FERRING
PHARMACEUTICALS

Protocol

Title of trial: A randomized, double-blind, placebo-controlled, parallel groups, multicenter trial investigating the efficacy and safety of FE 999049 in controlled ovarian stimulation in women aged 35-42 years undergoing assisted reproductive technology
NCT number: NCT03738618
Sponsor trial code: 000002
Date: Date of the original protocol: 25 April 2018 Date of the protocol amendment (1 amendment only): 19 March 2020

CLINICAL TRIAL PROTOCOL

A randomized, double-blind, placebo-controlled, parallel groups, multicenter trial investigating the efficacy and safety of FE 999049 in controlled ovarian stimulation in women aged 35-42 years undergoing assisted reproductive technology

Trial 000002

Recombinant FSH Investigation in the Treatment of Infertility with ART (RITA-2)

IND Number:	103040
Investigational Medicinal Product:	FE 999049, human recombinant follicle-stimulating hormone (rFSH), solution for subcutaneous injection
Indication:	Development of multiple follicles and pregnancy after fresh and/or cryopreserved embryo transfer in ovulatory women undergoing assisted reproductive technology (ART)
Phase:	3
Name and Address of Sponsor:	Ferring Pharmaceuticals, Inc. 100 Interpace Parkway Parsippany, NJ 07054 United States Tel: [redacted]
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A randomized, double-blind, placebo-controlled, parallel groups, multicenter trial investigating the efficacy and safety of FE 999049 in controlled ovarian stimulation in women aged 35-42 years undergoing assisted reproductive technology

Short title: Recombinant FSH Investigation in the Treatment of Infertility with ART (RITA-2)

SIGNATORY INVESTIGATOR

[redacted] M.D.
[redacted]

TRIAL SITES

Approximately 25 sites in the U.S.

PLANNED TRIAL PERIOD

First patient first visit:	Q3 2018
Last ongoing pregnancy after fresh and cryopreserved cycles:	Q2 2020
Last live birth after fresh and cryopreserved cycles:	Q4 2020
Last 1-year neonatal health follow-up after fresh and cryopreserved cycles:	Q4 2021

CLINICAL PHASE

3

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

The present trial is a randomized, placebo-controlled, phase 3 trial designed to demonstrate the efficacy and safety of the human-derived recombinant follicle-stimulating hormone (rFSH) preparation FE 999049 in women aged 35-42 years undergoing controlled ovarian stimulation for the development of multiple follicles for assisted reproductive technologies (ART). FE 999049 is expressed from a host cell line of human fetal retinal origin (PER.C6®), and is thereby the first rFSH from a human cell line. Ferring received marketing authorization approval for FE 999049 for the 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" from the European Commission in 2016. As of early

2018, FE 999049 is approved in 37 countries also including countries outside the European Union such as Australia, Switzerland, and Canada.

The primary endpoint is the cumulative ongoing pregnancy rate after the fresh cycle and cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation. The trial will be conducted in the U.S., and it is the first U.S. clinical registration trial with a cumulative endpoint covering outcomes from both the fresh and subsequent cryopreserved cycles and thus capturing the clinical efficacy of a single controlled ovarian stimulation cycle in a more complete manner.

OBJECTIVES

Primary Objective

- To demonstrate the efficacy and safety of FE 999049 in controlled ovarian stimulation

Secondary Objectives

- To establish the efficacy of FE 999049 in controlled ovarian stimulation with respect to pregnancy rates based on the fresh cycle and/or cryopreserved cycles
- To characterize the ovarian response, including follicular development, oocytes retrieved and endocrine profile, as well as the embryo development associated with controlled ovarian stimulation with FE 999049
- To characterize the safety profile of FE 999049 treatment, including adverse events, routine safety laboratory parameters, local tolerability and immunogenicity

ENDPOINTS

Primary Endpoint

- Cumulative ongoing pregnancy rate (at least one intrauterine viable fetus 8-9 weeks after transfer) after the fresh cycle and cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation

Secondary Endpoints

- Ongoing pregnancy rate (at least one intrauterine viable fetus 8-9 weeks after transfer) in the fresh cycle and in the cryopreserved cycles

- Time from start of controlled ovarian stimulation to ongoing pregnancy across the fresh and cryopreserved cycles, including duration and number of cycles before achieving ongoing pregnancy
- Ongoing implantation rate (number of intrauterine viable fetuses 8-9 weeks after transfer divided by number of blastocysts transferred) in the fresh cycle, the cryopreserved cycles and cumulatively
- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer) in the fresh cycle, the cryopreserved cycles and cumulatively
- Vital pregnancy rate (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer) in the fresh cycle, the cryopreserved cycles and cumulatively
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of blastocysts transferred) in the fresh cycle, the cryopreserved cycles and cumulatively
- Positive βhCG rate (positive serum βhCG test 10-14 days after transfer) in the fresh cycle, the cryopreserved cycles and cumulatively
- Proportion of subjects in the fresh cycle with triggering of final follicular maturation (with hCG, with GnRH agonist, and in total), cycle cancellation and transfer cancellation
- Number and size of follicles on stimulation day 5 and end-of-stimulation
- Number of oocytes retrieved and proportion of subjects with <4, 4-7, 8-14, 15-19 and ≥20 oocytes retrieved
- Number and percentage of metaphase II oocytes (only applicable for those inseminated using ICSI), number of fertilized oocytes, fertilization rate as well as number and quality of blastocysts on day 5 after oocyte retrieval
- Endometrial thickness and echogenicity pattern on stimulation day 5 and end-of-stimulation
- Oocyte utilization rate (number of blastocysts transferred or cryopreserved divided by the number of oocytes retrieved) and oocyte efficiency index (cumulative number of ongoing pregnancies per oocyte retrieved)
- Number and percentage of blastocysts surviving cryopreservation and number and percentage of blastocysts with re-expansion after cryopreservation
- Number of cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation, and number and percentage of cryopreserved cycles with blastocyst transfer
- Circulating concentrations of AMH, FSH, LH, estradiol, progesterone, inhibin A and inhibin B on stimulation day 5, end-of-stimulation and oocyte retrieval, and FSH population pharmacokinetic parameters
- Total gonadotropin dose, number of stimulation days and number of dose adjustments

- Frequency and intensity of adverse events
- Changes in circulating levels of clinical chemistry and hematology parameters and proportion of subjects with markedly abnormal changes
- Frequency and intensity of injection site reactions (redness, pain, itching, swelling and bruising) assessed by the subject during the stimulation period
- Proportion of subjects with treatment-induced anti-FSH antibodies, overall as well as with neutralizing capacity
- Frequency and intensity of immune-related adverse events
- Proportion of subjects with cycle cancellations due to an adverse event, including immune-related adverse events, or due to technical malfunctions of the administration pen
- Proportion of subjects with OHSS, overall and by grade, and proportion of subjects with moderate/severe OHSS
- Proportion of subjects hospitalized due to OHSS and proportion of subjects undergoing paracentesis due to OHSS
- Rate of multi-fetal gestation, biochemical pregnancy, spontaneous abortion, ectopic pregnancy (with and without medical/surgical intervention) and vanishing twins in the fresh cycle and in the cryopreserved cycles
- Technical malfunctions of the administration pen

POST-TRIAL INFORMATION

Post-trial Objectives

- To establish the efficacy of controlled ovarian stimulation with FE 999049 with respect to live birth rates based on the fresh cycle and/or cryopreserved cycles
- To characterize the neonatal health associated with controlled ovarian stimulation with FE 999049, including minor/major congenital anomalies at birth, 4 weeks and 1 year after birth in the fresh cycle and cryopreserved cycles

Post-trial Endpoints

- Cumulative live birth rate after the fresh cycle and cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation
- Live birth rate in the fresh cycle and in the cryopreserved cycles
- Live birth rate of singletons born at term (≥37 weeks of gestation) in the fresh cycle, the cryopreserved cycles and cumulatively

- Time from start of controlled ovarian stimulation to live birth of a singleton born at term across the fresh and cryopreserved cycles, including duration and number of cycles before achieving a live birth of a singleton born at term
- Rate of minor/major congenital anomalies at birth, 4 weeks and 1 year after birth in the fresh cycle and cryopreserved cycles

METHODOLOGY

This will be a randomized, double-blind, placebo-controlled, parallel groups, multicenter trial assessing the efficacy and safety of the rFSH preparation FE 999049 in subjects aged 35-42 years undergoing controlled ovarian stimulation for IVF / ICSI following a gonadotropin-releasing hormone (GnRH) antagonist protocol. The primary endpoint is the cumulative ongoing pregnancy rate after the fresh cycle and cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation. Thereby, the trial is designed to capture the clinical efficacy of a single controlled ovarian stimulation cycle in a more complete manner by following outcomes from both the fresh and subsequent cryopreserved cycles. Secondary endpoints include pharmacodynamic parameters of FSH action as well as efficacy and safety parameters related to controlled ovarian stimulation from the fresh cycle and subsequent cryopreserved cycles.

Controlled Ovarian Stimulation and Fresh Cycle

Subjects will be screened within 90 days prior to randomization for compliance with the inclusion and exclusion criteria. On day 2-3 of the menstrual cycle, subjects will be randomized in a 10:1 ratio to FE 999049 or placebo, and controlled ovarian stimulation will be initiated. FE 999049 and placebo will be self-administered subcutaneously using a pre-filled injection pen.

Subjects assigned to treatment with FE 999049 will receive a starting dose of 15 µg daily that is fixed for the first four stimulation days. Based on ovarian response, the dose may be adjusted by 3 µg, with dose increases implemented not more frequently than once every 2 days and dose decreases implemented per investigator's judgement. The minimum daily dose is 6 µg, and the maximum daily dose is 24 µg. Subjects assigned to placebo will have the injection pen dialed to the same value (dose) as if administered FE 999049. Subjects can be treated with FE 999049 or placebo for a maximum of 20 days. Coasting, use of dopamine agonist or any other drug to prevent early ovarian hyperstimulation syndrome (OHSS) with the exception of GnRH agonist for triggering of final follicular maturation, are not allowed.

During stimulation, subjects will be monitored by transvaginal ultrasound on stimulation days 1 and 5 and thereafter at least every second day. When the leading follicle reaches a diameter of ≥14 mm, transvaginal ultrasound will be performed daily. To prevent a premature luteinizing hormone (LH) surge, 250 µg GnRH antagonist (ganirelix acetate, GANIRELIX, Merck Sharp & Dohme) will be

initiated on stimulation day 5 for subjects with ≥3 follicles with a diameter of ≥10 mm. Subjects who fail to satisfy this GnRH antagonist criterion on stimulation day 5 will continue to be monitored at least every second day, and GnRH antagonist will be initiated when/if the criterion is met. The GnRH antagonist will be continued throughout the stimulation period. Triggering of final follicular maturation will be done as soon as ≥2 follicles with a diameter of ≥17 mm are observed. If there are <20 follicles with a diameter of ≥12 mm, 10,000 IU human chorionic gonadotropin (hCG; NOVAREL, Ferring Pharmaceuticals) will be administered. If there are ≥20 follicles with a diameter of ≥12 mm or the serum estradiol concentration is ≥3,000 pg/mL (local laboratory), 4.0 mg GnRH agonist (leuprolide acetate, LEUPROLIDE ACETATE, Sandoz) will be administered, and the fresh blastocyst transfer will be canceled. If after 8 days of stimulation, the investigator judges that the triggering criterion is not likely to be reached by day 20, the cycle will be canceled. If the triggering criterion is not met after 20 days of stimulation, the cycle will be canceled.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation, and oocytes will be inseminated by IVF or ICSI 4h (±1h) after retrieval. Rescue ICSI is not allowed. Fertilization and embryo development will be assessed. For subjects who undergo triggering of final follicular maturation with hCG and have <20 oocytes retrieved, transfer will be performed on day 5 (blastocyst stage) after oocyte retrieval. Subjects will have one blastocyst transferred if at least one good-quality (i.e. grade 3BB or above) blastocyst is available, or one or two blastocysts transferred if no good-quality blastocyst is available. Remaining blastocysts will be cryopreserved by vitrification. For subjects with ≥20 oocytes retrieved following hCG administration and for subjects who undergo triggering of final follicular maturation with GnRH agonist, no transfer will take place in the fresh cycle and blastocysts will instead be cryopreserved.

A subject who fails to reach the triggering criterion due to poor ovarian response or who has ≤3 oocytes retrieved will be offered medication and financial support for an ART cycle with an approved gonadotropin preparation outside of the trial.

Vaginal progesterone inserts (progesterone, ENDOMETRIN, Ferring Pharmaceuticals) 100 mg three times daily (TID) will be provided for luteal phase support from the day after oocyte retrieval and continuing until menses, negative β human chorionic gonadotropin (βhCG test), pregnancy loss or until ongoing pregnancy has been documented.

A serum βhCG test will be performed 10-14 days after transfer, clinical and vital pregnancy will be confirmed by transvaginal ultrasound 5-6 weeks after transfer, and ongoing pregnancy will be confirmed by transvaginal or abdominal ultrasound 8-9 weeks after transfer.

Blood samples will be collected for the purpose of evaluating the endocrine profile, clinical chemistry and hematology parameters as well as anti-FSH antibodies. Endocrine parameters will be assessed at screening, stimulation day 1, stimulation day 5, end-of-stimulation and oocyte retrieval. Clinical chemistry and hematology will be assessed at screening, end-of-stimulation, and end-of-cycle. Anti-FSH antibodies will be assessed on four occasions. The first sample will be taken at the

screening visit and will be used exclusively to re-establish the anti-drug antibody analytical assays. The subsequent three samples will be used for analysis of anti-FSH antibodies in individual subjects in the trial, and taken prior to dosing on stimulation day 1 and on two occasions post-dosing: 7-10 days after the last FE 999049 or placebo dose (this may coincide with the transfer visit) and 21-28 days after the last FE 999049 or placebo dose (this may coincide with the βhCG test visit). Subjects with a treatment-induced anti-FSH antibody response will be followed until the response has become negative, returned to the pre-dosing level, or for a maximum of 1 year after the second post-dose sampling. These subjects will be called in for assessments 2 months after the last post-dosing anti-FSH antibody sampling. If required, further assessments will be made at 3, 4, 6, 9 and 12 months after the last post-dosing anti-FSH antibody sampling. The follow-up will also be terminated if the subject commences a new treatment cycle with any gonadotropin preparation.

Local tolerability of FE 999049 and placebo following subcutaneous administration will be assessed by the subject three times daily: immediately, 30 minutes and 24 hours after each injection. The presence and intensity of injection site reactions will be rated as none, mild, moderate or severe. The assessments will be made throughout the stimulation period and recorded by the subject in a diary.

Cryopreserved Cycles

The trial covers cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation. Either a programmed or natural cycle can be selected for any cryopreserved cycle.

Any programmed cryopreserved cycle will be initiated within 3 days of start of menses with administration of estradiol (ESTRADIOL Tablets USP, Teva Pharmaceuticals USA, Inc.) 2 mg TID or 3 mg two times daily (BID) (or 3 mg TID at the investigator's discretion, if a daily dose of 6 mg has been shown to be insufficient in a previous cycle). If after 10-12 days of estradiol treatment the endometrial thickness is ≥8 mm, the subject will initiate daily intramuscular (IM) injections of 50 mg progesterone (PROGESTERONE Injection USP, West-ward Pharmaceutical Corp or Watson Pharma, Inc.) within the next 5 days in conjunction with the estradiol treatment. The ultrasound evaluation can be repeated within 7 days if the endometrial thickness criterion is not met. In programmed cryopreserved cycles, transfer of one or two blastocysts will occur on the 6th day from start of progesterone after warming and assessment of blastocyst survival and re-expansion. Subjects will have one blastocyst transferred if at least one good-quality (i.e. grade 3BB or above) blastocyst is available, or one or two blastocysts transferred if no good-quality blastocyst is available. Luteal phase support (estradiol and IM progesterone) will continue to be administered until menses, negative βhCG test, pregnancy loss or until ongoing pregnancy has been documented.

Any natural cryopreserved cycle will be initiated 7 days after start of menses with monitoring of urinary LH on a daily basis by the subject. The day after confirmation of LH surge by serum LH (local laboratory) and endometrial thickness of ≥8 mm, the subject will start luteal phase support with vaginal progesterone inserts (progesterone, ENDOMETRIN, Ferring Pharmaceuticals) 100 mg

TID. In a natural cryopreserved cycle, transfer of one or two blastocysts will occur on day LH surge +7 after warming and assessment of blastocyst survival and re-expansion. Subjects will have one blastocyst transferred if at least one good-quality (i.e. grade 3BB or above) blastocyst is available, or one or two blastocysts transferred if no good-quality blastocyst is available. Luteal phase support (vaginal progesterone) will continue to be administered until menses, negative βhCG test, pregnancy loss or until ongoing pregnancy has been documented.

Failure to achieve endometrial thickness ≥8 mm in the first cryopreserved cycle will result in cycle cancellation, and in the programmed cycles, administration of 100 mg IM progesterone (PROGESTERONE Injection USP, West-ward Pharmaceutical Corp or Watson Pharma, Inc.) to induce withdrawal bleeding. In subsequent cryopreserved cycles, blastocyst transfer can take place regardless of endometrial thickness at the investigator's discretion.

In both programmed and natural cryopreserved cycles, a serum βhCG test is performed 10-14 days after transfer, clinical and vital pregnancy will be confirmed by transvaginal ultrasound 5-6 weeks after transfer, and ongoing pregnancy will be confirmed by transvaginal or abdominal ultrasound 8-9 weeks after transfer.

After completion of the trial, the subject is allowed to use cryopreserved blastocysts in accordance with local guidelines and/or regulations.

Post-trial Activities

Post-trial activities cover pregnancy and neonatal health follow-up after the fresh cycle and cryopreserved cycles.

All subjects with an ongoing pregnancy obtained in the fresh cycle or in cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation will be followed until delivery to collect information on live birth rate. Furthermore, data will be collected on neonatal health, including minor/major congenital anomalies, at birth, 4 weeks and 1 year after birth.

Optional Exploratory Analyses

For subjects who have provided a separate informed consent, a blood sample and a saliva sample for potential future genome sequencing will be collected on stimulation day 1, and a tongue coat sample for potential future microbial profiling will be collected on stimulation day 1 and at the transfer visit(s) in the fresh and cryopreserved cycles, as applicable.

NUMBER OF SUBJECTS

It is planned to randomize 550 subjects in a 10:1 ratio to FE 999049 and placebo, i.e. 500 subjects assigned to FE 999049 and 50 subjects assigned to placebo. Blocked randomization will be utilized to distribute the placebo subjects randomly over the trial enrollment period. It is estimated that approximately 625 subjects should be screened to achieve 550 subjects eligible for the trial.

CRITERIA FOR INCLUSION / EXCLUSION

This trial will include women aged 35-42 years who are eligible for IVF or ICSI and who have undergone no more than one previous controlled ovarian stimulation cycle. They should have been diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or have partners diagnosed with male factor infertility. The allowed body mass index (BMI) is 17.5-38.0 kg/m^2. The exclusion criteria incorporate the contraindications for the use of gonadotropins and other concomitant fertility medications used in the trial. The complete list of inclusion and exclusion criteria is provided below.

Inclusion Criteria

1. Informed Consent Documents signed prior to any trial-related procedure.
2. In good physical and mental health in the judgement of the investigator.
3. Pre-menopausal females between the ages of 35 and 42 years. The subjects must be at least 35 years (including the 35th birthday) when they sign the informed consent and no more than 42 years (up to the day before the 43rd birthday) at the time of randomization.
4. Body mass index (BMI) between 17.5 and 38.0 kg/m^2 (both inclusive) at screening.
5. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility, eligible for in vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.
6. Documented history of infertility for at least 6 months before randomization (not applicable in case of tubal or severe male factor infertility, or when the use of donor sperm is indicated).
7. Regular menstrual cycles of 24-35 days (both inclusive).
8. Hysterosalpingography, hysteroscopy or saline infusion sonography, documenting a uterus consistent with expected normal function (e.g. no evidence of clinically interfering uterine fibroids defined as submucous fibroids of any size 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) at screening or within 1 year prior to screening.

9. Transvaginal ultrasound documenting presence and adequate visualization of both ovaries, without evidence of significant abnormality (e.g. enlarged ovaries which would contraindicate the use of gonadotropins) and normal adnexa (e.g. no hydrosalpinx) at screening. Both ovaries must be accessible for oocyte retrieval.
10. Early follicular phase (cycle day 2-4) serum levels of follicle-stimulating hormone (FSH) between 1 and 15 IU/L (results obtained within 3 months prior to randomization).
11. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests at screening or within 6 months prior to screening.
12. Willing to accept the blastocyst transfer policy for the fresh cycle and the cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation using blastocysts obtained in this trial, i.e. transfer of one blastocyst (if a good-quality blastocyst is available) or transfer of one or two blastocysts (if no good-quality blastocyst is available).
13. Willing and able to comply with trial procedures, including filling in the diary and attending scheduled visits as well as providing the neonatal health data up to 1 year after birth.

Exclusion Criteria

1. More than one previous controlled ovarian stimulation cycle for IVF/ICSI.
2. Known endometriosis stage III-IV (defined by the revised American Society for Reproductive Medicine (ASRM) classification, 2012).
3. Known history of anovulation.
4. One or more follicles ≥10 mm (including cysts) observed on the transvaginal ultrasound prior to randomization on stimulation day 1.
5. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy [excl. ectopic pregnancy] and before week 24 of pregnancy).
6. Known abnormal karyotype of subject or of her partner / sperm donor, as applicable, depending on source of sperm used for insemination in this trial. In case partner sperm will be used and the sperm production is severely impaired (concentration <1 million/mL), normal karyotype, including no Y-chromosome microdeletion, must be documented.
7. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
8. Known inherited or acquired thrombophilia.
9. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
10. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) with the exception of pharmacologically controlled sub-clinical hypothyroidism.
11. Known tumors of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
12. Known moderate or severe impairment of renal or hepatic function.

13. Any abnormal finding of clinical chemistry, hematology, thyroid-stimulating hormone (TSH) or prolactin, or vital signs at screening, which is judged clinically significant by the investigator.
14. Currently breast-feeding.
15. Undiagnosed vaginal bleeding.
16. Known abnormal cervical cytology of clinical significance observed within three years prior to randomization (unless the clinical significance has been resolved).
17. Findings at the gynecological examination at screening which preclude gonadotropin stimulation or are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
18. Pregnancy (negative urinary pregnancy tests must be documented at screening and prior to randomization) or contraindication to pregnancy.
19. Known current active pelvic inflammatory disease.
20. Use of fertility modifiers during the last menstrual cycle before randomization, including dehydroepiandrosterone (DHEA), metformin or cycle programming with oral contraceptives, progestogen or estrogen preparations.
21. Use of hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomization.
22. Known history of chemotherapy (except for gestational conditions) or radiotherapy.
23. Current or past (1 year prior to randomization) abuse of alcohol or drugs.
24. Current (last month) intake of more than 14 units of alcohol per week (one unit is equivalent to 12 fluid ounces of regular beer (5% alcohol), 5 fluid ounces of wine (12% alcohol), or 1.5 fluid ounces of 80 proof distilled spirits (40% alcohol).
25. Current or past (3 months prior to randomization) smoking habit of more than 10 cigarettes per day.
26. Known hypersensitivity to any active ingredient or excipients in the medicinal products used in this trial.
27. Any known clinical condition that would prevent the use of estrogen or progestin compounds.
28. Previous participation in this trial.
29. Use of any non-registered investigational drugs during the last 3 months prior to randomization.

MEDICINAL PRODUCTS

Investigational Medicinal Products (IMPs)

IMP name	*Drug type*	*Active ingredient; route of administration; concentration*	*Daily administration*
FE 999049	rFSH	FE 999049 in solution for subcutaneous injection in pre-filled injection pen; 72 µg/2.16 mL	Starting dose of 15 µg daily fixed for the first four stimulation days. Based on ovarian response, the dose may be adjusted by 3 µg, with dose increases implemented not more frequently than once every 2 days and dose decreases implemented per investigator's judgement. The minimum daily dose is 6 µg, and the maximum daily dose is 24 µg
Placebo to FE 999049	Placebo	Solution for subcutaneous injection in pre-filled injection pen	Pen will be dialed to the same value (dose) as if administered FE 999049

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

Controlled Ovarian Stimulation and Fresh Cycle

NIMP name	*Drug type*	*Active ingredient and route of administration*	*Dose*
GANIRELIX	GnRH antagonist	Ganirelix acetate in solution for subcutaneous injection	250 µg, daily injection
NOVAREL	hCG	Chorionic gonadotropin in solution for intramuscular injection	10,000 IU, single injection
LEUPROLIDE ACETATE	GnRH agonist	Leuprolide acetate in solution for subcutaneous injection	4.0 mg, single injection
ENDOMETRIN	Progesterone	Progesterone vaginal inserts for vaginal administration	100 mg, TID

Programmed Cryopreserved Cycles

NIMP name	*Drug type*	*Active ingredient and route of administration*	*Dose*
ESTRADIOL	Estradiol	Estradiol oral tablet	2 mg TID or 3 mg BID (or 3 mg TID at the investigator's discretion, if a daily dose of 6 mg has been shown insufficient in a previous cycle)
PROGESTERONE	Progesterone	Progesterone injection USP in sesame oil for intramuscular (IM) injection	50 mg, daily injection (100 mg, single injection for induction of withdrawal bleeding, as applicable)

Natural Cryopreserved Cycles

NIMP name	*Drug type*	*Active ingredient and route of administration*	*Dose*
ENDOMETRIN	Progesterone	Progesterone vaginal inserts for vaginal administration	100 mg, TID

DURATION OF TREATMENT

The maximum period of exposure to FE 999049 or placebo is 20 days.

STATISTICAL METHODS

The primary objective of this trial is to demonstrate the efficacy and safety of FE 999049 in controlled ovarian stimulation.

Sample Size

The proposed sample size of 550 subjects (FE 999049:placebo = 500:50) can adequately address both the efficacy and safety objectives of the trial:

- The cumulative ongoing pregnancy rate in the FE 999049-treated subjects aged 35-42 years is estimated to be approximately 30% according to results from clinical trials conducted in

the U.S. By comparison, the pregnancy rate in the placebo arm is expected not to exceed 3%, the monthly spontaneous pregnancy rate in infertile women. Therefore, the proposed sample size of 550 (FE 999049:placebo = 500:50) will provide at least 99% power for the primary efficacy comparison. Based on the estimated cumulative ongoing pregnancy rate, the cumulative live birth rate from the fresh and/or cryopreserved cycles is estimated to be approximately 27%, resulting in a power for the comparison of the cumulative live birth rate to be at least 99%.

- A key pharmacodynamic parameter in subjects aged 35-42 years is cycle cancellation due to poor follicular development, which may occur in approximately 5% of the population exposed to gonadotropins.
- The safety and tolerability of daily rFSH preparations as part of an ART treatment cycle have been well documented for the population studied in previous clinical trials. OHSS was reported to occur in 1.7% to 3.7% of the subjects, with moderate/severe OHSS occurring in 1.4% to 2.2% of the subjects. Other adverse events were pelvic pain, pelvic discomfort and headache, with those assessed to be related to trial treatments reported in 1.5% to 7.1% of the subjects.

  Table 1 shows that the planned sample size of 500 subjects exposed to FE 999049 provides a high probability to detect a rare adverse event or safety signal occurring in 0.5% or more subjects:

Table 1: Probabilities to Detect at Least One Rare Event

Incidence rate of rare event	Chance of detecting at least 1 event
0.5%	91.8%
0.6%	95.1%
1%	99.3%

Table 2 presents the margin width estimates of the 95% confidence intervals for a range of adverse event rates with the planned sample size.

Table 2: Estimated Margin Widths of 95% Confidence Intervals

Adverse event rate	Margin of error width estimate
5%	1.9%
10%	2.6%
15%	3.1%
20%	3.5%

Primary Endpoint

The hypothesis to be tested for the primary endpoint, cumulative ongoing pregnancy rate, is:

H_0: $\pi_{FE\ 999049} - \pi_{Placebo} \leq 0$ against the alternative H_A: $\pi_{FE\ 999049} - \pi_{Placebo} > 0$,

where $\pi_{FE\ 999049}$ and $\pi_{Placebo}$ denote the cumulative ongoing pregnancy rate after the fresh cycle and cryopreserved cycles in subjects aged 35-42 years treated with FE 999049 or placebo, respectively.

H_0 will be tested against the alternative H_A by constructing a two-sided 95% confidence interval for the difference in the cumulative ongoing pregnancy rates between the two treatment groups using the traditional Wald interval. If the lower limit of the two-sided 95% confidence interval is greater than 0, the null hypothesis H_0 will be rejected. In the case that the number of pregnancies observed in the placebo group is small (<5), then the one-sided Fisher's exact test will be used.

The primary endpoint will be determined as soon as the subject has achieved an ongoing pregnancy, or when all cryopreserved blastocysts have been exhausted, or after assessment of ongoing pregnancy status in cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation.

The efficacy analysis will be based on the modified intention-to-treat (mITT) analysis set, defined as all subjects who were randomized and received at least one dose of IMP (FE 999049 or placebo).

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LIST OF ABBREVIATIONS

βhCG	β unit of human chorionic gonadotropin
ASRM	American Society for Reproductive Medicine
AMH	anti-Müllerian hormone
ART	assisted reproductive technology
ATC	Anatomical Therapeutic Chemical Classification System
AUC	area under the time-concentration curve
BID	"bis in die", two times daily
BMI	body mass index
CHO	Chinese hamster ovary
CRO	contract research organization
DHEA	dehydroepiandrosterone
eCRF	electronic case report form
ESTHER	Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World
EU	European Union
FDA	Food and Drug Administration, USA
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
GMP	Good Manufacturing Practice
C_{max}	maximum concentration observed
hCG	human chorionic gonadotropin
HLT	high level term
ICH	International Conference on Harmonisation
ICSI	intracytoplasmic sperm injection
ID	identifier
Ig	immunoglobulin
IM	intramuscular
IMP	investigational medicinal product
IND	investigational new drug (application)

IRB	institutional review board
ITT	intention-to-treat
IU	international unit
IVF	in vitro fertilization
LH	luteinizing hormone
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
NCU	neonatal care unit
NICU	neonatal intensive care unit
NIMP	non-investigational medicinal product
NME	new molecular entity
OHSS	ovarian hyperstimulation syndrome
PCU	pediatric care unit
PGD	preimplantation genetic diagnosis
PGS	preimplantation genetic screening
PP	per-protocol
PT	preferred term
rFSH	recombinant follicle-stimulating hormone
RITA	Recombinant FSH Investigation in the Treatment of Infertility with ART
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SMQ	Standardised MedDRA Queries
SUSAR	suspected unexpected serious adverse reaction
TID	“ter in die”, three times daily
TSH	thyroid-stimulating hormone
U.S.	United States
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

FE 999049 is a human recombinant follicle-stimulating hormone (rFSH) belonging to the pharmaceutical class of gonadotropins. The current trial is intended to support the following indication being pursued for FE 999049 in the United States (U.S.): "Development of multiple follicles and pregnancy after fresh and/or cryopreserved embryo transfer in ovulatory women undergoing assisted reproductive technology (ART)".

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

Ferring received marketing authorization approval for FE 999049 for the 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" from the European Commission in 2016. As of early 2018, FE 999049 is approved in 37 countries also including countries outside the European Union (EU) such as Australia, Switzerland, and Canada.

There are no commercially available rFSH products derived from human cell lines in the U.S. The rFSH products currently approved in the U.S. for controlled ovarian stimulation in ovulatory women undergoing ART, e.g. follitropin alfa (GONAL-F, EMD Serono) and follitropin beta (FOLLISTIM, Merck), 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 α2,3 and α2,6 sialylation patterns, while CHO-derived rFSH products exclusively carry 2,3 linked sialic acid; this difference further contributes to the observed differences in glycosylation profiles between FE 999049 and CHO-derived rFSH products. For the purpose of clinical trials, FE 999049 is being treated as a new molecular entity (NME) by the Food and Drug Administration (FDA).

In total, eight previous clinical trials have been completed as part of the development program for FE 999049, covering four phase 1 trials, two phase 2 trials (one conducted in EU and one in Japan) and two phase 3 trials. A total of 1,927 subjects were included in these trials, of whom 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 patients were treated with FE 999049 in 1,012 treatment cycles. In addition, two phase 3 trials are currently ongoing; one in Japan and one in Pan-Asia.

The two completed phase 3 trials support the efficacy and safety of FE 999049 (ESTHER-1 / ESTHER-2: Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World). ESTHER-1 (Trial 000004)[1] was a randomized, controlled, assessor-blind trial conducted in 11 countries in women 18-40 years undergoing IVF/ICSI followed predominantly by single blastocyst transfer. The trial was designed to demonstrate non-inferiority of FE 999049 versus an approved recombinant FSH preparation (GONAL-F) with ongoing pregnancy rate and ongoing implantation rate as co-primary endpoints and also to prospectively evaluate the outcome of an individualized FE 999049 dosing regimen based on the serum anti-Müllerian hormone (AMH) concentration (measured by Elecsys® AMH Immunoassay, Roche Diagnostics) and body weight. The ESTHER-1 trial demonstrated non-inferiority of FE 999049 to GONAL-F for ongoing pregnancy rate and ongoing implantation rate for both the per-protocol (PP) and modified intention-to-treat (mITT; randomized and exposed) populations. For the overall trial population randomized and exposed to FE 999049, the ongoing pregnancy rate was 30.7% and the ongoing implantation rate was 35.2%. Among the women aged ≥35 years, the ongoing pregnancy rate with FE 999049 was 26.9% and the ongoing implantation rate was 30.9%. ESTHER-2 (Trial 000071)[2] was a safety immunogenicity trial covering up to two repeated treatment cycles in subjects who did not achieve an ongoing pregnancy in ESTHER-1. The trial confirmed the low immunogenicity potential with incidences of anti-FSH antibodies after exposure to FE 999049 of 0.8% in cycle 2 and 1.1% in cycle 3, which was not higher than the incidence of 1.1% in cycle 1 (ESTHER-1) or the incidence of pre-existing anti-FSH antibodies before exposure to FE 999049, which was 1.4%.[2] ESTHER-2 furthermore documented the efficacy of FE 999049 in repeated cycles with similar ongoing pregnancy rates between FE 999049 and GONAL-F as well as documented the safety of FE 999049 in an extended dose range up to 24 µg daily. Cryopreserved cycles using blastocysts derived from the controlled ovarian stimulation cycle in ESTHER-1 or ESTHER-2 and initiated within 1 year after start of stimulation in the subject's last stimulation cycle were followed and showed good efficacy of FE 999049 in cryopreserved cycles with an ongoing pregnancy rate of 32.3% per initiated cycle.

For further information regarding FE 999049, please refer to the current edition of the Investigator's Brochure.[3]

1.2 Scientific Justification for Conducting the Trial

A clinical development program for FE 999049 has been conducted outside the U.S. applying an individualized dosing regimen based on the patient's serum AMH concentration and body weight, and with a fixed dose throughout stimulation. As per FDA recommendations, the FE 999049 dosing regimen in phase 3 in the U.S. will not be based on AMH and body weight. Consequently, a phase 3 program is required for the U.S. to document the efficacy and safety of FE 999049 in the dosing regimen applied in the present trial (see section 3.5.4). The present phase 3 trial will be conducted in the U.S. and will meet the FDA requirements of exposure in the intended target population in the U.S.

The trial is designed to demonstrate the efficacy and safety of FE 999049 in women aged 35-42 years undergoing controlled ovarian stimulation for the development of multiple follicles and pregnancy after fresh and/or cryopreserved cycles.

Cryopreservation of surplus embryos for potential use after the fresh cycle is standard practice in ART treatment, and serves to improve chances of pregnancy from a single stimulation cycle. The development of the vitrification method for freezing of embryos has resulted in significant improvement in post-thaw embryo survival[4,5] with resulting ongoing pregnancy rates at least as good as those from fresh embryo transfer.[6,7] As a consequence, the percentage of transfer cycles involving cryopreserved embryos has steadily increased in the U.S. over the last years, with a doubling from 26.6% in 2011 to 52.4% in 2015.[8,9] The higher frequency of cryopreserved cycles also reflects an increase of "cryo-all" cycles (ovarian stimulation cycles with cryopreservation of all embryos), which when coupled to a gonadotropin-releasing hormone (GnRH) agonist trigger improves patient safety, by reducing the risk of early severe ovarian hyperstimulation syndrome (OHSS).[10] With the observed higher proportion of cryopreserved cycles, it becomes increasingly relevant to include these cycles in the assessment of pregnancy outcome following controlled ovarian stimulation. The present trial is the first U.S. clinical registration trial with a cumulative endpoint covering outcomes from both the fresh and subsequent cryopreserved cycles and thus capturing the clinical efficacy of a single controlled ovarian stimulation cycle in a more complete manner.

The primary endpoint of cumulative ongoing pregnancy rate will be based on the fresh cycle and cryopreserved cycles initiated within 12 months of the start of controlled ovarian stimulation. The cumulative nature of the primary endpoint selected for this trial reflects the evolution in clinical management of infertility. Contemporary approaches have also been applied to improve the safety of infertility treatment, with implementation of GnRH agonist triggering in patients with excessive response to reduce the risk of OHSS as well as implementation of a restrictive transfer policy guided by blastocyst quality and limited to no more than double blastocyst transfer to minimize the incidence of multiple gestation, thereby addressing the most common safety concerns.

1.3 Benefit / Risk Aspects

Benefits

Subjects who participate in this trial will undergo fertility screening procedures useful for their future clinical management. They will also be closely monitored and may benefit by achieving pregnancy. If subjects exhibit poor response to therapy (pre-established protocol criteria), they will be offered medication and financial support for an ART cycle with an approved gonadotropin preparation outside of the trial.

Risks

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

FE 999049

In the completed clinical trials of the development program for FE 999049, covering four phase 1 trials, two phase 2 trials and two phase 3 trials, a total of 1,927 subjects were included. 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 most frequently reported adverse drug reactions during 1,012 treatment cycles with FE 999049 in the phase 3 program 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 diarrhea, dizziness, mood swings, constipation, vomiting, abdominal discomfort, breast pain, breast tenderness, vaginal hemorrhage and somnolence. The incidence of injection site reactions was low after administration of FE 999049, and the severity of the injection site reactions was in general mild and comparable to that observed for GONAL-F.

Concerning well-known risks associated with the use of gonadotropin products for controlled ovarian stimulation, subjects are closely monitored throughout the trial. The most serious risk associated with gonadotropin treatment is OHSS. OHSS manifests itself with increasing degrees of severity. Moderate/severe OHSS is associated with marked ovarian enlargement, fluid accumulation and other complications. The incidence of early OHSS can be minimized by withholding gonadotropins, withholding human chorionic gonadotropin (hCG) or administering GnRH agonist for triggering of final follicular maturation. In the current trial, a GnRH agonist will be administered for triggering of final follicular maturation in subjects who might be at risk of OHSS (as per defined criteria), and transfer in the fresh cycle will be cancelled. In addition, subjects with excessive ovarian response after triggering with hCG (as per defined criteria) will also have transfer in the fresh cycle cancelled to

reduce the risk of late OHSS which would be amplified by pregnancy. In both instances, blastocysts will be cryopreserved. Very rare cases of serious allergic reactions have been reported after injection of gonadotropins. Concerning immunogenicity, the risk of treatment-induced anti-drug-antibodies following FE 999049 treatment is very low. In the ESTHER-1 and ESTHER-2 trials, the observed incidence of anti-FSH antibodies after treatment with FE 999049 was 1.1% in cycle 1, 0.8% in cycle 2 and 1.1% in cycle 3, which was not higher than the incidence of pre-existing anti-FSH antibodies of 1.4% before exposure of FE 999049.[2] In all instances, titers were undetectable or very low and without neutralizing capacity. No safety or efficacy concern has been identified with regard to immunogenicity with FE 999049.

Concomitant Fertility Medications

Subjects will receive concomitant fertility medication as part of the fresh cycle and the cryopreserved cycles in this trial. The most frequently reported adverse events with GnRH antagonist and hCG products are similar to those reported for FSH preparations and include headache, injection site reactions, pelvic pain, abdominal pain, abdominal distension and allergic reactions. Further, similar adverse events are expected after a single injection of GnRH agonist. Use of progesterone can cause skin reactions, fluid retention, somnolence, and arterial and venous thromboembolic events, including retinal thrombosis. Furthermore, the vaginal progesterone has been associated with vulvovaginal disorders and uterine spasms (at a frequency of 1-2%). Intramuscular progesterone can cause injection site reactions and sterile abscesses. Estrogen can cause breast tenderness, nausea, vomiting, skin reactions, headache, anaphylactic reactions, increase in blood pressure, and arterial and venous thromboembolic events, including retinal thrombosis. For detailed information on adverse events, please refer to the respective products Prescribing Information.

Procedures

Subjects will undergo standard ART treatment procedures (e.g. transvaginal ultrasound, blood sampling, oocyte retrieval and transfer). The transvaginal ultrasound examinations may be associated with mild discomfort and a very rare risk of infection. The blood sampling might be associated with mild discomfort, bruising and a very rare risk of infection. The oocyte retrieval procedure is associated with discomfort and very rarely infections and bleeding. The transfer procedure is associated with mild discomfort and very rarely infections and mild bleeding.

Pregnancy-related Events

Oocytes will be inseminated using IVF or ICSI and subsequently cultured to blastocyst stage (day 5 or later depending on embryo development). Although the frequency of cancellation of transfer is higher when culturing to blastocyst stage compared to culturing only to cleavage stage, the pregnancy rates per started cycle are at least as good with blastocyst transfer as with cleavage embryo transfer[11] and may even be higher.[12] A serious concern associated with ART cycles is the frequency of multiple

pregnancies / births and the related neonatal health problems. To minimize the incidence of multiple gestations, a restrictive transfer policy guided by blastocyst quality and limited to no more than double blastocyst transfer in both the fresh and the cryopreserved cycles is mandatory in this trial. 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 women 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, maternal and paternal genetic background, and sperm characteristics) and multiple pregnancies.

Benefits / Risks

Participation in this trial does not create extra risks for the subjects compared to routine controlled ovarian stimulation. The majority of subjects will receive active treatment, with an expected likelihood of conceiving similar to that in standard clinical practice. Subjects who exhibit poor response to therapy as per pre-established protocol criteria will be offered medication and financial support for an ART cycle with an approved gonadotropin preparation outside of the trial. In conclusion, the evaluation of benefits and risks indicate that participation in this trial is associated with a favorable benefit-risk ratio.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To demonstrate the efficacy and safety of FE 999049 in controlled ovarian stimulation

Secondary Objectives

- To establish the efficacy of FE 999049 in controlled ovarian stimulation with respect to pregnancy rates based on the fresh cycle and/or cryopreserved cycles
- To characterize the ovarian response, including follicular development, oocytes retrieved and endocrine profile, as well as the embryo development associated with controlled ovarian stimulation with FE 999049
- To characterize the safety profile of FE 999049 treatment, including adverse events, routine safety laboratory parameters, local tolerability and immunogenicity

Post-trial Objectives

- To establish the efficacy of controlled ovarian stimulation with FE 999049 with respect to live birth rates based on the fresh cycle and/or cryopreserved cycles
- To characterize the neonatal health associated with controlled ovarian stimulation with FE 999049, including minor/major congenital anomalies at birth, 4 weeks and 1 year after birth in the fresh cycle and cryopreserved cycles

2.2 Endpoints

Primary Endpoint

- Cumulative ongoing pregnancy rate (at least one intrauterine viable fetus 8-9 weeks after transfer) after the fresh cycle and cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation

Secondary Endpoints

- Ongoing pregnancy rate (at least one intrauterine viable fetus 8-9 weeks after transfer) in the fresh cycle and in the cryopreserved cycles
- Time from start of controlled ovarian stimulation to ongoing pregnancy across the fresh and cryopreserved cycles, including duration and number of cycles before achieving ongoing pregnancy
- Ongoing implantation rate (number of intrauterine viable fetuses 8-9 weeks after transfer divided by number of blastocysts transferred) in the fresh cycle, the cryopreserved cycles and cumulatively
- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer) in the fresh cycle, the cryopreserved cycles and cumulatively
- Vital pregnancy rate (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer) in the fresh cycle, the cryopreserved cycles and cumulatively
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of blastocysts transferred) in the fresh cycle, the cryopreserved cycles and cumulatively
- Positive βhCG rate (positive serum βhCG test 10-14 days after transfer) in the fresh cycle, the cryopreserved cycles and cumulatively
- Proportion of subjects in the fresh cycle with triggering of final follicular maturation (with hCG, with GnRH agonist, and in total), cycle cancellation and transfer cancellation
- Number and size of follicles on stimulation day 5 and end-of-stimulation
- Number of oocytes retrieved and proportion of subjects with <4, 4-7, 8-14, 15-19 and ≥20 oocytes retrieved
- Number and percentage of metaphase II oocytes (only applicable for those inseminated using ICSI), number of fertilized oocytes, fertilization rate as well as number and quality of blastocysts on day 5 after oocyte retrieval
- Endometrial thickness and echogenicity pattern on stimulation day 5 and end-of-stimulation
- Oocyte utilization rate (number of blastocysts transferred or cryopreserved divided by the number of oocytes retrieved) and oocyte efficiency index (cumulative number of ongoing pregnancies per oocyte retrieved)
- Number and percentage of blastocysts surviving cryopreservation and number and percentage of blastocysts with re-expansion after cryopreservation
- Number of cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation, and number and percentage of cryopreserved cycles with blastocyst transfer

- Circulating concentrations of AMH, FSH, LH, estradiol, progesterone, inhibin A and inhibin B on stimulation day 5, end-of-stimulation and oocyte retrieval, and FSH population pharmacokinetic parameters
- Total gonadotropin dose, number of stimulation days and number of dose adjustments
- Frequency and intensity of adverse events
- Changes in circulating levels of clinical chemistry and hematology parameters and proportion of subjects with markedly abnormal changes
- Frequency and intensity of injection site reactions (redness, pain, itching, swelling and bruising) assessed by the subject during the stimulation period
- Proportion of subjects with treatment-induced anti-FSH antibodies, overall as well as with neutralizing capacity
- Frequency and intensity of immune-related adverse events
- Proportion of subjects with cycle cancellations due to an adverse event, including immune-related adverse events, or due to technical malfunctions of the administration pen
- Proportion of subjects with OHSS, overall and by grade, and proportion of subjects with moderate/severe OHSS
- Proportion of subjects hospitalized due to OHSS and proportion of subjects undergoing paracentesis due to OHSS
- Rate of multi-fetal gestation, biochemical pregnancy, spontaneous abortion, ectopic pregnancy (with and without medical/surgical intervention) and vanishing twins in the fresh cycle and in the cryopreserved cycles
- Technical malfunctions of the administration pen

Post-trial Endpoints

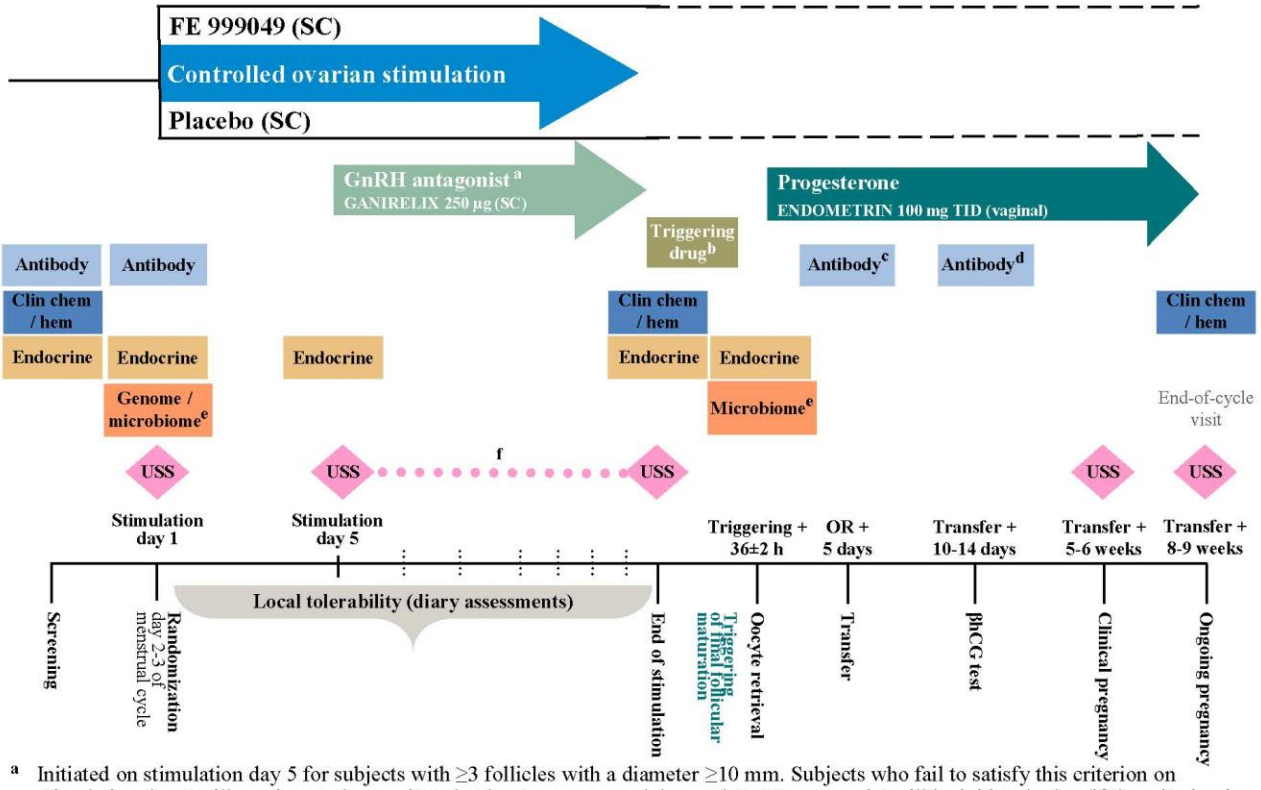
- Cumulative live birth rate after the fresh cycle and cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation
- Live birth rate in the fresh cycle and in the cryopreserved cycles
- Live birth rate of singletons born at term (≥37 weeks of gestation) in the fresh cycle, the cryopreserved cycles and cumulatively
- Time from start of controlled ovarian stimulation to live birth of a singleton born at term across the fresh and cryopreserved cycles, including duration and number of cycles before achieving a live birth of a singleton born at term
- Rate of minor/major congenital anomalies at birth, 4 weeks and 1 year after birth in the fresh cycle and cryopreserved cycles

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

A diagram illustrating the controlled ovarian stimulation and fresh cycle is presented in Figure 3-1.

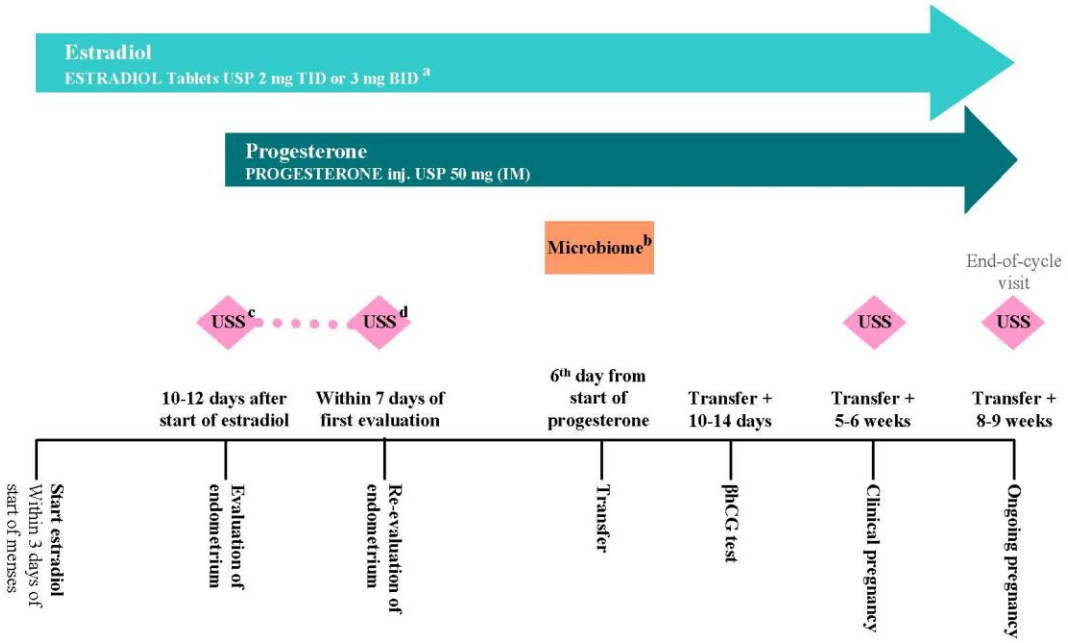


[a] Initiated on stimulation day 5 for subjects with ≥3 follicles with a diameter ≥10 mm. Subjects who fail to satisfy this criterion on stimulation day 5 will continue to be monitored at least every second day, and GnRH antagonist will be initiated when/if the criterion is met.
[b] hCG (NOVAREL 10,000 IU; SC) or GnRH agonist (LEUPROLIDE ACETATE 4 mg; SC), depending on number and size of follicles.
[c] 7-10 days after the last FE 999049 or placebo dose (may coincide with the transfer visit).
[d] 21-28 days after the last FE 999049 or placebo dose (may coincide with the βhCG test visit).
[e] Optional sampling for future potential exploratory analyses for subjects who have provided separate written informed consent.
[f] Stimulation days 1, 5 and thereafter at least every second day. When the leading follicle reaches a diameter of ≥14 mm, ultrasound will be performed daily.

SC: subcutaneous, OR: oocyte retrieval, TID: three times daily, USS: ultrasound sonography

Figure 3-1 Trial Diagram – Controlled Ovarian Stimulation and Fresh Cycle

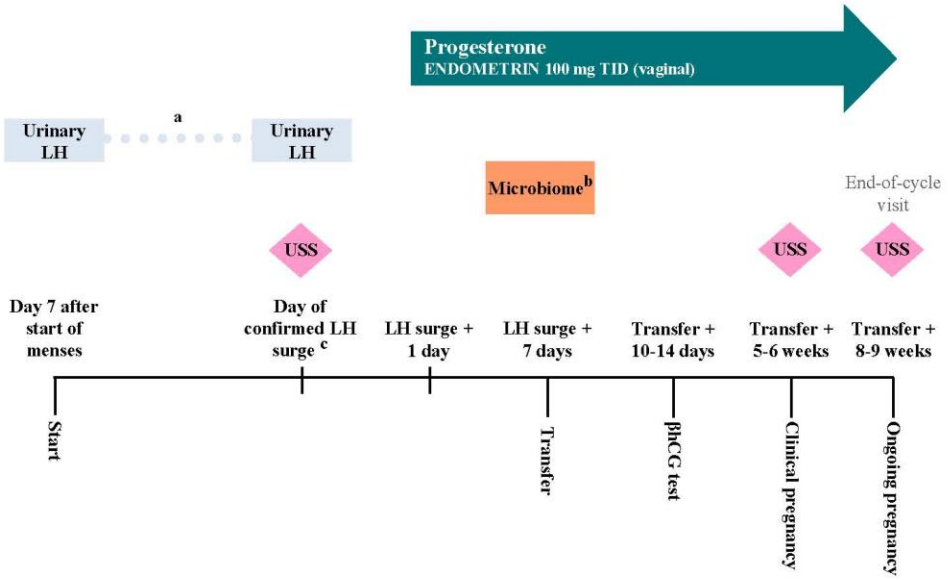
Diagrams illustrating the cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation are presented in Figure 3-2 for programmed cryopreserved cycles and in Figure 3-3 for natural cryopreserved cycles.



[a] 2 mg TID or 3 mg BID, or 3 mg TID at the investigator's discretion if a daily dose of 6 mg has been shown to be insufficient in a previous cycle.
[b] Optional sampling for future potential exploratory analyses for subjects who have provided separate written informed consent.
[c] If endometrial thickness is ≥8 mm, daily IM injections of 50 mg progesterone will be initiated within 5 days.
[d] Only for subjects with endometrial thickness <8 mm at the first evaluation. If endometrial thickness is ≥8 mm, subjects will initiate 50 mg IM progesterone within 5 days. Subjects who fail to achieve adequate endometrial thickness will discontinue estradiol and be administered 100 mg IM progesterone to induce withdrawal bleeding.

BID: two times daily, IM: intramuscular, TID: three times daily, USS: ultrasound sonography

Figure 3-2 Trial Diagram – Programmed Cryopreserved Cycles Initiated Within 12 Months From the Start of Controlled Ovarian Stimulation



[a] Monitoring of urinary LH will be done on a daily basis by the subject until confirmed LH surge.
[b] Optional sampling for future potential exploratory analyses for subjects who have provided separate written informed consent.
[c] Confirmation by serum LH.

LH: luteinizing hormone, TID: three times daily, USS: ultrasound sonography

Figure 3-3 Trial Diagram – Natural Cryopreserved Cycles Initiated Within 12 Months From the Start of Controlled Ovarian Stimulation

A diagram illustrating the post-trial activities for the fresh and cryopreserved cycles is shown in Figure 3-4.

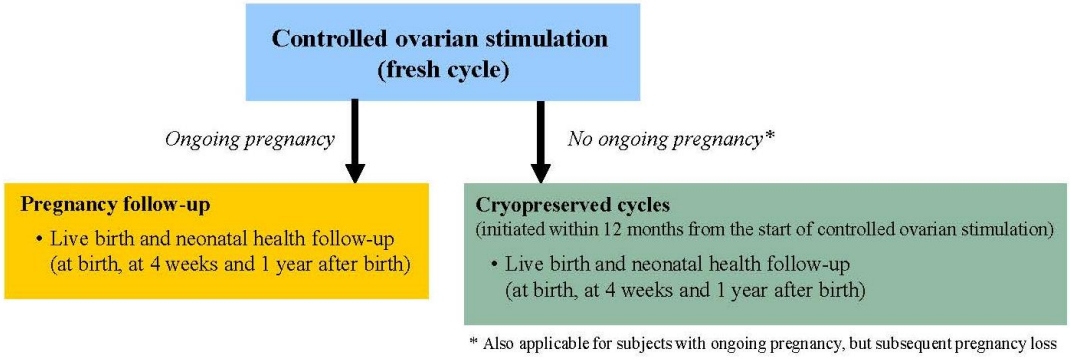


Figure 3-4 Trial Diagram – Post-trial Activities

3.1.2 Overall Design and Control Methods

This will be a randomized, double-blind, placebo-controlled, parallel groups, multicenter trial assessing the efficacy and safety of the rFSH preparation FE 999049 in subjects aged 35-42 years undergoing controlled ovarian stimulation for IVF / ICSI following a GnRH antagonist protocol. The primary endpoint is the cumulative ongoing pregnancy rate after the fresh cycle and cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation. Thereby, the trial is designed to capture the clinical efficacy of a single controlled ovarian stimulation cycle in a more complete manner by following outcomes from both the fresh and subsequent cryopreserved cycles. Secondary endpoints include pharmacodynamic parameters of FSH action as well as efficacy and safety parameters related to controlled ovarian stimulation from the fresh cycle and subsequent cryopreserved cycles.

Controlled Ovarian Stimulation and Fresh Cycle

Subjects will be screened within 90 days prior to randomization for compliance with the inclusion and exclusion criteria. On day 2-3 of the menstrual cycle, subjects will be randomized in a 10:1 ratio to FE 999049 or placebo, and controlled ovarian stimulation will be initiated. FE 999049 and placebo will be self-administered subcutaneously using a pre-filled injection pen.

Subjects assigned to treatment with FE 999049 will receive a starting dose of 15 µg daily that is fixed for the first four stimulation days. Based on ovarian response, the dose may be adjusted by 3 µg, with

dose increases implemented not more frequently than once every 2 days and dose decreases implemented per investigator's judgement. The minimum daily dose is 6 µg, and the maximum daily dose is 24 µg. Subjects assigned to placebo will have the injection pen dialed to the same value (dose) as if administered FE 999049. Subjects can be treated with FE 999049 or placebo for a maximum of 20 days. Coasting, use of dopamine agonist or any other drug to prevent early OHSS with the exception of GnRH agonist for triggering of final follicular maturation, are not allowed.

During stimulation, subjects will be monitored by transvaginal ultrasound on stimulation days 1 and 5 and thereafter at least every second day. When the leading follicle reaches a diameter of ≥14 mm, transvaginal ultrasound will be performed daily. To prevent a premature luteinizing hormone (LH) surge, 250 µg GnRH antagonist (ganirelix acetate, GANIRELIX, Merck Sharp & Dohme) will be initiated on stimulation day 5 for subjects with ≥3 follicles with a diameter of ≥10 mm. Subjects who fail to satisfy this GnRH antagonist criterion on stimulation day 5 will continue to be monitored at least every second day, and GnRH antagonist will be initiated when/if the criterion is met. The GnRH antagonist will be continued throughout the stimulation period. Triggering of final follicular maturation will be done as soon as ≥2 follicles with a diameter of ≥17 mm are observed. If there are <20 follicles with a diameter of ≥12 mm, 10,000 IU hCG (NOVAREL, Ferring Pharmaceuticals) will be administered. If there are ≥20 follicles with a diameter of ≥12 mm or the serum estradiol concentration is ≥3,000 pg/mL (local laboratory), 4.0 mg GnRH agonist (leuprolide acetate, LEUPROLIDE ACETATE, Sandoz) will be administered, and the fresh blastocyst transfer will be canceled. If after 8 days of stimulation, the investigator judges that the triggering criterion is not likely to be reached by day 20, the cycle will be canceled. If the triggering criterion is not met after 20 days of stimulation, the cycle will be canceled.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation, and oocytes will be inseminated by IVF or ICSI 4h (±1h) after retrieval. Rescue ICSI is not allowed. Fertilization and embryo development will be assessed. For subjects who undergo triggering of final follicular maturation with hCG and have <20 oocytes retrieved, transfer will be performed on day 5 (blastocyst stage) after oocyte retrieval. Subjects will have one blastocyst transferred if at least one good-quality (i.e. grade 3BB or above) blastocyst is available, or one or two blastocysts transferred if no good-quality blastocyst is available. Remaining blastocysts will be cryopreserved by vitrification. For subjects with ≥20 oocytes retrieved following hCG administration and for subjects who undergo triggering of final follicular maturation with GnRH agonist, no transfer will take place in the fresh cycle and blastocysts will instead be cryopreserved.

A subject who fails to reach the triggering criterion due to poor ovarian response or who has ≤3 oocytes retrieved will be offered medication and financial support for an ART cycle with an approved gonadotropin preparation outside of the trial.

Vaginal progesterone inserts (progesterone, ENDOMETRIN, Ferring Pharmaceuticals) 100 mg three times daily (TID) will be provided for luteal phase support from the day after oocyte retrieval and continuing until menses, negative β human chorionic gonadotropin (βhCG test), pregnancy loss or until ongoing pregnancy has been documented.

A serum βhCG test will be performed 10-14 days after transfer, clinical and vital pregnancy will be confirmed by transvaginal ultrasound 5-6 weeks after transfer, and ongoing pregnancy will be confirmed by transvaginal or abdominal ultrasound 8-9 weeks after transfer.

Blood samples will be collected for the purpose of evaluating the endocrine profile, clinical chemistry and hematology parameters as well as anti-FSH antibodies. Endocrine parameters will be assessed at screening, stimulation day 1, stimulation day 5, end-of-stimulation and oocyte retrieval. Clinical chemistry and hematology will be assessed at screening, end-of-stimulation, and end-of-cycle. Anti-FSH antibodies will be assessed on four occasions. The first sample will be taken at the screening visit and will be used exclusively to re-establish the anti-drug antibody analytical assays. The subsequent three samples will be used for analysis of anti-FSH antibodies in individual subjects in the trial, and taken prior to dosing on stimulation day 1 and on two occasions post-dosing: 7-10 days after the last FE 999049 or placebo dose (this may coincide with the transfer visit) and 21-28 days after the last FE 999049 or placebo dose (this may coincide with the βhCG test visit). Subjects with a treatment-induced anti-FSH antibody response will be followed until the response has become negative, returned to the pre-dosing level, or for a maximum of 1 year after the second post-dose sampling. These subjects will be called in for assessments 2 months after the last post-dosing anti-FSH antibody sampling. If required, further assessments will be made at 3, 4, 6, 9 and 12 months after the last post-dosing anti-FSH antibody sampling. The follow-up will also be terminated if the subject commences a new treatment cycle with any gonadotropin preparation.

Local tolerability of FE 999049 and placebo following subcutaneous administration will be assessed by the subject three times daily: immediately, 30 minutes and 24 hours after each injection. The presence and intensity of injection site reactions will be rated as none, mild, moderate or severe. The assessments will be made throughout the stimulation period and recorded by the subject in a diary.

Cryopreserved Cycles

The trial covers cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation. Either a programmed or natural cycle can be selected for any cryopreserved cycle.

Any programmed cryopreserved cycle will be initiated within 3 days of start of menses with administration of estradiol (ESTRADIOL Tablets USP, Teva Pharmaceuticals USA, Inc.) 2 mg TID or 3 mg two times daily (BID) (or 3 mg TID at the investigator's discretion, if a daily dose of 6 mg has

been shown to be insufficient in a previous cycle). If after 10-12 days of estradiol treatment the endometrial thickness is ≥8 mm, the subject will initiate daily intramuscular (IM) injections of 50 mg progesterone (PROGESTERONE Injection USP, West-ward Pharmaceutical Corp or Watson Pharma, Inc.) within the next 5 days in conjunction with the estradiol treatment. The ultrasound evaluation can be repeated within 7 days if the endometrial thickness criterion is not met. In programmed cryopreserved cycles, transfer of one or two blastocysts will occur on the 6th day from start of progesterone after warming and assessment of blastocyst survival and re-expansion. Subjects will have one blastocyst transferred if at least one good-quality (i.e. grade 3BB or above) blastocyst is available, or one or two blastocysts transferred if no good-quality blastocyst is available. Luteal phase support (estradiol and IM progesterone) will continue to be administered until menses, negative βhCG test, pregnancy loss or until ongoing pregnancy has been documented.

Any natural cryopreserved cycle will be initiated 7 days after start of menses with monitoring of urinary LH on a daily basis by the subject. The day after confirmation of LH surge by serum LH (local laboratory) and endometrial thickness of ≥8 mm, the subject will start luteal phase support with vaginal progesterone inserts (progesterone, ENDOMETRIN, Ferring Pharmaceuticals) 100 mg TID. In a natural cryopreserved cycle, transfer of one or two blastocysts will occur on day LH surge +7 after warming and assessment of blastocyst survival and re-expansion. Subjects will have one blastocyst transferred if at least one good-quality (i.e. grade 3BB or above) blastocyst is available, or one or two blastocysts transferred if no good-quality blastocyst is available. Luteal phase support (vaginal progesterone) will continue to be administered until menses, negative βhCG test, pregnancy loss or until ongoing pregnancy has been documented.

Failure to achieve endometrial thickness ≥8 mm in the first cryopreserved cycle will result in cycle cancellation, and in the programmed cycles, administration of 100 mg IM progesterone (PROGESTERONE Injection USP, West-ward Pharmaceutical Corp or Watson Pharma, Inc.) to induce withdrawal bleeding. In subsequent cryopreserved cycles, blastocyst transfer can take place regardless of endometrial thickness at the investigator's discretion.

In both programmed and natural cryopreserved cycles, a serum βhCG test is performed 10-14 days after transfer, clinical and vital pregnancy will be confirmed by transvaginal ultrasound 5-6 weeks after transfer, and ongoing pregnancy will be confirmed by transvaginal or abdominal ultrasound 8-9 weeks after transfer.

After completion of the trial, the subject is allowed to use cryopreserved blastocysts in accordance with local guidelines and/or regulations.

Post-trial Activities

Post-trial activities cover pregnancy and neonatal health follow-up after the fresh cycle and cryopreserved cycles.

All subjects with an ongoing pregnancy obtained in the fresh cycle or in cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation will be followed until delivery to collect information on live birth rate. Furthermore, data will be collected on neonatal health, including minor/major congenital anomalies, at birth, 4 weeks and 1 year after birth.

Optional Exploratory Analyses

For subjects who have provided a separate informed consent, a blood sample and a saliva sample for potential future genome sequencing will be collected on stimulation day 1, and a tongue coat sample for potential future microbial profiling will be collected on stimulation day 1 and at the transfer visit(s) in the fresh and cryopreserved cycles, as applicable.

3.1.3 Trial Schedule

First patient first visit:	Q3 2018
Last ongoing pregnancy after fresh and cryopreserved cycles:	Q2 2020
Last live birth after fresh and cryopreserved cycles:	Q4 2020
Last 1-year neonatal health follow-up after fresh and cryopreserved cycles:	Q4 2021

3.2 Planned Number of Trial Sites and Subjects

It is planned to randomize 550 subjects from approximately 25 sites in the U.S. It is estimated that approximately 625 subjects should be screened to achieve 550 subjects eligible for the trial.

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

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

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

The trial is designed to demonstrate the efficacy and safety of FE 999049 in controlled ovarian stimulation, taking into account the clinical outcome of the blastocysts transferred in the fresh cycle and subsequent cryopreserved cycles initiated within 12 months from start of controlled ovarian stimulation. It is the first U.S. clinical registration trial with a cumulative endpoint covering outcomes from both the fresh and subsequent cryopreserved cycles and thus capturing the clinical efficacy of a single controlled ovarian stimulation cycle in a more complete manner. Contemporary approaches have also been applied to improve the safety of infertility treatment, with implementation of GnRH agonist triggering in patients with excessive response to reduce the risk of OHSS as well as implementation of a restrictive transfer policy guided by blastocyst quality and limited to transfer of no more than two blastocyst to minimize the incidence of multiple gestation, thereby addressing the most common safety concerns.

The trial is a randomized, double-blind, placebo-controlled trial. The double-blind, placebo-controlled clinical trial has a long history as the standard for investigations of new drugs in the U.S., including those for the treatment of infertility (ClinicalTrials.gov NCT01976728). Moreover, the placebo response has not been rigorously characterized in the indicated trial population undergoing ART. A placebo solution has been manufactured for the purpose of this trial; it is indistinguishable from the active FE 999049 solution and is provided in identical pre-filled injection pens. Only placebo to FE 999049 is used in the trial and NIMPs will be supplied to subjects both in the placebo and FE 999049 treatment groups as per protocol description, facilitating a focused comparison of FE 999049 versus placebo to FE 999049. Clinical considerations have been made to maximize the probability for pregnancy in the placebo group, including that the criterion for starting the GnRH antagonist is based on follicular development and not fixed to a specific stimulation day. It will not be possible to distinguish between poor responders to FE 999049 and women in the placebo group, which supports the double-blinded design.

The double-blind design will ensure that the subjects, the investigator and other trial staff such as trial nurses, ultrasound technicians, local laboratory technicians and embryologists, as well as central laboratory personnel are blinded to individual treatment allocation throughout the trial, including the post-trial activities. Sponsor staff will also remain blinded to individual subject treatment allocation during the conduct of the trial.

The trial will be a multi-center 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 generalization of the results.

The trial covers a fresh cycle and cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation. Subjects will undergo controlled ovarian stimulation in a GnRH antagonist protocol with either FE 999049 or placebo. Subjects randomized to FE 999049 will receive a starting dose of 15 µg daily that is fixed for the first four stimulation days. Based on ovarian response, the dose may be adjusted by 3 µg, with dose increases implemented not more frequently than once every 2 days and dose decreases implemented per investigator's judgement. The minimum daily dose is 6 µg, and the maximum daily dose is 24 µg. For subjects randomized to placebo the injection pen will be dialed to the same value (dose) as if administered FE 999049. The selection of FE 999049 starting dose and dose adjustments is described in detail in section 3.5.4.

Oocytes will be inseminated by either IVF or ICSI reflecting the procedures used in the target population for the proposed indication, and embryo development parameters will be assessed. Blastocyst biopsy, assisted hatching, and preimplantation genetic diagnosis (PGD) / preimplantation genetic screening (PGS) are not allowed.

The present protocol has a restrictive transfer policy guided by blastocyst quality and limited to no more than double blastocyst transfer in both the fresh and the cryopreserved cycles. These criteria are stricter than the current American Society for Reproductive Medicine (ASRM) guidelines for embryo transfer but is justifiable to reduce the risk of multiple gestations.[13] There is increasing evidence suggesting that late stages of embryo progression are better predictors of clinical pregnancy than early embryo development parameters.[14] In good-prognosis patients, the transfer of blastocysts yields a higher live birth rate than that achieved with transfer of the same number of cleavage-stage embryos.

Concerning cryopreserved cycles, both the option of programmed cycles and natural cycles is being provided. The methodology has been standardized within each approach.

Subjects who achieve an ongoing pregnancy in the fresh cycle or in cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation will be followed until live birth to collect information on pregnancy outcome. In addition, neonatal health data will be collected at birth, 4 weeks and 1 year after birth.

3.5.2 Selection of Endpoints

The primary endpoint of cumulative ongoing pregnancy rate covers outcome from both the initial stimulated fresh cycle and the subsequent cryopreserved cycles and thereby captures the clinical efficacy of a single controlled ovarian stimulation cycle in a more complete manner.

It has been observed in previous clinical trials that most women who return to use their cryopreserved blastocysts undergo 2-3 cryopreserved cycles, and in this context 6 months would be a sufficient follow-up period if exclusively natural cycles were applied. In the present trial, the extent of

cryopreserved cycles is 12 months due to the option of the programmed cycle approach; this expansion to 12 months allows the trial to capture the greatest potential of the blastocysts derived from a single controlled ovarian stimulation cycle.

Positive βhCG, clinical pregnancy and vital pregnancy are included as secondary endpoints in the trial. Additional secondary endpoints include total dose of gonadotropins and pharmacodynamic parameters of FSH, such as ovarian response in terms of follicular development, endocrine profile and oocytes retrieved, and also oocyte / blastocyst quality, including blastocyst survival and re-expansion in the cryopreserved cycles. Follicular development and endocrine profile will be evaluated after the initial 4 days of ovarian stimulation (i.e. before any potential IMP dose adjustments and before start of the GnRH antagonist) as well as at the end of stimulation. The endocrine profile consists of AMH, FSH, LH, estradiol, progesterone, inhibin A and inhibin B.

Clinical safety endpoints cover adverse events, clinical chemistry and hematology parameters, local tolerability, immunogenicity, OHSS and pregnancy-related events (i.e. multi-fetal gestations, biochemical pregnancies, spontaneous abortions, ectopic pregnancies and vanishing twins). Pre-defined local tolerability reactions, i.e. redness, pain, itching, swelling and bruising, will be assessed by the subjects on three occasions after each subcutaneous IMP injection spanning from immediately to 24 hours after. Presence of anti-FSH antibodies will be evaluated 7-10 and 21-28 days after the last administration of FE 999049 for assessment of a potential immunoglobulin M (IgM) response and a fully mounted immunoglobulin G (IgG) immune response, respectively.[15] Technical malfunction of the pens used for administration of FE 999049 and placebo will also be monitored.

Live birth is the ultimate objective for couples starting infertility treatment. Nevertheless, it can be justified to use ongoing pregnancy rate as an endpoint indicative of the final treatment outcome as few pregnancy losses occur after confirmation of ongoing pregnancy.[16] In the ESTHER-1 trial, the absolute difference between live birth rate and ongoing pregnancy rate was -0.7% among the women aged ≥35 years. In the present trial, ongoing pregnancies in the fresh and cryopreserved cycles will be followed until live birth, allowing for evaluation of cumulative live birth rate. Neonatal health data at birth, 4 weeks and 1 year after birth will be collected for infants born after the fresh cycle and cryopreserved cycles to provide additional safety information.

In conclusion, the primary and secondary endpoints are appropriate for a phase 3 trial designed to document the efficacy and safety of a gonadotropin intended for controlled ovarian stimulation.

3.5.3 Blinding

The randomized, placebo-controlled, double-blind trial design will ensure random allocation of eligible subjects to the FE 999049 and placebo treatment groups. It will also allow for the unbiased evaluation

by the subject, the investigator and other site staff such as trial nurses, ultrasound technicians, local laboratory technicians and embryologists, as well as central laboratory personnel.

Sponsor staff (e.g., field monitor, data manager, statistician, clinical trial manager, medical writer, pharmacovigilance physician, pharmacovigilance manager, medical monitor and medical officer) will also be blinded to treatment allocation until breaking of the blind.

The pre-filled injection pens and solutions of FE 999049 and placebo will be identical in appearance to maintain the blinding. Central laboratory analysis results of endocrine parameters, including serum FSH, from blood samples drawn after stimulation day 1 will not be available to site or sponsor staff until after unblinding of the trial, and local laboratory analysis of serum FSH is prohibited.

The blind will be broken when the trial database is declared clean and released to the statistician.

3.5.4 Selection of Doses in the Trial

3.5.4.1 FE 999049

The dosing regimen for FE 999049 in women aged ≥35 years is a starting dose of 15 µg daily for the first four stimulation days, after which dose adjustments of 3 µg based on the individual subject's ovarian response can be implemented, with the minimum daily dose being 6 µg and the maximum daily dose being 24 µg.

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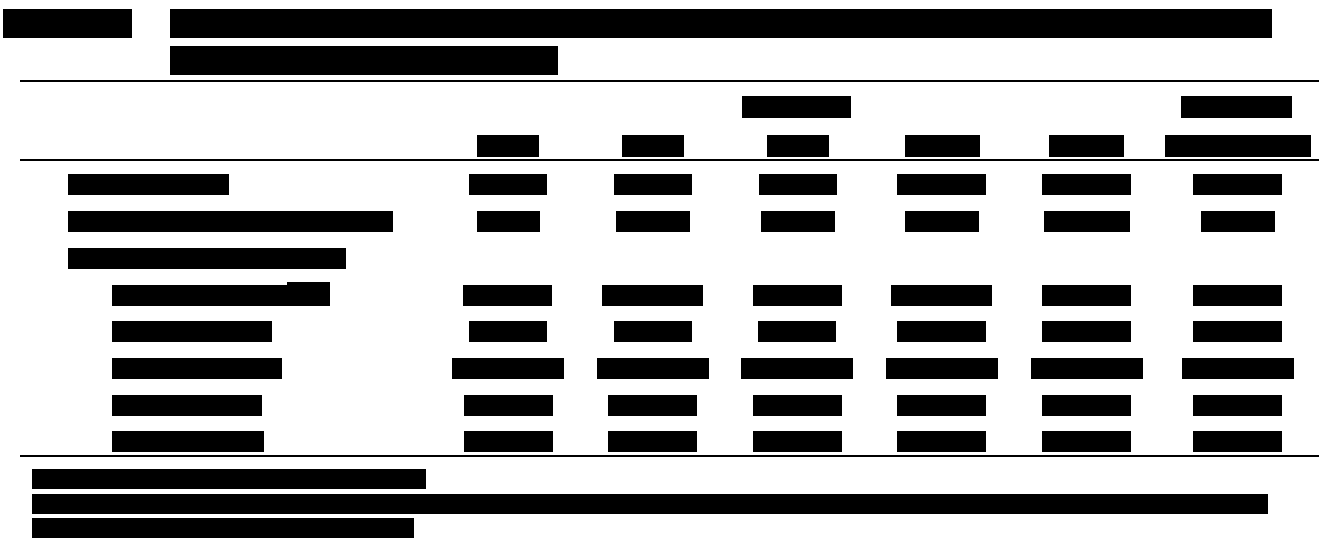

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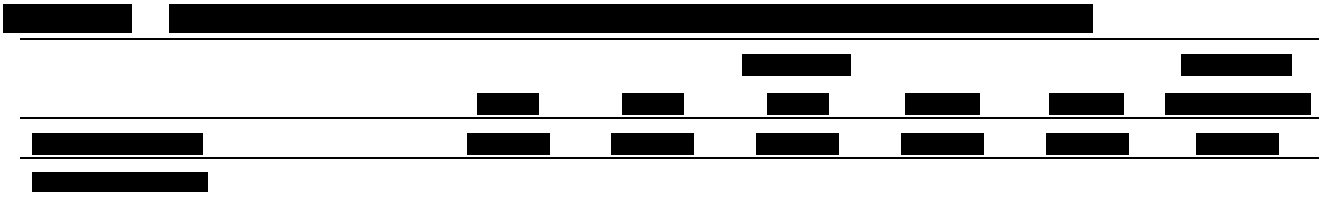

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3.5.4.2 Concomitant Fertility Medication

Controlled Ovarian Stimulation and Fresh Cycle

The doses and overall treatment regimens for the GnRH antagonist (GANIRELIX), hCG (NOVAREL) and progesterone (ENDOMETRIN) products are in line with the recommendations in the respective products' Prescribing Information and/or standard clinical practice within ART. The GnRH agonist (LEUPROLIDE ACETATE) is included as an option for triggering of final follicular maturation in subjects with ≥20 follicles with a diameter of ≥12 mm or serum estradiol concentration ≥3,000 pg/mL as this approach is associated with a decreased risk of early severe OHSS despite high ovarian response.[20,21,22,23,24] 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.[25,26,27] Although subjects with GnRH agonist triggering do not undergo blastocyst transfer in the fresh cycle, the trial design with cryopreserved cycles and a cumulative ongoing pregnancy endpoint means that the efficacy evaluation is not compromised.

Cryopreserved Cycles

For the programmed cryopreserved cycles, the doses and treatment regimens for estradiol (ESTRADIOL Tablets USP) and progesterone (PROGESTERONE Injection USP) are in line with standard clinical practice within ART.

For the natural cryopreserved cycles, the dose of progesterone (ENDOMETRIN) is in line with the Prescribing Information.

3.5.5 Selection of the Trial Population

This trial will include women aged 35-42 years who are eligible for IVF or ICSI and who have undergone no more than one previous controlled ovarian stimulation cycle. The subjects have been diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or have partners diagnosed with male factor infertility. The allowed body mass index (BMI) is 17.5-38.0 kg/m^2, thus including underweight, normal weight, overweight and obese subjects.

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

3.5.6 Follow-up Procedures

Post-trial Activities

Post-trial activities cover pregnancy and neonatal health follow-up at birth, 4 weeks and 1 year after birth, after the fresh cycle and all cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation.

It is foreseen that the long extent of follow-up will pose challenges. While the ongoing pregnancy visit will take place at the trial sites, later pregnancy monitoring and delivery does not occur at the trial site but at the subject's general practitioner, OB/GYN specialist, hospital etc. Likewise, neonatal health follow-up is not performed at the trial sites. Efforts will be made to capture the follow-up information described in the protocol by use of contact logs and other measures, but instances of missing data especially as the follow-up period advances cannot be ruled out.

Immunogenicity Follow-up

As a safety precaution, subjects with treatment-induced anti-FSH antibody response will be followed until the response has become negative or returned to the pre-dosing level, or for a maximum of 1 year after the second post-dose sampling. The follow-up procedure involves frequent visits/samples in the

beginning after detecting a positive signal, followed by longer intervals later in the follow-up period. The follow-up will be terminated if the subject commences a new treatment cycle with any gonadotropin preparation.

Access to Therapy after End-of-trial

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

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

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

1. Informed Consent Documents signed prior to any trial-related procedure.
2. In good physical and mental health in the judgement of the investigator.
3. Pre-menopausal females between the ages of 35 and 42 years. The subjects must be at least 35 years (including the 35th birthday) when they sign the informed consent and no more than 42 years (up to the day before the 43rd birthday) at the time of randomization.
4. Body mass index (BMI) between 17.5 and 38.0 kg/m^2 (both inclusive) at screening.
5. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility, eligible for in vitro fertilization (IVF) and/or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.
6. Documented history of infertility for at least 6 months before randomization (not applicable in case of tubal or severe male factor infertility, or when the use of donor sperm is indicated).
7. Regular menstrual cycles of 24-35 days (both inclusive).
8. Hysterosalpingography, hysteroscopy or saline infusion sonography, documenting a uterus consistent with expected normal function (e.g. no evidence of clinically interfering uterine fibroids defined as submucous fibroids of any size 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) at screening or within 1 year prior to screening.
9. Transvaginal ultrasound documenting presence and adequate visualization of both ovaries, without evidence of significant abnormality (e.g. enlarged ovaries which would contraindicate the use of gonadotropins) and normal adnexa (e.g. no hydrosalpinx) at screening. Both ovaries must be accessible for oocyte retrieval.
10. Early follicular phase (cycle day 2-4) serum levels of follicle-stimulating hormone (FSH) between 1 and 15 IU/L (results obtained within 3 months prior to randomization).
11. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests at screening or within 6 months prior to screening.
12. Willing to accept the blastocyst transfer policy for the fresh cycle and the cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation using blastocysts obtained in this trial, i.e. transfer of one blastocyst (if a good-quality blastocyst is available) or transfer of one or two blastocysts (if no good-quality blastocyst is available).

13. Willing and able to comply with trial procedures, including filling in the diary and attending scheduled visits as well as providing the neonatal health data up to 1 year after birth.

4.1.2 Exclusion Criteria

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

1. More than one previous controlled ovarian stimulation cycle for IVF/ICSI.
2. Known endometriosis stage III-IV (defined by the revised ASRM classification, 2012[28]).
3. Known history of anovulation.
4. One or more follicles ≥10 mm (including cysts) observed on the transvaginal ultrasound prior to randomization on stimulation day 1.
5. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy [excl. ectopic pregnancy] and before week 24 of pregnancy).
6. Known abnormal karyotype of subject or of her partner / sperm donor, as applicable, depending on source of sperm used for insemination in this trial. In case partner sperm will be used and the sperm production is severely impaired (concentration <1 million/mL), normal karyotype, including no Y-chromosome microdeletion, must be documented.
7. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
8. Known inherited or acquired thrombophilia.
9. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
10. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) with the exception of pharmacologically controlled sub-clinical hypothyroidism.
11. Known tumors of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
12. Known moderate or severe impairment of renal or hepatic function.
13. Any abnormal finding of clinical chemistry, hematology, thyroid-stimulating hormone (TSH) or prolactin, or vital signs at screening, which is judged clinically significant by the investigator.
14. Currently breast-feeding.
15. Undiagnosed vaginal bleeding.
16. Known abnormal cervical cytology of clinical significance observed within three years prior to randomization (unless the clinical significance has been resolved).
17. Findings at the gynecological examination at screening which preclude gonadotropin stimulation or are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
18. Pregnancy (negative urinary pregnancy tests must be documented at screening and prior to randomization) or contraindication to pregnancy.

19. Known current active pelvic inflammatory disease.
20. Use of fertility modifiers during the last menstrual cycle before randomization, including dehydroepiandrosterone (DHEA), metformin or cycle programming with oral contraceptives, progestogen or estrogen preparations.
21. Use of hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomization.
22. Known history of chemotherapy (except for gestational conditions) or radiotherapy.
23. Current or past (1 year prior to randomization) abuse of alcohol or drugs.
24. Current (last month) intake of more than 14 units of alcohol per week (one unit is equivalent to 12 fluid ounces of regular beer (5% alcohol), 5 fluid ounces of wine (12% alcohol), or 1.5 fluid ounces of 80 proof distilled spirits (40% alcohol).
25. Current or past (3 months prior to randomization) smoking habit of more than 10 cigarettes per day.
26. Known hypersensitivity to any active ingredient or excipients in the medicinal products used in this trial.
27. Any known clinical condition that would prevent the use of estrogen or progestin compounds.
28. Previous participation in this trial.
29. Use of any non-registered investigational drugs during the last 3 months prior to randomization.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

The participating subjects will be recruited among the patients attending the sites included in the trial. Advertisements may be used if approved by the Institutional Review Boards (IRBs).

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 Randomization

On day 2-3 of the menstrual cycle, subjects will be randomized in a 10:1 ratio to FE 999049 or placebo, and ovarian stimulation will be initiated.

Randomization is performed centrally through the electronic case report form (eCRF). When a subject is randomized to the trial, she will always be assigned to the lowest available randomization number. An independent statistician will prepare a computer-generated randomization list and randomization is performed in blocks to distribute placebo subjects randomly over the trial enrollment period. The block

size will only be revealed when the trial database is declared clean and released to the statistician. Details of subject enrolment will be recorded on a subject identification code list for all randomized subjects kept by the investigator.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

The subjects must not have used fertility modifiers, including DHEA, metformin or cycle programming with oral contraceptives, progestogen or estrogen preparations, or hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomization.

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

4.3.2 Prohibited Therapy

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

During the trial it is prohibited to administer any other fertility medication than the ones provided as part of the trial regimen. Metformin use as an ongoing treatment during the trial is not permitted, nor is the use of dopamine agonist as an intervention to prevent OHSS.

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

Every subject has the right to withdraw from the trial at any time for any reason, without the need to justify her decision. A subject's participation is to terminate immediately upon her request. However, the investigator should record the reason for the subject’s withdrawal, if possible.

Randomized subjects will be asked to attend an end-of-cycle visit, which will include all procedures outlined in section 6.1.12 for the fresh cycle, in section 6.2.1.7 for programmed cryopreserved cycles, and in section 6.2.2.8 for natural cryopreserved cycles.

The subject can also be withdrawn from the trial at any time at the discretion of the investigator. 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.

A subject that withdraws from the trial will not be replaced.

Withdrawal of Consent

If the subject withdraws her consent, data collected up to withdrawal will remain in the database, but no further data will be collected. Samples and recordings obtained before withdrawal may be analyzed. 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 Trial Stopping Criteria

Occurrence of the following adverse events or abnormal laboratory values may warrant consideration of trial termination:

- Life-threatening serious adverse events (SAEs) with suspected causality to the IMP, including but not limited to OHSS (section 8.3.1)
- Formation of treatment-induced neutralizing antibodies to FSH

The internal Safety Management Team at the sponsor will review each occurrence and provide a recommendation as to whether to terminate the trial. The responsibilities and composition of the internal Safety Management Team are provided in a separate charter document, available before the first subject's first visit.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Products

Subjects will be randomized in a 10:1 ratio to FE 999049:placebo. The dosing regimen for FE 999049 and placebo is described in Table 5-1.

Table 5-1 FE 999049 and Placebo Dosing Regimen

IMP	Dosing regimen
FE 999049	Starting dose of 15 µg daily fixed for the first four stimulation days. Based on the ovarian response, the dose may be adjusted by 3 µg, with dose increases implemented not more frequently than once every 2 days and dose decreases implemented per investigator's judgement. The minimum daily dose is 6 µg, and the maximum daily dose is 24 µg. Subcutaneous injection in the lower part of the abdomen.
Placebo to FE 999049	Pen will be dialed to the same value (dose) as if administered FE 999049. Subcutaneous injection in the lower part of the abdomen.

The investigational medicinal products (IMPs) will be self-administered by the subject as a daily subcutaneous injection in the lower part of the abdomen using a pre-filled injection pen. The start and end dates as well as daily dose of IMP will be recorded by the subject in a diary. To minimize local injection site reactions, it is advisable to change the injection site regularly, i.e. between the right and left lower part of the abdomen.

Administration of IMP after reaching the triggering criterion is not allowed.

For information on warnings and precautions, please refer to the Investigator's Brochure for FE 999049.[3]

5.1.2 Non-investigational Medicinal Products

The non-investigational medicinal products (NIMPs) are listed in Table 5-2 for the controlled ovarian stimulation and fresh cycle, in Table 5-3 for the programmed cryopreserved cycles, and in Table 5-4 for the natural cryopreserved cycles.

Table 5-2 NIMP Dosing Regimen – Controlled Ovarian Stimulation and Fresh Cycle

NIMP	Trade name (active ingredient)	Dosing regimen
GnRH antagonist	GANIRELIX (ganirelix acetate)	250 µg, daily injection Will be initiated on stimulation day 5 for subjects with ≥3 follicles with a diameter of ≥10 mm (subjects who fail to satisfy this GnRH antagonist criterion on stimulation day 5 will continue to be monitored at least every second day, and GnRH antagonist will be initiated when/if the criterion is met); will be continued throughout the stimulation period. The timing of the GnRH antagonist injections should be aligned with the IMP injections. Subcutaneous injection in the upper thigh (to distinguish from IMP injection site)
hCG	NOVAREL (chorionic gonadotropin)	10,000 IU, single injection Will be administered for triggering of final follicular maturation if there are <20 follicles with a diameter of ≥12 mm. 2 x 5,000 IU reconstituted in one vial with diluent. Intramuscular injection
GnRH agonist	LEUPROLIDE ACETATE (leuprolide acetate)	4.0 mg, single injection Will be administered for triggering of final follicular maturation if there are ≥20 follicles with a diameter of ≥12 mm or the serum estradiol concentration is ≥3,000 pg/mL (local laboratory). Subcutaneous injection
Progesterone	ENDOMETRIN (progesterone)	100 mg, TID Will be initiated the day after oocyte retrieval; will be continued until menses, negative βhCG, pregnancy loss or until ongoing pregnancy has been documented. Vaginal administration

Table 5-3 NIMP Dosing Regimen – Programmed Cryopreserved Cycles

NIMP	Trade name (active ingredient)	Dosing regimen
Estradiol	ESTRADIOL Tablets USP (estradiol)	2 mg TID or 3 mg BID (or 3 mg TID at the investigator's discretion, if a daily dose of 6 mg has been shown insufficient in a previous cycle). Will be initiated within 3 days of start of menses; will be continued until menses, negative βhCG, pregnancy loss or until ongoing pregnancy has been documented. Oral administration
Progesterone	PROGESTERONE Injection USP (progesterone)	50 mg, daily injection Will be initiated within 5 days of confirmed endometrial thickness ≥8 mm; will be continued until menses, negative βhCG, pregnancy loss or until ongoing pregnancy has been documented. Intramuscular injection 100 mg, single injection can be administered for induction of withdrawal bleeding, as applicable.

Table 5-4 NIMP Dosing Regimen – Natural Cryopreserved Cycles

NIMP	Trade name (active ingredient)	Dosing regimen
Progesterone	ENDOMETRIN (progesterone)	100 mg, TID Will be initiated the day after confirmed LH surge (local laboratory); will be continued until menses, negative βhCG, pregnancy loss or until ongoing pregnancy has been documented. Vaginal administration

The doses and treatment regimens of the NIMPs are in line with the recommendations in the respective products' Prescribing Information and/or standard clinical practice within ART. For information on warnings and precautions, please refer to the Prescribing Information for the NIMPs.

5.2 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 5-5 provides an overview of the presentation of each medicinal product.

Table 5-5 Characteristics of Medicinal Products

IMP / NIMP	Presentation	Manufacturer or Distributor
FE 999049	Pre-filled injection pen for multiple use containing 72 µg of FSH in 2.16 mL.	Ferring Pharmaceuticals
Placebo	Pre-filled injection pen for multiple use containing 2.16 mL of placebo.	Ferring Pharmaceuticals
GANIRELIX	Pre-filled syringe for single use delivering 250 µg of ganirelix acetate in 0.5 mL.	Merck Sharp & Dohme
NOVAREL	Vials with lyophilized powder and vials with diluent. After reconstitution, each vial delivers 5,000 IU chorionic gonadotropin.	Ferring Pharmaceuticals
LEUPROLIDE ACETATE	Vial containing 14 mg of leuprolide acetate in 2.8 mL.	Sandoz Inc.
ENDOMETRIN	Vaginal inserts of 100 mg of progesterone.	Ferring Pharmaceuticals
ESTRADIOL Tablets USP	Oral tablets of 1 mg estradiol.	Teva Pharmaceuticals USA, Inc.
PROGESTERONE Injection USP	Vial containing 500 mg of progesterone in 10 mL sesame oil solution.	West-ward Pharmaceutical Corp or Watson Pharma, Inc.

5.3 Packaging and Labelling

Packaging and labelling of the medicinal products will be performed under the responsibility of the Clinical Trial Supply department at Ferring in accordance with GMP and U.S. regulatory requirements. Details on the packaging of each medicinal product is provided in Table 5-6.

Table 5-6 Packaging of Medicinal Products

IMP / NIMP	Packaging
FE 999049	FE 999049 is provided in boxes containing 1 pre-filled injection pen for multiple use and single-use disposable needles.
Placebo	Placebo is provided in boxes containing 1 pre-filled injection pen for multiple use and single-use disposable needles.
GANIRELIX	GANIRELIX is provided in boxes containing 1 pre-filled syringe.
NOVAREL	NOVAREL is provided in boxes containing one vial with powder and one vial with diluent.
LEUPROLIDE ACETATE	LEUPROLIDE ACETATE is provided in boxes containing 1 vial and disposable syringes.
ENDOMETRIN	ENDOMETRIN is provided in boxes containing 21 vaginal inserts and 21 disposable vaginal applicators.
ESTRADIOL Tablets USP	ESTRADIOL Tablets USP is provided in bottles containing 100 tablets.
PROGESTERONE Injection USP	PROGESTERONE Injection USP is provided in boxes containing 1 vial.

All NIMPs are commercially available and will be purchased centrally. No modification from the usual commercial state of the NIMPs will be made, except for trial-specific labelling.

All products (IMPs and NIMPs) will be labelled with trial-specific labels, which contain a self-adhesive tear-off portion to be affixed to the subject dispensing log, maintained at the trial site.

5.4 Conditions for Storage and Use

The investigator will ensure that the medicinal products will be stored in appropriate conditions in a secure location with controlled access. The storage compartment shall be monitored regularly and the temperature shall be documented. Deviations in storage temperature must be reported to Ferring as instructed in the IMP/NIMP handling guideline.

The storage conditions for the IMPs and NIMPs will be as described in the trial-specific or commercial box labelling.

Information on how to administer the medicinal products will be provided in Instructions for Use prepared for the IMPs and in the Package Inserts for the NIMPs.

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.

5.5 Blinding / Unblinding

5.5.1 Blinding

The pre-filled injection pens with FE 999049 and placebo will be identical in appearance. Likewise, the FE 999049 and placebo solutions will be identical in appearance.

The IMP will be packaged according to a computer-generated randomization list. The randomization 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 investigators, other trial staff at site, central laboratory personnel, or sponsor staff during the trial.

5.5.2 Unblinding of Individual Subject Treatment

An emergency decoding possibility will be available to the investigator and designated persons at Ferring. 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 Ferring. Where the event requires immediate unblinding by the investigator, Ferring must be informed of the unblinding as soon as possible and provided with the rationale for unblinding. The investigator/person who unblinds a treatment will use the eCRF in which he/she is required to enter a password and record the reason for unblinding before the treatment code can be broken. The eCRF automatically records when and by whom the code is 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, the same procedure as for emergency unblinding must be followed, i.e. the person who is accidentally unblinded will enter a password in the eCRF and must record the reason for unblinding, while the eCRF records when and by whom the code is broken. In addition the event must also be recorded in the subject's medical record.

If Ferring needs to unblind a subject's treatment, the eCRF will be used for unblinding. It is required 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 standard operating 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 relevant health authorities and/or IRBs. In that situation, every effort will be made to maintain blinding of Ferring 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 Pharmacovigilance using the contact details given below.

Ferring Pharmacovigilance

US Toll-free number: [redacted]

If Ferring Pharmacovigilance cannot access the eCRF, a back-up procedure involving the eCRF vendor is in place.

5.6 Treatment Compliance, Dispensing and Accountability

The IMP will only be dispensed to subjects who meet the eligibility criteria and are randomized to a treatment group in the trial. The investigator (or his/her designated staff, e.g. trial nurse) will maintain a drug-dispensing log detailing the dates and quantities of IMPs/NIMPs dispensed to, and used by, each subject, as well as the batch numbers, IMP/NIMP numbers or other identifier used in the trial.

The monitor will verify the drug accountability during the trial and if applicable document any discrepancies.

In order to monitor compliance, the subjects are to return empty, partially used, and unused vials, pens, syringes, tablets or inserts to the investigator at each visit. The investigator (or his/her designated staff, e.g. trial nurse) will reconcile and document the return on the drug accountability log. Any discrepancies should be discussed with the subject at the time of the return.

5.7 Return and Destruction of Medicinal Products and Auxiliary Supplies

All dispensed IMP and NIMP is to be destroyed at the trial site in accordance with local legislation after the drug accountability has been finalized.

Used syringes and needles should be destroyed immediately after usage according to normal procedures at each trial site.

Any non-dispensed IMP/NIMP must be returned for destruction, as instructed by the Ferring Clinical Trial Supply Department, after the drug accountability has been finalized.

6 TRIAL PROCEDURES

6.1 Controlled Ovarian Stimulation and Fresh Cycle

The flow of the trial procedures for subjects in the controlled ovarian stimulation and fresh cycle is shown in Table 6-1.

Table 6-1 Trial Flow Chart – Subject Procedures – Controlled Ovarian Stimulation and Fresh Cycle

	Screening	Stimulation				OR	Transfer	Pregnancy monitoring			End
		During stimulation			End-of-stimulation	Oocyte retrieval	Transfer	βhCG	Clinical	Ongoing	End-of-cycle
Timing	<90 days before randomization	Day 1	Day 5	Day ≥6 to <20 [a]	End	36h ±2h after triggering	Day 5 after OR	10-14 days after transfer	5-6 weeks after transfer	8-9 weeks after transfer	[b]
Written informed consent(s)	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,d]									X [d]
Physical examination	X										X
Gynecological examination	X										X
Urine pregnancy test	X	X [c]									
Ultrasound sonography[e]		X [c]	X	X	X				X	X	
Randomization		X									
Vital signs	X	X [f]									X
Blood collection, clin chem / hem	X				X						X
Blood collection, endocrine	X	X [f]	X [g]		X [g]	X					
Blood collection, antibodies [h]	X [i]	X [f]					X [j]	X [k]			X [k]
Blood collection, estradiol			X	X	X						
Blood collection, genome [l]		X									
Saliva collection, genome [l]		X									
Tongue coat collection, microbiome [l]		X					X				
IMP dispensing		X	X [m]	X [m]							
NIMP dispensing			X [n]	X	X	X	X	X	X		
Local tolerability (diary)		X	X	X	X						
Oocyte retrieval						X					
Blastocyst transfer / cryo							X				
βhCG test (local lab)								X			
Drug accountability			X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
End-of-cycle form											X

a) Visits must be scheduled at least every second day; when the leading follicle reaches ≥14 mm visits must be performed daily.
b) End-of-cycle assessments must be performed at the subject's last scheduled visit: at the earliest 21-28 days after the last IMP dose.
c) Performed before randomization.
d) Only body weight.
e) Transvaginal ultrasound with exception of the ongoing pregnancy visit, where it can be either transvaginal or abdominal ultrasound.
f) Performed before the first IMP dose.
g) Performed at least 8 h after IMP administration (and NIMP administration at end-of-stimulation visit).
h) All subjects with a treatment-induced antibody response must be followed until the response is negative or has returned to pre-dosing level.
i) Sample exclusively used to re-establish the anti-drug antibody analytical assays.
j) Blood sampling for antibody assessment must be done 7-10 days after the last IMP dose (this may coincide with the transfer visit; alternatively, a separate visit must be scheduled).
k) Blood sampling for antibody assessment must be done 21-28 days after the last IMP dose (this may coincide with the βhCG test visit; alternatively, a separate visit must be scheduled).
l) Optional sampling for future potential exploratory analyses for subjects who have provided separate written informed consent.
m) The starting dose of 15 µg FE 999049 is fixed for the first 4 stimulation days. Based on the ovarian response, the daily dose may be adjusted by 3 µg, with dose increases implemented not more frequently than once every 2 days and dose decreases implemented per investigator's judgement. The minimum dose is 6 µg, and the maximum dose is 24 µg.
n) GnRH antagonist will be initiated on stimulation day 5 for subjects with ≥3 follicles with a diameter of ≥10 mm. Subjects who fail to satisfy this GnRH antagonist criterion on stimulation day 5 will continue to be monitored at least every second day, and GnRH antagonist will be initiated when/if the criterion is met.

βhCG: β human chorionic gonadotropin; IMP: investigational medicinal product; NIMP: non-investigational medicinal product; OR: oocyte retrieval

6.1.1 Screening

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

The following must take place during the screening period:

- Signed and dated written informed consent for participation in the trial, obtained prior to any trial-related procedures
- Signed and dated written informed consent for parental consent to data collection on the neonate, obtained prior to randomization
- Signed and dated written informed consent for exploratory analyses covering potential future genome sequencing and microbial profiling (*optional*), obtained prior to sampling
- 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
- Gynecological examination
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Urine pregnancy test – must be negative
- Blood collection for central laboratory analysis of:
  - clinical chemistry and hematology parameters [*note*: the results must be available prior to randomization]
  - endocrine parameters (screening panel: AMH, TSH and prolactin) [*note*: the results for TSH and prolactin must be available prior to randomization]
  - anti-FSH antibodies [exclusively used to re-establish the anti-drug antibody analytical assays]

- 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 subject's menstrual cycle.

In case of positive findings of HBsAg, HCV or HIV antibody tests obtained at screening, it is the investigator's responsibility to ensure that standard reporting and referral procedures at the sites are followed in line with local regulations.

6.1.2 Stimulation Day 1

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

The following must take place prior to randomization:

- Ensure that the subject is still eligible for participation in the trial
- Check those inclusion and exclusion criteria that were not possible during screening
- Body weight
- Urine pregnancy test – must be negative
- Transvaginal ultrasound of uterus (endometrial thickness, echogenicity pattern) and ovaries (number and size of follicles, ovarian volume)

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

- Randomization, i.e. assignment to the lowest available subject number and thereby allocation to either FE 999049 or placebo

The following must take place after randomization but before administration of the first dose of IMP (FE 999049 or placebo):

- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Blood collection for central laboratory analysis of:
  - endocrine parameters (AMH, FSH, LH, estradiol, progesterone, inhibin A and inhibin B)
  - anti-FSH antibodies

- Blood collection for future potential genome sequencing (*applicable for subjects who have provided a separate informed consent*)
- Saliva collection for future potential genome sequencing (*applicable for subjects who have provided a separate informed consent*)
- Tongue coat collection for future potential microbial profiling (*applicable for subjects who have provided a separate informed consent*)

Once the above has been completed, the following must be performed:

- Hand out the diary for recording of local tolerability to the subject.
  The subject must be instructed to assess and record local tolerability after each IMP administration throughout the entire stimulation period. The first evaluation of local tolerability reactions at the injection site is done immediately after the injection of IMP, followed by a second evaluation 30 minutes after injection of IMP and a third evaluation 24 hours after injection of IMP (before the next day's injection of IMP). In case the subject has any concern related to an injection site reaction, the investigator should be contacted for possible further assessment, prior to the next IMP injection.
- Dispense IMP according to randomization and instruct the subject on how to administer the IMP. The subject will self-administer the IMP (at the trial site or at home) as a subcutaneous injection in the lower part of the abdomen. The starting dose for the first 4 days is fixed at 15 µg.

Finally, the following must be done before the subject leaves the site:

- Recording of use of any concomitant medication
- Recording of adverse events

The IMP should preferably be administered at the same time each day during the stimulation period (with the possible exception of stimulation day 1).

6.1.3 Stimulation Day 5

The following must take place on stimulation day 5:

- Transvaginal ultrasound of uterus (endometrial thickness, echogenicity pattern) and ovaries (number and size of follicles)
- Blood collection for central laboratory analysis of:

  - endocrine parameters (AMH, FSH, LH, estradiol, progesterone, inhibin A and inhibin B) – the blood sample must be drawn at least 8 hours after the latest IMP administration

- Blood collection for local laboratory analysis of estradiol (optional; can be used for assessing potential IMP dose adjustment)
- Dispensing of IMP
- Implementation of potential dose adjustments
  From stimulation day 5 and onwards, the daily dose may be adjusted by 3 µg, with dose increases implemented not more frequently than once every 2 days and dose decreases implemented per investigator's judgement. The minimum daily dose is 6 µg, and the maximum daily dose is 24 µg. In case of dose adjustments, the reason will be collected.
- Dispensing of GnRH antagonist, as applicable
  Daily administration of 250 µg GnRH antagonist will be initiated on stimulation day 5 for subjects with ≥3 follicles with a diameter of ≥10 mm. Subjects who fail to satisfy this GnRH antagonist criterion on stimulation day 5 will continue to be monitored at least every second day, and GnRH antagonist will be initiated when/if the criterion is met. The subject will self-administer the GnRH antagonist as a subcutaneous injection in the upper thigh throughout the stimulation period. The timing of the GnRH antagonist injections should be aligned with the IMP injections.
- Collection of local tolerability data (diary pages)
- Drug accountability of IMP
- Recording of use of any concomitant medication
- Recording of adverse events

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

- Remind the subject to assess and record local tolerability immediately, 30 minutes and 24 hours after each IMP administration

After the stimulation day 5 visit, visits must be scheduled at least every second day throughout the remaining stimulation period.

6.1.4 Stimulation Days ≥6 to <20

Visits will take place at least every second day throughout the remaining stimulation period. When the leading follicle reaches ≥14 mm, visits must be performed daily. Coasting or use of dopamine agonist as preventive intervention of OHSS are not allowed. The maximum period of stimulation is 20 days.

The following must take place at the visits throughout the remainder of the stimulation period (with the exception of the end-of-stimulation visit, which is described in section 6.1.5):

- Transvaginal ultrasound of uterus (endometrial thickness, echogenicity pattern) and ovaries (number and size of follicles, ovarian volume)
- Blood collection for local laboratory analysis of estradiol (optional; can be used for assessing potential IMP dose adjustment)
- Dispensing of IMP
- Implementation of potential dose adjustments
  From stimulation day 5 and onwards, the daily dose may be adjusted by 3 µg, with dose increases implemented not more frequently than once every 2 days and dose decreases implemented per investigator's judgement. The minimum daily dose is 6 µg, and the maximum daily dose is 24 µg. In case of dose adjustments, the reason will be collected.
- Dispensing of GnRH antagonist, as applicable
  For subjects who did not initiate GnRH antagonist on stimulation day 5, initiation should be performed when the criterion of ≥3 follicles with a diameter of ≥10 mm is met. A daily dose of 250 µg should be continued throughout the stimulation period.
- Collection of local tolerability data (diary pages)
- Drug accountability of IMP and GnRH antagonist
- Recording of use of any concomitant medication
- Recording of adverse events
- Remind the subject to assess and record local tolerability immediately, 30 minutes and 24 hours after each IMP administration

6.1.5 End-of-stimulation

The end-of-stimulation visit will take place when the subject reaches the criterion for triggering of final follicular maturation or if the cycle is canceled. Administration of hCG or GnRH agonist must take place the same day as the criterion for triggering of final follicular maturation, i.e. ≥2 follicles with a diameter of ≥17 mm, is met. Administration of FE 999049 or placebo after reaching the triggering criterion is not allowed.

Criterion for triggering of final follicular maturation with 10,000 IU hCG:

- <20 follicles with a diameter of ≥12 mm

Criterion for triggering of final follicular maturation with 4 mg GnRH agonist:

- ≥20 follicles with a diameter of ≥12 mm or serum estradiol concentration ≥3,000 pg/mL (local laboratory)

If after 8 days of stimulation, the investigator judges that the triggering criterion, i.e. ≥2 follicles with a diameter of ≥17 mm, is not likely to be reached by day 20, the cycle will be canceled. If the triggering criterion is not met after 20 days of stimulation, the cycle will be canceled.

The investigator also has the option of canceling the cycle for other relevant medical reasons, including adverse events and technical malfunctions of the administration pen. In the latter event, the option of replacing the administration pen and continuing treatment should be considered.

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

- Transvaginal ultrasound of uterus (endometrial thickness, echogenicity pattern) and ovaries (number and size of follicles, ovarian volume)
- Blood collection for central laboratory analysis of:
  - clinical chemistry and hematology parameters
  - endocrine parameters (AMH, FSH, LH, estradiol, progesterone, inhibin A and inhibin B) – the blood sample must be drawn at least 8 hours after the latest administration of IMP and GnRH antagonist
- Blood collection for local laboratory analysis of estradiol (used to determine the triggering drug)
- Dispensing of hCG or GnRH agonist, as applicable
- Collection of local tolerability data (diary pages)
- Drug accountability of IMP and GnRH antagonist
- Recording of use of any concomitant medication
- Recording of adverse events

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

For subjects with cycle cancellation, the next visit is the first post-dosing anti-FSH antibody blood sampling visit 7-10 days after the last FE 999049 or placebo dose (section 6.1.8.2).

6.1.6 Oocyte Retrieval

Oocyte retrieval must take place 36h (±2h) after hCG or GnRH agonist administration. All oocytes from follicles with an estimated diameter of ≥12 mm should be retrieved. The procedures related to subjects attending the oocyte retrieval visit are listed below, while procedures related to the oocytes are described in section 6.1.7.

The following must take place at the oocyte retrieval visit:

- Blood collection for central laboratory analysis of:
  - endocrine parameters (AMH, FSH, LH, estradiol, progesterone, inhibin A and inhibin B)
- Oocyte retrieval
- Dispensing of progesterone vaginal inserts for luteal phase 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 or GnRH agonist, as applicable
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with <20 oocytes retrieved following hCG administration, the next visit is the transfer visit 5 days after oocyte retrieval (section 6.1.8.1).

For subjects with ≥20 oocytes retrieved following hCG administration and for subjects with oocytes retrieved following GnRH agonist administration the fresh blastocyst transfer will be canceled. The oocytes will undergo the procedures described in section 6.1.7 and blastocysts will be cryopreserved by vitrification. The next visit for these subjects is the first post-dosing anti-FSH antibody assessment visit which must be scheduled 7-10 days after the last FE 999049 or placebo dose (section 6.1.8.2).

For subjects with no oocytes retrieved, the next visit is the first post-dosing anti-FSH antibody assessment visit which must be scheduled 7-10 days after the last FE 999049 or placebo dose (section 6.1.8.2).

6.1.7 Oocyte / Blastocyst Evaluation

The laboratory procedures regarding handling and evaluations of oocytes and blastocysts are described in a trial-specific manual. This section provides an overview of the procedures and assessments to be made from oocyte retrieval until transfer at the blastocyst stage. The flow of the trial procedures for

oocytes is shown in Table 6-2.

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

	Day 0 (OR)		Day 1 after OR	Day 5 after OR
Timing	-4h (±1h)	0h	19h (±2h)	Day 5
Oocyte retrieval (OR)	X			
Assessment of maturity stage (applicable for oocytes undergoing ICSI)	X			
Insemination by IVF and/or ICSI		X		
Assessment of oocyte fertilization			X	
Assessment of blastocyst quality				X
Transfer of one or two blastocysts of the highest quality available: – Subjects with at least one good-quality blastocyst (i.e. grade 3BB or above) will have one blastocyst transferred – Subjects with no good-quality blastocysts available (i.e. lower than grade 3BB) will have one or two blastocysts transferred				X
Cryopreservation of blastocysts by vitrification, as applicable				X[a]

[a] In case the embryologist judges that a blastocyst/morula is still developing, continued culturing and cryopreservation on day 6 is allowed.
ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization; OR: oocyte retrieval

Blastocyst biopsy, assisted hatching and PGD/PGS are prohibited.

Day 0 (Oocyte Retrieval)

- Oocyte retrieval at 4h (±1h) before start of the insemination procedure
- Assessment of maturity stage (applicable for oocytes undergoing ICSI)
- Insemination at 0h using IVF or ICSI using ejaculated sperm (fresh or frozen) from partner or donor

Day 1 after Oocyte Retrieval

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

Day 5 after Oocyte Retrieval

- Assessment of blastocyst quality

- Transfer of blastocyst(s) (section 6.1.8.1)
- Cryopreservation of blastocysts by vitrification, as applicable. In case the embryologist judges that a blastocyst/morula is still developing, continued culturing and cryopreservation on day 6 is allowed

6.1.8 Transfer

6.1.8.1 Blastocyst Transfer

Transfer is performed on day 5 (blastocyst stage) after oocyte retrieval. Transfer of day 6 (or later) blastocysts is not allowed in the fresh cycle.

The subject-related procedures are described below.

- Blood collection for central laboratory analysis of anti-FSH antibodies (first post-dosing assessment)
- Tongue coat collection for future potential microbial profiling (*applicable for subjects who have provided a separate informed consent*)
- Transfer of one or two blastocysts of the highest quality available (per judgement of the site embryologist):
  - Subjects with at least one good-quality blastocyst (i.e. grade 3BB or above[a]) will have one blastocyst transferred
  - Subjects with no good-quality blastocysts available (i.e. lower than grade 3BB) will have one or two blastocysts transferred
- Dispensing of progesterone vaginal inserts for luteal phase support, if applicable
- Drug accountability of progesterone vaginal inserts
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with blastocyst transfer, the next visit is the βhCG test visit which must be scheduled 10-14 days after transfer (section 6.1.9.1).

[a] 3BB and above defined as: 6AA, 6AB, 6AC, 6BA, 6BB, 6BC, 6CA, 6CB, 6CC, 5AA, 5AB, 5AC, 5BA, 5BB, 5BC, 5CA, 5CB, 5CC, 4AA, 4AB, 4AC, 4BA, 4BB, 4BC, 4CA, 4CB, 4CC, 3AA, 3AB, 3AC, 3BA, or 3BB.

6.1.8.2 First Post-dosing Anti-FSH Antibody Assessment (7-10 Days after Last IMP Dose)

Subjects who have been exposed to FE 999049 or placebo must have the first post-dosing anti-FSH antibody assessment performed 7-10 days after the last FE 999049 or placebo dose. This may coincide with the transfer visit (section 6.1.8.1).

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

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

6.1.9 βhCG Test

6.1.9.1 βhCG Test

Subjects who have undergone transfer must attend a visit 10-14 days after transfer.

The following must take place:

- Blood collection for local laboratory analysis of βhCG
- Blood collection for central laboratory analysis of anti-FSH antibodies (second post-dosing assessment)
- Dispensing of progesterone vaginal inserts, if applicable
- Drug accountability of progesterone vaginal inserts
- Recording of use of any concomitant medication
- Recording of adverse events

The blood sample for βhCG will be analyzed by the local laboratory and evaluated according to the local reference ranges. In case of a doubtful / inconclusive βhCG result, the test may be repeated, preferably within 2 days, and the conclusive result recorded. Subjects with a positive βhCG test must attend a clinical pregnancy visit 5-6 weeks after transfer (section 6.1.10). Subjects with a negative βhCG test must proceed to the end-of-cycle assessments (section 6.1.12).

6.1.9.2 Second Post-dosing Anti-FSH Antibody Assessment (21-28 Days after Last IMP Dose)

Subjects who have been exposed to FE 999049 or placebo must have the second post-dosing anti-FSH antibody assessment performed 21-28 days after the last FE 999049 or placebo dose. This may coincide with the βhCG test visit (section 6.1.9.1).

For subjects who do not attend the βhCG test visit, this second post-dosing anti-FSH antibody assessment may be done in connection with the end-of-cycle assessments (section 6.1.12) if applicable or a separate visit must be scheduled, at which the following must take place:

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

6.1.10 Clinical Pregnancy

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

The following must take place:

- Transvaginal ultrasound of uterus to assess any clinical pregnancy
- Dispensing of progesterone vaginal inserts for luteal phase support, if applicable
- Drug accountability of progesterone vaginal inserts
- Recording of use of any concomitant medication
- Recording of adverse events

If at least one gestational sac (either intrauterine or ectopic) is observed, this confirms a clinical pregnancy. If at least one intrauterine gestational sac with fetal heart beat is observed, this confirms a vital pregnancy. For subjects with a vital pregnancy, the next visit is the ongoing pregnancy visit (section 6.1.11). Subjects with no vital pregnancy must undergo end-of-cycle assessments (section 6.1.12).

6.1.11 Ongoing Pregnancy

If a vital pregnancy has been documented, the subject must attend a visit 8-9 weeks (56-69 days) after transfer.

The following must take place:

- Ultrasound (transvaginal or abdominal) of uterus to assess any ongoing pregnancy
- Drug accountability of progesterone vaginal inserts
- Recording of use of any concomitant medication
- Recording of adverse events

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

6.1.12 End-of-cycle

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

Due to the timing of the mandatory anti-FSH antibody assessments, the end-of-cycle assessments can at the earliest be performed 21-28 days after the last FE 999049 or placebo dose. This may coincide with the βhCG visit for subjects with a negative βhCG test.

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

- Body weight
- Physical examination
- Gynecological examination
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Blood collection for central laboratory analysis of:
  - clinical chemistry and hematology parameters
  - anti-FSH antibodies (second post-dosing assessment) [*note*: only applicable for subjects who have not already had a blood sample taken for the second post-dosing anti-FSH antibodies assessment as described in section 6.1.9.2]

- Drug accountability, if applicable
- Recording of use of any concomitant medication
- Recording of adverse events
- Complete end-of-cycle form

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

6.2 Cryopreserved Cycles

The trial covers cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation. Either a programmed cycle (section 6.2.1) or a natural cycle (section 6.2.2) can be selected for any cryopreserved cycle.

6.2.1 Programmed Cryopreserved Cycles

The flow of the trial procedures in the programmed cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation is shown in Table 6-3.

Table 6-3 Trial Flow Chart – Subject and Blastocyst Procedures – Programmed Cryopreserved Cycles Initiated Within 12 Months From the Start of Controlled Ovarian Stimulation

	Preparation of the endometrium			Transfer	Pregnancy monitoring			End
	Start estradiol[a)]	Evaluate endometrium[b)]	Re-evaluate endometrium[c)]	Transfer	βhCG	Clinical	Ongoing	End-of-cycle
Timing	Within 3 days of start of menses	10-12 days after start of estradiol	Within 7 days of first evaluation	6th day from start of progesterone	10-14 days after transfer	5-6 weeks after transfer	8-9 weeks after transfer	[d)]
Physical examination	X							X
Gynecological examination	X							X
Urine pregnancy test	X[e)]							
Vital signs	X							X
Ultrasound sonography[f)]		X	X			X	X	
NIMP dispensing	X	X	X	X	X	X		
Assessment of blastocyst survival and re-expansion				X				
Blastocyst transfer				X				
Tongue coat collection, microbiome[g)]				X				
βhCG test (local lab)					X			
Drug accountability		X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
End-of-cycle form								X

a) Estradiol (ESTRADIOL Tablets USP) 2 mg TID or 3 mg BID (or 3 mg TID, if a daily dose of 6 mg has been shown to be insufficient in a previous cycle).
b) If endometrial thickness is ≥8 mm, IM progesterone will be initiated within 5 days.
c) Only for subjects with endometrial thickness <8 mm at the first evaluation. If endometrial thickness is ≥ 8 mm, IM progesterone will be initiated within 5 days. Subjects who fail to achieve adequate endometrial thickness will discontinue estradiol and be administered 100 mg IM progesterone to induce withdrawal bleeding.
d) End-of-cycle assessments must be performed at the subject's last scheduled visit in each cryopreserved cycle.
e) Performed before start of estradiol treatment.
f) Transvaginal ultrasound with exception of the ongoing pregnancy visit, where it can be either transvaginal or abdominal ultrasound.
g) Optional sampling for future potential exploratory analyses for subjects who have provided separate written informed consent.

βhCG: β human chorionic gonadotropin; NIMP: non-investigational medicinal product

6.2.1.1 Cycle Initiation / Preparation of the Endometrium

Start of Estradiol

Any programmed cryopreserved cycle is to be initiated within 3 days of start of menses when subjects starts preparation of the endometrium with estradiol.

At that time, the following must be performed:

- Physical examination
- Gynecological examination
- Urine pregnancy test – must be negative
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Dispensing of estradiol
  The subject will start endometrial preparation with estradiol 2 mg TID or 3 mg BID (or 3 mg TID, if a daily dose of 6 mg has been shown to be insufficient in a previous cycle)
- Recording of use of any concomitant medication
- Recording of adverse events

Evaluation of Endometrium

After 10-12 days of estradiol treatment the following must be performed:

- Transvaginal ultrasound of uterus to measure endometrial thickness
  Based on the results of the endometrial evaluation one of the following will take place:
  - If endometrial thickness is ≥8 mm, the estradiol dose will be continued and daily intramuscular (IM) injections of 50 mg progesterone will be initiated within 5 days
  - If endometrial thickness is <8 mm, the estradiol dose will be continued and endometrial thickness measurement repeated within 7 days
- Dispensing of IM progesterone, if applicable
- Dispensing of estradiol
- Drug accountability of estradiol
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with an endometrial thickness ≥8 mm, the next visit is the transfer visit on the 6th day from start of progesterone treatment (section 6.2.1.3).

For subjects with endometrial thickness <8 mm, the endometrial thickness measurement will be repeated within 7 days. If the criterion of endometrial thickness ≥8 mm is reached at the repeated measurement, daily IM injections of 50 mg progesterone will be initiated within 5 days.

Subjects who fail to achieve adequate endometrial thickness will discontinue estradiol and will be administered 100 mg IM progesterone to induce withdrawal bleeding. In subsequent cryopreserved cycles, blastocyst transfer can take place regardless of endometrial thickness at the investigator's discretion.

6.2.1.2 Blastocyst Evaluation

The laboratory procedures regarding handling and evaluations of warmed blastocysts are described in a trial-specific manual. This section provides an overview of the procedures and assessments to be made from warming until transfer.

Cryopreserved blastocysts must be warmed in order of quality, using the best quality blastocysts first.

On the day of warming, the following must take place:

- Assessment of blastocyst survival 0h (+0.5h) after thawing
  - In case of survival, the blastocyst proceeds to the re-expansion assessment
- Assessment of blastocyst re-expansion 2.5h (±0.5h) after thawing

6.2.1.3 Transfer

On the 6th day from start of progesterone, one or two cryopreserved blastocysts will be transferred after warming and assessment of blastocyst survival and re-expansion.

The subject-related procedures are described below:

- Tongue coat collection for future potential microbial profiling (*applicable for subjects who have provided a separate informed consent*)

- Transfer of one or two blastocysts of the highest quality available (per judgement of the site embryologist):
  - Subjects with at least one good-quality blastocyst (i.e. grade 3BB or above[b]) will have one blastocyst transferred
  - Subjects with no good-quality blastocysts available (i.e. lower than grade 3BB) will have one or two blastocysts transferred
- Dispensing of estradiol
- Dispensing of IM progesterone
- Drug accountability of estradiol and IM progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with blastocyst transfer, the next visit is the βhCG test visit which must be scheduled 10-14 days after transfer (section 6.2.1.4).

6.2.1.4 βhCG Test

Subjects who have undergone transfer must attend a visit 10-14 days after transfer.

The following must take place:

- Blood collection for local laboratory analysis of βhCG
- Dispensing of estradiol, if applicable
- Dispensing of IM progesterone, if applicable
- Drug accountability of estradiol and IM progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

The blood sample for βhCG will be analyzed by the local laboratory and evaluated according to the local reference ranges. In case of a doubtful / inconclusive βhCG result, the test may be repeated, preferably within 2 days, and the conclusive result recorded. Subjects with a positive βhCG test must attend a clinical pregnancy visit 5-6 weeks after transfer (section 6.2.1.5). Subjects with a negative

[b] 3BB and above defined as: 6AA, 6AB, 6AC, 6BA, 6BB, 6BC, 6CA, 6CB, 6CC, 5AA, 5AB, 5AC, 5BA, 5BB, 5BC, 5CA, 5CB, 5CC, 4AA, 4AB, 4AC, 4BA, 4BB, 4BC, 4CA, 4CB, 4CC, 3AA, 3AB, 3AC, 3BA, or 3BB.

βhCG test must proceed to the end of-cycle assessments (section 6.2.1.7).

6.2.1.5 Clinical Pregnancy

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

The following must take place:

- Transvaginal ultrasound of uterus to assess any clinical pregnancy
- Dispensing of estradiol, if applicable
- Dispensing of IM progesterone, if applicable
- Drug accountability of estradiol and IM progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

If at least one gestational sac (either intrauterine or ectopic) is observed, this confirms a clinical pregnancy. If at least one intrauterine gestational sac with fetal heart beat is observed, this confirms a vital pregnancy. For subjects with a vital pregnancy, the next visit is the ongoing pregnancy visit (section 6.2.1.6). Subjects with no vital pregnancy must undergo end-of-cycle assessments (section 6.2.1.7).

6.2.1.6 Ongoing Pregnancy

If a vital pregnancy has been documented, the subject must attend a visit 8-9 weeks (56-69 days) after transfer.

The following must take place:

- Ultrasound (transvaginal or abdominal) of uterus to assess any ongoing pregnancy
- Drug accountability of estradiol and IM progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

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

6.2.1.7 End-of-cycle

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

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

- Physical examination
- Gynecological examination
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Drug accountability, if applicable
- Recording of use of any concomitant medication
- Recording of adverse events
- Complete end-of-cycle form

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

6.2.2 Natural Cryopreserved Cycles

The flow of the trial procedures in the natural cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation is shown in Table 6-4.

Table 6-4 Trial Flow Chart – Subject and Blastocyst Procedures – Natural Cryopreserved Cycles Initiated Within 12 Months From the Start of Controlled Ovarian Stimulation

	Start of cryopreserved cycle / monitoring of LH surge[a]		Transfer	Pregnancy monitoring			End
			Transfer[b]	βhCG	Clinical	Ongoing	End-of-cycle
Timing	7 days after start of menses[c]	LH surge	LH surge + 7 days	10-14 days after transfer	5-6 weeks after transfer	8-9 weeks after transfer	[d]
Physical examination	X						X
Gynecological examination	X						X
Urine pregnancy test	X						
Vital signs	X						X
Urinary LH assessment	X						
Serum LH (local lab)		X					
Ultrasound sonography[e]		X[f]			X	X	
NIMP dispensing		X[g]	X	X	X		
Assessment of blastocyst survival and re-expansion			X				
Blastocyst transfer			X				
Tongue coat collection, microbiome[h]			X				
βhCG test (local lab)				X			
Drug accountability			X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
End-of-cycle form							X

a) Monitoring of urinary LH will be done on a daily basis by the subject until confirmed LH surge.
b) One cryopreserved blastocyst will be transferred 7 days after confirmed LH surge (day LH surge + 7).
c) Natural cryopreserved cycles will be initiated on day 7 after start of menses in a subsequent menstrual cycle.
d) End-of-cycle assessments must be performed at the subject's last scheduled visit in each cryopreserved cycle.
e) Transvaginal ultrasound with exception of the ongoing pregnancy visit, where it can be either transvaginal or abdominal ultrasound.
f) To confirm endometrial thickness ≥8 mm. If the endometrial thickness is <8 mm, the cycle will be canceled.
g) Progesterone will be initiated on day LH surge + 1.
h) Optional sampling for future potential exploratory analyses for subjects who have provided separate written informed consent.

βhCG: β human chorionic gonadotropin; LH: luteinizing hormone; NIMP: non-investigational medicinal product

6.2.2.1 Cycle Initiation

Any natural cryopreserved cycle is to be initiated 7 days after start of menses in a subsequent menstrual cycle.

The following must take place at cycle initiation:

- Physical examination
- Gynecological examination

- Urine pregnancy test – must be negative
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Urinary LH assessment
- Recording of use of any concomitant medication
- Recording of adverse events

6.2.2.2 Confirmation of LH Surge

The following must take place on the day of confirmation of LH surge:

- Confirmation of LH surge by:
  - blood collection for local laboratory analysis of serum LH, and
  - transvaginal ultrasound to confirm endometrial thickness ≥8 mm.
    If the endometrial thickness is <8 mm in the first cryopreserved cycle, the cycle will be canceled. In subsequent cryopreserved cycles, blastocyst transfer can take place regardless of endometrial thickness at the investigator's discretion.
- Dispensing of progesterone vaginal inserts for luteal phase support – must be started on the day after confirmed LH surge (day LH surge + 1).
- Recording of use of any concomitant medication
- Recording of adverse events

6.2.2.3 Blastocyst Evaluation

The laboratory procedures regarding handling and evaluations of warmed blastocysts are described in a trial-specific manual. This section provides an overview of the procedures and assessments to be made from warming until transfer.

Cryopreserved blastocysts must be warmed in order of quality, using the best quality blastocysts first.

On the day of warming, the following must take place:

- Assessment of blastocyst survival 0h (+ 0.5h) after thawing
  - In case of survival, the blastocyst proceeds to the re-expansion assessment.
- Assessment of blastocyst re-expansion 2.5h (± 0.5h) after thawing

6.2.2.4 Transfer

Seven days after confirmed LH surge (day LH surge + 7), one cryopreserved blastocyst will be transferred after warming and assessment of blastocyst survival and re-expansion.

The subject-related procedures are described below:

- Tongue coat collection for future potential microbial profiling (*applicable for subjects who have provided a separate informed consent*)
- Transfer of one or two blastocysts of the highest quality available (per judgement of the site embryologist):
  - Subjects with at least one good-quality blastocyst (i.e. grade 3BB or above[c]) will have one blastocyst transferred
  - Subjects with no good-quality blastocysts available (i.e. lower than grade 3BB) will have one or two blastocysts transferred
- Dispensing of progesterone vaginal inserts, if applicable
- Drug accountability of progesterone vaginal inserts
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with blastocyst transfer, the next visit is the βhCG test visit which must be scheduled 10-14 days after transfer (section 6.2.2.5).

6.2.2.5 βhCG Test

Subjects who have undergone transfer must attend a visit 10-14 days after transfer.

The following must take place:

- Blood collection for local laboratory analysis of βhCG
- Dispensing of progesterone vaginal inserts, if applicable
- Drug accountability of progesterone vaginal inserts
- Recording of use of any concomitant medication

[c] 3BB and above defined as: 6AA, 6AB, 6AC, 6BA, 6BB, 6BC, 6CA, 6CB, 6CC, 5AA, 5AB, 5AC, 5BA, 5BB, 5BC, 5CA, 5CB, 5CC, 4AA, 4AB, 4AC, 4BA, 4BB, 4BC, 4CA, 4CB, 4CC, 3AA, 3AB, 3AC, 3BA, or 3BB.

- Recording of adverse events

The blood sample for βhCG will be analyzed by the local laboratory and evaluated according to the local reference ranges. In case of a doubtful / inconclusive βhCG result, the test may be repeated, preferably within 2 days, and the conclusive result recorded. Subjects with a positive βhCG test must attend a clinical pregnancy visit 5-6 weeks after transfer (section 6.2.2.6). Subjects with a negative βhCG test must proceed to the end of-cycle assessments (section 6.2.2.8).

6.2.2.6 Clinical Pregnancy

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

The following must take place:

- Transvaginal ultrasound of uterus to assess any clinical pregnancy
- Dispensing of progesterone vaginal inserts, if applicable
- Drug accountability of progesterone vaginal inserts
- Recording of use of any concomitant medication
- Recording of adverse events

If at least one gestational sac (either intrauterine or ectopic) is observed, this confirms a clinical pregnancy. If at least one intrauterine gestational sac with fetal heart beat is observed, this confirms a vital pregnancy. For subjects with a vital pregnancy, the next visit is the ongoing pregnancy visit (section 6.2.2.7). Subjects with no vital pregnancy must undergo end-of-cycle assessments (section 6.2.2.8).

6.2.2.7 Ongoing Pregnancy

If a vital pregnancy has been documented, the subject must attend a visit 8-9 weeks (56-69 days) after transfer.

The following must take place:

- Ultrasound (transvaginal or abdominal) of uterus to assess any ongoing pregnancy
- Drug accountability of progesterone vaginal inserts
- Recording of use of any concomitant medication

- Recording of adverse events

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

6.2.2.8 End-of-cycle

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

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

- Physical examination
- Gynecological examination
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Drug accountability, if applicable
- Recording of use of any concomitant medication
- Recording of adverse events
- Complete end-of-cycle form

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

6.3 Post-trial Activities

All subjects with an ongoing pregnancy obtained in the fresh cycle, or in cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation, will be followed until delivery to collect information on live birth rate. Furthermore, data will be collected on neonatal health, including minor/major congenital anomalies, at birth, 4 weeks and 1 year after birth. These follow-up data can be obtained from the subject, unless medical judgement is required. The subject will be contacted by telephone and a contact log will be maintained at the trial site. These data will be reported separately.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Efficacy Endpoints

7.1.1 Ongoing Pregnancy

A transvaginal or abdominal ultrasound of the uterus will be performed 8-9 weeks after transfer in the fresh cycle and in the cryopreserved cycles. Ongoing pregnancy will be defined as at least one intrauterine viable fetus. For ongoing pregnancies, the number of intrauterine viable fetuses will be recorded.

7.1.2 Time to Ongoing Pregnancy

Based on the recordings of start of controlled ovarian stimulation (date) and confirmation of ongoing pregnancy (date), the time to ongoing pregnancy will be calculated. Furthermore, based on the recording of which cycle the ongoing pregnancy occurred in, the number of cycles before achieving an ongoing pregnancy will be determined.

7.1.3 Ongoing Implantation

Ongoing implantation is determined based on the ultrasound performed at the ongoing pregnancy visit in the fresh cycle and in the cryopreserved cycles. Ongoing implantation rate will be defined as the number of intrauterine viable fetuses 8-9 weeks after blastocyst transfer divided by number of blastocysts transferred.

7.1.4 Clinical Pregnancy

A transvaginal ultrasound of the uterus will be performed 5-6 weeks after transfer in the fresh cycle and in the cryopreserved cycles. 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.[29,d] For intrauterine and ectopic pregnancies, the number of gestational sacs with fetal heart beat as well as without fetal heart beat will be recorded.

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

7.1.5 Vital Pregnancy

Vital pregnancy is determined based on the transvaginal ultrasound performed at the clinical pregnancy visit in the fresh cycle and in the cryopreserved cycles. Vital pregnancy will be defined as at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after blastocyst transfer.

7.1.6 Implantation

Implantation is determined based on the transvaginal ultrasound performed at the clinical pregnancy visit in the fresh cycle and in the cryopreserved cycles. Implantation rate will be defined as the number of gestational sacs 5-6 weeks after blastocyst transfer divided by number of blastocysts transferred.

7.1.7 Positive βhCG

A blood serum βhCG test must be obtained 10-14 days after blastocyst transfer in the fresh cycle and in the cryopreserved cycles. If the test is positive according to the local laboratory's reference ranges, this confirms a positive βhCG. In case of a doubtful / inconclusive βhCG result, a second test will be performed, preferably within 2 days, and the conclusive result recorded.

7.1.8 Triggering of Final Follicular Maturation, Cycle Cancellation and Transfer Cancellation

The drug used for triggering of final follicular maturation, i.e. hCG or GnRH agonist, will be recorded.

The reason for each cycle cancellation will be recorded.

The reason for each transfer cancellation will be recorded. Transfer cancellation due to adverse events such as the Medical Dictionary for Regulatory Activities preferred terms (MedDRA PTs) 'ovarian hyperfunction' and 'ovarian hyperstimulation syndrome' in subjects with blastocysts available for transfer will be considered as transfer cancellations due to risk of OHSS. Similarly, transfer cancellations in subjects with ≥20 oocytes retrieved will be considered as transfer cancellations due to risk of OHSS.

7.1.9 Number and Size of Follicles during Stimulation

Transvaginal ultrasound will be performed at all visits during the controlled ovarian stimulation period to count the number of follicles and measure the size of the follicles. Each follicle will be measured in 2 dimensions, and its diameter will be calculated as the mean of the largest diameter and its perpendicular value.

The total number of follicles and number of follicles with a diameter of 8-9 mm, 10-11 mm, 12-14 mm, 15-16 mm, and ≥17 mm on stimulation day 5 and at end-of-stimulation will be recorded. Data will be recorded separately for the right and left ovary.

7.1.10 Number and Distribution of Oocytes Retrieved

The number of oocytes retrieved will be recorded at the oocyte retrieval visit. The proportion of subjects with <4 oocytes, 4-7 oocytes, 8-14 oocytes, 15-19 oocytes and ≥20 oocytes will be calculated.

7.1.11 Number of Metaphase II Oocytes

Maturity stage will be assessed prior to insemination for oocytes that will undergo ICSI. Maturity stage will be categorized as germinal vesicle, metaphase I, metaphase II, degenerated or other.

7.1.12 Number of Fertilized Oocytes and Fertilization Rate

The number of pronuclei will be counted at 19h (±2h) after insemination and recorded as 0, 1, 2 or >2. Fertilized oocytes with 2 pronuclei (2PN) will be regarded as correctly fertilized. Fertilization rate is the number of 2PN oocytes divided by the number of oocytes retrieved.

7.1.13 Number and Quality of Blastocysts on Day 5

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 & Schoolcraft,[30] 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 3 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.

In the event of continued culture, blastocyst grading will be recorded after day 5.

In the fresh cycle, the number of transferred and cryopreserved blastocysts will be recorded. In each cryopreserved cycle, the number of transferred blastocysts will be recorded.

7.1.14 Endometrial Thickness and Echogenicity Pattern

Transvaginal ultrasound of the uterus to assess the endometrial thickness and endometrial echogenicity pattern will be conducted on stimulation day 1, stimulation day 5, stimulation days 6 to 20, and at end-of-stimulation.

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

7.1.15 Oocyte Utilization Rate and Oocyte Efficiency Index

Based on the recordings of the number of oocytes retrieved and the number of blastocysts transferred or cryopreserved, the oocyte utilization rate will be calculated.

Based on the recordings of the number of oocytes retrieved and the cumulative number of ongoing pregnancies, the oocyte efficiency index rate will be calculated.

7.1.16 Blastocyst Survival and Re-expansion after Cryopreservation

Blastocyst survival after cryopreservation will be assessed for all thawed blastocysts at 0h (+0.5h) after thawing. Furthermore, re-expansion will be assessed for all surviving blastocysts at 2.5h (±0.5h) after thawing.

7.1.17 Number of Cryopreserved Cycles

A programmed cryopreserved cycle is considered as initiated if the subject has started estradiol treatment.

A natural cryopreserved cycle is considered as initiated if the subject has started LH surge monitoring.

The number of cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation, and the number of cryopreserved cycles with blastocyst transfer will be recorded.

7.1.18 Circulating Levels of Endocrine Parameters

The following endocrine parameters will be evaluated during controlled ovarian stimulation: AMH, FSH, LH, estradiol, progesterone, inhibin A and inhibin B.

Blood samples will be drawn on stimulation day 1, stimulation day 5, end-of-stimulation and oocyte retrieval. The sample on stimulation day 1 (baseline) will be collected prior to the first dose of IMP,

samples drawn on stimulation day 5 will be collected at least 8 hours after the previous IMP administration, and samples drawn at end-of-stimulation will be collected at least 8 hours after the previous IMP and GnRH antagonist administration. The samples will be analyzed at a central laboratory.

The endocrine parameters include pharmacokinetic and pharmacodynamic markers of FSH therapy, and therefore to maintain blinding of treatment allocation the laboratory results from samples drawn after stimulation day 1 will not be made available to the investigator, other trial staff at site, or sponsor staff.

7.1.19 Total Gonadotropin Dose, Number of Stimulation Days and Number of Dose Adjustments

The administration dates as well as daily dose of IMP will be recorded by the subject in a diary. These data will be used to calculate the total dose of FE 999049 or placebo (actual and intended dose) administered, the number of stimulation days, and the number of dose adjustments.

In addition, the reason for dose adjustment will be recorded by the investigator, using the following categories: a) inadequate follicular development, b) inadequate serum estradiol level, c) inadequate follicular development and inadequate serum estradiol level, d) excessive follicular development, e) excessive serum estradiol level, f) excessive follicular development and excessive serum estradiol level.

7.2 Assessments Related to Safety Endpoints

7.2.1 Adverse Events

Adverse events will be recorded from the time of signed informed consent for participation in the trial until the end-of-cycle visit in the fresh cycle. In any cryopreserved cycle, adverse events will be recorded from cycle initiation until the end-of-cycle visit. For each adverse event the following parameters will be recorded by the investigator on the Adverse Event Log: description of event, date and time of onset, intensity, causal relation to IMP, action taken to IMP, other actions taken, seriousness of the adverse event, date and time of outcome, and outcome. Definitions of adverse events are provided in section 8.

7.2.2 Clinical Chemistry and Hematology Parameters

The following clinical chemistry and hematology parameters will be analyzed at a central laboratory:

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

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

Blood samples will be drawn at screening, end-of-stimulation and end-of-cycle in the fresh cycle. The sample at the screening visit will be used for eligibility evaluation of the subject before randomization. The investigator will review the laboratory results from all visits and evaluate and document whether the abnormal results are non-clinically or clinically significant. The laboratory report will be signed and dated by the investigator.

7.2.3 Injection Site Reactions

Every day throughout the stimulation period, the subjects will assess the local tolerability of subcutaneous injections of FE 999049 and placebo 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 paper diary and the diary data will subsequently be transcribed to the eCRF.

In case a subject has any concern related to an injection site reaction, the investigator should be contacted for possible further assessment, prior to the next IMP injection.

7.2.4 Anti-FSH Antibodies

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

- Screening [*note*; this sample is exclusively used to re-establish anti-drug antibody analytical assays]

- Stimulation day 1, prior to dosing (baseline; pre-dosing sample)
- 7-10 days after the last FE 999049 or placebo dose
  This may coincide with the transfer visit. Subjects not reaching transfer must be called in for this extra visit.
- 21-28 days after the last FE 999049 or placebo dose
  This may coincide with the βhCG visit. In case of discontinuation before the βhCG visit, this assessment should be done at the end-of-cycle visit scheduled 21-28 days after the last FE 999049 or placebo dose.

Ferring has developed the following assays for evaluating the immunogenicity of FE 999049:

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

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

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

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

Assay 5 A cell-based assay determining the neutralizing antibody response titer of any positive result in assay 4.

Assay 6 A confirmatory assay based on native FSH, in order to assess cross-reactivity with native FSH of any anti-FSH antibodies confirmed to be specific towards exogenous FSH in assay 2, using a cut-point approach with a 1% false positive rate.

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

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

All positive samples in the confirmatory assay (assay 2) will be further characterized for titer, neutralizing capacity (qualitatively and titer, if applicable) and cross-reactivity. A subject is defined to have treatment-induced anti-FSH antibodies with neutralizing capacity if she has a positive outcome of assay 4 after IMP administration and if she was negative for anti-FSH antibodies with neutralizing capacity at pre-dosing. Ferring will report treatment-induced neutralizing antibodies to the FDA.

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

Subjects with a treatment-induced anti-FSH antibody response (both with and without neutralizing capacity) will be followed until the response is negative or has returned to pre-dosing level or after a maximum of 1 year. These subjects will be called in for assessments 2 months after the last post-dosing anti-FSH antibody sampling. If required, further assessments will be made at 3, 4, 6, 9 and 12 months after the last post-dosing anti-FSH antibody sampling. The assessments will be terminated when two consecutive assessments are negative or indicate that the pre-dosing level has been reached, or after a maximum of 1 year. The assessments will also be terminated if the subject commences a new treatment cycle with any gonadotropin preparation.

7.2.5 Immune-related Adverse Events

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

[e] The fold increase in titers is determined by minimum significant ratio (MSR) experiments during assay validation and will be stated in the validation report and the clinical trial report.

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

The reason for each cycle cancellation will be recorded, allowing subsequent tabulation of cycle cancellations due to adverse events, including immune-related adverse events (see section 7.2.5), and technical malfunctions of the administration pen.

7.2.7 Ovarian Hyperstimulation Syndrome

All cases of OHSS will be reported as adverse events with further details on signs and symptoms recorded on a specific OHSS form. Golan's classification system[31] (see section 8.3.1 for details) will be used for grading of each OHSS case as mild, moderate or severe. In the fresh cycle, early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation, and late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation.

7.2.8 Hospitalizations and Paracentesis due to Ovarian Hyperstimulation Syndrome

Based on the recordings in the OHSS form, the cases of hospitalization due to OHSS and paracentesis due to OHSS will be identified. Associated parameters to be recorded include dates of admission and discharge from the hospital, and volume of fluid, respectively.

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

Data related to multi-fetal gestation defined as a pregnancy with more than one fetus will be recorded. Furthermore, data related to the occurrence of biochemical pregnancy, spontaneous abortion, ectopic pregnancy (with and without medical/surgical interventions) and vanishing twins will also be recorded (section 8.3.2).

7.2.10 Technical Malfunctions of the Administration Pen

In case of technical malfunction of an administration pen that results in a replacement of the pen, all relevant details (including time, date, a description of the malfunction and whether dosing was affected) of the incidence should be reported in the eCRF, the pen should be replaced and the treatment continued. Human errors such as misunderstanding of instructions or incorrect handling of the device should not be regarded as technical malfunctions.

In case of adverse events caused by malfunction of the administration pen, these will be identified and described.

7.3 Other Assessments

7.3.1 Demographics

Demographic information will be obtained during the screening period, including the following: date of birth, ethnicity (Hispanic or Latino, Not Hispanic or Latino) and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White).

7.3.2 Medical History

Any relevant medical history will be recorded during the screening period. This includes diagnosis / symptoms, and start and end dates (or marked ongoing in case it has not been resolved).

7.3.3 Infertility History

Information about the causes 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.

7.3.4 Menstrual History

Information about the menstrual history (average cycle length and onset of last menstrual cycle prior to the screening visit) will be obtained during the screening period.

7.3.5 Reproductive History

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

7.3.6 Body Measurements

Body weight will be measured at screening, stimulation day 1, and at end-of-cycle in the fresh cycle. Body weight will be measured without shoes and coat, using a calibrated scale.

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

7.3.7 Physical Examination

A complete physical examination will be performed at screening and end-of-cycle in the fresh cycle. In any cryopreserved cycle, a complete physical examination will be performed at cycle initiation and at

end-of-cycle. 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.

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 each end-of-cycle visit, potential changes from screening to end-of-cycle in the fresh cycle or from cycle initiation to end-of-cycle in any cryopreserved cycle 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-cycle in the fresh cycle and from cycle initiation to end-of-cycle in any cryopreserved cycle must be recorded as adverse events.

7.3.8 Gynecological Examination

A complete gynecological examination will be performed at screening and end-of-cycle in the fresh cycle. In any cryopreserved cycle, a complete gynecological examination will be performed at cycle initiation and at end-of-cycle. Information will be recorded for breast, external genitalia, vagina, cervix, uterus, ovaries and fallopian tubes.

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 each end-of-cycle visit, potential changes from screening to end-of-cycle in the fresh cycle or from cycle initiation to end-of-cycle in any cryopreserved cycle 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-cycle in the fresh cycle and from cycle initiation to end-of-cycle in any cryopreserved cycle must be recorded as adverse events.

7.3.9 Endocrine Parameters at Screening

At screening, the following panel of endocrine parameters will be evaluated: AMH, TSH and prolactin.

The sample will be analyzed at a central laboratory.

The results for TSH and prolactin must be available prior to randomization. The investigator will review and evaluate the laboratory results. The laboratory report will be signed and dated by the investigator.

7.3.10 Vital Signs

Systolic and diastolic blood pressure and pulse will be measured at screening, on stimulation day 1, and at end-of-cycle in the fresh cycle. In any cryopreserved cycle, vital signs will be measured at cycle initiation and at end-of-cycle. Assessments of blood pressure and heart rate are to be measured while the subject is in supine position after resting for 3 minutes.

7.3.11 Ovarian Volume

As part of the transvaginal ultrasounds performed on stimulation day 1, stimulation days 6 to 20, and end-of-stimulation, the size – length, width and depth (recorded in mm) – of each ovary is measured and used for subsequent calculation of ovarian volume.

7.3.12 Endometrial Evaluation in Cryopreserved Cycles

Transvaginal ultrasound of the uterus to measure the endometrial thickness prior to transfer will be conducted in the cryopreserved cycles. In programmed cryopreserved cycles, the transvaginal ultrasound will be performed after 10-12 days of estradiol treatment (a second assessment may be performed within 7 additional days, if applicable). In natural cryopreserved cycles, the transvaginal ultrasound will be performed on the day of confirmation of LH surge.

7.3.13 Concomitant Medication

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

7.3.14 Drug Dispensing and Accountability

For all medicinal products used in the fresh cycle and the cryopreserved cycles, dates of administration and dose administered will be recorded. Furthermore, time of administration will also be recorded for IMP, GnRH antagonist, hCG and GnRH agonist in the fresh cycle. Details on drug dispensing and accountability are provided in section 5.6.

7.3.15 End-of-cycle Form

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

7.4 Assessments Related to Post-trial Endpoints

7.4.1 Live Birth

Each cycle with an ongoing pregnancy will be followed until delivery. The outcome of each delivery, i.e. live birth or stillbirth, will be recorded.

7.4.2 Live Birth of Singletons Born at Term

Based on recordings of timing of blastocyst transfer as well as timing and outcome of delivery, the live birth rate of singletons born at term (≥37 weeks of gestation) will be calculated.

7.4.3 Time to Live Birth of a Singleton Born at Term

Based on the recordings of start of controlled ovarian stimulation (date) as well as timing (date) and outcome of delivery, the time to live birth of a singleton born at term will be calculated. Furthermore, based on the recording of which cycle the live birth of a singleton at term occurred in, the number of cycles before achieving this will be determined.

7.4.4 Minor/Major Congenital Anomalies

All neonates will be followed as part of the post-trial follow-up. Congenital anomalies detected at birth, 4 weeks and 1 year after birth for all infants born after the fresh cycle and after the cryopreserved cycles will be reported and classified as minor or major as described in section 8.5.1.

7.5 Other Post-trial Assessments

Gender, birth weight and length, and Apgar score after 1 and 5 minutes will be recorded.

Furthermore, admission to neonatal intensive care unit (NICU), neonatal care unit (NCU) or pediatric care unit (PCU) will be recorded as described in section 8.5.1. At 4 weeks and 1 year after birth, the information collected will include minor/major congenital anomalies, admission to NICU, NCU or PCU and any other relevant medical conditions.

7.6 Optional Exploratory Analyses

7.6.1 Genome Sequencing

For subjects who have provided a separate informed consent, a blood sample and a saliva sample for potential future genome sequencing will be collected on stimulation day 1. The informed consent for these optional exploratory analyses signed by the subject must be obtained prior to the sampling.

Resultant sequence data may be used in exploratory pharmacogenomic analyses aimed at identifying novel relationships between ovarian response/associated outcomes and subjects' genomic variants.

Results of these potential future exploratory analyses will not be provided to the sites.

7.6.2 Microbial Profiling

For subjects who have provided a separate informed consent, a tongue coat sample for potential future microbial profiling will be collected on stimulation day 1 and at the transfer visit(s) in the fresh and cryopreserved cycles, as applicable. The informed consent for these optional exploratory analyses signed by the subject must be obtained prior to the sampling.

Subjects will be asked to rinse and gargle twice with sterile water prior to using a tongue scraper to collect the tongue coat from the posterior middle area to the anterior middle area.

Analyses may be performed to identify relationships between ovarian response/associated outcomes and subjects' microbiome.

Results of these potential future exploratory analyses will not be provided to the sites.

7.7 Handling of Biological Samples

A trial-specific laboratory manual will be provided to the participating sites, describing in detail how to handle, store and transport the biological samples (blood) in this trial. Biological samples will be analyzed at central laboratories and will be maintained in storage and destruction will take place within 2 years after reporting of the trial. Exceptions are the blood, saliva and tongue coat samples collected for potential future genome sequencing and microbial profiling, as well as blood samples for which methods / results have not been adequately validated; these will be stored for a maximum of 10 years after reporting of the trial prior to destruction in line with local regulations. Blood samples analyzed by a local laboratory, e.g. in connection with eligibility criteria, estradiol for monitoring of ovarian response, and the βhCG tests, will be destroyed after analysis. For all biological samples collected in the trial, it applies that analyses beyond those described in the protocol can only be performed after obtaining the required approvals. The processes related to handling of biological samples will be described in the informed consent documents, and biobank / data protection legislation 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 unfavorable 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 gynecological examination assessed as clinically significant by the investigator [*note*: pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not adverse events, but are recorded as medical history].
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.

All adverse events will be coded by Ferring Global Pharmacovigilance using MedDRA (the version effective at trial start).

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The investigator must monitor the condition of the subject throughout the trial from the time of signed informed consent for participation in the trial until the end-of-cycle visit in the fresh cycle. In any cryopreserved cycle, adverse events will be recorded from cycle initiation until the end-of-cycle 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. hospitalization).

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.[f]

Note: a procedure is not an adverse event; the reason for conducting the procedure is. Hospitalization is not an adverse event; the reason for hospitalization 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).

[f] 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 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 recognized 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 Ovarian Hyperstimulation Syndrome

Symptoms and Classification

OHSS is an adverse event of special interest during controlled ovarian stimulation. Investigators will record OHSS symptoms using a classification system based on Golan's classification system[31] 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 (Based on Golan's Classification System)

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

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

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

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

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

e) Hospitalization is defined as admission exceeding 24 hours.

All cases of OHSS must be reported as adverse events and followed until the adverse event has an outcome of recovered. Any case of OHSS that requires hospitalization (admission exceeding 24 hours) or surgical/medical intervention (e.g. paracentesis) should be considered severe. All cases of severe OHSS should be reported as an SAE.

Please note, that the classification of '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), but to the grades in Golan's Classification System described above.

Subject narratives will be prepared for all OHSS cases.

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

Investigations in Case of OHSS

The investigator should report signs, symptoms and laboratory assessments used to diagnose and classify all cases of OHSS in the eCRF. The following investigations must be conducted when OHSS symptoms are first observed and repeated when there are clinically relevant changes in the OHSS presentation suggestive of a worsening, i.e. higher grading:

- Body weight
- Ultrasound of ovarian size and if applicable, measurement of pelvic/abdominal/thoracic fluid
- Vital signs
- Blood sample for central laboratory analysis of the following:
  - Progesterone and estradiol
  - CBC (red blood cells, red blood cell morphology, white blood cells, white blood cell morphology, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin 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 Pregnancy Losses

The following terminology should be used for reporting of pregnancy losses as adverse events:

Biochemical pregnancy:	Positive βhCG test but no gestational sac is observed on later transvaginal ultrasound, or menstruation is reported
Spontaneous abortion:	Positive βhCG test but all intrauterine gestational sacs are without fetal heart beat as documented by ultrasound, or there are no viable fetuses observed by ultrasound
Vanishing twin:	Spontaneous disappearance of at least one 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. a positive βhCG test but no ongoing pregnancy at 8-9 weeks after transfer) will be defined as an early pregnancy loss, while a pregnancy loss occurring after ongoing pregnancy (i.e. at least one intrauterine viable fetus at 8-9 weeks after transfer but no live birth) during the post-trial follow-up will be defined as a late pregnancy loss.

8.4 Events Requiring Special Handling

8.4.1 Injection Site Reactions

Injection site reactions after administration of IMP (FE 999049 or placebo) are only to be reported as adverse events if they require active management, i.e. discontinuation of IMP, additional investigations or treatment of the injection site reaction. Local tolerability of IMP constitutes a secondary endpoint and will be evaluated in detail based on the subjects' recordings in the diary.

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

8.4.2 Treatment-induced Anti-FSH Antibodies

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

8.4.3 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.

8.4.4 Multiple Pregnancies

Multi-fetal gestations are not to be reported as adverse events.

8.5 Serious Adverse Events

8.5.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined a serious adverse event (SAE) if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is *per se* not an event, but an outcome.
is **life-threatening**	The term life-threatening refers to an adverse event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient **hospitalization** or prolongation of existing hospitalization	The term hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization 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 hospitalization. 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). Hospitalizations for administrative or social purposes do not constitute an SAE. 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 hospitalization but might jeopardize 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 hospitalization, or development of drug dependency or drug abuse.

Elective Termination

In connection with elective termination due to a congenital anomaly, the congenital anomaly of the fetus should be reported as an SAE.

The congenital anomaly leading to elective termination will be coded using both MedDRA and ICD-10 and classified as minor or major.[g]

Serious Adverse Events during Post-trial Activities

Pregnancy outcome will be gathered for all subjects with an ongoing pregnancy in the fresh or any cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation. Furthermore, data will be collected on neonatal health, including minor/major congenital anomalies, at birth, 4 weeks and 1 year after birth. These data will be reported separately.

The following untoward medical occurrences reported as part of this post-trial follow-up information will be recorded as SAEs:

- Death of mother in connection with pregnancy or labor
- Death of neonate / infant
- Stillbirth[h]
- Neonate admitted to the neonatal intensive care unit (NICU) regardless of duration, or neonate / infant admitted to the neonatal care unit (NCU) / pediatric care unit (PCU) for more than 2 hours
- Congenital anomaly / birth defect
- Medically important event

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

Congenital anomalies will be coded by Ferring using both MedDRA and ICD-10 and classified as minor or major.[32]

[g] Minor anomalies: relatively frequent structural anomaly not likely to cause any medical or cosmetic problems. 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.

[h] Stillbirth: gestational age ≥24 weeks + 0 days, calculated from the day of day 5 blastocyst transfer + 19 days

8.5.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

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

The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

SAE Report Form

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

Ferring Pharmacovigilance
E-mail: [redacted]
US Fax: [redacted]

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

Additional information relevant to the SAE such as hospital records, results from investigations, e.g. laboratory parameters (that are not already uploaded in the eCRF), invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring Pharmacovigilance using the contact details in the section above. In any case this information must be supplied by the investigator upon request from Ferring. On any copies provided, 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 IRB with any additional requested information such as results of post-mortem examinations and hospital records.

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

Ferring will report SAEs according to local regulations.

8.6 Follow-up of Adverse Events and Serious Adverse Events

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

During the trial, the investigator must follow-up on each adverse event until it is resolved or until the medical condition of the subject is stable.

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

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

For post-trial SAEs in neonates, where the neonate has not recovered at the 1-year follow-up assessment, the investigator must follow up until the SAE has resolved. If the SAE is a chronic condition or the medical condition of the neonate is stable, the investigator and Ferring may agree that further follow-up is not required.

8.6.3 Collection of Serious Adverse Events with Onset after End-of-trial

If an investigator becomes aware of an SAE after the subject's last visit in the trial, and he/she assesses the SAE to have a reasonable possible causality to the IMP or to the NIMP where Ferring is the NDA holder (i.e., ENDOMETRIN and NOVAREL), the case will have to be reported to Ferring Pharmacovigilance, regardless how long after the end of the trial this takes place.

9 STATISTICAL METHODS

This section details the planned statistical analyses for the primary endpoint and outlines the analysis plan for the secondary endpoints. All analyses and further descriptions of the statistical methodology for the primary and secondary endpoints will be included in the statistical analysis plan (SAP). The SAP will be available before the first subject is randomized in the trial. A separate SAP will be prepared to cover the post-trial information.

9.1 Determination of Sample Size

The proposed sample size of 550 (FE 999049:placebo = 500:50) can adequately address both the efficacy and safety objectives of the trial:

- The cumulative ongoing pregnancy rate in the FE 999049-treated subjects aged 35-42 years is estimated to be approximately 30% according to results from clinical trials conducted in the U.S.[33] By comparison, the pregnancy rate in the placebo arm is expected not to exceed 3%, the monthly spontaneous pregnancy rate in infertile women.[34] Therefore, the proposed sample size of 550 (FE 999049:placebo=500:50) will provide at least 99% power for the primary efficacy comparison. Based on the estimated cumulative ongoing pregnancy rate, the cumulative live birth rate from the fresh and/or cryopreserved cycles is estimated to be approximately 27%, resulting in a power for the comparison of the cumulative live birth rate to be at least 99%.
- A key pharmacodynamic parameter in subjects aged 35-42 years is cycle cancellation due to poor follicular development, which may occur in approximately 5% of the population exposed to gonadotropins.
- The safety and tolerability of daily rFSH preparations as part of an ART treatment cycle have been well documented for the population studied in previous clinical trials.[1,35] OHSS was reported to occur in 1.7% to 3.7% of the subjects, with moderate/severe OHSS occurring in 1.4% to 2.2% of the subjects. Other adverse events were pelvic pain, pelvic discomfort and headache, with those assessed to be related to trial treatments reported in 1.5% to 7.1% of the subjects.

  Table 9-1 shows that the planned sample size of 500 subjects exposed to FE 999049 provides a high probability to detect a rare adverse event or safety signal occurring in 0.5% or more subjects.

Table 9-1 Probabilities to Detect at Least One Rare Event

Incidence rate of rare event	Chance of detecting at least 1 event
0.5%	91.8%
0.6%	95.1%
1%	99.3%

Table 9-2 presents the margin width estimates of the 95% confidence intervals for a range of adverse event rates with the planned sample size.

Table 9-2 Estimated Margin Widths of 95% Confidence Intervals

Adverse event rate	Margin of error width estimate
5%	1.9%
10%	2.6%
15%	3.1%
20%	3.5%

9.2 Subject Disposition

All screened subjects will be accounted for. Screened subjects who discontinue from the trial prior to randomization are regarded as screening failures. Screening failures and their primary reason for screening failure will be tabulated. Screening failures will not otherwise be accounted for.

Subject disposition with respect to analysis sets will be tabulated. A separate table will summarize the subject disposition with respect to analysis sets by trial site. Subject attendance at selected trial visits and adherence to selected trial procedures will be tabulated. The number of completed and discontinued subjects including reason for discontinuation will also be tabulated.

Subject disposition with respect to analysis sets will be listed for all randomized 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

The rating of protocol deviations as ‘minor’ and ‘major’, as well as the criteria for major protocol deviations with the implication of exclusions from the per-protocol (PP) analysis set will be decided by the medical officer, medical monitor and statistician on the basis of a blinded review of data before declaration of clean file and lock of database.

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 summarized and listed by subject.

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.

9.4 Analysis Sets

Intention-to-Treat Analysis Set

The intention-to-treat (ITT) analysis set comprises all randomized subjects. Subjects will be analyzed according to planned treatment.

Modified Intention-to-Treat Analysis Set

The modified intention-to-treat (mITT) analysis set comprises all randomized and exposed subjects. Subjects will be analyzed according to planned treatment.

Per-Protocol Analysis Set

The PP analysis set comprises all mITT subjects except those excluded as a result of major protocol deviations as described in section 9.3.

Safety Analysis Set

The safety analysis set comprises all randomized and exposed treated subjects. Subjects will be analyzed according to actual treatment received.

9.5 Trial Population

9.5.1 General Considerations

All relevant baseline data will be summarized in tables including both treatment groups and a total column. The purpose of these tabulations is to characterize the treatment groups and assess the degree of similarity achieved by the randomization. Baseline data will not be compared using statistical tests. Unless otherwise noted, tabulations will be produced overall for the mITT analysis set, as well as in the ITT analysis set if the ITT analysis set differs from the mITT 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 mITT.

Unless otherwise noted, missing data will not be imputed.

9.5.2 Trial Population Parameters

Demographics and other Baseline Characteristics

Demographics and other baseline characteristics (body measurements, ultrasound parameters, vital signs, and endocrine parameters) obtained before first exposure to IMP will be listed by subject and presented in summary tables.

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 summarized for each medical item.

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 Gynecological Examination

Physical examination and gynecological examination performed during screening will be summarized per category.

Concomitant Medication

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

- Prior medication, i.e. medication taken exclusively prior to treatment (i.e. with stop date/time before date/time of 1st IMP administration)

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

Concomitant medication will be presented separately for the fresh cycle and the cryopreserved cycles.

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 Exposure and Treatment Compliance

9.6.1 General Considerations

Duration of treatment (days) is defined as the number of days from first exposure to the day of last exposure (both inclusive). Tabulations will be produced for the mITT analysis set.

9.6.2 Controlled Ovarian Stimulation (Fresh Cycle)

IMP

Exposure to gonadotropins, including total dose, duration of stimulation and number of dose adjustments is covered by a secondary endpoint (section 9.7.3.19).

NIMPs

Exposure to GnRH antagonist will be summarized as the total dose administered (µg) and duration of treatment (days).

Exposure to drug used for triggering of final follicular maturation, i.e. hCG or GnRH agonist, is covered by a secondary endpoint (section 9.7.3.8).

Exposure to progesterone will be summarized as the total dose administered (mg) and duration of treatment (days).

9.6.3 Cryopreserved Cycles

In the programmed cryopreserved cycles, exposure to estradiol will be summarized by cycle as the total dose administered (mg) and duration of treatment (days), and exposure to IM progesterone will be summarized by cycle as the total dose administered (mg) and duration of treatment (days).

In the natural cryopreserved cycles, exposure to vaginal progesterone will be summarized by cycle as the total dose administered (mg) and duration of treatment (days).

9.6.4 Treatment Compliance

Non-compliance to IMP is expected to be limited and will be presented in listings. Similarly, listings will be prepared for subjects with deviations in the NIMP schedules for the fresh and cryopreserved cycles.

9.7 Efficacy Endpoints Assessments

9.7.1 General Considerations

Primary Endpoint and Secondary Efficacy Endpoints

Upon achieving statistical significance about the primary endpoint at the 0.05 alpha level, the cumulative live birth rate will be formally tested at the 0.05 alpha level for inferential conclusions.

The secondary endpoints related to pregnancy and implantation parameters are considered supportive of the primary endpoint (cumulative ongoing pregnancy rate). The secondary efficacy endpoints related to ovarian response and embryo development parameters are intended to provide additional characterization of FE 999049.

Analysis and Presentation of Primary and Secondary Efficacy Endpoints

Summary tables and treatment comparisons for the primary endpoint will be presented for both the mITT and PP analysis sets. In case that the mITT and ITT analysis sets are not identical (i.e. at least one subject is randomized but not exposed) the summary tables and treatment comparisons will also be presented for the ITT analysis set. As applicable for the secondary endpoints, summary tables and treatment comparisons may be presented for the mITT and PP analysis sets.

All tabulations will be presented by treatment group. 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 mITT.

Multiplicity

In order to handle the formal testing procedures for the primary endpoint of cumulative ongoing pregnancy rate and the key post-trial endpoint of cumulative live birth rate, the overall type-I error will be controlled by the use of a hierarchical inferential approach. Statistical significance of the primary endpoint at the 0.05 alpha level is required before drawing inferential conclusions about the key post-trial endpoint of the cumulative live birth rate. This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.05 level.

All additional analyses of the primary endpoint and secondary efficacy endpoints are considered as supportive. Adjustments for multiplicity will therefore not be applied.

Missing Data

Missing observations for the primary endpoint of cumulative ongoing pregnancy rate will be imputed as 'negative' irrespective of the reason why data are not recorded. Similarly, for other pregnancy endpoints (βhCG, clinical pregnancy and vital pregnancy) missing data will be imputed as 'negative' with the exception of a later observation in that cycle confirming that an earlier missing observation was in fact 'positive', e.g. in case of a missing βhCG test result and a confirmed clinical pregnancy in the same cycle then the βhCG test result will be imputed as 'positive'.

For subjects with transfer but missing observations on the number of viable fetuses 8-9 weeks after transfer the number of viable fetuses will be imputed as zero irrespective of why data is not recorded. For subjects with transfer but missing information on the number of gestational sacs 5-6 weeks after transfer, the number of gestational sacs will be imputed as the number of viable fetuses 8-9 weeks after transfer.

For subjects with cycle cancellation, the numbers of oocytes retrieved, metaphase II oocytes, fertilized oocytes, and blastocysts on day 5 will be imputed as zero.

Missing values will not be imputed for any of the other secondary endpoints, unless otherwise noted.

9.7.2 Primary Endpoint

The hypothesis to be tested for the primary endpoint, cumulative ongoing pregnancy rate, is:

H_0: $\pi_{FE\ 999049} - \pi_{Placebo} \leq 0$ against the alternative H_A: $\pi_{FE\ 999049} - \pi_{Placebo} > 0$,

where $\pi_{FE\ 999049}$ and $\pi_{Placebo}$ denote the cumulative ongoing pregnancy rate after the fresh cycle and cryopreserved cycles in subjects aged 35-42 years treated with FE 999049 or placebo, respectively.

H_0 will be tested against the alternative H_A by constructing a two-sided 95% confidence interval for the difference in the cumulative ongoing pregnancy rates between the two treatment groups using the traditional Wald interval. If the lower limit of the two-sided 95% confidence interval is greater than 0, the null hypothesis H_0 will be rejected. In the case that the number of pregnancies observed in the placebo group is small (<5), then the one-sided Fisher's exact test will be used.

The primary endpoint will be determined as soon as the subject has achieved an ongoing pregnancy, or when all cryopreserved blastocysts have been exhausted, or after assessment of ongoing pregnancy status in cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation.

The efficacy analysis will be based on the mITT analysis set, defined as all subjects who were randomized and received at least one dose of IMP (FE 999049 or placebo).

Sensitivity Analyses

The primary analysis will be repeated for the subjects in the PP analysis set as sensitivity analysis, as well as in the ITT analysis set if the ITT analysis set differs from the mITT analysis set. The outcomes of these analyses are considered supportive.

The primary analyses described above will be repeated restricted to subjects with oocytes retrieved and to subjects undergoing blastocyst transfer.

Missing data for the primary endpoint is expected to be limited due to the trial design, but may occur if the subject is lost to follow-up before ongoing pregnancy is assessed. If one or more such subjects have a positive pregnancy test result (βhCG test, clinical pregnancy or vital pregnancy) prior to lost to follow-up, the impact of imputing the ongoing pregnancy will be investigated in a sensitivity analysis.

Subgroup Displays

The primary endpoint will also be displayed by the following subgroups:

- Primary reason for infertility (unexplained infertility, tubal infertility, male factor, endometriosis stage I/II, other)
- Method of insemination (IVF, ICSI, IVF/ICSI)
- Age (35-37, 38-40, 41-42 years)
- Body weight (≤75, >75 kg)
- AMH on stimulation day 1 (<7.5, 7.5-<15, 15-<25, ≥25 pmol/L)
- Center

For each subgroup factor, descriptive statistics for the cumulative ongoing pregnancy rate will be presented by subgroup level and treatment group. These subgroup displays will be prepared for the mITT and PP analysis sets.

9.7.3 Secondary Efficacy Endpoints

Secondary efficacy endpoints will be analyzed based on the mITT analysis set. As specified below, for selected endpoints, analyses will be repeated on the PP analysis set.

9.7.3.1 Ongoing Pregnancy Rate

The ongoing pregnancy rate will be calculated for the fresh cycle, for each cryopreserved cycle, and for cryopreserved cycles cumulatively based on both the total number of subjects in the treatment group and the total number of subjects who started the respective cycle. For subjects with an ongoing pregnancy, the number of intrauterine viable fetuses will be tabulated. Analyses similar to that used for the primary endpoint will be applied as applicable and will be applied to both the mITT and PP analysis sets.

9.7.3.2 Time to Ongoing Pregnancy

For subjects who achieve ongoing pregnancy following a fresh or cryopreserved transfer, time to ongoing pregnancy across the fresh and cryopreserved cycles will be calculated as the number of days from the start of controlled ovarian stimulation to the visit confirming ongoing pregnancy, as well as the number of cycles until ongoing pregnancy is achieved. Descriptive statistics will be presented by treatment group, and will be applied to both the mITT and PP analysis sets.

9.7.3.3 Ongoing Implantation Rate

The ongoing implantation rate will be calculated for the fresh cycle, for each cryopreserved cycle, cumulatively for the cryopreserved cycles, and cumulatively across the fresh and cryopreserved cycles for subjects with at least one transferred blastocyst in the applicable cycles. For subjects where the number of viable fetuses 8-9 weeks after transfer is greater than the number of blastocysts transferred, the number of viable fetuses will be set to the number of blastocyst transferred in the analysis. Descriptive statistics will be presented by treatment group and the two treatment groups will be compared using the nonparametric Wilcoxon rank-sum test as applicable. The analyses will be applied to both the mITT and PP analysis sets.

9.7.3.4 Clinical Pregnancy Rate

The clinical pregnancy rate will be calculated for the fresh cycle, for each cryopreserved cycle, cumulatively for the cryopreserved cycles, and cumulatively across the fresh and cryopreserved cycles based on both the total number of subjects in the treatment group and the total number of subjects who started the respective cycle. The analyses will be conducted in a similar manner as ongoing pregnancy rate and will be applied to both the mITT and PP analysis sets. For subjects with clinical pregnancy, the type of clinical pregnancy (intrauterine or ectopic) will be tabulated.

9.7.3.5 Vital Pregnancy Rate

The vital pregnancy rate will be calculated and analyzed in a similar manner as ongoing pregnancy rate and will be applied to both the mITT and PP analysis sets.

9.7.3.6 Implantation Rate

The implantation rate will be calculated and analyzed in a similar manner as ongoing implantation rate and will be applied to both the mITT and PP analysis sets.

9.7.3.7 Positive βhCG Rate

The positive βhCG rate will be calculated and analyzed in a similar manner as ongoing pregnancy rate and will be applied to both the mITT and PP analysis sets.

9.7.3.8 Triggering of Final Follicular Maturation, Cycle Cancellation and Transfer Cancellation

The proportion of subjects with triggering of final follicular maturation will be tabulated by triggering drug (hCG, GnRH agonist) and in total. The proportion of subjects with cycle cancellation or transfer cancellation in the cycle will also be tabulated, including the reasons.

9.7.3.9 Number and Size of Follicles during Stimulation

The follicle cohort on stimulation day 5 and end-of-stimulation will be summarized 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 Wilcoxon's test. Categorical data will be compared between treatment groups using the chi-square test or Fisher's exact test in case of sparse data. The analyses will be applied to both the mITT and PP analysis sets.

9.7.3.10 Number and Distribution of Oocytes Retrieved

The number of oocytes retrieved will be tabulated including summary statistics. Furthermore, a frequency table with subjects grouped according to number of oocytes retrieved will be prepared using these categories: <4, 4-7, 8-14, 15-19 and ≥20 oocytes. Subjects with cycle cancellation due to poor ovarian response will be included in the <4 oocytes group. Continuous data will be compared between treatment groups using Wilcoxon's test. Categorical data will be compared between treatment groups using the chi-square test or Fisher's exact test in case of sparse data. The analyses will be applied to both the mITT and PP analysis sets.

9.7.3.11 Number of Metaphase II Oocytes

Oocytes undergoing ICSI will have their maturity stage assessed prior to insemination. The number of metaphase II (MII) oocytes per subject will be tabulated including both summary statistics and a frequency table. Furthermore, the percentage of MII oocytes to oocytes retrieved for subjects where all oocytes are inseminated using ICSI will be tabulated. Continuous data will be compared between treatment groups using Wilcoxon's test. Categorical data will be compared between treatment groups using the chi-square test or Fisher's exact test in case of sparse data. The analyses will be applied to both the mITT and PP analysis sets.

9.7.3.12 Number of Fertilized Oocytes and Fertilization Rate

An oocyte is defined as fertilized if it is scored as 2PN at 19h (±2h). The number of fertilized oocytes per subject will be tabulated including both summary statistics and a frequency table. Furthermore, for subjects with oocytes retrieved, the rate of fertilized oocytes to oocytes retrieved (and also the rate of fertilized oocytes to metaphase II oocytes for those inseminated using ICSI) will be tabulated overall and by method of insemination. Continuous data will be compared between treatment groups using Wilcoxon's test as applicable. Categorical data will be compared between treatment groups using the chi-square test or Fisher's exact test in case of sparse data. The analyses will be applied to both the mITT and PP analysis sets.

9.7.3.13 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. Tables will be produced overall and by method of insemination. The percentage of subjects with at least one good-quality blastocyst, i.e. of grade 3BB or above[i], will be reported. Further, for subjects with oocytes retrieved, the rate of blastocysts to oocytes retrieved will be summarized overall and by quality score. Continuous data will be compared between treatment groups using Wilcoxon's test. Categorical data will be compared between treatment groups using the chi-square test or Fisher's exact test in case of sparse data. The analyses will be applied to both the mITT and PP analysis sets.

9.7.3.14 Endometrial Thickness and Echogenicity Pattern

Endometrial thickness on stimulation day 5 and at end-of-stimulation will be tabulated including summary statistics. Endometrial echogenicity pattern on stimulation day 5 and at end-of-stimulation will be tabulated. Continuous data will be compared between treatment groups using Wilcoxon's test. Categorical data will be compared between treatment groups using the chi-square test or Fisher's exact test in case of sparse data. The analyses will be applied to both the mITT and PP analysis sets.

9.7.3.15 Oocyte Utilization Rate and Oocyte Efficiency Index

The oocyte utilization rate (number of blastocysts transferred or cryopreserved divided by the number of oocytes retrieved) will be analyzed in a similar manner as ongoing implantation rate and will be applied to both the mITT and PP analysis sets.

[i] 3BB and above defined as: 6AA, 6AB, 6AC, 6BA, 6BB, 6BC, 6CA, 6CB, 6CC, 5AA, 5AB, 5AC, 5BA, 5BB, 5BC, 5CA, 5CB, 5CC, 4AA, 4AB, 4AC, 4BA, 4BB, 4BC, 4CA, 4CB, 4CC, 3AA, 3AB, 3AC, 3BA, or 3BB.

The oocyte efficiency index (cumulative number of ongoing pregnancies per oocyte retrieved) will be analyzed in a similar manner as ongoing implantation rate and will be applied to both the mITT and PP analysis sets.

9.7.3.16 Blastocyst Survival and Re-expansion after Cryopreservation

The number and percentage of blastocysts surviving cryopreservation will be tabulated. Further, among the blastocysts that survived cryopreservation, the number and percentage of blastocysts with re-expansion will be tabulated.

9.7.3.17 Number of Cryopreserved Cycles

The number of cryopreserved cycles initiated (i.e. cycles with subjects starting estradiol treatment), as well as the number and percentage of cryopreserved cycles with blastocyst transfer will be tabulated. Further, the total number of blastocysts transferred in fresh and cryopreserved cycles will be tabulated.

9.7.3.18 Circulating Levels of Endocrine Parameters

Blood samples drawn on stimulation day 1, stimulation day 5, end-of-stimulation, and oocyte retrieval will be analyzed for AMH, 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 5, end-of-stimulation and oocyte retrieval. For each parameter the change from baseline will be compared between treatment groups using a log-normal model. In this model change from baseline in log-transformed measurements will be the dependent variable and the linear predictor will include treatment as factor and baseline measurement (log-transformed) as covariate. The estimated treatment difference with 95% confidence interval will be presented on the original scale of measurement (i.e. exp-transformation applied to the log-transformed measurement) and accompanied by the p-value for test of no treatment difference.

Further, a population pharmacokinetic model will be used for evaluating the effects of subject characteristics on FSH concentrations and for assessing the variability in exposure. The modelling analysis will be described in a modelling analysis plan and the results reported separately from the clinical trial report.

9.7.3.19 Total Gonadotropin Dose, Number of Stimulation Days, and Number of Dose Adjustments

The total gonadotropin dose will be tabulated by treatment group. For the placebo group, both the actual total dose administered and the intended total dose (i.e. the sum of the dialed doses recorded by the subject) will be presented. In addition, the average daily dose, i.e. the total dose divided by the number of stimulation days, will be tabulated by treatment group.

The number of stimulation days will be tabulated by treatment group.

Investigator-requested decreases and increases of the gonadotropin dose will be captured during the stimulation period. The requested dose change (decrease / increase / no change) on stimulation day 5 will be tabulated. Furthermore, the total number of dose increase requests and dose decrease requests per subject will be tabulated.

These tables will be produced for all subjects who started stimulation, and for subjects who underwent triggering of final follicular maturation as well as separately according to whether triggering was done with hCG or GnRH agonist.

9.8 Safety Endpoints Assessments

9.8.1 General Considerations

Analyses for the safety analysis set will be conducted according to the actual treatment received.

Data will be presented by summary tables and listings. Categorical data will be summarized by treatment using the number and percentage of subjects in each category. For calculation of percentages, the denominator will be the total number of subjects in the respective treatment group in the safety analysis set. Continuous data will be summarized by treatment using number, mean, standard deviation, median, minimum, and maximum.

All individual subject data will be listed per subject and treatment as observed including any derived values.

Missing Data

Missing values will be treated as missing, except for causality, intensity, seriousness, and outcome of adverse events. A worst-case approach will be used: if causality is missing, the adverse event will be regarded as related to the IMP; if the intensity of an adverse event is missing, the adverse event will be regarded as severe; if seriousness is missing, the adverse event will be regarded as serious; if outcome

is missing, and no date of outcome is present, the outcome is regarded as 'ongoing'.

9.8.2 Secondary Safety Endpoints

9.8.2.1 Adverse Events

Adverse events will be coded using MedDRA. The version of MedDRA will be documented. Adverse events will be 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 in the fresh cycle, i.e. any adverse event occurring after start of IMP and before the end-of-cycle 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-cycle visit.
- Adverse events in cryopreserved cycles, i.e. any adverse event occurring after initiation of a cryopreserved cycle and before the end-of-cycle visit, or a pre-existing medical condition that worsens in intensity after initiation of a cryopreserved cycle and before the end-of-cycle visit.

Treatment-emergent adverse events and adverse events in cryopreserved cycles 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, SAEs 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 alphabetically and 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 treatment-emergent adverse events, treatment-emergent adverse events by causality (reasonable possibility / no reasonable possibility), treatment-emergent adverse events leading to death, adverse events by intensity (mild / moderate / severe), treatment-emergent adverse reactions by intensity (mild / moderate / severe), serious treatment-emergent adverse events, treatment-emergent adverse events leading to discontinuation, treatment-emergent adverse events with an incidence of ≥5% in any treatment group, and non-serious treatment-emergent adverse events with an incidence of ≥5% in any treatment group.

Similar displays will be prepared for the adverse events in cryopreserved cycles.

9.8.2.2 Clinical Chemistry and Hematology Parameters

The circulating levels of clinical chemistry and hematology 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-cycle values, using a categorization 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.

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.

9.8.2.3 Injection Site Reactions

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

9.8.2.4 Treatment-induced Anti-FSH Antibodies

The proportion of subjects with treatment-induced anti-FSH antibodies as well as the proportion of subjects with treatment-induced anti-FSH antibodies with neutralizing capacity will be tabulated. Furthermore, all assessments of anti-FSH antibodies will be listed for subjects with a positive result in assay 2.

9.8.2.5 Immune-related Adverse Events

Potential immune-related adverse events will be tabulated using the SMQs, PTs and HLTs mentioned in section 7.2.5.

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

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

9.8.2.7 Ovarian Hyperstimulation Syndrome

OHSS will for each treatment group be tabulated by classification (mild, moderate, severe) and grade (1, 2, 3, 4, 5). The tabulation will also include the total incidence of OHSS and the incidence of moderate/severe OHSS. OHSS will be presented overall and by timing (early, late, and early and late combined). Separate tabulations will be made for the fresh and the cryopreserved cycles.

9.8.2.8 Hospitalization and Paracentesis due to Ovarian Hyperstimulation Syndrome

The number and percentage of subjects hospitalized due to OHSS as well as the number and percentage of subjects who underwent paracentesis due to OHSS will be tabulated. Separate tabulations will be made for the fresh and the cryopreserved cycles.

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

Summary tables will be prepared for these endpoints. Separate tabulations will be made for the fresh and the cryopreserved cycles.

9.8.2.10 Technical Malfunctions of the Administration Pen

The frequency of technical malfunctions of the administration pen will be presented in a summary table.

9.9 Additional Safety Evaluations

Vital Signs

Vital signs and their change from stimulation day 1 (baseline) to end-of-cycle will be summarized. Shift tables will be prepared to compare the baseline values with the end-of-cycle values using the categorization 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-cycle in the fresh cycle compared to screening will be summarized in shift tables and all subjects with any abnormal finding will be listed per subject. For each cryopreserved cycle, physical examination at end-of-cycle in the cryopreserved cycle compared to cycle initiation in the respective cycle will be summarized in shift tables and all subjects with any abnormal finding will be listed per subject.

Gynecological Examination

Gynecological examination at end-of-cycle in the fresh cycle compared to screening will be summarized in shift tables and all subjects with any abnormal finding will be listed per subject. For each cryopreserved cycle, gynecological examination at end-of-cycle in the cryopreserved cycle compared to cycle initiation in the respective cycle will be summarized in shift tables and all subjects with any abnormal finding will be listed per subject.

9.10 Post-trial Activities

9.10.1 Post-trial Endpoints

9.10.1.1 Cumulative Live Birth Rate

The live birth rate will be calculated cumulatively across the fresh and cryopreserved cycles. Subjects with no information on live birth will be defaulted to a negative response. Descriptive statistics will be presented by treatment group.

9.10.1.2 Live Birth Rate

The live birth rate will be calculated for the fresh cycle, for each cryopreserved cycle, and cumulatively for the cryopreserved cycles. Subjects with no information on live birth will be defaulted to a negative response. Descriptive statistics will be presented by treatment group.

9.10.1.3 Live Birth Rate of Singletons Born at Term

The live birth rate of singletons born at term will be calculated for the fresh cycle, for each cryopreserved cycle, cumulatively for the cryopreserved cycles, and cumulatively across the fresh and cryopreserved cycles. Subjects with no information on live birth will be defaulted to a negative response. Descriptive statistics will be presented by treatment group.

9.10.1.4 Time to Live Birth of a Singleton Born at Term

For subjects who achieve live birth of a singleton born at term, time to live birth of a singleton born at term across the fresh and cryopreserved cycles will be calculated as the number of days from the start of controlled ovarian stimulation to delivery, as well as the number of cycles until delivery. Descriptive statistics will be presented by treatment group.

9.10.1.5 Minor/Major Congenital Anomalies

The rate of minor/major congenital anomalies at birth, 4 weeks and 1 year after birth in the fresh cycle and cryopreserved cycles will be calculated. Descriptive statistics will be presented by treatment group.

9.10.2 Other Post-trial Evaluations

Gender, birth weight and length, and Apgar score will be tabulated. Descriptive statistics will be presented by treatment group.

9.11 Optional Exploratory Analyses

Results on the potential future genome sequencing and microbial profiling will be reported separately from the clinical trial report.

9.12 Interim Analysis

No interim analysis intended to compare treatment groups with respect to efficacy or safety 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 identifier [ID], subject ID)
- Informed consent(s) (date and time of oral information, date and time of handing out Informed Consent Documents, date and time of obtaining written informed consent(s))
- Eligibility for participation in the trial (documenting all inclusion/exclusion criteria)
- Relevant medical history, infertility history, menstrual history and reproductive history
- Body weight measurements (fresh cycle + cryopreserved cycles)
- Visit dates (fresh cycle + cryopreserved cycles)
- Dates of administration of IMP
- Dates and daily doses of NIMP (fresh cycle + cryopreserved cycles)
- Dates and daily doses of concomitant medication (fresh cycle + cryopreserved cycles)

- Date of oocyte retrieval and number of oocytes retrieved
- Date of transfer and number and quality of blastocysts transferred (fresh cycle + cryopreserved cycles)
- Number and quality of blastocysts cryopreserved
- Number of blastocysts thawed, number of surviving blastocysts, quality of surviving blastocysts (cryopreserved cycles)
- Confirmation of LH surge (natural cryopreserved cycles)
- Results of βhCG test and ultrasound at clinical and ongoing pregnancy visits (fresh cycle + cryopreserved cycles)
- Pregnancy outcome, i.e. live birth or pregnancy loss (fresh cycle + cryopreserved cycles), and neonatal health at birth, 4 weeks and 1 year after birth (fresh cycle + cryopreserved cycles)
- Injection site reactions after IMP administration – diary
- Adverse events (description as well as start/stop date and time) (fresh cycle + cryopreserved cycles)
- OHSS symptoms, investigations and treatments
- Reason for discontinuation (fresh cycle + cryopreserved cycles)
- Event of unblinding, including the reason for unblinding
- Follow-up on treatment-induced anti-FSH antibody response

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

If the trial sites use electronic medical record systems, the sponsor will decide if the electronic medical records qualify for the trial and document the decision. If the electronic medical records system does not qualify for the trial, it may be considered to utilize paper data sheets for source data as an exception.

The source data for the endocrine parameters, clinical chemistry and hematology parameters as well as anti-FSH antibodies will be available at the central laboratory. Laboratory reports will be available at the sites for clinical chemistry and hematology parameters.

10.2 eCRF

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

Trial data should be entered into the eCRF in a timely manner. The time-frame will be specified in the investigator agreement.

The investigator will approve/authorize the eCRF entries for each subject, with an electronic signature which is equivalent to a handwritten signature.

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

Entry 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.

The data management plan will also include information about the intended use of computerized systems, a description of the security measures employed to protect the data, and a description of the electronic data flow.

10.4 Provision of Additional Information

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

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of 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 co-operate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits.

When the first subject is randomized at the trial site, a monitoring visit will take place shortly afterwards. For this trial, the frequency of the monitoring visits per site will be determined by the enrolment rate, observed data quality, overall site performance and will be detailed in the Monitoring Plan.

The source data verification process and definition of key variables to be monitored will be described in detail in the Monitoring Plan for the trial.

11.2 Audit and Inspection

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

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki and all other relevant regulations.

The subjects must be informed by the investigator and in the Informed Consent Documents that authorized Ferring representatives and representatives from regulatory authorities and IRBs 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/randomization number will appear on these copies.

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

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, and, if applicable, agreed upon by the investigator and Ferring prior to its implementation. Amendments may be submitted for consideration to the approving IRBs and FDA, in accordance with U.S. regulations. Changes to the protocol to eliminate immediate hazard(s) to trial subjects may be implemented prior to IRBs approval/favorable 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, either as answer to a query in the eCRF, in a protocol deviation report or a combination of both. A log of protocol deviation reports will be maintained by Ferring. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and the Trial Master File.

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. The appropriate authorities and IRBs will be informed.

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

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring and submitted for comments and signature to the signatory investigator. Furthermore, the data and information collected during the post-trial follow-up activities will be reported in clinical trial report addendums, including live birth, neonatal health at birth, 4 weeks and 1 year after birth in the fresh cycle and the cryopreserved cycles, respectively.

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 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 will 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 U.S. regulatory requirements. A summary of the trial results is made publicly available in accordance with U.S. regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Institutional Review Board (IRB)

An IRB will review the protocol and any amendments and advertisements used for recruitment. The IRB will review the Subject Information Sheet and the Informed Consent Form, their updates (if any), and any written materials given to the subjects. A list of all IRBs to which the protocol has been submitted and the name of the committee chairmen will be included in the Clinical Trial Report.

14.2 Regulatory Authority Notification

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

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

The end of the trial is defined as the date of last patient last visit (LPLV), i.e. when the last subject completes the last end-of-cycle visit in a cryopreserved cycle. This date is also the primary completion date.

Post-trial follow-up will cover the period from LPLV to the end of the 1-year follow-up of the neonates.

The IRBs will be notified about the completion of the clinical trial and the post-trial follow-up according to local legislation.

In the case of early termination for safety reasons, Ferring will notify the relevant authorities and IRBs about the end of the trial as soon as possible, clearly explain the reasons, and describe follow-up measures, if any.

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

14.5 Subject Information and Consent

This trial will use three sets of Informed Consent Documents (consisting of Subject Information and Informed Consent Form): one covering trial participation, one covering potential future genome

sequencing and microbial profiling, and one covering data collection on the neonate. The latter two documents will only describe the aspects relevant to the exploratory analyses or to the neonate and should be read in conjunction with the Informed Consent Document for the general trial. Participation in the investigation of exploratory analyses is optional.

Informed Consent Documents regarding Participation in the Trial – Subject

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

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

The subject will receive a copy of the Subject Information and her signed Informed Consent Form.

If new important information becomes available that may be relevant to the trial subject's willingness to continue participation in the trial, a new Subject Information and Informed Consent Form will be forwarded to the IRBs (and FDA, if required). The trial subjects will be informed about this new information and re-consent will be obtained.

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

Informed Consent Documents regarding Exploratory Analyses – Subject (*Optional*)

The investigator (or the person delegated by the investigator) will obtain a freely given written consent from the subject after an appropriate explanation of the potential future genome sequencing and microbial profiling and after information that participation in these exploratory analyses is optional.

The trial subject must be given ample time to consider participation in these exploratory analyses, before the consent is obtained. The Informed Consent Documents must be signed and dated by the subject and the investigator, or the person delegated by the investigator, who has provided information to the subject regarding the exploratory analyses, before any associated samples are collected.

The investigator (or the person delegated by the investigator) will explain that the subject is completely free to refuse to consent to these exploratory analyses or to withdraw consent at any time, without any consequences for her further care and without the need to justify her decision.

The subject will receive a copy of the Subject Information and her signed Informed Consent Form.

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

Informed Consent Documents regarding Data Collection on the Neonate – Parental Consent

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

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

The child-custody holders will receive a copy of the Subject Information and their signed Informed Consent Form.

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

14.6 Subject Participation Card

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

- That she is participating in a clinical trial.
- That the trial involves controlled ovarian stimulation, and the subject receives/has received either a recombinant FSH under clinical development in the U.S., or placebo.
- The name and phone number of the investigator.
- The name, address and phone number of Ferring contact (as required by local regulations).

The subjects will be asked to keep the Subject Participation Card in their possession at all times during the trial and to return it at the last 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 Checklist for Pregnancy Follow-up

In addition to the trial participation card, the subject will be provided with a checklist for pregnancy follow-up, where the subject will be reminded to report the following information to the investigator:

<u>At delivery:</u>

- Date of delivery
- Way of delivery (vaginal / vacuum extraction / forceps / caesarean section)
- Position of neonate (head / breech / transverse / other – please specify)
- Gender
- Birth weight
- Birth length
- Apgar score after 1 and 5 minutes
- Admission to NICU regardless of duration
- Admission to NCU for more than 2 hours
- Any medically important event
- Congenital anomaly
- Neonatal death

4 weeks after delivery:

Relevant important conditions since birth:

- Admission to NICU regardless of duration
- Admission to NCU for more than 2 hours
- Any medically important event
- Any congenital anomaly discovered since birth
- Neonatal death

1 year after delivery:

Relevant important conditions since the 4-weeks follow-up:

- Admission to NICU regardless of duration
- Admission to NCU/PCU for more than 2 hours
- Any medically important event
- Any congenital anomaly discovered since the 4-weeks follow-up
- Death of infant

14.8 Compliance Reference Documents

The Helsinki Declaration, the consolidated ICH-GCP and other national law(s) in the U.S. shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor and the investigator are defined in the ICH-GCP consolidated guideline, and applicable regulatory requirements in the U.S. The investigator is responsible for adhering to the ICH-GCP responsibilities of investigators, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

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

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 15 years after the completion or discontinuation of the trial, if no further instructions are given by Ferring.

The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and anonymous 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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CLINICAL TRIAL PROTOCOL
SUMMARY OF CHANGES #01

A randomized, double-blind, placebo-controlled, parallel groups, multicenter trial investigating the efficacy and safety of FE 999049 in controlled ovarian stimulation in women aged 35-42 years undergoing assisted reproductive technology

Trial 000002

Recombinant FSH Investigation in the Treatment of Infertility with ART (RITA-2)

IND Number:	103040
Investigational Medicinal Product:	FE 999049, human recombinant follicle-stimulating hormone (rFSH), solution for subcutaneous injection
Indication:	Development of multiple follicles and pregnancy after fresh and/or cryopreserved embryo transfer in ovulatory women undergoing assisted reproductive technology (ART)
Phase:	3
Name and Address of Sponsor:	Ferring Pharmaceuticals, Inc. 100 Interpace Parkway Parsippany, NJ 07054 United States Tel: [redacted]
Amendment Number:	01
Sites where Effective:	All trial sites
Date of Original Protocol:	25 Apr 2018

This Protocol Amendment
- implications for continued trial conduct -
is issued as urgent safety measures due to COVID-19 required to protect subjects against immediate hazard to their health and safety and is implemented immediately

DOCUMENT INFORMATION:

Protocol change intended to eliminate an apparent immediate hazard to subjects.

REASON FOR CHANGE TO THE CLINICAL TRIAL PROTOCOL:

- The COVID-19 pandemic has caused extensive restrictions on the movement of local populations in countries worldwide and recommendations to focus health care resources on essential activities only. Subsequently, clinical trial participants are experiencing increased difficulty in attending scheduled visits and trial sites are operating at reduced capacity.

- On 17 March 2020, the American Society for Reproductive Medicine (ASRM) issued a guidance on patient management and clinical recommendations, including: *"Suspend initiation of new treatment cycles…. Strongly consider cancellation of all embryo transfers whether fresh or frozen… Continue to care for patients who are currently "in-cycle""*.

- On 18 March 2020, the Food and Drug Administration (FDA) issued a guidance on conduct of clinical trials of medicinal products during the COVID-19 pandemic, including general considerations for how to ensure the safety of trial participants, maintain compliance with GCP and minimize risks to trial integrity.

Ferring has conducted a risk assessment, which led to this change to the clinical trial protocol. This document outlines the deliberations and decisions.

SUMMARY OF MAIN CHANGES TO CLINICAL TRIAL PROTOCOL:

Recruitment to the trial has been completed and all fresh cycles have been completed up to the ongoing pregnancy visit. The current activities are cryopreserved cycles initiated within 12 months from the start of controlled ovarian stimulation as well as pregnancy follow-up to birth, 4 weeks and 1 year after birth in the fresh and cryopreserved cycles.

Ferring is issuing guidance for continued trial conduct and management of subjects included in the trial. The table below provides guidance for how to manage the subjects according to stage in the trial.

Continued trial conduct for management of subjects included in the trial
• Cryopreserved cycles: o Cycles not yet initiated: do not initiate until this COVID-19 related temporary deferral of cryopreserved cycles has been lifted o Cycles already initiated and where transfer has not occurred: continue per protocol and document any deviations o Cycles where transfer has occurred: continue per protocol and document any deviations o *Note:* timelines for cryopreserved cycles will be extended by the approximate duration of the temporary deferral of cryopreserved cycles required by this change to the protocol • Pregnancy follow-up: continue per protocol and document any deviations

In case subjects are prevented from attending scheduled visits, the investigator (or designee) will attempt to contact the subject by phone or other ways to inquire about potential adverse events and changes to concomitant medication.

IMPLICATIONS OF CHANGE:

The implications of these changes to the protocol are summarized below. The actions are considered urgent safety measures due to COVID-19 required to protect subjects against immediate hazard to their health and safety and are therefore implemented immediately.

- Trial sites, regulatory authorities and independent research boards will be informed.
- Subjects will be verbally informed by the investigator of potential changes to the course of action, as applicable for the individual subject. This will be documented in the subject's medical records.
- Protocol deviations (including deviations to the aspects described in this 'change to protocol') should be avoided whenever possible except where necessary to eliminate an immediate hazard to the subject. If deviations occur they will be documented as per standard practice, with additional specification whether they were related to the COVID-19 situation.
- Ferring will continuously monitor the situation and will resume the trial activities as per protocol when it is judged that the situation allows for this. Ferring will notify sites, regulatory authorities and independent research boards accordingly.