.
- b) In case of triggering of final follicular maturation with a GnRH agonist, a GnRH agonist nasal spray such as SUPRECUR (buserelin acetate, Sanofi / Mochida Pharmaceuticals Co., Ltd) or NASANYL (nafarelin acetate, Pfizer) can be used according to local availability and at a dose according to site-specific procedures, e.g. a single dose of 300 μ g SUPRECUR or 400 μ g NASANYL.

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

As the injections of gonadotropin (FE 999049 or FOLLISTIM) and GnRH antagonist preferably are done in the evening, the last injections of these preparations occur the evening before the criterion for triggering of final follicular maturation is met and the triggering drug (hCG or GnRH agonist) is administered.

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

- Blood collection for central laboratory analysis of:
 - Clinical chemistry and haematology parameters
 - Endocrine parameters – the blood sample must be drawn at least 8 hours after the previous administration of FE 999049 or FOLLISTIM and GnRH antagonist, as applicable
- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial echogenicity pattern, number and size of follicles)
- Administration of hCG (or GnRH agonist, if applicable)
- Drug accountability of FE 999049 or FOLLISTIM and GnRH antagonist
- Collection of diary pages
- 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 (± 2 h) after administration of the triggering drug.

Subjects with cycle cancellation will proceed to end-of-trial assessments.

6.3 Oocyte Retrieval

Oocyte retrieval must take place 36h (± 2 h) after administration of the triggering drug. 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:

- Oocyte retrieval
- Dispensing of progesterone for luteal support – must be started on the day after oocyte retrieval [*note*: only applicable for subjects who underwent triggering of final follicular maturation with hCG and who had oocytes retrieved]
- Drug accountability of hCG
- 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 5 days after oocyte retrieval. For subjects with oocytes retrieved following GnRH agonist administration, the oocytes will undergo the procedures described in section 6.4 and blastocysts will be cryopreserved as according to local practice and declaration by JSOG.

Subjects with no oocytes retrieved will proceed to end-of-trial assessments.

6.4 Oocyte / Embryo / Blastocyst Evaluation

The laboratory procedures regarding handling and evaluations of oocytes, embryos and blastocysts are described in detail 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 blastocyst stage. The flow of the trial procedures for embryos is shown in Table 6-2.

Table 6-2 Trial Flow Chart – Oocyte / Embryo / Blastocyst Procedures

| Timing | Day 0 (OR) | | Day 1 | Day 3 | Day 5 |
|---|---------------|----|---------------|---------------|-----------------|
| | -2h (± 2h) | 0h | 19h (± 2h) | 68h (± 2h) | 120h (± 3h) |
| Oocyte retrieval (OR) | X | | | | |
| Assessment of maturity stage (applicable for oocytes undergoing ICSI) | X | | | | |
| Insemination by IVF or ICSI | | X | | | |
| Assessment of oocyte fertilisation | | | X | | |
| Assessment of embryo/blastocyst quality | | | | X | X |
| Transfer of a single blastocyst ^{a)} | | | | | X |
| Cryopreservation of blastocysts | | | | | X ^{b)} |

a) In the absence of a viable blastocyst, a single morula may be used for transfer.

b) Cryopreservation may also occur after day 5.

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

Day 0 (Oocyte Retrieval)

- Oocyte retrieval at 2h (± 2h), i.e. 0-4 hrs, before start of any insemination procedure. Oocytes must be cultured individually in separate dishes / droplets
- Procedures between oocyte retrieval and insemination:
 - Assessment of maturity stage (applicable for oocytes undergoing ICSI)
- Insemination using IVF or ICSI using ejaculated sperm (fresh or frozen) from partner

Day 1 after Oocyte Retrieval

- Assessment of fertilisation (number of pronuclei) at 19h (± 2h) post-insemination

Day 3 after Oocyte Retrieval

- Assessment of embryo quality at 68h (± 2h) post-insemination

Day 5 after Oocyte Retrieval

- Assessment of blastocyst quality at 120h (± 3h) post-insemination
- Transfer of a single blastocyst at 120h (± 3h) post-insemination (section 6.5)

- Cryopreservation at 120h (\pm 3h) post-insemination, in line with local practice and declaration by JSOG [*note*: cryopreservation may also occur after day 5]

6.5 Blastocyst Transfer

Transfer is performed on day 5 (blastocyst stage) after oocyte retrieval.

The subject-related procedures are described below.

- Transfer of a single blastocyst of the best quality available
[*note*: only applicable for subjects who underwent triggering of final follicular maturation with hCG. Subjects who were administered GnRH agonist will not undergo transfer in this cycle]
- Dispensing of progesterone for luteal phase support. Progesterone support should be continued until the day of the clinical pregnancy visit, but can be terminated earlier in case of menses, a negative β hCG test or pregnancy loss.
- Drug accountability of progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with blastocyst transfer, the next visit is the β hCG test visit which must be scheduled 13-15 days after transfer (section 6.6). Subject with no blastocyst transfer will proceed to end-of-trial assessments.

6.6 β hCG Test

Subjects who have undergone transfer must attend a visit 13-15 days after transfer, unless the subject experiences a full menstrual bleeding following transfer, then the β hCG test must be performed 7-15 days after transfer. The β hCG test is mandatory for all subjects who have undergone transfer, irrespective of bleeding.

The following must take place:

- Blood collection for central laboratory analysis of β hCG
- 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 will be analysed for β hCG by a central laboratory and evaluated according to the central laboratory's reference ranges. In case of a doubtful β hCG result, the test may be repeated.

Subjects with a positive β hCG test must attend a clinical pregnancy visit 5-6 weeks after transfer (section 6.7). Subjects with a negative β hCG test must proceed to the end-of-trial assessments (section 6.8).

6.7 Clinical Pregnancy

Subjects with a positive β hCG 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, if applicable
- 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.

6.8 End-of-Trial

Subjects who have a positive β hCG test and continue to the clinical pregnancy visit will have end-of-trial assessments done at that visit. Subjects who have a negative β hCG test will proceed directly to end-of-trial assessments. Subjects experiencing a full menstrual bleeding following transfer can also proceed to the end-of-trial visit and have the β hCG test performed as part of the end-of-trial assessments, if this occurs 7-15 days after transfer.

The following must take place at the end-of-trial visit:

- Body measurements (body weight)
- Physical examination
- Gynaecological examination
- Vital signs
- Blood collection for central laboratory analysis of clinical chemistry and haematology parameters
- 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.

6.9 Pregnancy Follow-up

Pregnancy progress and outcome data will be gathered for subjects with a vital pregnancy. Data will be collected on ongoing pregnancy (10-11 weeks after transfer) and pregnancy outcome as well as neonatal health at birth and at 4 weeks after birth. The pregnancy follow-up does not include any interventions but only data collection. The pregnancy follow-up data will be based on reports obtained from the subject's gynaecologist / obstetrician and the subject's Maternal and Child Health Handbook. The data will be retrieved by the trial site, either via the subject's gynaecologist / obstetrician, the subject herself, or other sources, as applicable.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Primary Endpoint

7.1.1 Number of Oocytes Retrieved

The number of oocytes retrieved will be recorded at the oocyte retrieval visit.

7.2 Assessments Related to Important Secondary Endpoint

7.2.1 Clinical Pregnancy

The clinical pregnancy rate is considered an important secondary endpoint. A transvaginal ultrasound of the uterus will be performed 5-6 weeks after transfer. Clinical pregnancy will be defined as at least one gestational sac, either intrauterine or ectopic. The inclusion of ectopic pregnancies and the lack of specification of heart beat in the definition of clinical pregnancy is in line with the current International Committee Monitoring Assisted Reproductive Technologies (ICMART) and World Health Organization (WHO) glossary on ART terminology.^{b,27}

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

7.3 Assessments Related to Secondary Endpoints

7.3.1 β hCG Test

A blood β hCG test must be obtained 13-15 days after transfer, unless the subject experiences a full menstrual bleeding following transfer, then the β hCG test must be performed 7-15 days after transfer. If the test is positive according to the central laboratory's reference ranges, this confirms a positive β hCG. The β hCG test is mandatory for all subjects who have undergone transfer, irrespective of bleeding.

7.3.2 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.

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

7.3.3 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 blastocysts transferred.

7.3.4 Cycle Cancellation due to Poor or Excessive Ovarian Response or Blastocyst 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 ≥ 25 follicles with a diameter ≥ 12 mm are observed (in case of 25-35 follicles with a diameter ≥ 12 mm, GnRH agonist may be administered). The reason for each blastocyst 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", "ovarian hyperstimulation syndrome" and "high progesterone" in subjects with blastocysts available for transfer will be considered as transfer cancellations due to excessive response / OHSS risk.

7.3.5 Ovarian Response

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.

7.3.6 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.

7.3.7 Preventive Interventions for Early OHSS

Preventive interventions for early OHSS cover cycle cancellation due to excessive ovarian response, triggering of final follicular maturation with GnRH agonist and administration of dopamine agonist (the latter is only considered as preventive intervention in subjects with ≥ 20 follicles of ≥ 12 mm).

7.3.8 Early OHSS (including Moderate/Severe) 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 8.3.1 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, triggering of final follicular maturation with GnRH agonist and administration of dopamine agonist (the latter is only considered as preventive intervention in subjects with ≥ 20 follicles of ≥ 12 mm).

7.3.9 Late OHSS (including Moderate/Severe)

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 8.3.1 for details) and all OHSS cases will be graded as mild, moderate or severe.

7.3.10 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.

7.3.11 Fertilisation Rate

The number of pronuclei will be counted at 19h (± 2 h) post-insemination and recorded as 0, 1, 2 or >2 . Fertilised oocytes with 2 pronuclei will be regarded as correctly fertilised.

7.3.12 Number and Quality of Embryos on Day 3

Each embryo will be evaluated 68h (± 2 h) post-insemination. The quality evaluation will consist of assessment of cleavage stage and embryo morphology parameters (blastomere uniformity, cell size, degree of fragmentation and visual signs of multinucleation).

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

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

Cell size will be classified as stage-specific cell size or not stage-specific cell size.

Degree of fragmentation will be classified as one of the following: 0%, 1-10%, 11-20%, 21-25%, 26-30%, 31-50% or $>50\%$ fragmentation, or totally fragmented (no blastomeres recognised).

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

7.3.13 Number and Quality of Blastocysts on Day 5

Blastocyst Expansion and Hatching Status, Blastocyst Inner Cell Mass Grading and Trophectoderm Grading

The quality evaluation of blastocysts on day 5 after oocyte retrieval will consist of assessment of three parameters: blastocyst expansion and hatching status, blastocyst inner cell mass grading and trophectoderm grading. The scoring is based on the classification system by Gardner & Schoolcraft²⁸ with the addition of D-categories for inner cell mass and trophectoderm.

Blastocyst expansion and hatching status will be assessed as one of the following:

1. An early blastocyst, blastocoel being less than half volume of that of the embryo
2. A blastocyst with a blastocoel whose volume is half of, or greater than half of, that of the embryo
3. A blastocyst with a blastocoel completely filling the embryo
4. An expanded blastocyst with a blastocoel volume larger than that of the early embryo, with a thinning zona
5. A hatching blastocyst with the trophectoderm starting to herniate through the zona
6. A hatched blastocyst, in which the blastocyst has completely escaped from the zona

For blastocysts with expansion and hatching status 3-6, blastocyst inner cell mass grading and trophectoderm grading will be evaluated.

Blastocyst inner cell mass grading will be assessed as one of the following:

- A. Tightly packed, many cells
- B. Loosely grouped, several cells
- C. Very few cells
- D. Degenerative or no inner cell mass

Trophectoderm grading will be assessed as one of the following:

- A. Many cells forming a cohesive epithelium
- B. Few cells forming a loose epithelium
- C. Very few, large cells
- D. Degenerative or very large cells

Blastocysts with expansion and hatching status 3-6 will have a score combining the three parameters (blastocyst expansion and hatching status, inner cell mass and trophectoderm); e.g. 4AB for a blastocyst with blastocyst expansion and hatching status 4, inner cell mass grading A and trophectoderm grading B.

7.3.14 Circulating Levels of Endocrine Parameters

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

Blood samples will be drawn at stimulation day 1^c, 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 FOLLISTIM, 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, FOLLISTIM 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.

7.3.15 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 FOLLISTIM dose administered and the number of stimulation days.

7.3.16 Adverse Events

Adverse events will be recorded from the signed informed consent 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 gonadotropin (i.e. FE 999049 / FOLLISTIM), action taken, seriousness of the adverse event, date and time of outcome, and outcome. Definitions are provided in section 8.

^c AMH will also be included in the stimulation day 1 analyses.

7.3.17 Clinical Chemistry and Haematology Parameters

Blood samples for analysis of circulating levels of clinical chemistry and haematology parameters will be drawn on the following occasions: screening, end-of-stimulation and end-of-trial.

All samples will be analysed at a central laboratory for the following clinical chemistry and haematology parameters:

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

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

The investigator will review the laboratory results and evaluate and document whether the abnormal results are non-clinically or clinically significant. The results from the screening sample will be reviewed prior to randomisation. The Laboratory Report will be signed and dated by the investigator.

7.3.18 Injection Site Reactions to IMP

Every day throughout the stimulation period, the subjects will assess the local tolerability of subcutaneous injections of FE 999049 or FOLLISTIM 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 eCRF.

7.3.19 Pen Malfunctions

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

7.4 Other Assessments

7.4.1 Demographics

Demographic information will be obtained during the screening period, including date of birth and confirmation that the subject is Japanese.

7.4.2 Medical History

Any relevant medical history will be recorded during the screening period. This includes diagnosis / symptoms, and whether it is a past or ongoing occurrence.

7.4.3 Infertility History

Information about the reasons of infertility and duration of infertility will be obtained during the screening period. This will also cover information about any previous treatment for infertility, including type of treatment and gonadotropin preparations used.

7.4.4 Menstrual History

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

7.4.5 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.

7.4.6 Body Measurements

Body weight will be measured at screening, stimulation day 1 and end-of-trial. In addition, height will be measured at screening. Body weight will be done 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.

7.4.7 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.

7.4.8 Gynaecological Examination

A complete gynaecological examination will be performed at screening and end-of-trial. Information will be recorded for breasts, 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 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.

7.4.9 Endocrine Parameters at Screening

At screening, the following panel of endocrine parameters will be evaluated: AMH, TSH and prolactin. The AMH level at screening will be used for stratification (<15 pmol/L and ≥ 15 pmol/L) and will furthermore be used for dose determination for subjects randomised to FE 999049.

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.

7.4.10 Vital Signs

Systolic and diastolic blood pressure as well as pulse will be measured at 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.

7.4.11 Ovarian Size and Volume

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

7.4.12 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 and echogenicity pattern.

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 echogenicity pattern will be recorded as hypoechoic, isoechoic, hyperechoic, or not possible to evaluate.

7.4.13 Maturity Stage

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.

7.4.14 Blastocyst Transfer Procedure

Any difficulty and eventuality during transfer procedure will be noted.

7.4.15 Concomitant Medication

The use of any concomitant medication within the last 3 months prior to informed consent (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.

7.4.16 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 as well as GnRH antagonist and

hCG or GnRH agonist, as applicable. Details on drug dispensing and accountability are provided in section 5.7.

7.4.17 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.

7.5 Assessments Related to Pregnancy Follow-up Information

The source data for the pregnancy follow-up data will be reports obtained from the subject's gynaecologist / obstetrician and the subject's Maternal and Child Health Handbook (or a copy of the relevant pages). The data will be retrieved by the trial site, either via the subject's gynaecologist/obstetrician, the subject herself, or other sources, as applicable.

Ongoing Pregnancy Rate and Live Birth Rate

For all subjects with a vital pregnancy, data will be collected on ongoing pregnancy, defined as at least one intrauterine viable fetus 10-11 weeks after transfer. Pregnancy losses after vital pregnancy will be recorded. Furthermore, information on pregnancy outcome, e.g. live birth, stillbirth, will also be collected. These data will be reported separately in a Clinical Trial Report Addendum.

Neonatal Health

Neonatal health data will be collected at birth and at 4 weeks after birth for all children born. At birth, the data collected will include date of birth, gender, birth weight and length as well as information on minor/major congenital anomalies and admission to neonatal intensive care unit (NICU), neonatal care unit (NCU) or growing care unit (GCU). At 4 weeks after birth, the data collected will include minor/major congenital anomalies, hospitalisations and any other relevant medical conditions. These data will be reported separately in a Clinical Trial Report Addendum.

7.6 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 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. An exception is the blood sample for β hCG which is analysed by a central laboratory and subsequently destroyed. 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 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 Department 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 last 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 eCRF 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.^d

Note: A procedure is not an adverse event; the reason for conducting the procedure is. Hospitalisation is not an adverse event; the reason for hospitalisation is. Death is not an adverse event, but the cause of death is (an exception is sudden death of unknown cause, which is an adverse event).

^d Exception: if an adverse event with onset before the first IMP administration (i.e. a pre-treatment adverse event) worsens in intensity, this must be recorded as two separate events. The initial adverse event should be recorded with outcome "not 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.

Date and Time of Onset

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

Intensity

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

- Mild: Awareness of signs or symptoms, but no disruption of usual 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 (the event is improving)
- Not recovered
- Fatal

8.3 Adverse Events of Special Interest

8.3.1 OHSS

OHSS is an adverse event of special interest during controlled ovarian stimulation. Investigators will record OHSS symptoms and will use Golan's system²⁹ as shown in Table 8-1 to grade (1, 2, 3, 4, or 5) each OHSS case.

Table 8-1 Classification of Mild, Moderate and Severe OHSS

| | |
|----------------------|--|
| <i>Mild OHSS</i> | |
| Grade 1 | Abdominal distension and discomfort. |
| Grade 2 | Features of grade 1 plus nausea, vomiting, and/or diarrhoea. Ovaries enlarged to 5 to 12 cm. |
| <i>Moderate OHSS</i> | |
| Grade 3 | Features of mild OHSS plus ultrasonic evidence of ascites. |
| <i>Severe OHSS</i> | |
| Grade 4 | Features of moderate OHSS plus clinical evidence of ascites and/or hydrothorax or breathing difficulties. |
| 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. |

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 OHSS cases.

Concerning timing, early OHSS will be defined as OHSS with onset \leq 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.

OHSS rate will be evaluated in the context of whether triggering of final follicular maturation was done with hCG or GnRH agonist and also whether the cycle was cancelled.

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
- Administration of dopamine agonist (this is only considered as preventive intervention in subjects with ≥ 20 follicles of ≥ 12 mm)

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 (for all OHSS)
- Blood sample for central lab 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/FOLLISTIM) are only to be reported as adverse events if they require active management, i.e. discontinuation of FE 999049 or FOLLISTIM, additional investigations or treatment of the injection site reaction. Local tolerability is a secondary endpoint and will be evaluated in detail based on the subjects' recordings in the diary.

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

8.3.3 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.

8.3.4 Pregnancy Losses

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

| | |
|------------------------|---|
| Biochemical pregnancy: | Positive β hCG test but no gestational sac is observed on later transvaginal ultrasound, or menstruation is reported |
| Spontaneous abortion: | Positive β hCG 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 during the pregnancy follow-up will be defined as a late pregnancy loss.

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 <i>per se</i> 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 in Connection with Pregnancy Outcome and Neonatal Health

The following untoward medical occurrences reported as part of the pregnancy outcome and neonatal health data collection will be reported as serious adverse events:

- Death of mother in connection with pregnancy or labour
- Death of neonate
- Stillbirth (occurring after gestational age 24 weeks + 0 days and calculated from the day of transfer + 19 days)
- Neonate admitted to the NICU irrespective of duration, or neonate admitted to NCU or GCU for at least 2 hours
- Congenital anomaly / birth defect
- Medically important event

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

Congenital anomalies will be coded using both MedDRA and International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) and classified as minor or major^e in accordance with the European Medicines Agency (EMA) guideline.³⁰

8.4.2 Collection, Recording and Reporting of Serious Adverse Events in Core Trial

Reporting by the Investigator

All serious adverse events must be reported immediately to Ferring Pharmacovigilance (i.e., Global Pharmacovigilance at Ferring Pharmaceuticals A/S and Ferring Pharmaceuticals Co., Ltd.) 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 SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the serious adverse event. The process is as follows:

- Report to Ferring Global Pharmacovigilance in English language using the serious adverse event (SAE) Report Form in the eCRF system (the form must be completed and submitted according to the instructions provided on the form).

^e 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.

Back-up Procedure

In case the eCRF cannot be accessed and hence the SAE Report Form cannot be filled in within the eCRF system, the English paper SAE Report Form should be sent according to the above timelines to Ferring Pharmacovigilance by fax, [REDACTED]

When the eCRF again can be accessed the information from the paper SAE Report Form should be entered in the eCRF.

Serious Adverse Event Information

The investigator must capture information for each serious adverse event on the SAE Report Form as described below.

A meaningful description of the serious adverse event and a narrative with relevant details including the clinical course leading up to an event should be made. The description should be written by the investigator and should be similar to the epicrisis generally written at disease termination/discharge. Course of event(s) must be stated as accurately and thoroughly as possible. The scope of the narrative is to give a full overview of the cause of event(s), making the case understandable to people without existing knowledge of the subject and without access to the subject's hospital records. Information relevant for the assessment of the case must be enclosed, e.g., medical history, concomitant medications, outcome, copies of source records, results from laboratory or other tests, surgery reports, hospital discharge letters, autopsy reports, etc. If laboratory results are presented, reference ranges should be included. If the subject was hospitalised, dates of hospital admission and discharge should be included. In any case this information must be supplied by the investigator upon request from Ferring. On any copies provided, details such as subject's name, address, and hospital identification number should be concealed and instead subject number should be provided.

Information to be Entered / Updated in the eCRF

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 eCRF for Ferring Global Pharmacovigilance to access the information.

Overdoses and medication errors of IMP with and without clinical consequences will be tracked in the eCRF and reviewed by Ferring GPV on an ongoing basis.

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 eCRF), 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 most recent Investigator's Brochure for FE 999049 and the Product Information for FOLLISTIM.

Serious adverse events will be considered reportable regardless of whether or not these medicinal products were used in accordance with the provisions in the protocol and Investigator's Brochure and labelling.

8.4.3 Collection, Recording and Reporting of Serious Adverse Events in Pregnancy Follow-up

All serious adverse events reported as part of the pregnancy outcome and neonatal health data collection must be reported immediately to Ferring Pharmacovigilance 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 SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the serious adverse event. The process is as follows:

- Report to Ferring Global Pharmacovigilance in English language using the serious adverse event (SAE) Report Form in the eCRF system (the form must be completed and submitted according to the instructions provided on the form).

Back-up Procedure

In case the eCRF cannot be accessed and hence the SAE Report Form cannot be filled in within the eCRF system, the English paper SAE Report Form should be sent according to the above timelines to Ferring Pharmacovigilance by fax, [REDACTED]

8.5 Follow-up of Adverse Events and Serious Adverse Events

Follow-up of Adverse Events with Onset during the Trial

During the trial, i.e. from the time of obtaining informed consent until the end-of-trial visit (for each subject individually), 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.

Adverse events on NIMPs during the trial

In case an adverse event is recognised as an adverse drug reaction caused by a concomitant NIMP, investigators should report to each Marketing Authorisation Holder. For adverse drug reactions caused by an NIMP where Ferring is the Marketing Authorisation Holder, the case will have to be reported to Ferring.

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 or an NIMP where Ferring is Marketing Authorisation Holder, the case will have to be reported to Ferring, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

The Ferring Global Biometrics Department will be responsible for the statistical analyses of the primary and 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 patient is randomised.

9.1 Determination of Sample Size

The primary objective of this trial is to demonstrate non-inferiority of FE 999049 compared with FOLLISTIM with respect to number of oocytes retrieved in Japanese IVF/ICSI patients undergoing controlled ovarian stimulation. The non-inferiority margin for the difference between treatments (FE 999049 versus FOLLISTIM) is -3.0 oocytes. The standard deviation for the primary endpoint is estimated to 8.1 oocytes based on historical data with FOLLISTIM.

The sample size is determined to obtain 90% power to achieve the primary objective for the per-protocol (PP) analysis set for a 1:1 randomisation ratio between FE 999049 and FOLLISTIM and a one-sided t-test at a 2.5% significance level. Assuming the two treatments to be equally effective and a standard deviation of 8.1 oocytes, a sample size of 155 randomised subjects per treatment group would give 90% power. The proportion of subjects with major protocol deviations is assumed to be at most 5% and hence 328 randomised subjects are needed to provide 155 subjects/group in the PP analysis set.

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 and by AMH stratum (screening AMH: <15 pmol/L, ≥15 pmol/L) 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 AMH stratum.

A subject is considered a completer if she attends all scheduled trial visits and undergoes the end-of-trial assessments. Likewise, a subject is considered a non-completer if she does not attend all scheduled trial visits and does not undergo the end-of-trial assessments.

The number of subjects completed and discontinued (including reason) will be summarised for the following trial parts: stimulation, triggering of final follicular maturation, oocyte retrieval, transfer, and pregnancy monitoring. This table will be produced for the full analysis set (FAS) overall and by AMH 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 that may 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 or investigator
- IMP regimen (treatment not in accordance with randomisation or non-compliance with IMP for two or more days)
- Non-compliance with the triggering criterion

The rating of protocol deviations as ‘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 unforeseen deviations deemed to impact the primary endpoint, these will also be rated as major deviations.

The list of major protocol deviations will be detailed and documented in the clean file document prior to database release. Major protocol deviations will be summarised and listed by subject for the intention-to-treat (ITT) analysis set.

9.4 Analysis Sets

Intention-to-Treat (ITT) Analysis Set

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

The Full Analysis Set (FAS)

The FAS is defined as all randomised and exposed subjects. Subjects will be analysed according to planned (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 AMH 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 only be produced for the FAS.

9.5.2 Trial Population Parameters

Demographics and other Baseline Characteristics

Demographics and other baseline characteristics (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 only be produced overall (i.e. not by AMH 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 only be produced overall (i.e. not by AMH stratum) for the FAS.

Concomitant Medication

Concomitant medications will be coded using the 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 the following parameters:

- 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 only be produced overall (i.e. not by AMH 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 (number of oocytes retrieved) is essential for the non-inferiority claim. The analyses of the important secondary endpoint and the other secondary endpoints are intended to provide additional characterisation of the safety and efficacy of FE 999049. However, non-inferiority does not need to be established for these endpoints.

Analysis and Presentation of Primary and Secondary Endpoints

Summary tables and treatment comparisons for the primary endpoint, the important secondary endpoint and the secondary efficacy endpoints will be presented overall and by AMH stratum for both the FAS and the PP analysis set. In addition, summary tables per age group will be provided as applicable.

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. Listings will only be produced for the FAS.

Multiplicity

No adjustment for multiplicity is required for the primary endpoint since there is only one hypothesis and one analysis set (FAS). Concerning the secondary endpoints, no formal adjustment for multiplicity will be utilised.

Missing Data

For the primary endpoint, number of oocytes retrieved, no missing data are expected. Subjects that discontinue stimulation, do not continue from stimulation to triggering of final follicular maturation, or do not undergo the oocyte retrieval procedure, will be regarded as having zero oocytes retrieved.

For the secondary endpoints, positive β hCG rate, clinical pregnancy rate, vital pregnancy rate, and implantation rate occurrence of missing data is unlikely but may occur in case the assessment was not done. For these endpoints, a subject's response is considered as 'negative' unless recorded as 'positive'. An exception to this is if a later observation confirms that a previous missing observation was in fact positive. If, for example, the β hCG test result is missing but clinical pregnancy is recorded as 'positive', then the β hCG test result will be imputed as 'positive'.

9.7.2 Primary Endpoint

The primary endpoint 'number of oocytes retrieved' will be analysed using an analysis of variance model with treatment and AMH stratum as fixed factors. The 2-sided 95% confidence limits for the mean treatment differences (FE 999049 - FOLLISTIM) will be calculated based on the fitted model for the FAS.

The hypotheses to be tested is:

$$H_0: OR_{FE\ 999049} - OR_{FOLLISTIM} \leq -3.0$$

$$H_1: OR_{FE\ 999049} - OR_{FOLLISTIM} > -3.0$$

where $OR_{FE\ 999049}$ and $OR_{FOLLISTIM}$ denote the number of oocytes retrieved with respective treatment.

The null hypothesis (H_0) will be tested against the alternative (H_1) by constructing a two-sided 95% confidence interval for the difference in number of oocytes retrieved. The null hypothesis will be rejected if the lower-limit of the two-sided 95% confidence interval is greater than the non-inferiority limit (-3.0 oocytes) for the FAS. In this case it will be claimed that FE 999049 is non-inferior to FOLLISTIM with respect to number of oocytes retrieved in women undergoing controlled ovarian stimulation.

Primary Endpoint: Number Oocytes Retrieved – Sensitivity Analysis and Additional Analysis and Descriptions

The FAS is the primary analysis population for this trial, and the analysis of the PP analysis set is only considered supportive for the application in Japan. In the EMA guideline "Points to consider on switching between superiority and non-inferiority"³¹, the FAS and the PP analysis sets are considered equally important. FE 999049 is a compound under global development. Therefore, for applications in countries applying the EMA guideline, Ferring would intend to demonstrate non-inferiority for both the FAS and PP analysis sets, and in such a case both would be considered as confirmatory analyses.

The primary analysis will be repeated using the PP analysis set. This sensitivity analysis will address the assay sensitivity of the primary analysis by excluding subjects with major protocol deviations, e.g. substantial non-compliance with randomised treatment.

To investigate the possibility for different treatment differences in the two AMH strata, an analysis of variance model will be fitted where the treatment-by-stratum interaction is included. In addition, subgroup analyses will be performed for the two AMH strata separately (using a simpler model with only treatment as factor). The trial is not powered to show non-inferiority in the two strata separately and these analyses should only be regarded as descriptive.

Additional descriptions will be made based only on subjects with oocytes retrieved. The purpose of this is purely descriptive.

9.7.3 Important Secondary Endpoint

Clinical Pregnancy Rate

Clinical pregnancy is defined as at least one gestational sac 5-6 weeks after transfer. The clinical pregnancy rate will be summarised for all subjects, for subjects with at least one oocyte retrieved and for subjects with transfer. The difference between FE 999049 and FOLLISTIM in clinical pregnancy rate will be estimated by constructing a two-sided 95% confidence interval. The Mantel-Haenszel method will be used to combine results across AMH strata. In brief, this corresponds to deriving a weighted average across AMH strata where the weight depends on the number of observations in each treatment group in each AMH stratum.

9.7.4 Secondary Endpoints

Secondary endpoints will be evaluated based on the FAS.

Positive β hCG Rate

Positive β hCG is defined as positive serum β hCG test 13-15 days after transfer. The positive β hCG rate will be summarised and analysed in a similar manner as the clinical pregnancy rate.

Vital Pregnancy Rate

Vital pregnancy is defined as at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer. The vital pregnancy rate will be summarised and analysed in a similar manner as the clinical pregnancy rate. 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

Implantation rate is defined as the number of gestational sacs 5-6 weeks after transfer divided by number of blastocysts transferred. The implantation rate will be summarised and analysed in a similar manner as the vital pregnancy rate. The transferred blastocysts are the experimental unit.

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

For this endpoint, treatment groups will be compared using a logistic regression model with treatment and AMH stratum as fixed factors. If both factors are significant then the possibility of an interaction will be investigated. 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 will be used as alternative.

The analysis will be performed for the composite endpoint and the separate components defined as: 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 blastocyst transfer cancellation due to excessive ovarian response/ OHSS risk.

Ovarian Response

The number of oocytes retrieved will be tabulated 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. For each definition the proportion of subjects will be tabulated. This endpoint will be analysed in a similar manner as the proportion of subjects with cycle cancellation.

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. This endpoint will be analysed in a similar manner as the proportion of subjects with cycle cancellation.

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, moderate or 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 this includes OHSS with onset before triggering and OHSS with onset during stimulation where triggering is not performed.

This endpoint will be tabulated in a similar manner as the proportion of subjects with cycle cancellation. Analyses will be performed for subjects with early OHSS, subjects with early OHSS of moderate or severe grade, subjects with preventive interventions for early OHSS, subjects with early OHSS and/or preventive interventions for early OHSS, and subjects with early OHSS of moderate or severe grade and/or preventive interventions for early OHSS.

The risk of preventive interventions for early OHSS and/or early OHSS is related to the ovarian response potential. 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.

For each endpoint two different logistic regression models will be fitted assuming an increasing risk with increasing AMH as follows:

$$\text{LOGIT}(\pi) = \beta_0 + \beta_1 \log(\text{AMH}),$$

where π denotes the risk and the β 's denotes the regression coefficients.

A comparison of the two treatment regimens with respect to the risk will be performed by adding treatment group as factor and the interaction term between treatment group and $\log(\text{AMH})$ to the model as follows:

$$\text{LOGIT}(\pi) = \beta_0 + \beta_1 \text{Treatment} + \beta_2 \log(\text{AMH}) + \beta_3 \text{Treatment} * \log(\text{AMH})$$

The two models will be compared using the likelihood ratio test. Adjusted odds ratio estimates (comparing FE 999049 to FOLLISTIM) and associated 95% Wald CI will be provided.

The adequacy of the model fits will be evaluated using the Hosmer-Lemeshow goodness-of-fit test. The estimated risks based on the models will be plotted as a function of AMH, i.e. overall and for each treatment group.

Late OHSS (Including OHSS of Moderate/Severe Grade)

OHSS will for each treatment group be tabulated by classification (mild, moderate, severe, moderate and 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 subjects with late OHSS, and subjects with late OHSS of moderate or severe grade.

OHSS (Early and/or Late) and/or Preventive Interventions for Early OHSS

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

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 van Elteren test stratified for AMH and within each AMH stratum using the Wilcoxon's test. Categorical data will be compared between treatment groups using a logistic regression model with treatment and AMH stratum as fixed factors and within each AMH stratum the chi-square test.

Fertilisation Rate

An oocyte is defined as fertilised if it is scored as 2 pronuclei at 19 hours. 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. Number of fertilised oocytes and fertilisation rate will be compared between treatment groups using van Elteren test stratified for AMH and within each AMH stratum using the Wilcoxon's test. Categorical data will be compared between treatment groups using a logistic regression model with treatment and AMH stratum as fixed factors and within each AMH stratum the chi-square 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 van Elteren

test stratified for AMH and within each AMH stratum using the Wilcoxon's test. Categorical data will be compared between treatment groups using a logistic regression model with treatment and AMH stratum as fixed factors and within each AMH stratum the chi-square test.

Number and Quality of Blastocysts on Day 5

The number of blastocysts on day 5 including a breakdown in quality scores will be tabulated including both summary statistics and frequency tables. The number of subjects with at least one good-quality blastocyst, i.e. of grade 3BB or higher, will be reported. Further, for subjects with oocytes retrieved, the rate of blastocysts to oocytes retrieved will be summarised overall and by quality score. Continuous data will be compared between treatment groups using van Elteren test stratified for AMH and within each AMH stratum using the Wilcoxon's test. Categorical data will be compared between treatment groups using a logistic regression model with treatment and AMH stratum as fixed factors and within each AMH stratum the chi-square 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. 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. For each parameter the change from baseline will be compared between treatment groups using an analysis of covariance model (ANCOVA). In this model change from baseline in ln-transformed measurements will be the dependent variable and the linear predictor will include treatment and AMH stratum as fixed factors and the baseline measurement (ln-transformed) as covariate. The estimated treatment ratio (FE 999049/FOLLISTIM) with 95% confidence interval will be presented accompanied by the p-value for test of no treatment difference.

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 van Elteren test stratified for AMH and within each AMH stratum using the Wilcoxon's test.

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 $\geq 5\%$ in any treatment group, and non-serious adverse events with an incidence of $\geq 5\%$ 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 screening. 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 to IMP

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).

Pen Malfunction

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

9.8 Additional Safety Evaluations

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.

Physical Examination

Physical examination at end-of-trial compared to baseline (screening) 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 (screening) 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.

9.9 Pregnancy Follow-up Information

For all subjects with a vital pregnancy, data will be collected on ongoing pregnancy. Ongoing pregnancy rate will be analysed similar to the pregnancy endpoints.

Pregnancy losses between clinical and ongoing pregnancy will also be tabulated. Furthermore, information on pregnancy outcome, e.g. live birth, stillbirth or late pregnancy loss will be tabulated.

Live birth rate will be summarised overall and by the same subgroups as the pregnancy endpoints.

Neonatal health data will be collected and tabulated at birth and at 4 weeks after birth for all children born.

9.10 Interim Analyses

No interim analysis is planned.

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 (date and time of oral information, date and time of handing out Informed Consent Documents, date and time of obtaining written informed consent)
- Eligibility for participation in the trial (documenting all inclusion / exclusion criteria)
- Relevant medical history, infertility history, menstrual history and reproductive history
- Visit dates
- Dates and daily dose of IMP administration
- Dates and daily doses of concomitant fertility medication
- Dates and daily doses of concomitant medication
- Date of oocyte retrieval and number of oocytes retrieved
- Date of transfer and number of blastocysts transferred

- Results of serum β hCG test and ultrasound at the clinical pregnancy visit
- Pregnancy progress, i.e. ongoing pregnancy information
- Pregnancy outcome, i.e. live birth or pregnancy loss, and neonatal health at birth and 4 weeks after birth
- Injection site reactions after IMP administration – diary
- Adverse events (description as well as start/stop date and time)
- Reason for discontinuation
- Event of unblinding, including the reason for unblinding

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

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

The source data for the endocrine parameters, clinical chemistry, haematology parameters and β hCG will be available at the central laboratory. Laboratory reports will be available at the sites.

The source data for the pregnancy follow-up data will be reports obtained from the subject's gynaecologist / obstetrician / paediatrician, and the subject's Maternal and Child Health Handbook (or a copy of the relevant pages) and information by the subject herself, or other sources, as applicable.

10.2 eCRF

An eCRF 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 Ferring 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 eCRF 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 equals a handwritten signature.

The eCRF 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 the Global Biometrics Department, 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 eCRF is revoked.

Errors occurring in the eCRF 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), Japanese Good Clinical Practice (J-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of eCRF 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 cooperate 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 monitoring visits per site will be determined through a risk-based approach depending on recruitment rate, observed data quality and overall site performance. The source data verification process and definition of key variables to be monitored will be described in detail in the Monitoring Plan for the trial.

For the pregnancy follow-up data, accuracy and verifiability of the eCRF entries compared to the reports obtained from the subject's gynaecologist / obstetrician / paediatrician the subject's Maternal and Child Health Handbook (or a copy of the relevant pages), information by the subject herself, or other sources, as applicable, will be ensured.

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 IRBs/ECs 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 and J-GCP including the Declaration of Helsinki 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 IRBs/ECs 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 IRB/EC.

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the eCRF 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 (Global Sponsor), and agreed upon by the investigator and Ferring prior to its implementation.

Amendments may be submitted for consideration to the approving IRBs/ECs 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 IRB/EC 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 eCRF. A log of protocol deviation reports will be available in the eCRF. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and 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 IRBs/ECs 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 (Global Sponsor) 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 International Committee of Medical Journal Editors (ICMJE) criteria (see current official version: <http://www.ICMJE.org>). 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 CRO 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 comments prior to submission. Comments will be given within four 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 public 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 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

IRBs/ECs will review the protocol, any potential protocol amendments and potential advertisements used for recruitment. The IRBs/ECs will review the Informed Consent Documents, their updates (if any), and any written materials given to the subjects. All IRB/EC 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 IRBs/ECs to which the protocol has been submitted and the name of the IRB/EC chairmen will be included in the Clinical Trial Report.

14.2 Regulatory Authority Notification

The sponsor will submit the clinical trial notification to the regulatory authorities in accordance with applicable regulatory requirements. Within the following 15 days of evaluation by the regulatory authority, no subject can be exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial and End-of-Trial Notification

The end-of-trial is defined as the date of the last visit of the last subject participating in the trial. Ferring shall notify the regulatory authorities of declaration of termination of the clinical trial.

For each clinical site, after confirmation of end of trial activities, the investigator must submit the end-of-trial notification to the head of institution. The head of institution must then notify the end-of-trial to IRBs/ECs and Ferring. A second end-of-trial notification is submitted by the investigator after completion of pregnancy follow-up if applicable in accordance with SOPs at each site.

In the case of early termination, Ferring must notify the end of the trial to the national regulatory authorities and the head of institutions immediately and at the latest within 15 days after the trial is halted, clearly explain the reasons, and describe follow-up measures, if any, taken for safety reasons. The head of institutions must notify to IRBs/ECs and investigator immediately.

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, J-GCP and applicable regulatory requirements.

14.5 Subject Information and Consent

The subject information describes both the clinical trial and the pregnancy follow-up data collection, and freely written consent to both parts will be obtained.

The investigator will obtain a freely given written consent from each subject and her partner after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial and pregnancy follow-up data collection which are relevant to the decision to participate. The subject and her partner must be given ample time to consider participation in the trial and acceptance of the pregnancy follow-up data collection before consents to both activities are obtained. The Informed Consent Documents (consisting of the Subject Information and the Informed Consent Form) must be signed and dated before the subject is exposed to any trial-related procedure, including screening tests for eligibility. The following persons must sign and date the Informed Consent Documents: the subject, the subject's partner, the investigator providing the explanation, the person providing the supplementary explanation, and the investigator obtaining the consent information.

The investigator will explain that the subject and her partner are completely free to refuse to enter the trial, refuse to agree to the pregnancy follow-up data collection or to withdraw their consent at any time, without any consequences for their further care and without the need to justify their decision.

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

If new information becomes available that may be relevant to the subject's and her partner's willingness to continue participation, a new Subject Information and Informed Consent Form will be forwarded to the IRBs/ECs (and regulatory authorities, if required). The subject and her partner will be informed about this new information and re-consent will be obtained.

Each subject will be informed that the monitor(s) and quality assurance auditor(s) mandated by Ferring, IRB/EC representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review her and her 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, as a minimum bearing the following information:

- That she is participating in a clinical trial
- That the trial involves controlled ovarian stimulation with recombinant FSH (randomisation to an FSH preparation under clinical development in Japan or to an FSH product approved in Japan)

- The name and phone number of the investigator

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

Additionally, 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 Compliance Reference Documents

The Declaration of Helsinki, the consolidated ICH-GCP, J-GCP and other national laws in Japan 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 and J-GCP consolidated guideline, and applicable local regulatory requirements. The investigator is responsible for adhering to the ICH-GCP and J-GCP responsibilities of investigators, for dispensing the IMP in accordance with the protocol or an amendment reviewed by the regulatory authorities, and for the secure storage and safe handling of medicinal products 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 eCRF 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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