Cover page for Protocol

Sponsor name	Ferring Pharmaceuticals A/S
NCT Number:	NCT03809429
Sponsor trial ID:	000304
Official title of trial:	A randomised, controlled, open label, parallel group, multicentre trial comparing the efficacy and safety of individualised FE 999049 (follitropin delta) dosing, using a long GnRH agonist protocol and a GnRH antagonist protocol in women undergoing controlled ovarian stimulation
Document Date:	09 Dec 2020

CLINICAL TRIAL PROTOCOL

A randomised, controlled, open label, parallel group, multicentre trial comparing the efficacy and safety of individualised FE 999049 (follitropin delta) dosing, using a long GnRH agonist protocol and a GnRH antagonist protocol in women undergoing controlled ovarian stimulation

Trial 000304

BEYOND

EudraCT Number:	2017-002783-40
Investigational Medicinal Product:	FE 999049, human recombinant follicle-stimulating hormone (rFSH), solution for subcutaneous injection
Indication:	Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle
Phase:	3b
Name and Address of Sponsor:	Ferring Pharmaceuticals A/S Global Clinical R&D International PharmaScience Center Kay Fiskers Plads 11 2300 Copenhagen S Denmark [redacted]
Version:	3.0 (Consolidated protocol; changes introduced with protocol amendment 02 implemented)
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A randomised, controlled, open label, parallel group, multicentre trial comparing the efficacy and safety of individualised FE 999049 (follitropin delta) dosing, using a long GnRH agonist protocol and a GnRH antagonist protocol in women undergoing controlled ovarian stimulation

SIGNATORY INVESTIGATOR

Professor Anja Pinborg, The Fertility Clinic, Rigshospitalet, Copenhagen University Hospital, Denmark

TRIAL SITES

Approximately 15 sites in 5-7 countries

PLANNED TRIAL PERIOD		**CLINICAL PHASE**
First patient first visit (FPFV):	Q1 2019	3b
Last patient first visit (LPFV):	Q3 2021	
Last patient last visit (LPLV) / end-of-trial:	Q1 2022	
Post-trial follow-up completed:	Q4 2022	

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

FE 999049 (follitropin delta) is a novel human recombinant follicle-stimulating hormone (rFSH) under global development by Ferring Pharmaceuticals. FE 999049 is individually dosed based on the patient's body weight and serum anti-Müllerian hormone (AMH) level. In December 2016, Ferring received Marketing Authorisation approval from the European Commission for FE 999049 under the trade name REKOVELLE. During 2017, FE 999049 was approved in Australia, Brazil, Israel and Switzerland, and in 2018, also in Canada and Mexico. The indication is: "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."

All clinical phase 2 and 3 trials conducted with FE 999049 have applied the gonadotropin-releasing hormone (GnRH) antagonist protocol and the FE 999049 dosing algorithm has not yet been studied in a long GnRH agonist protocol. Previous studies comparing the efficacy and safety of a GnRH antagonist protocol with a long GnRH agonist protocol using rFSH derived from Chinese hamster ovary (CHO) cell lines have consistently indicated that the cohort of recruited follicles is slightly smaller in GnRH antagonist cycles. The difference in the largest

randomised controlled trial was -1.0 oocyte (95% confidence interval [CI] -1.8; -0.2) which is in agreement with the estimated difference of -1.07 oocyte (95% CI -1.52; -0.61) in a Cochrane review including 27 randomised controlled trials. The evidence available suggests that the long GnRH agonist protocol compared to the GnRH antagonist protocol is generally associated with one more oocyte retrieved, one more day of stimulation, and consequently a higher total dose of exogenous FSH equivalent to one more day of dosing.

The impact on ovarian response and efficacy when applying the long GnRH agonist protocol instead of the GnRH antagonist protocol with FE 999049 is hypothesised to be similar to those described in the literature for existing rFSH preparations. In the pivotal phase 3 trial ESTHER-1, the mean number of oocytes retrieved was 9.6± 5.8 in the FE 999049 group and 10.1 ± 6.6 in the GONAL-F group for all randomised subjects. For subjects with triggering of final follicular maturation the mean number of oocytes retrieved was 10.0 ± 5.6 in the FE 999049 group and 10.4 ± 6.5 in the GONAL-F group. When analysed by AMH, the mean number of oocytes retrieved was 8.0 ± 4.3 in the FE 999049 group versus 7.0 ± 3.9 in the GONAL-F group among patients with AMH <15 pmol/L, and 11.6 ± 5.9 in the FE 999049 group versus 13.3 ± 6.9 oocytes in the GONAL-F group among patients with AMH ≥15 pmol/L.

This prospective, comparative trial is designed to document the ovarian response following the application of the individualised FE 999049 dosing regimen in a long GnRH agonist protocol compared to a GnRH antagonist protocol. The trial will describe the impact of the protocol on the mean number of oocytes retrieved, the mean number of oocytes retrieved in patients with AMH <15 pmol/L and AMH ≥15 pmol/L as well as the distribution of the number of oocytes retrieved (<4, 4-7, 8-14, 15-19, ≥20 oocytes).

OBJECTIVES

Primary objective

- To evaluate the effect of individualised FE 999049 treatment on ovarian response in a long GnRH agonist protocol versus a GnRH antagonist protocol

Secondary objectives

- To evaluate the effect of individualised FE 999049 treatment on other pharmacodynamic parameters in a long GnRH agonist protocol versus a GnRH antagonist protocol
- To evaluate the effect of individualised FE 999049 treatment on pregnancy rates in a long GnRH agonist protocol versus a GnRH antagonist protocol
- To evaluate the safety of individualised FE 999049 treatment in a long GnRH agonist protocol versus a GnRH antagonist protocol

ENDPOINTS

Primary endpoint

- Number of oocytes retrieved

Secondary endpoints

- Proportion of subjects with cycle cancellation due to poor ovarian response or excessive ovarian response
- Proportion of subjects with blastocyst transfer cancellation after oocyte retrieval due to (risk of) ovarian hyperstimulation syndrome (OHSS)
- Number and size of follicles on stimulation day 6 and end-of-stimulation
- Proportion of subjects with <4, 4-7, 8-14, 15-19 and ≥20 oocytes retrieved
- Number of metaphase II oocytes (only applicable for those inseminated using ICSI), fertilisation rate as well as number and quality of embryos on day 3 and blastocysts on day 5 after oocyte retrieval
- Circulating concentrations of FSH, luteinising hormone (LH), estradiol, progesterone and inhibin B on stimulation day 6, end-of-stimulation and at oocyte retrieval
- Total gonadotropin dose and number of stimulation days
- Positive βhCG rate (positive serum βhCG test 13-15 days after transfer)
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of blastocysts transferred)
- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer)
- Vital pregnancy rate (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer)
- Ongoing pregnancy rate (at least one intrauterine viable fetus 10-11 weeks after transfer
- Ongoing implantation rate (number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of blastocysts transferred)
- Proportion of subjects with early OHSS (including OHSS of moderate/severe grade)
- Proportion of subjects with late OHSS (including OHSS of moderate/severe grade)
- Frequency and intensity of adverse events
- Technical malfunctions of the prefilled injection pen

POST-TRIAL INFORMATION

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

METHODOLOGY

This will be a randomised, controlled, open label, parallel group, multicentre trial comparing the efficacy and safety of individualised FE 999049 dosing in first cycle patients aged 18-40 years undergoing controlled ovarian stimulation for IVF/ICSI following either a long GnRH agonist protocol or a GnRH antagonist protocol. The trial has been designed to describe potential differences in the mean number of oocytes retrieved with adequate precision.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. Randomisation may take place as soon as all eligibility criteria are met. Randomisation does not necessarily need to take place at a physical visit, but can be done by delegated trial staff without the subject being present at the clinic. However, the subject will be contacted prior to randomisation to confirm eligibility. Subjects will be randomised in a 1:1 ratio to controlled ovarian stimulation with FE 999049 in a long GnRH agonist protocol or to controlled ovarian stimulation with FE 999049 in a GnRH antagonist protocol. Randomisation will be stratified by centre and according to age (<35, 35-37 and 38-40 years). The subject will be informed of treatment allocation and when to start treatment by the delegated trial staff.

Subjects randomised to treatment with FE 999049 in the long GnRH agonist protocol will start down-regulation with GnRH agonist (triptorelin acetate, GONAPEPTYL) 0.1 mg/day subcutaneously in the mid-luteal phase (i.e. cycle day 21-24) of their menstrual cycle. Ovarian stimulation with FE 999049 will start after 14 days (±1 day) if the subject has experienced withdrawal bleeding and the following down-regulation criteria are fulfilled: 1) a thin endometrium (<5 mm) is observed by transvaginal ultrasound, and 2) no ovarian follicles ≥10 mm (including cysts that cannot be punctured prior to stimulation) are observed by transvaginal ultrasound. In case achievement of down-regulation is doubtful or it is deemed helpful, serum estradiol is to be measured (<50 pg/mL or 180 pmol/L; local laboratory). If down-regulation is confirmed and ovarian stimulation is initiated, treatment with GnRH agonist is continued throughout the stimulation period. If the subject has not experienced withdrawal bleeding after 14 days (±1 day), a urinary pregnancy test is to be performed. If the subject is not pregnant and down-regulation is not confirmed, treatment with GnRH agonist will be continued and stimulation will be postponed until down-regulation is confirmed. Subsequent visit(s) for confirmation of down-regulation will be scheduled according to local practice. If down-regulation is not achieved after 28 days, treatment with GnRH agonist will be stopped and the subject will be withdrawn from the trial.

Subjects randomised to treatment with FE 999049 in the GnRH antagonist protocol will start stimulation with FE 999049 on day 2 or 3 of their menstrual cycle. To prevent a premature LH surge, a GnRH antagonist (cetrorelix acetate, CETROTIDE) 0.25 mg/day subcutaneously will be initiated on stimulation day 6 and continued throughout the stimulation period.

Subjects will have their individual FE 999049 dose determined on the basis of their AMH level at screening and their body weight on stimulation day 1. The daily FE 999049 dose will be fixed

throughout the stimulation period. For subjects with AMH <15 pmol/L the daily FE 999049 dose is 12 µg, irrespective of body weight. For subjects with AMH ≥15 pmol/L the daily FE 999049 dose is on a continuous scale ranging from 0.19 to 0.10 µg/kg, i.e. dependent on actual AMH and body weight. AMH will be measured by Elecsys® AMH Plus Immunoassay (Roche Diagnostics). The maximum allowed daily FE 999049 dose is 12 µg. Subjects can be treated with FE 999049 for a maximum of 20 days, and coasting is not allowed.

During stimulation, subjects will be monitored by transvaginal ultrasound on stimulation day 1 and 6 and hereafter at least every second day. When the leading follicle reaches ≥15 mm, visits must be performed daily. Triggering of final follicular maturation will be done as soon as ≥3 follicles with a diameter ≥17 mm are observed. If there are <25 follicles with a diameter ≥12 mm, a single dose of human chorionic gonadotropin (hCG) (OVITRELLE) 250 µg will be administered. If there are ≥25 follicles with a diameter ≥12 mm, the cycle will be cancelled. If it is judged by the investigator that ≥3 follicles with a diameter ≥17 mm cannot be reached, but 1 or 2 follicles with a diameter ≥17 mm are observed, the cycle may either be cancelled due to poor follicular development or triggering of final follicular maturation is to be induced, as judged by the investigator.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation and the oocytes can be inseminated by IVF and/or ICSI. Fertilisation and embryo development will be assessed from oocyte retrieval to the day of transfer. For all subjects blastocyst transfer is performed on day 5 after oocyte retrieval. Subjects <38 years at randomisation will have single blastocyst transfer. Subjects ≥38 years at randomisation will have single blastocyst transfer if they have a good-quality blastocyst available, i.e. a blastocyst of grade 3BB or higher; otherwise they may have double blastocyst transfer. Remaining blastocysts may be cryopreserved and used by the subject after completion of the trial, in accordance with local guidelines and/or regulations. All procedures and assessments related to cryopreserved cycles will take place outside this protocol and will not be paid for by Ferring.

Vaginal progesterone tablets (LUTINUS) 100 mg three times daily will be provided for luteal phase support from the day after oocyte retrieval and until the serum βhCG test. Luteal phase support may be continued after a positive βhCG is obtained if this is local practice. A serum βhCG test is performed 13-15 days after transfer, clinical pregnancy will be confirmed by transvaginal ultrasound 5-6 weeks after transfer, and ongoing pregnancy will be confirmed by transvaginal or abdominal ultrasound 10-11 weeks after transfer.

Blood samples will be collected throughout the trial for the purpose of evaluating the endocrine profile assessed at screening, stimulation day 1, stimulation day 6, end-of-stimulation and at oocyte retrieval.

Post-trial Activities

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

NUMBER OF SUBJECTS

It is planned to randomise approximately 400 subjects of whom approximately 200 will be randomised to the long GnRH agonist protocol and approximately 200 will be randomised to the GnRH antagonist protocol. It is estimated that up to 500 subjects should be screened to achieve 400 randomised and treated subjects.

CRITERIA FOR INCLUSION / EXCLUSION

This trial applies similar inclusion/exclusion criteria as ESTHER-1. Women undergoing their first IVF/ICSI cycle and aged 18-40 years will be included. They have been diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or have partners diagnosed with male factor infertility, and are considered eligible for IVF or ICSI. The allowed body mass index (BMI) is 17.5-32.0 kg/m^2, thus including underweight, normal weight, overweight and obese patients. The exclusion criteria incorporate the contraindications for the use of gonadotropins.

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

Inclusion Criteria

1. Informed Consent Forms signed prior to screening evaluations.
2. In good physical and mental health.
3. The subjects must be at least 18 years (including the 18th birthday) when they sign the Informed Consent Form and no more than 40 years (up to the day before the 41st birthday) at the time of randomisation.
4. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility, eligible for in vitro fertilisation (IVF) and/or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.
5. Infertility for at least one year before randomisation for subjects <38 years or for at least 6 months for subjects ≥38 years (not applicable in case of tubal or severe male factor infertility).
6. The trial cycle will be the subject's first controlled ovarian stimulation cycle for IVF/ICSI.
7. Regular menstrual cycles of 24-35 days (both inclusive), presumed to be ovulatory.

8. Hysterosalpingography, hysteroscopy, saline infusion sonography, or transvaginal ultrasound documenting a uterus consistent with expected normal function (e.g. no evidence of clinically interfering uterine fibroids defined as submucous or intramural fibroids larger than 3 cm in diameter, no polyps and no congenital structural abnormalities which are associated with a reduced chance of pregnancy) within 1 year prior to randomisation.
9. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. no endometrioma greater than 2 cm or enlarged ovaries which would contraindicate the use of gonadotropins) and normal adnexa (e.g. no hydrosalpinx) within 1 year prior to randomisation. Both ovaries must be accessible for oocyte retrieval.
10. Early follicular phase (cycle day 2-5) serum levels of FSH between 1 and 15 IU/L at screening.
11. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests within 1 year prior to randomisation.
12. Body mass index (BMI) between 17.5 and 32.0 kg/m^2 (both inclusive) at screening.
13. If <38 years willing to accept single blastocyst transfer. If ≥38 years willing to accept transfer of a single good-quality blastocyst (double blastocyst transfer may be performed if no good-quality blastocyst is available).

Exclusion Criteria

1. AMH >35 pmol/L at screening.
2. Strong preference of the subject for either treatment protocol.
3. Known endometriosis stage III-IV (defined by the revised American Society for Reproductive Medicine [ASRM] classification, 1996).
4. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy (excl. ectopic pregnancy) and before week 24 of pregnancy).
5. Known abnormal karyotype of subject or of her partner / sperm donor, as applicable, depending on source of sperm used for insemination in this trial.
6. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
7. Known inherited or acquired thrombophilia disease.
8. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
9. Known porphyria.
10. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) with the exception of controlled thyroid function disease.

11. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
12. Known moderate or severe impairment of renal or hepatic function.
13. Currently breast-feeding.
14. Undiagnosed vaginal bleeding.
15. Known abnormal cervical cytology of clinical significance observed within 3 years prior to randomisation (unless the clinical significance has been resolved).
16. Findings at the gynaecological examination at screening which preclude gonadotropin stimulation or are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
17. Pregnancy (negative pregnancy test must be documented at screening) or contraindication to pregnancy.
18. Known current active pelvic inflammatory disease.
19. Use of fertility modifiers during the last menstrual cycle before randomisation, including dehydroepiandrosterone (DHEA), metformin or cycle programming with oral contraceptives, progestogen or estrogen preparations.
20. Use of hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomisation.
21. Known history of chemotherapy (except for gestational conditions) or radiotherapy.
22. Current or past (1 year prior to randomisation) abuse of alcohol or drugs and/or current (last month) intake of more than 14 units of alcohol per week.
23. Current or past (3 months prior to randomisation) smoking habit of more than 10 cigarettes per day.
24. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
25. Previous participation in the trial.
26. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.

Withdrawal Criteria

1. One or more follicles ≥10 mm (including cysts that cannot be punctured prior to stimulation) observed on the transvaginal ultrasound on stimulation day 1 / day of confirmation of down-regulation.
2. Down-regulation not achieved within 28 days after the first GnRH agonist administration.
3. Pregnancy (positive pregnancy test) between screening and stimulation day 1.

4. Use of fertility modifiers between randomisation and stimulation day 1, including DHEA, metformin or cycle programming with oral contraceptives, progestogen or estrogen preparations.
5. Use of hormonal preparations (except for thyroid medication and trial medication) between randomisation and stimulation day 1.

MEDICINAL PRODUCTS

Investigational Medicinal Product (IMP)

IMP name	*Drug type*	*Active ingredient, route of administration and concentration*	*Daily dose*
FE 999049 REKOVELLE (follitropin delta)	rFSH	FE 999049 in solution for subcutaneous injection; 72 µg follitropin delta in 2.16 mL pre-filled injection pen	AMH <15 pmol/L: 12 µg AMH ≥15 pmol/L: ranging from 0.19 to 0.10 µg/kg, i.e. depending on actual AMH Dose is fixed throughout stimulation The maximum daily dose is 12 µg

FE 999049 Dosing Regimen

AMH (pmol/L)	<15	15-16	17	18	19-20	21-22	23-24	25-27	28-32	33-39	≥40 [a]
Fixed daily dose of FE 999049	12 µg	0.19	0.18	0.17	0.16	0.15	0.14	0.13	0.12	0.11	0.10
		µg/kg [b]									

[a] The cut-off limit for AMH in this trial is 35 pmol/L, i.e. only subjects with AMH level ≤35 pmol/L will be included in the trial.
[b] The maximum daily FE 999049 dose is 12 µg.

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

NIMP name	*Drug type*	*Active ingredient and route of administration*	*Dose*
GONAPEPTYL	GnRH agonist	Triptorelin acetate in solution for subcutaneous injection	0.1 mg, daily dose
CETROTIDE	GnRH antagonist	Cetrorelix acetate powder and solvent for solution for subcutaneous injection	0.25 mg, daily dose
OVITRELLE	hCG	Choriogonadotropin alfa in solution for subcutaneous injection	250 µg, single dose
LUTINUS	Progesterone	Progesterone tablet for vaginal administration	100 mg vaginal tablets three times daily

DURATION OF TREATMENT

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

STATISTICAL METHODS

The primary analyses of the efficacy endpoints will be based on the full analysis set (FAS), including all randomised subjects, regardless of whether they started FE 999049 treatment or not. However, subjects that discontinued before starting FE 999049 treatment due to the COVID-19 pandemic (e.g. due to operational and/or societal issues) will be excluded from the FAS. Subjects will be analysed according to randomised protocol. Safety endpoints will be analysed using the safety analysis set, including all randomised subjects that were exposed to FE 999049.

The primary objective of this trial is to evaluate the effect of individualised FE 999049 treatment on ovarian response using a long GnRH agonist protocol versus a GnRH antagonist protocol. The primary endpoint is the number of oocytes retrieved. The estimand of interest is the difference between FE 999049 treatment in the long GnRH agonist protocol versus FE 999049 treatment in the GnRH antagonist protocol for all randomised subjects, assuming that all subjects start treatment with FE 999049. In the statistical analyses, subjects that discontinue after randomisation but before start of FE 999049 treatment (except for subjects that never started treatment due to the COVID-19 pandemic) will have their endpoint data imputed from subjects who started FE 999049 treatment in the same protocol, using a multiple imputation method. The mean number of oocytes retrieved will be compared between the long GnRH agonist protocol and the GnRH antagonist protocol using a negative binomial regression model with protocol, age stratum, and AMH (<15 pmol/L or ≥15 pmol/L) at screening as factors. A logarithmic link function will be used for the mean in the model. From this model, the mean difference between the two protocols in number of oocytes retrieved will be estimated, and a 95% CI for the estimate will be calculated using the delta method. The same models (without AMH as factor) will be used to compare the mean number of oocytes retrieved between the two protocols in the two sub-groups defined by AMH <15 pmol/L and AMH ≥15 pmol/L at screening.

The distribution of the number of oocytes retrieved will be further characterised and compared between the two protocols. The empirical distributions will be described with special focus on the proportion of subjects with <4, 4-7, 8-14, 15-19, and ≥20 oocytes retrieved. Additional descriptions will be made for the two subgroups defined by AMH level at screening.

Secondary endpoints will be described for the two protocols, both for the full group of subjects and for the subgroups defined by AMH level at screening.

Sample size calculation

The purpose of this trial is to gain clinical experience with the use of FE 999049 when applied in a long GnRH agonist protocol. The trial is descriptive and does not include any hypothesis testing. The sample size is based on achieving a reasonable precision in the estimate of the difference in mean number of oocytes retrieved between treatment with FE 999049 in a long GnRH agonist protocol versus treatment with FE 999049 in a GnRH antagonist protocol.

In the ESTHER-1 trial the standard deviation for the number of oocytes retrieved was 5.8 in the

FE 999049 treatment group. Due to a potentially higher number of oocytes retrieved in the long GnRH agonist protocol the standard deviation in this trial may be slightly higher. Assuming a standard deviation of 7.0, a sample size of 400 subjects (200 subjects per group) will give a 95% CI that ranges from -1.4 to +1.4 of the observed mean difference, i.e. the interval from the observed mean difference -1.4 to the observed mean difference +1.4 will with 95% probability include the true mean difference. This is regarded to be reasonably precise for describing the comparability of individualised FE 999049 dosing using the two protocols.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

α	alfa
AMH	anti-Müllerian hormone
ART	assisted reproductive technologies
ASRM	American Society for Reproductive Medicine
ATC	Anatomical Therapeutic Chemical Classification System
β	beta
βhCG	beta unit of human chorionic gonadotropin
BMI	body mass index
CHO	Chinese hamster ovary
CI	confidence interval
CRO	contract research organisation
DHEA	dehydroepiandrosterone
e-CRF	electronic case report form
EMA	European Medicines Agency
EU	European Union
FAS	full analysis set
FPFV	first patient first visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GnRH	gonadotropin-releasing hormone
h	hours
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICH	International Conference on Harmonisation
ICMART	International Committee Monitoring Assisted Reproductive Technologies

ICMJE	International Committee of Medical Journal Editors
ICSI	intracytoplasmic sperm injection
IMP	investigational medicinal product
IEC	independent ethics committee
IU	international unit
IVF	in vitro fertilisation
kg	kilogram
L	litre
LH	luteinising hormone
LLOQ	lower limit of quantification
LPFV	last patient first visit
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	millilitre
NCU	neonatal care unit
NIMP	non-investigational medicinal product
NICU	neonatal intensive care unit
NLM	National Library of Medicine
OHSS	ovarian hyperstimulation syndrome
PCU	pediatric care unit
PER.C6®	host cell line of human fetal retinal origin
PICU	pediatric intensive care unit
pmol	picomol
PT	preferred term
rFSH	recombinant follicle-stimulating hormone
SmPC	Summary of Product Charateristics
SOC	system organ class
TSH	thyroid-stimulating hormone
µg	microgram
WHO	World Health Organization

Definition of Terms

Gestational age	Gestational age is calculated from the day of transfer + 19 days to the outcome of the pregnancy (e.g. delivery).
Major congenital anomaly	A life threatening structural anomaly or one likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment.[1,2]
Minor congenital anomaly	Relatively frequent structural anomaly not likely to cause any medical or cosmetic problems.[1,2]

Medicinal Product Names

Product	***Trade name used in protocol***	***Trade name in participating countries***	***Company name used in protocol***	***Company name in participating countries***
FE 999049 Follitropin delta	REKOVELLE	REKOVELLE	Ferring Pharmaceuticals	Ferring Pharmaceuticals
Cetrorelix acetate	CETROTIDE	CETROTIDE	Merck	Merck
Choriogonadotropin alfa	OVITRELLE	OVITRELLE	Merck	Merck
Triptorelin acetate	GONAPEPTYL	GONAPEPTYL / DECAPEPTYL / FERTIPEPTIL	Ferring Pharmaceuticals	Ferring Pharmaceuticals
Progesterone	LUTINUS	LUTINUS [a)]	Ferring Pharmaceuticals	Ferring Pharmaceuticals

a) Other common tradename is ENDOMETRIN.

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

1 INTRODUCTION

1.1 Background

FE 999049 is a human recombinant follicle-stimulating hormone (rFSH) under global development by Ferring Pharmaceuticals. It is intended for the following indication: "Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle". Ferring has received Marketing Authorisation approval from the European Commission for FE 999049 under the trade name REKOVELLE (December 2016). During 2017, FE 999049 was approved in Australia, Brazil, Israel and Switzerland, and in 2018, also in Canada and Mexico.

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

There are no other commercially available rFSH products derived from human cell lines. Currently approved rFSH products for the proposed indication, such as follitropin alfa (GONAL-F, Merck Serono) and follitropin beta (PUREGON, MSD), are derived from Chinese hamster ovary (CHO) cell lines. The amino acid sequence of FE 999049 is the native human FSH sequence and is identical to that in CHO-derived rFSH products. Differences in glycosylation, as shown by glycan and isoform profiles, have been documented between FE 999049 and rFSH products from CHO cell lines. Comparison between the FE 999049 and the GONAL-F and PUREGON profiles indicate differences in acidity and carbohydrate side chains. As CHO cells lack enzymatic functions to construct more complex carbohydrate structures found in humans, the FE 999049 glycosylation profile is likely to be more similar to native human FSH as compared with CHO-derived rFSH products. In addition, sialic acid linkage in position 2,6 in FE 999049 is absent from CHO-derived rFSH products which exclusively carry 2,3 linked sialic acid; this difference further contributes to the observed differences in glycosylation profiles between FE 999049 and CHO-derived rFSH products.

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

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

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

The efficacy and safety of the FE 999049 individualised dosing regimen based on the woman's serum AMH and body weight has been confirmed in a large phase 3 trial, ESTHER-1 (Evidence-based Stimulation Trial with Human rFSH in Europe and Rest of World)[3], conducted in 11 countries including Europe, North America and Latin America. The ESTHER-1 trial was conducted in 1,326 IVF/ICSI patients who were randomised 1:1 to controlled ovarian stimulation with one of the following treatments: 1) FE 999049 in its individualised dosing regimen with the daily dose fixed throughout simulation, or 2) an approved CHO-derived rFSH product (follitropin alfa, GONAL-F) at a standard starting dose of 150 IU/day followed by dose adjustments based on the subject's follicular response during stimulation. FE 999049 in its individualised dosing regimen was demonstrated to be non-inferior to follitropin alfa with respect to ongoing pregnancy rate (30.7% versus 31.6%) and ongoing implantation rate (35.2% versus 35.8%). In subjects with triggering of final follicular maturation there was no statistically significant difference between treatment groups in terms of number of oocytes retrieved, with an average of 10.0 for FE 999049 and 10.4 for follitropin alfa. Nevertheless, the individualised FE 999049 dosing regimen in comparison to follitropin alfa led to statistically significantly more oocytes retrieved among patients with AMH <15 pmol/L (population at risk of hyporesponse) with an average of 8.0 versus 7.0 and statistically significantly fewer oocytes among patients with AMH ≥15 pmol/L (population at risk of hyperresponse) with an average of 11.6 versus 13.3. The immediate clinical relevance of this shift in ovarian response with FE 999049 therapy was realised as statistically significantly fewer patients with extreme ovarian response compared to follitropin alfa, i.e. <4 oocytes among patients with AMH <15 pmol/L (12% versus 18%) and ≥15 or ≥20 oocytes among patients with AMH ≥15 pmol/L (28% versus 35%, and 10% versus 16%). Despite implementation of dose adjustments during stimulation for 37% of the patients in the follitropin alfa group, an appropriate ovarian response, defined as 8-14 oocytes, was reached by a higher proportion of patients treated with FE 999049 compared to follitropin alfa, i.e. 43% versus 38%. A statistically significantly lower total gonadotropin dose in the FE 999049 group compared to the follitropin alfa group was observed with an average of 90 µg and 104 µg, respectively. When data where analysed for all subjects randomised, there was also no statistically significant difference between treatment groups in terms of number of oocytes retrieved, with an average of 9.6 for FE 999049 and 10.1 for follitropin alfa. In comparison to follitropin alfa, the individualised FE 999049 dosing regimen led to statistically significantly more oocytes retrieved among patients with AMH <15 pmol/L with an average of 7.5 versus 6.6 and statistically significantly fewer oocytes among patients with AMH ≥15 pmol/L) with an average of 11.2 versus 13.2. Fewer patients with extreme ovarian

response was observed for FE 999049 compared to follitropin alfa, i.e. <4 oocytes among patients with AMH <15 pmol/L (16% versus 22%) and ≥15 or ≥20 oocytes among patients with AMH ≥15 pmol/L (27% versus 35%, and 10% versus 16%). Implementation of dose adjustments during stimulation was performed for 37% of the patients in the follitropin alfa group, yet an appropriate ovarian response, defined as 8-14 oocytes, was reached by a higher proportion of patients treated with FE 999049 compared to follitropin alfa, i.e. 42% versus 37%.

For further information regarding FE 999049, please refer to the Summary of Product Characteristics (SmPC).[4]

1.2 Scientific Justification for Conducting the Trial

All clinical phase 2 and 3 trials conducted with FE 999049 have applied the gonadotropin-releasing hormone (GnRH) antagonist protocol and the FE 999049 dosing algorithm has not yet been studied in a long GnRH agonist protocol. Previous studies comparing the efficacy and safety of a GnRH antagonist protocol with a long GnRH agonist protocol using rFSH derived from CHO cell lines have consistently indicated that the cohort of recruited follicles is slightly smaller in GnRH antagonist cycles. The difference in the largest randomised controlled trial[5] was -1.0 oocyte (95% CI 1.8; -0.2) which is in agreement with the estimated difference of -1.07 oocyte (95% CI -1.52; -0.61) in a Cochrane review including 27 randomised controlled trials.[6] The evidence available suggests that the long GnRH agonist protocol compared to the GnRH antagonist protocol is generally associated with one more oocyte retrieved, one more day of stimulation, and consequently a higher total dose of exogenous FSH equivalent to one more day of dosing.

This prospective, comparative trial is designed to document the ovarian response following the application of the individualised FE 999049 dosing regimen in a long GnRH agonist protocol compared to a GnRH antagonist protocol. The trial will describe the impact of the protocol on the overall number of oocytes retrieved, the number of oocytes retrieved in patients with AMH <15 pmol/L and AMH ≥15 pmol/L as well as the distribution of the number of oocytes retrieved (<4, 4-7, 8-14, 15-19, ≥20 oocytes).

1.3 Benefit / Risk Aspects

Benefits

The treatment cycle is provided to the participating subjects free of charge, as Ferring compensates the investigational sites for their expenses. Subjects participating in this trial may benefit by achieving a pregnancy. Furthermore, subjects who do not achieve an ongoing pregnancy will also have the option of cryopreserved cycles. All procedures and assessments related to cryopreserved cycles will take place outside this protocol and will not be paid for by Ferring. Subjects in this trial will be closely monitored, and they will have either the same or more frequent visits to the clinic compared to routine treatment, depending on local practice. In addition, the data obtained from the treatment cycle may provide useful information for optimising the ovarian response and for clinical

planning of subsequent treatment cycles.

Risks

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

Gonadotropins

As part of the development programme for FE 999049, a total of 1,927 subjects have to date been included in four phase 1 trials, two phase 2 trials (one conducted in EU and one in Japan) and two phase 3 trials. 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 ESTHER-1 and ESTHER-2, 665 IVF/ICSI subjects were treated with FE 999049 in 1,012 treatment cycles. The overall adverse event profile of the individualised FE 999049 dosing regimen appeared to be comparable to that of the comparator GONAL-F with the exception of fewer cases of ovarian hyperstimulation syndrome (OHSS) and/or preventive interventions for OHSS with FE 999049. The most frequently reported adverse drug reactions during 1,012 treatment cycles with FE 999049 in the phase 3 programme were headache, pelvic discomfort, OHSS, pelvic pain, adnexa uteri pain, nausea and fatigue (all reported as common, i.e. 1% to <10%). Uncommon adverse drug reactions reported with FE 999049 were diarrhoea, dizziness, mood swings, constipation, vomiting, abdominal discomfort, breast pain, breast tenderness, vaginal haemorrhage and somnolence. FE 999049 was administered with an injection pen containing a replaceable cartridge and was well-tolerated with a low incidence of local injection site reactions. The severity of local injection site reactions was in general mild and comparable to that reported for GONAL-F administrated with a pre-filled pen. In the current trial, FE 999049 will be administered using the pre-filled FE 999049 injection pen.

Concerning well-known risks associated with the use of gonadotropin products for ovarian stimulation, subjects are closely monitored throughout the trial. The most serious risk associated with gonadotropin treatment is OHSS. OHSS manifests itself with increasing degrees of severity. Moderate/severe OHSS is associated with marked ovarian enlargement, fluid accumulation and other complications. The incidence of early OHSS can be minimised by withholding gonadotropins, withholding human chorionic gonadotropin (hCG) or administering GnRH agonist for triggering of final follicular maturation. In this trial, administering GnRH agonist for triggering of final follicular maturation cannot be allowed as half the subjects are treated in a long GnRH agonist protocol and the main statistical analysis compares the number and distribution of oocytes for all subjects, i.e. the full analysis set (FAS). Very rare cases of serious allergic reactions have been reported after injection of gonadotropins. Concerning immunogenicity, the risk of treatment-induced anti-drug-antibodies for gonadotropin products is very low (estimated to be 0-2%[7,8,9,10,11,12,13]). In the phase 3 trial ESTHER-1, the incidence of treatment-induced anti-FSH antibodies was 1.05% in the

FE 999049 group. None of the anti-FSH antibodies were of neutralising capacity. No safety or efficacy concern has been identified with regards to immunogenicity with FE 999049.

Procedures and Concomitant Fertility Medications

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

Pregnancy-related Events

Oocytes will be inseminated using IVF or ICSI and subsequently cultured to day 5 (blastocyst stage) after oocyte retrieval. Although the frequency of cancellation of transfer is higher when culturing to blastocyst stage compared to culturing only to cleavage stage[14], the pregnancy rates per started cycle are at least as good with blastocyst transfer as with cleavage embryo transfer[14] and may even be higher.[15] A serious concern associated with ART cycles is the frequency of multiple pregnancies / births and the related neonatal health problems. To minimise the risk of multiple gestations, single blastocyst transfer is mandatory for women <38 years, as these women in general have a very good prognosis for obtaining pregnancy. In women ≥38 years, the transfer policy depends on the quality of the available blastocysts, i.e. single blastocyst transfer if they have at least one good-quality blastocyst, and double blastocyst transfer may be performed if they have no good-quality blastocysts. The incidence of miscarriage and ectopic pregnancy is higher in women undergoing controlled ovarian stimulation than in women conceiving spontaneously, though the risk of ectopic pregnancy is mainly higher in patients with a history of tubal infertility. Furthermore, the prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions; this is thought to be due to differences in parental characteristics (e.g. maternal age and sperm characteristics) and multiple pregnancies.

Benefits / Risks

Participation in this trial is not expected to have a negative influence on the subject's likelihood of conceiving compared to normal clinical practice. Furthermore, participation does not imply extra risks for the subjects in comparison to routine controlled ovarian stimulation. In conclusion, the

evaluation of benefits and risks indicate that participation is this trial is associated with a favourable benefit-risk ratio.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To evaluate the effect of individualised FE 999049 treatment on ovarian response in a long GnRH agonist protocol versus a GnRH antagonist protocol

Secondary Objectives

- To evaluate the effect of individualised FE 999049 treatment on other pharmacodynamic parameters in a long GnRH agonist protocol versus a GnRH antagonist protocol
- To evaluate the effect of individualised FE 999049 treatment on pregnancy rates in a long GnRH agonist protocol versus a GnRH antagonist protocol
- To evaluate the safety of individualised FE 999049 treatment in a long GnRH agonist protocol versus a GnRH antagonist protocol

2.2 Endpoints

Primary Endpoint

- Number of oocytes retrieved

Secondary Endpoints

- Proportion of subjects with cycle cancellation due to poor ovarian response or excessive ovarian response
- Proportion of subjects with blastocyst transfer cancellation after oocyte retrieval due to (risk of) OHSS
- Number and size of follicles on stimulation day 6 and end-of-stimulation
- Proportion of subjects with <4, 4-7, 8-14, 15-19 and ≥20 oocytes retrieved
- Number of metaphase II oocytes (only applicable for those inseminated using ICSI), fertilisation rate as well as number and quality of embryos on day 3 and blastocysts on day 5 after oocyte retrieval
- Circulating concentrations of FSH, luteinising hormone (LH), estradiol, progesterone and inhibin B on stimulation day 6, end-of-stimulation and at oocyte retrieval
- Total gonadotropin dose and number of stimulation days
- Positive βhCG rate (positive serum βhCG test 13-15 days after transfer)
- Implantation rate (number of gestational sacs 5-6 weeks after transfer divided by number of blastocysts transferred)
- Clinical pregnancy rate (at least one gestational sac 5-6 weeks after transfer)

- Vital pregnancy rate (at least one intrauterine gestational sac with fetal heart beat 5-6 weeks after transfer)
- Ongoing pregnancy rate (at least one intrauterine viable fetus 10-11 weeks after transfer)
- Ongoing implantation rate (number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of blastocysts transferred)
- Proportion of subjects with early OHSS (including OHSS of moderate/severe grade)
- Proportion of subjects with late OHSS (including OHSS of moderate/severe grade)
- Frequency and intensity of adverse events
- Technical malfunctions of the pre-filled injection pen

Post-trial Information

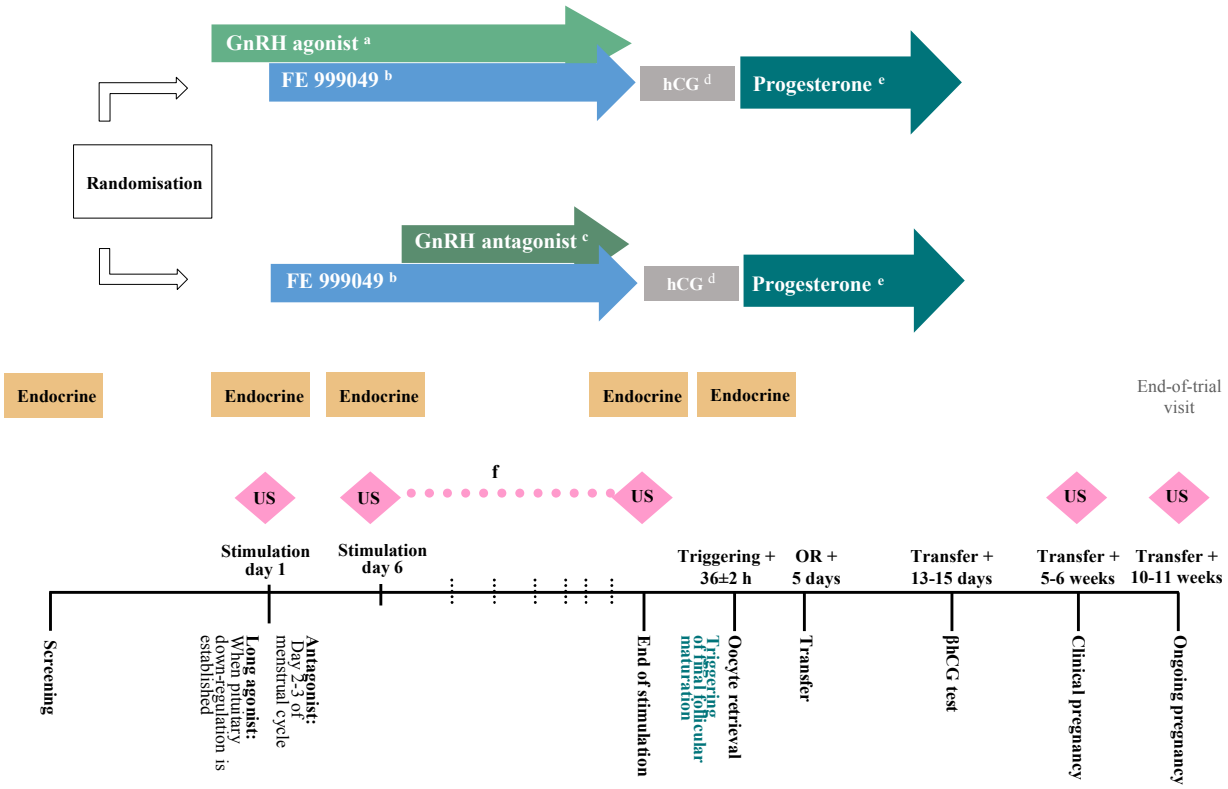
- Live birth rate and neonatal health, including minor/major congenital anomalies, at birth and at 4 weeks after birth

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

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



a. GnRH agonist (GONAPEPTYL 0.1 mg/day) from the mid-luteal phase (i.e. day 21-24) of the subject's menstrual cycle and continued throughout the stimulation period.
b. The FE 999049 dose is based on the subject's AMH at screening and body weight on stimulation day 1. In the GnRH agonist protocol, stimulation with FE 999049 starts when down-regulation is established. In the GnRH antagonist protocol, stimulation with FE 999049 starts on day 2-3 of the subject's menstrual cycle.
c. GnRH antagonist (CETROTIDE 0.25 mg/day) from stimulation day 6 and continued throughout the stimulation period.
d. hCG (OVITRELLE 250 µg single dose) when triggering criterion is met.
e. Progesterone (LUTINUS 3x100 mg/day) from the day after oocyte retrieval and continued until the day of the βhCG visit. Luteal phase support may be continued after a positive βhCG test is obtained if this is local practice.
f. Stimulation day 1, 6 and hereafter at least every second day. When the leading follicle reaches ≥15 mm, visits will be scheduled daily.
OR: oocyte retrieval, US: ultrasound

Figure 3-1 Trial Diagram – Trial Period

A diagram illustrating the post-trial activities is shown in Figure 3-2.

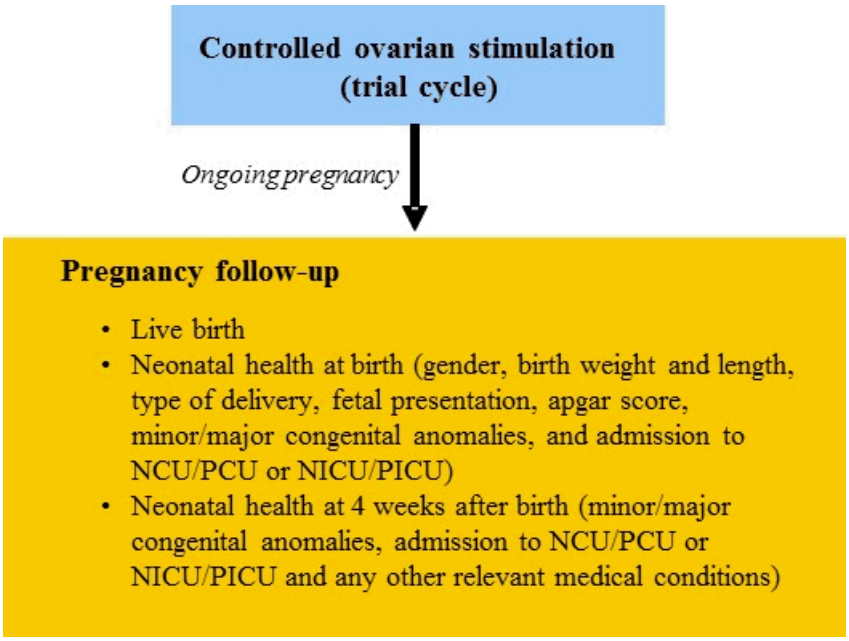


Figure 3-2 Trial Diagram – Post-trial Activities

3.1.2 Overall Design and Control Methods

Trial Design

This will be a randomised, controlled, open label, parallel group, multicentre trial comparing the efficacy and safety of individualised FE 999049 dosing in first cycle patients aged 18-40 years undergoing controlled ovarian stimulation for IVF/ICSI following either a long GnRH agonist protocol or a GnRH antagonist protocol. The trial has been designed to describe potential differences in the mean number of oocytes retrieved with adequate precision.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. Randomisation may take place as soon as all eligibility criteria are met. Randomisation does not necessarily need to take place at a physical visit, but can be done by delegated trial staff without the subject being present at the clinic. However, the subject will be contacted prior to randomisation to confirm eligibility. Subjects will be randomised in a 1:1 ratio to controlled ovarian stimulation with FE 999049 in a long GnRH agonist protocol or to controlled ovarian stimulation with FE 999049 in a GnRH antagonist protocol. Randomisation will be stratified by centre and according to age (<35, 35-37 and 38-40 years). The subject will be informed of treatment allocation and when to start treatment by the delegated trial staff.

Subjects randomised to treatment with FE 999049 in the long GnRH agonist protocol will start down-regulation with GnRH agonist (triptorelin acetate, GONAPEPTYL) 0.1 mg/day

subcutaneously in the mid-luteal phase (i.e. cycle day 21-24) of their menstrual cycle. Ovarian stimulation with FE 999049 will start after 14 days (±1 day) if the subject has experienced withdrawal bleeding and the following down-regulation criteria are fulfilled: 1) a thin endometrium (<5 mm) is observed by transvaginal ultrasound, and 2) no ovarian follicles ≥10 mm (including cysts that cannot be punctured prior to stimulation) are observed by transvaginal ultrasound. In case achievement of down-regulation is doubtful or it is deemed helpful, serum estradiol is to be measured (<50 pg/mL or 180 pmol/L; local laboratory). If down-regulation is confirmed and ovarian stimulation is initiated, treatment with GnRH agonist is continued throughout the stimulation period. If the subject has not experienced withdrawal bleeding after 14 days (±1 day), a urinary pregnancy test is to be performed. If the subject is not pregnant and down-regulation is not confirmed, treatment with GnRH agonist will be continued and stimulation will be postponed until down-regulation is confirmed. Subsequent visit(s) for confirmation of down-regulation will be scheduled according to local practice. If down-regulation is not achieved after 28 days, treatment with GnRH agonist will be stopped and the subject will be withdrawn from the trial.

Subjects randomised to treatment with FE 999049 in the GnRH antagonist protocol will start stimulation with FE 999049 on day 2 or 3 of their menstrual cycle. To prevent a premature LH surge, a GnRH antagonist (cetrorelix acetate, CETROTIDE) 0.25 mg/day subcutaneously will be initiated on stimulation day 6 and continued throughout the stimulation period.

Subjects will have their individual FE 999049 dose determined on the basis of their AMH level at screening and their body weight on stimulation day 1. The daily FE 999049 dose will be fixed throughout the stimulation period. For subjects with AMH <15 pmol/L the daily FE 999049 dose is 12 µg, irrespective of body weight. For subjects with AMH ≥15 pmol/L the daily FE 999049 dose is on a continuous scale ranging from 0.19 to 0.10 µg/kg, i.e. dependent on actual AMH and body weight. AMH will be measured by Elecsys® AMH Plus Immunoassay (Roche Diagnostics). The maximum allowed daily FE 999049 dose is 12 µg. Subjects can be treated with FE 999049 for a maximum of 20 days, and coasting is not allowed.

During stimulation, subjects will be monitored by transvaginal ultrasound on stimulation day 1 and 6 and hereafter at least every second day. When the leading follicle reaches ≥15 mm, visits must be performed daily. Triggering of final follicular maturation will be done as soon as ≥3 follicles with a diameter ≥17 mm are observed. If there are <25 follicles with a diameter ≥12 mm, a single dose of hCG (OVITRELLE) 250 µg will be administered. If there are ≥25 follicles with a diameter ≥12 mm, the cycle will be cancelled. If it is judged by the investigator that ≥3 follicles with a diameter ≥17 mm cannot be reached, but 1 or 2 follicles with a diameter ≥17 mm are observed, the cycle may either be cancelled due to poor follicular development or triggering of final follicular maturation is to be induced, as judged by the investigator.

Oocyte retrieval will take place 36h (±2h) after triggering of final follicular maturation and the oocytes can be inseminated by IVF and/or ICSI. Fertilisation and embryo development will be assessed from oocyte retrieval to the day of transfer. For all subjects blastocyst transfer is performed on day 5 after oocyte retrieval. Subjects <38 years at randomisation will have single

blastocyst transfer. Subjects ≥38 years at randomisation will have single blastocyst transfer if they have a good-quality blastocyst available, i.e. a blastocyst of grade 3BB or higher; otherwise they may have double blastocyst transfer. Remaining blastocysts may be cryopreserved and used by the subject after completion of the trial, in accordance with local guidelines and/or regulations. All procedures and assessments related to cryopreserved cycles will take place outside this protocol and will not be paid for by Ferring.

Vaginal progesterone tablets (LUTINUS) 100 mg three times daily will be provided for luteal phase support from the day after oocyte retrieval and until the serum βhCG test. Luteal phase support may be continued after a positive βhCG is obtained if this is local practice. A serum βhCG test is performed 13-15 days after transfer, clinical pregnancy will be confirmed by transvaginal ultrasound 5-6 weeks after transfer, and ongoing pregnancy will be confirmed by transvaginal or abdominal ultrasound 10-11 weeks after transfer.

Blood samples will be collected throughout the trial for the purpose of evaluating the endocrine profile assessed at screening, stimulation day 1, stimulation day 6, end-of-stimulation and at oocyte retrieval.

Post-trial Activities

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

3.1.3 Trial Schedule

First patient first visit (FPFV):	Q1 2019
Last patient first visit (LPFV):	Q3 2021
Last patient last visit (LPLV) / end-of-trial:	Q1 2022
Post-trial follow-up completed:	Q4 2022

3.2 Planned Number of Trial Sites and Subjects

It is planned to randomise approximately 400 subjects from approximately 15 sites. Approximately 200 will be randomised to the long GnRH agonist protocol and approximately 200 will be randomised to the GnRH antagonist protocol. It is estimated that up to 500 subjects should be screened to achieve 400 randomised and treated subjects.

3.3 Interim Analysis

No interim analysis is planned.

3.4 Data Monitoring Committee

No Data Monitoring Committee will be established for this trial.

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

The primary objective of the trial is to evaluate the effect of individualised FE 999049 treatment on ovarian response in a long GnRH agonist protocol versus a GnRH antagonist protocol.

This is a randomised controlled trial with a parallel group design which is preferred over a cross-over design in fertility trials. The trial will be open label as a double–blind design is not feasible due to the required GnRH agonist treatment prior to start of stimulation in a long GnRH agonist protocol. In contrast, in a GnRH antagonist protocol, the GnRH antagonist is only started during the mid-follicular phase of the stimulation period. Prior to start of stimulation in a long GnRH agonist protocol, down-regulation needs to be confirmed based on ultrasound findings, thus neither patients nor the assessors in this trial can be blinded. The lack of blinding may result in different withdrawal patterns for the two protocols. To minimise this, only subjects without strong preference for one of the protocols will be included. The trial will be a multicentre, multinational trial. This set-up ensures that the required number of subjects can be recruited within a reasonable time and also has the advantage that it should facilitate subsequent generalisation of the results.

Randomisation will be stratified by age group (<35, 35-37 and 38-40 years). Age is known to influence ovarian response, e.g. the primary endpoint, number of oocytes retrieved, as well as pregnancy endpoints such as clinical pregnancy rate and ongoing pregnancy rate. Stratification by age group will ensure that within each age group, a similar number of subjects is randomised to each protocol. This will increase the precision of the trial and facilitate separate presentations by age group. In addition, randomisation is stratified by centre as ovarian response and pregnancy outcome may differ between centres.

Subjects will undergo controlled ovarian stimulation with an individualised dosing regimen of FE 999049 based on the subject's AMH level and body weight, following either a long GnRH agonist protocol or a GnRH antagonist protocol. The daily FE 999049 dose is fixed throughout the stimulation period in this trial. The selection of doses is described in detail in section 3.5.4. Monitoring of ovarian response by transvaginal ultrasound and blood sampling for assessment of several endocrine parameters will be performed regularly during stimulation.

In this trial, subjects with ≥25 follicles of ≥12 mm at end of stimulation will be cancelled, meaning that hCG will be withhold in both treatment groups. Subjects in the GnRH antagonist group with

such high ovarian response could in principle receive GnRH agonist for triggering of final follicular maturation, but this approach is not allowed as an identical cancellation policy for both treatment groups is essential for a valid comparative analysis of the primary endpoint. However, the anticipated number of subjects that needs to be cancelled in the current trial is anticipated to be low. In the previous phase 3 trial ESTHER-1, there was no upper cut-off level for AMH, and only 2.5% of all subjects had ≥25 follicles ≥12 mm at the end of stimulation. The incidence was only 1.2% for FE 999049 treated subjects with AMH ≤35 pmol/L. In this phase 3b trial, subjects with AMH >35 pmol/L will be excluded which will lower the frequency of potential high responders, such as subjects with polycystic ovarian syndrome (PCOS) who have an increased risk of developing OHSS. Based on the incidence of 1.2% in the ESTHER-1 trial, only 5 subjects of the planned 400 randomised subjects are expected to be cancelled due to this criterion.

Oocytes will be inseminated by either IVF or ICSI reflecting the procedures used in the target population for the proposed indication. Embryos will be cultured for 5 days and embryo development will be assessed from oocyte retrieval till the day of transfer, allowing evaluation of embryo development until blastocyst stage.

The present protocol requires single blastocyst transfer on day 5 for all women <38 years and for women ≥38 years with at least one good-quality blastocyst available. Women ≥38 years with no good-quality blastocyst may have double blastocyst transfer. The scientific justification for incorporating these features is that it will ensure that the data obtained in this trial are in line with the current clinical directions taken for maintaining efficacy (i.e. ongoing pregnancy rates) and minimising risks (i.e. multiple pregnancies).[16,17,18] Further, there is increasing evidence suggesting that late stages of embryo progression are better predictors of clinical pregnancy than early embryo development parameters.[19] 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.[15]

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

3.5.2 Selection of Endpoints

In the phase 3 trial ESTHER-1 it was demonstrated that individualised FE 999049 dosing based on the subjects AMH and body weight in comparison to conventional rFSH treatment increased the number of oocytes retrieved in subjects with low AMH (<15 pmol/L) and decreased the number of oocytes retrieved in subjects with high AMH (≥15 pmol/L), the latter reducing the occurrence of preventive interventions for early OHSS.

The primary endpoint of this trial, the number of oocytes retrieved, is an endpoint reflecting the pharmacological effect of FSH on follicular development and growth, and it is associated with the risk of OHSS. Previous comparative trials with GnRH antagonist versus long GnRH agonist protocols, including meta-analyses, have demonstrated that following rFSH treatment in a GnRH antagonist protocol, less oocytes are retrieved and accordingly a lower risk of OHSS is observed.[5,20]

The primary endpoint of this trial will allow the comparison of distribution of the number of oocytes retrieved following each GnRH analogue protocol, and more specifically in subjects with low AMH (<15 pmol/L) and high AMH (≥15 pmol/L). Based on current knowledge about the difference in ovarian response following treatment with CHO-derived rFSH in either protocol[20] an overall treatment difference of at least 1 oocyte is to be anticipated, the difference being smaller in subjects with low AMH than in subjects with high AMH. This treatment difference, especially in subjects with high AMH, will indicate whether the FE 999049 dosing algorithm remains safe and effective when applied in a GnRH agonist protocol.

Secondary endpoints include standard efficacy endpoints in fertility treatment such as pregnancy outcomes, e.g. clinical pregnancy rate and ongoing pregnancy rate. Cycle cancellation due to poor or excessive ovarian response, blastocyst transfer cancellation due to (risk of) OHSS, distribution of number of oocytes retrieved, total gonadotropin dose and number of stimulation days will also be assessed.

Secondary endpoints related to safety include adverse events, early OHSS and late OHSS. Technical malfunction of the pre-filled injection pen used for administration of FE 999049 will also be monitored.

Other secondary endpoints include pharmacodynamic parameters such as ovarian response in terms of follicular development, endocrine profile and also embryo and blastocyst quality. Follicular development will be evaluated on day 6 as well as at end-of-stimulation. The endocrine profile consists of FSH, LH, estradiol, progesterone, and inhibin B and will be evaluated on stimulation day 6, end-of-stimulation and at oocyte retrieval.

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

3.5.3 Blinding

This trial is open label and unblinded due to the different protocols being compared and no measures are taken to prevent investigators, delegated trial staff or subjects from knowing the treatment allocation or dose of FE 999049 administered. It would be impractical to blind the protocols as they differ in respect to when treatment with GnRH agonist and GnRH antagonist, respectively, is initiated, and when the subject is to start stimulation with FE 999049.

3.5.4 Selection of Doses in the Trial

FE 999049

Modelling and simulation based on the efficacy and safety data obtained in the European phase 2 trial (000009) have been used to identify the overall dosing regimen for FE 999049. The objective

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

AMH and body weight were found to influence the dose-response with regard to obtaining the aim of the model of the FE 999049 dosing regimen. The impact of body weight on ovarian response is clinically relevant for low dose levels of FE 999049, while the effect is only minor at dose levels of 12 µg and above. The proposed individualised dosing regimen of FE 999049 is described in detail in section 5.1 and is summarised as follows: for subjects with AMH <15 pmol/L the daily FE 999049 dose is 12 µg, irrespective of body weight, and for subjects with AMH ≥15 pmol/L the daily FE 999049 dose is on a continuous scale ranging from 0.19 to 0.10 µg/kg, i.e. dependent on actual AMH and body weight. The safety and efficacy of this dosing regimen has been confirmed in the phase 3 trial ESTHER-1, and the dosing regimen of FE 999049 in this trial will be the same dosing regimen that was evaluated in the phase 3 trial and according to the labelling.

Concomitant Fertility Medication

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

3.5.5 Selection and Timing of Dose for Each Subject

The proposed individualised dosing regimen of FE 999049 is described in detail in section 5.1.

3.5.6 Selection of the Trial Population

This trial applies similar inclusion/exclusion criteria as ESTHER-1 and will include women undergoing their first IVF/ICSI cycle, as this group of patients is considered the most appropriate population for a trial using different treatment protocols. The subjects have been diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or have partners diagnosed with male factor infertility, and are considered eligible for IVF or ICSI. The trial will include women up to 40 years of age and will thereby cover the patient age span in which most ART treatments are performed.[21] The allowed body mass index (BMI) is 17.5-32.0 kg/m^2, thus including underweight, normal weight, overweight and obese patients.

Subjects with an AMH level > 35 pmol/L at screening will be excluded from the trial as these subjects are likely to have polycystic ovaries and may have an increased risk of OHSS. Subjects with a strong preference for either treatment protocol will also be excluded from the trial. For example, some subjects may prefer the short term GnRH antagonist protocol or suffer from needle

fobia which could cause more premature discontinuations among subjects randomised to the GnRH agonist protocol. Furthermore, the exclusion criteria incorporate the contraindications for the use of gonadotropins.

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

3.5.7 Withdrawal Criteria

Description of specific withdrawal criteria for the individual subject is listed in section 4.4.

3.5.8 Follow-up Procedures

Post-trial Activities

Post-trial activities includes follow-up of ongoing pregnancies and neonatal health follow-up at birth and at 4 weeks after birth.

Safety Follow-up

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 investigational medicinal product (IMP) until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to Ferring. If the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

Access to Therapy after End-of-trial

In December 2016, Ferring received Marketing Authorisation approval from the European Commission for FE 999049 and the product is approved under the trade name REKOVELLE in all countries included in this trial. Commercial availability may vary across countries.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

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

1. Informed Consent Forms signed prior to screening evaluations.
2. In good physical and mental health.
3. The subjects must be at least 18 years (including the 18th birthday) when they sign the Informed Consent Form and no more than 40 years (up to the day before the 41st birthday) at the time of randomisation.
4. Infertile women diagnosed with tubal infertility, unexplained infertility, endometriosis stage I/II or with partners diagnosed with male factor infertility, eligible for in vitro fertilisation (IVF) and/or intracytoplasmic sperm injection (ICSI) using fresh or frozen ejaculated sperm from male partner or sperm donor.
5. Infertility for at least one year before randomisation for subjects <38 years or for at least 6 months for subjects ≥38 years (not applicable in case of tubal or severe male factor infertility).
6. The trial cycle will be the subject's first controlled ovarian stimulation cycle for IVF/ICSI.
7. Regular menstrual cycles of 24-35 days (both inclusive), presumed to be ovulatory.
8. Hysterosalpingography, hysteroscopy, saline infusion sonography, or transvaginal ultrasound documenting a uterus consistent with expected normal function (e.g. no evidence of clinically interfering uterine fibroids defined as submucous or intramural fibroids larger than 3 cm in diameter, no polyps and no congenital structural abnormalities which are associated with a reduced chance of pregnancy) within 1 year prior to randomisation.
9. Transvaginal ultrasound documenting presence and adequate visualisation of both ovaries, without evidence of significant abnormality (e.g. no endometrioma greater than 2 cm or enlarged ovaries which would contraindicate the use of gonadotropins) and normal adnexa (e.g. no hydrosalpinx) within 1 year prior to randomisation. Both ovaries must be accessible for oocyte retrieval.
10. Early follicular phase (cycle day 2-5) serum levels of FSH between 1 and 15 IU/L at screening.
11. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) antibody tests within 1 year prior to randomisation.
12. Body mass index (BMI) between 17.5 and 32.0 kg/m^2 (both inclusive) at screening.
13. If <38 years willing to accept single blastocyst transfer. If ≥38 years willing to accept transfer of a single good-quality blastocyst (double blastocyst transfer may be performed if no good-quality blastocyst is available).

4.1.2 Exclusion Criteria

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

1. AMH >35 pmol/L at screening.
2. Strong preference of the subject for either treatment protocol.
3. Known endometriosis stage III-IV (defined by the revised ASRM classification, 1996[22]).
4. Known history of recurrent miscarriage (defined as three consecutive losses after ultrasound confirmation of pregnancy (excl. ectopic pregnancy) and before week 24 of pregnancy).
5. Known abnormal karyotype of subject or of her partner / sperm donor, as applicable, depending on source of sperm used for insemination in this trial.
6. Any known clinically significant systemic disease (e.g. insulin-dependent diabetes).
7. Known inherited or acquired thrombophilia disease.
8. Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events.
9. Known porphyria.
10. Any known endocrine or metabolic abnormalities (pituitary, adrenal, pancreas, liver or kidney) with the exception of controlled thyroid function disease.
11. Known tumours of the ovary, breast, uterus, adrenal gland, pituitary or hypothalamus which would contraindicate the use of gonadotropins.
12. Known moderate or severe impairment of renal or hepatic function.
13. Currently breast-feeding.
14. Undiagnosed vaginal bleeding.
15. Known abnormal cervical cytology of clinical significance observed within three years prior to randomisation (unless the clinical significance has been resolved).
16. Findings at the gynaecological examination at screening which preclude gonadotropin stimulation or are associated with a reduced chance of pregnancy, e.g. congenital uterine abnormalities or retained intrauterine device.
17. Pregnancy (negative pregnancy test must be documented at screening) or contraindication to pregnancy.
18. Known current active pelvic inflammatory disease.
19. Use of fertility modifiers during the last menstrual cycle before randomisation, including dehydroepiandrosterone (DHEA), metformin or cycle programming with oral contraceptives, progestogen or estrogen preparations.
20. Use of hormonal preparations (except for thyroid medication) during the last menstrual cycle before randomisation.
21. Known history of chemotherapy (except for gestational conditions) or radiotherapy.

22. Current or past (1 year prior to randomisation) abuse of alcohol or drugs and/or current (last month) intake of more than 14 units of alcohol per week.
23. Current or past (3 months prior to randomisation) smoking habit of more than 10 cigarettes per day.
24. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.
25. Previous participation in the trial.
26. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

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

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

4.2.2 Randomisation

Randomisation may take place as soon as all eligibility criteria are met. Subjects will be randomised in a 1:1 ratio to controlled ovarian stimulation with FE 999049 in a long GnRH agonist protocol or to controlled ovarian stimulation with FE 999049 in a GnRH antagonist protocol. Randomisation is performed centrally through the electronic case report form (e-CRF) and will be stratified by centre and according to age (<35, 35-37 and 38-40 years). The randomisation number will be allocated to the subject together with the treatment allocation. When a subject is randomised to the trial, she will always be assigned to the lowest available randomisation number. An independent statistician at the Ferring Global Biometrics Department will prepare a computer-generated randomisation list and randomisation is performed in blocks. Blocks will be maintained within centres, i.e. the randomisation will be stratified by centre. The block size will only be revealed when the trial database is declared clean and locked. An overview of recruitment will be recorded on a subject identification code list for all randomised subjects kept by the investigator.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

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

4.3.2 Prohibited Therapy

Additional to the medicinal products listed in section 4.3.1 it is prohibited to administer other gonadotropins than FE 999049 and concomitant fertility medication provided as part of the trial regimen.

It is prohibited to administer medication for prevention of OHSS to subjects not showing symptoms of OHSS. For subjects with symptoms of OHSS, medication can be administered according to local practice.

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

4.4 Withdrawal Criteria

Withdrawal from Trial

The subjects have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the investigator should record the reason for the subject's withdrawal, if possible. The investigator must withdraw subjects if one of the following criteria is met:

Withdrawal Criteria

1. One or more follicles ≥10 mm (including cysts that cannot be punctured prior to stimulation) observed on the transvaginal ultrasound on stimulation day 1 / day of confirmation of down-regulation.
2. Down-regulation not achieved within 28 days after the first GnRH agonist administration.
3. Pregnancy (positive pregnancy test) between screening and stimulation day 1.
4. Use of fertility modifiers between randomisation and stimulation day 1, including DHEA, metformin or cycle programming with oral contraceptives, progestogen or estrogen preparations.
5. Use of hormonal preparations (except for thyroid medication and trial medication) between randomisation and stimulation day 1.

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

Withdrawal of Consent

If the subject withdraws her consent, no further data will be obtained. However, already obtained samples may be analysed. This will be described in the Informed Consent Form.

4.5 Subject Replacement

A subject can only be assigned one screening number and one randomisation number. Subjects who discontinue prematurely from the trial after randomisation are not to be replaced, i.e. randomisation numbers are uniquely linked to each subject and cannot be re-used. Withdrawn subjects will not be replaced.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Product

Subjects will be randomised in a 1:1 ratio to controlled ovarian stimulation with FE 999049 (follitropin delta) in a long GnRH agonist protocol or to controlled ovarian stimulation with FE 999049 in a GnRH antagonist protocol. All subjects will be treated with FE 999049 in a pre-filled injection pen.

FE 999049 Dosing Regimen

Subjects will have their individual FE 999049 dose determined on the basis of their AMH level at screening and their body weight on stimulation day 1. For subjects with low AMH (<15 pmol/L) the daily FE 999049 dose is 12 µg, irrespective of body weight. For subjects with high AMH (≥15 pmol/L) the daily FE 999049 dose is on a continuous scale ranging from 0.19 to 0.10 µg/kg, i.e. dependent on actual AMH and body weight.

The daily FE 999049 dose will be fixed throughout the stimulation period. The maximum allowed daily FE 999049 dose is 12 µg. Dosing will continue until the criterion for triggering of final follicular maturation has been met. Subjects can be treated with FE 999049 for a maximum of 20 days. Coasting is not allowed. Overdose and medication errors of FE 999049 with and without clinical consequences will be tracked in the e-CRF and reviewed ongoing by Ferring Global Pharmacovigilance.

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

Table 5-1 FE 999049 Dosing Regimen

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

AMH concentration will be rounded off to integers. The cut-off limit for AMH in this trial is 35 pmol/L, i.e. only subjects with AMH level ≤35 pmol/L will be included in the trial.
Subjects can be treated for a maximum of 20 days.

The FE 999049 preparation is administered as daily subcutaneous injection(s) in the abdomen.[a] To minimise local injection site reactions, it is advisable to change injection site regularly.

The first FE 999049 injection will take place at the clinic and will be performed either by the delegated trial staff or the subject under supervision by the delegated trial staff. Subsequent injections can be done at home or at the clinic. The delegated trial staff will give the subject instructions for how to administer FE 999049.

Calculation of the FE 999049 Dose and Setting the Dose on the FE 999049 Pre-filled Injection Pen

The subject's serum AMH concentration will be available from the blood sample taken at screening and analysed by a central laboratory using a qualified assay. The AMH concentration will be provided from the central laboratory directly to the e-CRF. The subject's body weight will be measured on stimulation day 1 using a calibrated scale and performed without shoes and overcoat. The body weight result will be entered into the e-CRF. The FE 999049 dosing algorithm has been programmed in the e-CRF, which calculates the FE 999049 dose based on the subject's AMH and body weight.

The FE 999049 pre-filled injection pen has a dosing scale numbered from 0 to 20 µg. Each number is separated by two lines, each representing 0.33 µg. Thus, the pre-filled injection pen can be set to supply doses rounded to the nearest 0.33 µg. Rounding off of the calculated dose may be needed, as

[a] It will be allowed to split the dose if the pre-filled injection pen does not contain enough FE 999049 for the daily dose to be administered. The remaining part of the dose will then be administered using a new FE 999049 pre-filled injection pen.

in this example of a subject weighing 75.0 kg with an AMH level of 24 pmol/L for whom the calculated dose is 10.5 µg (0.14 µg/kg * 75.0 kg) which will then be rounded to 10.66 µg, i.e. 10 µg + 2 lines on the pen. The e-CRF will provide the calculated dose in an output that matches the numbers and lines on the pre-filled injection pen; i.e. any rounding off will be done automatically prior to providing the subject's calculated dose.

The delegated trial staff will be instructed and trained in the correct use of the pre-filled injection pen, so that correct instructions can be provided to the subjects.

5.1.2 Non-Investigational Medicinal Product

As concomitant therapy in the controlled ovarian stimulation cycle, subjects will use the following non-investigational medicinal products (NIMPs) as illustrated in Table 5-2.

Table 5-2 Non-Investigational Medicinal Products

NIMP	Trade name	Dose
GnRH agonist	GONAPEPTYL	0.1 mg subcutaneous injection once daily, starting in the mid-luteal phase of the subject's menstrual cycle (i.e. day 21-24) and continued throughout the stimulation period.
GnRH antagonist	CETROTIDE	0.25 mg subcutaneous injection once daily, starting on stimulation day 6 and continued throughout the stimulation period.
hCG	OVITRELLE	A single 250 µg subcutaneous injection as soon as reaching the criterion for triggering of final follicular maturation (≥3 follicles with a diameter ≥17 mm and <25 follicles with a diameter ≥12 mm).
Progesterone	LUTINUS	100 mg vaginal tablets three times daily, starting on the day after oocyte retrieval and continued until the day of the βhCG test. Progesterone will be terminated earlier in case of no transfer, menses, negative βhCG or pregnancy loss.

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

5.2 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). It should be noted that Ferring will only provide progesterone for luteal phase support until the serum βhCG test. Table 5-3 provides an overview of the presentation and manufacturer of each medicinal product.

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

IMP / NIMP	Presentation	Manufacturer
FE 999049 (rFSH)	FE 999049 is provided as a pre-filled injection pen for multiple use containing 72 µg of follitropin delta in 2.16 mL solution.	Ferring Pharmaceuticals
GONAPEPTYL (GnRH agonist)	GONAPEPTYL (triptorelin acetate) is provided as a pre-filled syringe (1 mL) for single use delivering 0.1 mg triptorelin acetate.	Ferring Pharmaceuticals
CETROTIDE (GnRH antagonist)	CETROTIDE (cetrorelix acetate) is provided as powder and solvent for solution for injection. After reconstitution, 1 mL solvent contains 0.25 mg cetrorelix acetate.	Merck
OVITRELLE (hCG)	OVITRELLE (choriogonadotropin alfa) is provided as a pre-filled syringe (0.5 mL) for single use delivering 250 µg choriogonadotropin alfa.	Merck
LUTINUS (progesterone)	LUTINUS is provided as vaginal tablets, each containing 100 mg of progesterone.	Ferring Pharmaceuticals

5.3 Packaging and Labelling

Packaging and labelling of the medicinal products will be performed under the responsibility of the Clinical Trial Supply Department at Ferring in accordance with GMP and national regulatory requirements.

All medicinal products will be labelled with trial-specific labels containing a unique IMP number to ensure traceability.

Details on the packaging of each medicinal product are provided in Table 5-4.

Table 5-4 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.
GONAPEPTYL (GnRH agonist)	GONAPEPTYL is provided in boxes containing 7 pre-filled syringes for single use.
CETROTIDE (GnRH antagonist)	CETROTIDE is provided in boxes with 1 vial with powder and 1 pre-filled syringe with 1 mL solvent.
OVITRELLE (hCG)	OVITRELLE is provided in boxes containing 1 pre-filled syringe for single use.
LUTINUS (progesterone)	LUTINUS is provided in boxes containing 1 vaginal applicator and 21 vaginal tablets, packed individually in a sealed foil pouch.

5.4 Conditions for Storage and Use

The delegated trial staff will ensure that the medicinal products will be stored in appropriate conditions as stated in the labelling and in a secure location with controlled access. The storage compartment shall be monitored regularly and the temperature shall be documented.

Excursions in storage temperature must be reported to the sponsor as instructed in a trial specific guideline.

In case of technical malfunction of a pre-filled injection pen, all relevant details (including time, date, a description of the malfunction and whether dosing was affected) of the incidence should be reported to the sponsor in a timely manner according to instructions in a trial specific guideline. The pen should be replaced and the treatment continued.

For information on warnings, precautions and treatment of overdose, please refer to the SmPCs for FE 999049, GONAPEPTYL, CETROTIDE, OVITRELLE, and LUTINUS.

5.5 Blinding / Unblinding

5.5.1 Blinding

Not applicable as this is an open label trial.

5.5.2 Unblinding of Individual Subject Treatment

Not applicable as this is an open label trial.

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

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

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

5.6.2 Assessment of Compliance

The IMP and NIMP will only be dispensed by authorised trial staff to subjects who meet the eligibility criteria and are randomised to a treatment group in the trial. All medication will be dispensed at the trial site and the subject will enter dates and time of IMP, GnRH antagonist and hCG administration, dose of IMP administered, and date of first and last GnRH agonist and progesterone administration in a trial specific diary. For each day between first and last GnRH agonist administration and between first and last progesterone administration, information about whether the drug was administered will also be entered in the trial specific diary. This will later be entered into the e-CRF by delegated and trained trial staff (*for GnRH agonist and progesterone administration between first day and last day of administration, summary information will be entered into the e-CRF*). In case the subject has taken an incorrect IMP dose, this will be captured in the e-CRF as a medication error.

5.7 Auxiliary Supplies

Ferring will supply safety containers for the collection of used injection pens and needles.

5.8 Return and Destruction of Medicinal Products and Auxiliary Supplies

Used / dispensed IMP and NIMP can be destroyed at the site in accordance with local legislation after drug accountability has been verified by the monitor.

Unused / non-dispensed IMP and NIMP will be returned for destruction as instructed by the Ferring Clinical Trial Supply Department after drug accountability has been verified by the monitor.

6 TRIAL PROCEDURES

6.1 Trial Flow Chart

Table 6-1 Trial Flow Chart – Subject Procedures

	Screening	Rando-misation	GnRH agonist group	Stimulation				Oocyte retrieval	Transfer	Pregnancy monitoring			End
			Down-regulation period	During stimulation			End-of-stimu-lation	OR	Transfer	βhCG	Clinical	Ongoing	End-of-trial
Timing	<90 d before rando-misation	a)	b)	SD 1	SD 6	SD ≥7 to <20 c)	End	36h ±2h after triggering	Day 5 after OR	13-15 days after transfer	5-6 weeks after transfer	10-11 weeks after transfer	d)
Written informed consent	X												
Inclusion/exclusion criteria	X	X											
Withdrawal criteria			X e	X f									
Demographics	X												
Medical history	X												
Infertility history	X												
Menstrual history	X												
Reproductive history	X												
Smoking and alcohol habits	X												
Body weight and height	X			X f,g									
Physical exam	X												
Gynaecological exam	X												
Pregnancy test (local lab)	X		X h	X f									
Ultrasound			X	X f,i	X	X	X				X	X	
Randomisation		X											
Blood collection, endocrine	X j			X f,k	X k		X k	X k					
Confirmation of down-reg			X l										
Serum E_2 (local lab)			X m										
IMP dispensing				X	X	X							
GnRH agonist dispensing			X n ·····				X						
GnRH antagonist dispensing					X o ·····		X						
hCG dispensing							X p						
Oocyte retrieval								X					
Progesterone dispensing								X	X q				
Blastocyst transfer									X				
Serum βhCG test (local lab)										X			
Drug accountability			X		X	X	X	X	X	X			X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
End-of-trial form													X

a) Randomisation does not necessarily need to take place at a physical visit by the subject, but can be done by the delegated trial staff without the subject being present at the clinic
b) Subjects randomised to treatment with FE 999049 in the long GnRH agonist protocol will attend a mandatory visit where down-regulation will be initiated and a mandatory visit after 14 days (±1 day) for confirmation of down-regulation The number of subsequent visits for subjects who are not down-regulated after 14 days (±1 day) will depend on local practice
c) Visits must be scheduled at least every second day; when the leading follicle reaches ≥15 mm visits must be scheduled daily
d) End-of-trial is the subject's last scheduled visit
e) Withdrawal criteria will be checked at different time points during the down-regulation period
f) Performed before the first IMP dose
g) Only body weight
h) A pregnancy test will be made at start of down-regulation and repeated after 14 days (±1 day) if the subject has not experienced withdrawal bleeding
i) For subject randomised to treatment with FE 999049 in the long GnRH agonist protocol, the ultrasound assessments on stimulation day 1 can be combined with the ultrasound performed to confirm down-regulation if the subject fulfils the criteria for continuing to stimulation day 1
j) Endocrine parameters consist of a screening panel (AMH, FSH, prolactin and TSH: central laboratory)
k) Endocrine parameters consist of a treatment panel (estradiol, FSH, inhibin B, LH and progesterone: central laboratory) and AMH (at SD 1 only)
l) Confirmation of down-regulation will be assessed after 14 days (±1 day) If down-regulation is not confirmed and the subject is not pregnant, treatment with triptorelin acetate is continued and stimulation is postponed until down-regulation is confirmed Subsequent visit(s) for confirmation of down-regulation will be scheduled according to local practice If down-regulation is not achieved after 28 days, the subject is withdrawn from the trial
m) In case achievement of down-regulation is doubtful or it is deemed helpful, serum estradiol is to be measured (<50 pg/mL or 180 pmol/L)
n) Only applicable for subjects randomised to treatment with FE 999049 in the long GnRH agonist protocol
o) Only applicable for subjects randomised to treatment with FE 999049 in the GnRH antagonist protocol
p) Triggering of final follicular maturation will be done as soon as ≥3 follicles with a diameter of ≥17 mm are observed
q) Progesterone for luteal phase support will be administered from the day after oocyte retrieval and until the serum βhCG test Luteal phase support may be continued after a positive βhCG test is obtained if this is local practice

6.2 Screening

Potential participants will be scheduled to come to the clinic for the screening assessments. Screening must be initiated within 90 days before randomisation.

The following must take place during the screening period:

- Signed and dated written informed consent, obtained prior to any trial-related procedures
- Allocation of a screening number
- Check of inclusion and exclusion criteria (those which are possible to check at screening) [*note:* if the results of the examinations for eligibility according to inclusion criteria 8, 9 and 11 are older than required per protocol or not available, respective examinations should be performed during the screening period. Blood collection for Negative serum HBsAg, HCV and HIV antibody tests will be performed at the local laboratory, if applicable]
- Demographics (age, ethnicity, race)
- Collection of the following data:
  - Medical history
  - Infertility history
  - Menstrual history
  - Reproductive history
  - Smoking and alcohol habits
- Body measurements (body weight, height) [*note*: these are used for calculation of BMI]
- Physical examination
- Gynaecological examination
- Pregnancy test – must be negative
- Blood collection for central laboratory analysis of endocrine parameters (screening panel; AMH, FSH, prolactin and thyroid-stimulating hormone [TSH]) [*note*: the results must be available prior to randomisation and reviewed by the investigator to assess the eligibility of the subject]
- 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 randomisation which may take place as soon as all eligibility criteria are met but within 90 days from the screening visit.

6.3 Randomisation

Randomisation does not necessarily need to take place at a physical visit, but can be done by delegated trial staff without the subject being present at the clinic.

The following must take place prior to randomisation:

- Ensure that the subject is still eligible for participation in the trial
- Check those inclusion and exclusion criteria that were not possible during screening
- Recording of use of concomitant medication
- Recording of adverse events

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

- Randomisation, i.e. assignment to the lowest available subject number and thereby allocation to controlled ovarian stimulation with FE 999049 in either a long GnRH agonist protocol or a GnRH antagonist protocol
- Provide the completed subject participation card to the subject (or at the next scheduled visit if randomisation is not performed at a physical visit)

The subject will be informed of treatment allocation by the delegated trial staff.

Subjects randomised to controlled ovarian stimulation with FE 999049 in a long GnRH agonist protocol will proceed to a down-regulation visit where down-regulation will be initiated. Subjects randomised to controlled ovarian stimulation with FE 999049 in a GnRH antagonist protocol will proceed to the stimulation day 1 visit (section 6.6.1).

6.4 Down-regulation

Subjects randomised to controlled ovarian stimulation with FE 999049 in a long GnRH agonist protocol will start down-regulation in the mid-luteal phase (i.e. cycle day 21-24) of their menstrual cycle.

The following must take place at the down-regulation visit prior to GnRH agonist administration:

- Check withdrawal criteria and ensure that the subject is still eligible for participation in the trial
- Urinary pregnancy test – must be negative

Once the above has been done, the subject will start down-regulation with GnRH agonist:

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

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

- In the first 30 min following the GnRH agonist administration, the delegated trial staff must observe the subject's general health with emphasis on symptoms of an acute allergic reaction
- Instruct the subject to administer the GnRH agonist at a daily dose of 0.1 mg throughout the stimulation period
- Recording of use of any concomitant medication
- Recording of adverse events
- Hand out the diary to the subject. The subject must be instructed to record administration of GnRH agonist

A new visit must be scheduled for confirmation of down-regulation after 14 days (±1 day) of GnRH agonist treatment.

6.5 Confirmation of Down-regulation

Subjects randomised to controlled ovarian stimulation with FE 999049 in a long GnRH agonist protocol who have started down-regulation will attend a visit for confirmation of down-regulation after 14 days (±1 day) of GnRH agonist treatment. The following criteria must be fulfilled before the subject can proceed to stimulation with FE 999049:

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

The ultrasound performed to confirm down-regulation can be combined with the ultrasound assessments performed on stimulation day 1 if the subject fulfills the three criteria (see section 6.6.1). In case achievement of down-regulation is doubtful or it is deemed helpful, serum estradiol is to be measured (<50 pg/mL or 180 pmol/L; local laboratory).

In case the subject has not experienced withdrawal bleeding after 14 days (±1 day), a urinary pregnancy test is to be performed. If the subject is not pregnant and down-regulation is not confirmed, treatment with GnRH agonist will be continued and stimulation will be postponed. Subsequent visit(s) for confirmation of down-regulation will be scheduled according to local practice (*note: only the data from the visit where down-regulation is confirmed will be reported in the e-CRF*). If down-regulation is not achieved after 28 days, treatment with GnRH agonist will be stopped and the subject will be withdrawn from the trial (*note: in this case, the data from the last visit for confirmation of down-regulation will be reported in the e-CRF*).

If down-regulation is confirmed, the subject may proceed to controlled ovarian stimulation with FE 999049 and undergo the stimulation day 1 assessments on the same day as down-regulation is confirmed. A new visit must be scheduled for stimulation day 1 if the subject does not proceed directly to the stimulation day 1 assessments (*note: this visit must take place within 2 days after down-regulation is confirmed)*.

6.6 Stimulation

6.6.1 Stimulation Day 1

Subjects randomised to controlled ovarian stimulation with FE 999049 in a long GnRH agonist protocol will attend the stimulation day 1 visit after down-regulation is confirmed (*note: this can be on the same day as the visit for confirmation of down-regulation or within 2 days after down-regulation is confirmed)*.

Subjects randomised to controlled ovarian stimulation with FE 999049 in a GnRH antagonist protocol will attend the stimulation day 1 visit on day 2-3 of the menstrual cycle.

The following must take place before administration of the first dose of FE 999049:

- Check withdrawal criteria and ensure that the subject is still eligible for participation in the trial
- Body measurements (body weight) [once the body weight has been entered into the e-CRF, the FE 999049 dose will be calculated and displayed within the system]
- Pregnancy test – must be negative
- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, ovarian volume, number and size of follicles). If a cyst ≥10 mm is observed (functional or not), it should be punctured before treatment is initiated.[b] If the cyst was present at the screening visit, it should have been recorded on the medical history form. If the cyst presented between screening and stimulation day 1, it should be recorded on the adverse event form.
- Blood collection for central laboratory analysis of endocrine parameters (treatment panel; FSH, LH, inhibin B, progesterone and estradiol, and additionally AMH)

Once the above has been completed, the following must be performed by the delegated trial staff:

- Dispense FE 999049 to the subject and instruct the subject on how to administer FE 999049

[b] Treatment can be initiated the same day. If puncture is not possible, stimulation may be postponed to the next menstrual cycle for subjects randomised to controlled ovarian stimulation with FE 999049 in the GnRH antagonist protocol, assuming that the cyst will disappear, that the subject fulfils the inclusion criteria and that stimulation day 1 can take place within 90 days from screening.

- Administer the 1st dose of FE 999049 according to AMH level at screening and body weight at stimulation day 1 [administration of FE 999049 takes place at the clinic and can be done by either the delegated trial staff or the subject under supervision by the delegated trial staff]
- Dispensing of GnRH agonist as needed [*note*: only applicable for subjects randomised to controlled ovarian stimulation with FE 999049 in a long GnRH agonist protocol]
- Recording of use of any concomitant medication
- Recording of adverse events
- Hand out the diary to the subjects randomised to controlled ovarian stimulation with FE 999049 in a GnRH antagonist protocol.
- All subjects must be instructed to record administration of FE 999049

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

- Take precautions in the event that the subject experiences an acute allergic reaction. In the first 30 min following the FE 999049 administration, the delegated trial staff (or another qualified trial staff) must observe the subject's general health with emphasis on symptoms of an acute allergic reaction. The trial sites are requested to have facilities (i.e. medication, equipment and trained staff) and procedures in place for diagnosis and treatment of acute allergic reactions.

The next visit must be scheduled for stimulation day 6.

6.6.2 Stimulation Day 6

The following must take place at stimulation day 6:

- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial triple-layer structure, endometrial echogenicity pattern, number and size of follicles)
- Blood collection for central laboratory analysis of endocrine parameters (treatment panel) – the blood sample must be drawn at least 8 hours after the latest administration of FE 999049 and, if applicable, prior to administration of GnRH antagonist
- Dispensing of FE 999049 as needed
- Dispensing of GnRH agonist as needed [*note*: only applicable for subjects randomised to controlled ovarian stimulation with FE 999049 in a long GnRH agonist protocol]
- Dispensing and administration of GnRH antagonist [*note*: only applicable for subjects randomised to controlled ovarian stimulation with FE 999049 in a GnRH antagonist protocol; the first administration of GnRH antagonist takes place at the clinic and can be done by either the delegated trial staff or the subject under supervision by the delegated trial staff]
- Drug accountability of FE 999049 and, if applicable, GnRH agonist
- Recording of use of any concomitant medication

- Recording of adverse events
- The subjects randomised to controlled ovarian stimulation with FE 999049 in a GnRH antagonist protocol must be instructed to record administration of GnRH antagonist

Finally, this must be done before the subject leaves the clinic [*note*: only applicable to subjects randomised to controlled ovarian stimulation with FE 999049 in a GnRH antagonist protocol]:

- In the first 30 min following the GnRH antagonist administration, the trial medication delegate (or another qualified trial staff) must observe the subject's general health with emphasis on symptoms of an acute allergic reaction.
- Instruct the subject to administer the GnRH antagonist at a daily dose of 0.25 mg throughout the stimulation period.

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

6.6.3 Stimulation Days ≥7 to <20

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

The following must take place at all visits throughout the remainder of the stimulation period (with the exception of the end-of-stimulation visit, which is described in section 6.6.4):

- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial triple-layer structure, endometrial echogenicity pattern, number and size of follicles)
- Dispensing of FE 999049 as needed
- Dispensing of GnRH agonist or GnRH antagonist, as applicable and as needed
- Drug accountability of FE 999049 and GnRH agonist or GnRH antagonist, as applicable
- Recording of use of any concomitant medication
- Recording of adverse events

6.6.4 End-of-stimulation

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

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

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

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

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

- Transvaginal ultrasound of uterus and ovaries (endometrial thickness, endometrial triple-layer structure, endometrial echogenicity pattern, ovarian volume, number and size of follicles)
- Blood collection for central laboratory analysis of endocrine parameters (treatment panel) – the blood sample must be drawn at least 8 hours after the latest administration of FE 999049 and GnRH agonist or GnRH antagonist, as applicable
- Dispensing of hCG, if applicable
- Drug accountability of FE 999049 and GnRH agonist or GnRH antagonist, as applicable
- Recording of use of any concomitant medication
- Recording of adverse events

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

Subjects with cycle cancellation will undergo end-of-trial assessments (section 6.13).

6.7 Oocyte Retrieval

Oocyte retrieval must take place 36h (±2h) after hCG administration. All oocytes from follicles with an estimated diameter ≥12 mm should be retrieved. Below are listed the procedures related to the subjects attending the oocyte retrieval visit, while procedures related to the oocytes are described in section 6.8.

The following must take place at the oocyte retrieval visit:

- Blood collection for central laboratory analysis of endocrine parameters (treatment panel) preferably before oocyte retrieval procedure
- Oocyte retrieval
- Dispensing of progesterone for luteal support – must be started on the day after oocyte retrieval [*note*: only applicable for subjects who had oocytes retrieved]
- Drug accountability of hCG
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with oocytes retrieved, the next visit is the transfer visit 5 days after oocyte retrieval (section 6.9). Subjects having no oocytes retrieved will undergo end-of-trial assessments (section 6.13).

6.8 Oocyte / Embryo / Blastocyst Evaluation

The laboratory procedures regarding handling and evaluations of oocytes, embryos and blastocysts are described in detail in a trial-specific manual. This section provides an overview of the procedures and assessments to be made from oocyte retrieval till transfer at the blastocyst stage. The flow of the trial procedures for oocytes is shown in Table 6-3.

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

	Day 0 (OR)	Day 1 after OR	Day 3 after OR	Day 5 after OR
Oocyte retrieval (OR)	X			
Assessment of maturity stage (applicable for oocytes undergoing ICSI)	X			
Insemination by IVF and/or ICSI	X			
Assessment of oocyte fertilisation		X		
Assessment of embryo / blastocyst quality			X	X
Transfer of blastocyst(s)[a] of the highest quality available: – Subjects <38 years at randomisation: • single blastocyst transfer – Subjects ≥38 years at randomisation: • single blastocyst transfer if a good-quality[b] blastocyst is available • double blastocyst transfer may be performed if a good-quality[b] blastocyst is not available				X

[a] In the absence of blastocysts, compacted (not compacting) morulas could take the place of blastocysts for transfer.

[b] A good-quality blastocyst is defined as a grade 3BB or above.

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

Day 0 (Oocyte Retrieval)

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

Day 1 after Oocyte Retrieval

- Assessment of fertilisation (number of pronuclei)

Day 3 after Oocyte Retrieval

- Assessment of embryo quality

From day 3 and onwards, embryos must be cultured separately to ensure individual assessment.

Day 5 after Oocyte Retrieval

- Assessment of blastocyst quality
- Transfer of blastocyst(s) according to transfer policy (section 6.9)
- Remaining blastocysts may be cryopreserved in accordance with local guidelines and/or regulations. All procedures and assessments related to cryopreserved cycles will take place outside this protocol

6.9 Transfer

Transfer is performed on day 5 (blastocyst stage) after oocyte retrieval. The subject-related procedures are described below.

- Transfer of blastocyst(s) of the highest quality available according to this policy:

Subjects <38 years at randomisation:	• single blastocyst transfer
Subjects ≥38 years at randomisation:	• single blastocyst transfer if a good-quality blastocyst (i.e. grade 3BB or above) is available • double blastocyst transfer may be performed if a good-quality blastocyst (i.e. grade 3BB or above) is not available

Note: only blastocysts of acceptable quality as judged by the investigator or embryologist should be transferred. If only low-quality blastocysts are available, the investigator or

embryologist may decide not to transfer any blastocysts without this being a protocol violation. In the absence of viable blastocysts, compacted (not *compacting*) morulas could be used for transfer.

- Dispensing of progesterone for luteal phase support
- Drug accountability of progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

For subjects with blastocyst transfer, the next visit is the βhCG test visit which must be scheduled 13-15 days after transfer (section 6.10)

6.10 βhCG Test

Subjects who have undergone transfer must attend a visit 13-15 days after transfer. Subjects experiencing a full menstrual bleeding may have the βhCG test performed as part of the end-of-trial assessments if this occurs 13-15 days after transfer.

The following must take place:

- Blood collection for local laboratory analysis of βhCG
- Drug accountability of progesterone
- Recording of use of any concomitant medication
- Recording of adverse events

The blood sample for βhCG will be analysed by the local laboratory and evaluated according to the local reference ranges. In case of a doubtful / inconclusive βhCG result, the test should be repeated, preferably within 2 days. Subjects with a positive βhCG test must attend a clinical pregnancy visit 5-6 weeks after transfer (section 6.11). Subjects with a negative βhCG test must proceed to the end-of-trial assessments (section 6.13).

6.11 Clinical Pregnancy

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

The following must take place:

- Transvaginal ultrasound of uterus to assess any clinical pregnancy
- 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 6.12). Subjects with no vital pregnancy must undergo end-of-trial assessments (section 6.13).

6.12 Ongoing Pregnancy

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

The following procedures / assessments must take place:

- Ultrasound (transvaginal or abdominal) of uterus to assess any intrauterine viable fetus
- 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.

6.13 End-of-trial

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

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

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

6.14 Post-trial Activities

All subjects with an ongoing pregnancy will be followed till delivery to gather information on live birth rate. Furthermore, data will be gathered on neonatal health, including minor/major congenital anomalies, at birth and at 4 weeks after birth.

7 TRIAL ASSESSMENTS

7.1 Assessment Related to Primary Endpoint

7.1.1 Number of Oocytes Retrieved

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

7.2 Assessment Related to Secondary Endpoints

7.2.1 Cycle Cancellation due to Poor Ovarian Response or Excessive Ovarian Response

The reason for each cycle cancellation will be recorded. Cycle cancellations related to inappropriate ovarian response will include poor and excessive follicular development. Cycle cancellation due to poor follicular development is implemented when the investigator judges that ≥3 follicles with a diameter ≥17 mm cannot be reached by stimulation day 20. Cycle cancellation due to excessive follicular development is implemented when >25 follicles with a diameter ≥12 mm are observed.

7.2.2 Transfer Cancellation due to (Risk of) OHSS

The reason for each blastocyst transfer cancellation will be recorded. Transfer cancellation due to adverse events such as the Medical Dictionary for Regulatory Activities preferred terms (MedDRA PTs) ”ovarian hyperfunction”, “ovarian hyperstimulation syndrome” and “high progesterone” in subjects with blastocysts available for transfer will be considered as transfer cancellations due to excessive response / (risk of) OHSS.

7.2.3 Number and Size of Follicles during Stimulation

Transvaginal ultrasound will be performed at all visits during the stimulation period to count the number of follicles and measure the size of the follicles. Data will be recorded separately for the right and left ovary.

7.2.4 Proportion of subjects with <4, 4-7, 8-14, 15-19 and ≥20 Oocytes Retrieved

The proportion of subjects with <4 oocytes (low response), 4-7 oocytes (moderate response), 8-14 oocytes (targeted response), 15-19 oocytes (hyperresponse) and ≥20 oocytes (severe hyperresponse) will be calculated.

7.2.5 Metaphase II Oocytes

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

7.2.6 Fertilisation Rate

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

7.2.7 Number and Quality of Embryos on Day 3

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

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

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

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

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

7.2.8 Number and Quality of Blastocysts on Day 5

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

The quality evaluation of blastocysts on day 5 after oocyte retrieval will consist of assessment of three parameters: blastocyst expansion and hatching status, blastocyst inner cell mass grading and trophectoderm grading. The scoring is based on the classification system by Gardner & Schoolcraft[23] 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 visible

Trophectoderm grading will be assessed as one of the following:

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

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

Compaction Assessment in Morulas

Embryos that have not reached the blastocyst stage on day 5, but are morulas, will also be evaluated. Morulas will be categorised as one of the following three options:

- *Compacted:* Complete compaction. Tightly compacted cells. Individual cell membranes are no longer visible.
- *Compacting:* Early stage. Cells can be distinguished.
- *Abnormal compaction:* Regional or partial compaction, or few cells (<8) in compaction.

7.2.9 Circulating Levels of Endocrine Parameters

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

Blood samples will be drawn at stimulation day 1[c], stimulation day 6, end-of-stimulation and at the oocyte retrieval visit. The sample on stimulation day 1 (baseline) will be collected prior to the first dose of FE 999049, and samples drawn at stimulation day 6 and the end-of-stimulation visit will be

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

collected at least 8 hours after the previous administration of FE 999049 and GnRH agonist or GnRH antagonist, as applicable. The sample drawn at the oocyte retrieval visit should preferably be collected before the oocyte retrieval procedure. The samples will be analysed at a central laboratory. The investigator will review and evaluate the laboratory results. The Laboratory Report will be signed and dated by the investigator.

7.2.10 Total Gonadotropin Dose and Number of Stimulation Days

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

7.2.11 βhCG Test

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

7.2.12 Implantation

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

7.2.13 Clinical Pregnancy

A transvaginal ultrasound of the uterus will be performed 5-6 weeks after transfer. Clinical pregnancy will be defined as at least one gestational sac, either intrauterine or ectopic. The inclusion of ectopic pregnancies and the lack of specification of heart beat in the definition of clinical pregnancy is in line with the current International Committee Monitoring Assisted Reproductive Technologies (ICMART) and World Health Organization (WHO) glossary on ART terminology.[d,24] For intrauterine and ectopic pregnancies, the number of gestational sacs with fetal heart beat as well as without fetal heart beat will be recorded.

7.2.14 Vital Pregnancy

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

[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.

7.2.15 Ongoing Pregnancy

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

7.2.16 Ongoing Implantation

Ongoing implantation is determined based on the ultrasound performed at the ongoing pregnancy visit. Ongoing implantation rate will be defined as the number of intrauterine viable fetuses 10-11 weeks after transfer divided by number of blastocysts transferred.

7.2.17 Early OHSS (including Moderate/Severe)

Early OHSS is defined as OHSS with onset ≤9 days after triggering of final follicular maturation. Classification of grade is according to a classification system based on Golan's classification system (see section 8.3.1 for details) and all OHSS cases will be graded as mild, moderate or severe.

7.2.18 Late OHSS (including Moderate/Severe)

Late OHSS is defined as OHSS with onset >9 days after triggering of final follicular maturation. Classification of grade is according to a classification system based on Golan's classification system (see section 8.3.1 for details) and all OHSS cases will be graded as mild, moderate or severe.

7.2.19 Adverse Events

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

7.2.20 Pen Malfunction

Incidences of technical malfunctions of the pre-filled injection pen will be recorded.

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). In countries where it is not allowed to collect 'date of birth' according to national regulations, 'age' will be collected at the screening and randomisation visits.

7.3.2 Medical History

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

7.3.3 Infertility History

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

7.3.4 Menstrual History

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

7.3.5 Reproductive History

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

7.3.6 Smoking and Alcohol Habits

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

7.3.7 Body Measurements

Body measurements will be made at screening and stimulation day 1. Body weight will be measured without shoes and overcoat and using a calibrated scale. The body weight at stimulation day 1 will be used for dose calculation in the FE 999049 group. Height will only be measured at

screening and will be used to calculate BMI.

7.3.8 Physical Examination

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

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

7.3.9 Gynaecological Examination

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

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

7.3.10 Endocrine Parameters at Screening

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

The results of the screening panel must be available prior to randomisation. The investigator will review and evaluate the laboratory results. The Laboratory Report will be signed and dated by the investigator.

7.3.11 Ovarian Volume

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

7.3.12 Endometrial Status

Transvaginal ultrasound of the uterus to assess the endometrial status will be conducted at all visits during the stimulation period. The endometrial status assessments consist of the following

parameters: endometrial thickness, endometrial triple-layer structure and endometrial echogenicity pattern (*note*: the latter two are not assessed on stimulation day 1).

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

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

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

7.3.13 Blastocyst Transfer Procedure

Any difficulty or eventuality during the transfer procedure will be noted.

7.3.14 Concomitant Medication

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

7.3.15 Drug Dispensing and Accountability

For IMP, GnRH antagonist and hCG, dates and time of administration will be recorded. Furthermore, the dose of IMP administered will be recorded. For GnRH agonist and progesterone, only date of first and last administration will be recorded. For each day between first and last GnRH agonist administration and between first and last progesterone administration, information about whether the drug was administered will be recorded. If progesterone is continued after the positive βhCG test is obtained, information about progesterone administration hereafter will not be recorded in the trial specific diary but will be entered on the concomitant medication form in the e-CRF. Details on drug dispensing and accountability are provided in section 5.6.1.

7.3.16 End-of-trial Form

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

7.4 Assessments related to Post-trial Information

7.4.1 Pregnancy Follow-up

For subjects with an ongoing pregnancy in the fresh cycle, information on the pregnancy period, including any relevant interventions performed and incidence of second or third trimester losses, as well as the pregnancy outcome, e.g. live birth, will be gathered. Further, neonatal health data will be collected at birth and at 4 weeks after birth for all children born. At birth, the data collected will include gender, birth weight and length, type of delivery, fetal presentation and apgar score as well as information on minor/major congenital anomalies and admission to neonatal intensive care unit (NICU)/pediatric intensive care unit (PICU) or neonatal care unit (NCU)/pediatric care unit (PCU). At 4 weeks after birth, the data collected will include minor/major congenital anomalies, hospitalisations and any other relevant medical conditions. These follow-up data can be obtained from the subject, unless medical judgement is required, and will be reported separately.

7.5 Handling of Biological Samples

A trial-specific laboratory manual will be provided to the participating sites, describing in detail how to handle, store and transport the biological samples (blood) in this trial. All biological samples will be analysed at central laboratories and will be destroyed after the end of the trial. Exceptions are the blood samples for estradiol, if applicable, and βhCG which are analysed by a local laboratory at the trial clinic / hospital and subsequently destroyed. AMH back-up samples will be stored for up to 4 years after submission of the clinical trial report and may be used for additional AMH measurement with any AMH assay or for recalibration against a new reference standard. 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.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

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

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

All adverse events will be coded by Ferring Global Pharmacovigilance using MedDRA.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the end-of-trial visit.

The sources of adverse events cover:

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

8.2.2 Recording of Adverse Events

The investigator must record all adverse events in the Adverse Event Log provided in each subject's e-CRF with information about:

- Adverse event

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

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

Adverse Event

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

If a subject suffers from the same adverse event more than once and the subject recovers in between the events, the adverse events should be recorded separately. If an adverse event changes in intensity, a worst-case approach should be used when recording the event, i.e. the highest intensity and the longest duration of the event.[e]

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

Date and Time of Onset

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

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

Intensity

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

Mild:	Awareness of signs or symptoms, but no disruption of usual activity
Moderate:	Event sufficient to affect usual activity (disturbing)
Severe:	Inability to work or perform usual activities (unacceptable)

Causal Relationship to IMP

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

Reasonable possibility:

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

Examples:

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

No reasonable possibility:

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

Examples:

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

Action Taken to IMP

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

- No change (medication schedule maintained or no action taken)
- Discontinued
- Interrupted

- Dose reduced
- Dose increased

Other Action Taken

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

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

Date and Time of Outcome

The date and time the subject recovered or died.

Outcome

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

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

8.3 Adverse Events of Special Interest

8.3.1 Ovarian Hyperstimulation Syndrome (OHSS)

Symptoms and Classification

OHSS is an adverse event of special interest during controlled ovarian stimulation. Investigators will record OHSS symptoms using a classification system based on Golan's system[25] 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

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

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

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

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

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

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

Subject narratives will be prepared for all OHSS cases.

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

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

Investigations in case of OHSS

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

- Body weight and maximum abdominal circumference (for all OHSS)
- Vital signs
- Blood sample for central laboratory analysis of the following (for moderate/severe OHSS):
  - Progesterone and estradiol
  - Complete Blood Count: red blood cells, red blood cell morphology, white blood cells, white blood cell morphology, haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, platelets
  - CHEM-20: albumin, alanine transaminase, 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 during the trial:

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

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

8.4 Events Requiring Special Handling

8.4.1 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.

8.4.2 Multiple Pregnancies

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

8.5 Serious Adverse Events

8.5.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined a serious adverse event if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is *per se* not an event, but an outcome.
is **life-threatening**	The term life-threatening refers to an adverse event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
requires in-patient **hospitalisation** or prolongation of existing hospitalisation	The term hospitalisation means that the subject was admitted to hospital or that existing hospitalisation was extended as a result of an event. Hospitalisation describes a period of at least 24 hours. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalisation. However, medical judgement must always be exercised and when in doubt the case should be considered serious (i.e. if case fulfils the criterion for a medically important event). Hospitalisations for administrative or social purposes do not constitute a serious adverse event. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability / incapacity**	Disability / incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgement by the investigator.
is an **important medical event**	Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Elective Termination

In connection with elective termination due to a congenital anomaly, the congenital anomaly of the fetus should be reported as a serious adverse event.

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

Serious Adverse Events during Post-Trial Follow-up

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

- Death of mother in connection with pregnancy or labour
- Death of neonate / infant
- Stillbirth[g]
- Neonate admitted to NICU/PICU regardless of duration or NCU/PCU for at least 2 hours
- Congenital anomaly / birth defect[h]
- Medically important event

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

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

[f] 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.

[g] Stillbirth: gestational age ≥24 weeks + 0 days. Gestational age is calculated from the day of transfer + 19 days.

[h] Congenital anomaly / birth defect in any off spring of the subject conceived during treatment with the IMP.

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

8.5.2 Collection, Recording and Reporting of Serious Adverse Events

Serious Adverse Event Reporting by the Investigator

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

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

Serious Adverse Event Report Form

The Serious Adverse Event Report Form is included in the e-CRF system, and must be completed and submitted according to the instructions provided on the form. In case the e-CRF cannot be accessed and hence the Serious Adverse Event Report Form cannot be filled in within the e-CRF system, a paper Serious Adverse Event Report Form should be used and sent to Ferring Global Pharmacovigilance using the contact details below. As soon as the e-CRF is accessible again, the serious adverse event must be entered and notified to Ferring Global Pharmacovigilance.

Global Pharmacovigilance, Ferring Pharmaceuticals A/S
E-mail: [redacted]
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 e-CRF for Ferring Global Pharmacovigilance to access the information.

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

The investigator will supply Ferring and the Independent Ethics Committee (IEC) 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 e-CRF and reviewed by Ferring Global Pharmacovigilance on an ongoing basis.

Ferring will report serious adverse events 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 Global Pharmacovigilance. Follow-up should continue until the outcome of recovered, recovered with sequelae or fatal, has been reached. If the event is a chronic condition, the investigator and Ferring may agree that further follow-up is not required.

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

If an investigator becomes aware of a serious adverse event after the end of the trial, and he/she assesses the serious adverse event to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring Global Pharmacovigilance, regardless how long after the end of the trial this takes place.

8.6.3 Follow-up of Serious Adverse Events with Onset during Post-trial

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

8.6.4 Adverse Events on Non-investigational Medicinal Products

During the trial, any case of adverse event that is recognised as an adverse drug reaction caused by a concomitant NIMP where Ferring is the Marketing Authorisation Holder (i.e. GONAPEPTYL and LUTINUS), must be reported to Ferring Global Pharmacovigilance.

If an investigator becomes aware of an adverse event with onset after the end of the trial, and he/she assesses the adverse event to have a reasonable possible causality to a concomitant NIMP where Ferring is the Marketing Authorisation Holder (i.e. GONAPEPTYL and LUTINUS), the case will

have to be reported to Ferring Global Pharmacovigilance.

8.6.5 Pregnancy during Down-regulation

If spontaneous pregnancy occurs during the down-regulation period it should be reported to Ferring Global Pharmacovigilance. An electronic pregnancy form should be filled out and sent to Ferring Global Pharmacovigilance using the contact information mentioned in section 8.5.2.

9 STATISTICAL METHODS

The Global Biometrics department of Ferring Pharmaceuticals will be responsible for the statistical analyses. All analyses will be detailed in a separate Statistical Analysis Plan.

9.1 Determination of Sample Size

The purpose of this trial is to gain clinical experience with the use of FE 999049 when applied in a long GnRH agonist protocol. The trial is descriptive and does not include any hypothesis testing. The sample size is based on achieving a reasonable precision in the estimate of the difference in mean number of oocytes retrieved between treatment with FE 999049 in a long GnRH agonist protocol versus treatment with FE999049 in a GnRH antagonist protocol.

In the ESTHER-1 trial, the standard deviation for the number of oocytes retrieved was 5.8 in the FE 999049 treatment group. Due to a potentially higher number of oocytes retrieved in the long agonist protocol, the standard deviation in this trial may be slightly higher. Assuming a standard deviation of 7.0, a sample size of 400 subjects (200 subjects per group) will give a 95% CI that ranges from -1.4 to +1.4 of the observed mean difference, i.e. the interval from the observed mean difference 1.4 to the observed mean difference +1.4 will with 95% probability include the true mean difference. This is regarded to be reasonably precise for describing the comparability of individualised FE 999049 dosing using the two protocols.

9.2 Subject Disposition

All subjects screened and randomised will be accounted for. All post-randomisation discontinuations will be summarised by time of, and reason for, discontinuation. Discontinuations will be classified as occurring before or after start of FE 999049 treatment. The number of subjects screened and not randomised will be presented.

9.3 Protocol Deviations

Important protocol deviations will be summarised and listed by subject. The impact of important protocol deviations on the trial results may be addressed in additional sensitivity analyses.

9.4 Analysis Sets

9.4.1 Full Analysis Set

The FAS will consist of all subjects that were randomised, regardless of whether they started FE 999049 treatment or not. However, subjects that discontinued before starting FE 999049 treatment due to the COVID-19 pandemic (e.g. due to operational and/or societal issues) will be excluded from the FAS. Subjects will be analysed according to the protocol to which they were randomised.

9.4.2 Safety Analysis Set

The safety analysis set will consist of all subjects that were randomised in the trial and were exposed to FE 999049. Subjects will be analysed according to the protocol they were actually treated with.

9.5 Trial Population

9.5.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics (body measurements, infertility history, menstrual history, reproductive history, smoking and alcohol habits, physical examination, and gynaecological examination) will be presented for the FAS. In addition, a summary of demographic characteristics will be presented by trial site.

9.5.2 Medical History and Concomitant Medication

Medical history and concomitant medication will be presented for the FAS. Medical history recorded at the screening visit will be coded using MedDRA and summarised. The version of MedDRA will be documented. Prior and concomitant medication will be summarised by ATC classification 1st level (alphabetically) and ATC classification 2nd level (in decreasing order of frequency). These medications will be tabulated separately for:

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

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

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

Concomitant medications will be listed by subject.

9.6 Endpoint Assessments

9.6.1 General Considerations

The primary objective of the trial is to evaluate the effect of individualised FE 999049 treatment on ovarian response in a long GnRH agonist protocol versus a GnRH antagonist protocol. The primary endpoint is the number of oocytes retrieved.

The estimand of interest is the difference between FE 999049 treatment in the long GnRH agonist protocol versus treatment with FE 999049 in the GnRH antagonist protocol for all randomised subjects, assuming that all subjects start treatment with FE 999049. In the statistical analyses, subjects that discontinue after randomisation but before start of FE 999049 treatment (except for subjects that never started treatment due to the COVID-19 pandemic) will have their endpoint data imputed from subjects who started FE 999049 treatment in the same protocol, using a multiple imputation method. No imputation will be done for subjects who discontinue the trial after starting FE 999049 treatment. For these subjects, the actual data will be used and not be regarded as missing. Therefore, the number of oocytes retrieved will be regarded as zero and pregnancy outcomes will be regarded as negative.

The trial is descriptive and no formal hypothesis will be tested. The statistical analyses aims at estimating any potential differences between FE 999049 treatment when applied in the two different GnRH protocols. The results will generally be described as an estimated mean treatment difference or treatment ratio and an associated 95% CI.

Since the trial is descriptive without any hypothesis testing, no corrections for multiplicity will be applied.

All analyses and descriptions for ovarian response endpoints and other pharmacodynamics endpoints will be based on the FAS. Analyses and descriptions for pregnancy endpoints will be based on the FAS but excluding subjects that had transfer cancellation due to the COVID-19 pandemic. Additional descriptions will be made based on the FAS. Analyses and descriptions of safety endpoints and exposure will be based on the safety analysis set.

9.6.2 Primary Endpoint

The primary endpoint will be analysed using a negative binomial regression model with protocol (long GnRH agonist protocol or GnRH antagonist protocol), age stratum (<35, 35-37, or 38-40 years), and AMH at screening (<15 pmol/L or or ≥15 pmol/L) as factors. A logarithmic link function will be used for the mean in the model. From this model, the mean difference between the two protocols in number of oocytes retrieved will be estimated, and a 95% CI for the estimate will be calculated using the delta method. The analyses will be done using the multiple imputation method described below.

Age stratum is included as factor in the model since randomisation is stratified by age. AMH at screening is additionally included as a factor since AMH is known to influence the number of oocytes retrieved. Although randomisation is stratified by centre, centre and the interaction between centre and age stratum are not included in the model as all centres may not randomise subjects from all age strata, and therefore the inclusion of the interaction in the model is likely to give empty cells in the analysis. The potential influence of centre differences on the results will instead be investigated in a sensitivity analysis.

For subjects in the FAS who discontinue the trial after randomisation but before start of FE 999049 treatment, the number of oocytes retrieved will be imputed from subjects who started FE 999049 treatment in the same protocol, using the following multiple imputation method:

- First, a negative binomial regression model with age stratum and AMH at screening as factors will be fitted to data from subjects who started FE 999049 treatment for each protocol separately.
- In the second step, 1000 complete datasets will be constructed. For the construction of each complete dataset, a set of parameter values will be sampled from a normal distribution with characteristics determined by the estimated parameters and covariance matrix for the two models in the first step. Missing individual subject data will then be imputed from a negative binomial distribution with the sampled parameters.
- In the third step, each complete dataset will be analysed using the negative binomial regression model described in the first paragraph of this section.
- In the final step, the estimated mean differences and the standard deviations from the 1000 analyses will be combined using Rubin's formula:

$$m_{MI} = \frac{1}{1000}\sum_{i=1}^{1000} m_{i,} \quad SD_{MI} = \sqrt{\frac{1}{1000}\sum_{i=1}^{1000} {SD_i}^2 + \left(1+\frac{1}{1000}\right)\left(\frac{1}{1000-1}\right)\sum_{i=1}^{1000}(m_i - m_{MI})^2}$$

  Where m_i and SD_i are the estimated mean differences and standard deviations for the differences for the 1000 copies of the dataset (derived using the delta method), and m_{MI} and SD_{MI} are the pooled estimates.

- The mean difference in number of oocytes retrieved between the long GnRH agonist protocol and the GnRH antagonist protocol will be estimated as m_{MI}, and the 95% CI for the estimate will be calculated as $m_{MI} \pm 1.96 * SD_{MI}$.

The assumption underlying the above imputation procedure is that all randomised subjects could have started FE 999049 treatment, and that their outcome would not have differed in any systematic way from the subjects that started FE 999049 treatment.

For subjects who discontinue the trial after start of FE 999049 treatment but before oocyte retrieval the number of oocytes retrieved will be regarded as zero.

Sensitivity Analyses and Additional Descriptions for the Primary Endpoint

The potential influence of centre differences on the results for the primary endpoint will be investigated by repeating the analyses of the 1000 complete datasets generated above, with the addition of centre and the interaction between centre and age strata as factors in the model.

Additional analyses will be made for two subgroups based on AMH at screening (<15 pmol/L or ≥15 pmol/L) and for the three age strata (<35, 35-37, or 38-40 years). These analyses will be based on the 1000 complete datasets used for the primary analyses and will use the same analysis model, except that age stratum will not be included as factor in the age strata analyses and AMH will not be included in the AMH subgroup analyses. The results of the subgroup analyses will be illustrated in forest plots.

9.6.3 Secondary Endpoints

Proportion of Subjects with Cycle Cancellation due to Poor Ovarian Response or Excessive Ovarian Response

The proportion of subjects with cycle cancellation due to poor ovarian response or excessive ovarian response will be described. Additional descriptions will be made for the two subgroups based on AMH at screening (<15 pmol/L or ≥15 pmol/L) and for the three age strata (<35, 35-37, or 38-40 years).

Proportion of Subjects with Blastocyst Transfer Cancellation after Oocyte Retrieval due to (Risk of) OHSS

The proportion of subjects with blastocyst transfer cancellation after oocyte retrieval due to (risk of) OHSS will be described. Additional descriptions will be made for the two subgroups based on AMH at screening (<15 pmol/L or ≥15 pmol/L) and for the three age strata (<35, 35-37, or 38-40 years).

Number and Size of Follicles on Stimulation Day 6 and End-of-stimulation

The follicle cohort on stimulation day 6 and end-of-stimulation will be summarised by protocol 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).

Proportion of Subjects with <4, 4-7, 8-14, 15-19 and ≥20 Oocytes Retrieved

The distribution of the number of oocytes retrieved will be described for the two protocols using histograms. The percentage of subjects with <4, 4-7, 8-14, 15-19 and ≥20 oocytes retrieved will be described. Additional descriptions will be made for the two subgroups based on AMH at screening (<15 pmol/L or ≥15 pmol/L) and for the three age strata (<35, 35-37, or 38-40 years).

Number of Metaphase II Oocytes

Oocytes undergoing ICSI will have their maturity stage assessed prior to insemination. The total number of metaphase II oocytes will be compared between the long GnRH agonist protocol and the GnRH antagonist protocol using the same analysis method as for the primary endpoint.

Fertilisation Rate

An oocyte is defined as fertilised if it is scored as 2 pronuclei on day 1 after oocyte retrieval. The total number of fertilised oocytes will be compared between the long GnRH agonist protocol and the GnRH antagonist protocol using the same analysis method as for the primary endpoint. The proportion of fertilised oocytes will be described.

Number and Quality of Embryos on Day 3 after Oocyte Retrieval

The number and the quality of embryos on day 3 will be described.

Number and Quality of Blastocysts on Day 5 after Oocyte Retrieval

The number and the quality of blastocysts on day 5 will be described.

The total number of good-quality blastocysts (grade 3BB or higher) will be compared between the long GnRH agonist protocol and the GnRH antagonist protocol using the same analysis method as for the primary endpoint.

Circulating Concentrations of FSH, LH, Estradiol, Progesterone and Inhibin B on Stimulation Day 6, End-of-stimulation and at Oocyte Retrieval

For each parameter, the concentrations on stimulation day 6, end-of-stimulation, and at oocyte retrieval will be described and compared for the long GnRH agonist protocol versus the GnRH antagonist protocol using analysis of variance models with age stratum and AMH at screening as factors. Multiplicative models will be used, i.e. the concentrations will be log-transformed before analysis. The results of the analyses will be back-transformed and presented as estimated geometric means for each parameter, and the mean ratios for long GnRH agonist protocol versus GnRH antagonist protocol with 95% CIs. Values below the lower limit of quantification (LLOQ) will be estimated with LLOQ/2.

Total Gonadotropin Dose and Number of Stimulation Days

The total gonadotropin dose and the number of stimulation days will be described for each of the two protocols and for subgroups based on age strata and AMH at screening.

Pregnancy Rates

The percentage of subjects with positive βhCG, clinical pregnancy, vital pregnancy, and ongoing pregnancy will be described for each of the two protocols and for subgroups based on age strata and AMH. Pregnancy rates will be compared between the long GnRH agonist protocol and the GnRH antagonist protocol using a logistic regression model with protocol (long GnRH agonist or GnRH antagonist), age stratum (<35, 35-37, or 38-40 years), and AMH at screening (<15 pmol/L or ≥15 pmol/L) as factors. The results of this analysis (in terms of odds for pregnancy) will be converted into proportions, differences in proportions, and 95% CIs for differences in proportions using the delta method.

To account for subjects withdrawing from the trial before starting FE 999049 treatment, the multiple imputation method applied for the primary endpoint will be used, using a logistic regression model instead of a negative binomial regression model. Pregnancy data for subjects with pregnancies occurring before start of FE 999049 treatment will not be included in the analysis. These subjects are withdrawn and their data will be imputed.

Missing pregnancy assessments will be assumed to indicate a negative test. If, however, a subsequent test is positive, a previous missing assessment will be considered as positive (if e.g. the clinical pregnancy assessment is missing but the ongoing pregnancy assessment is positive, the missing clinical pregnancy assessment will be regarded as positive).

Implantation Rates

The implantation rate will be calculated as the number of gestational sacs 5-6 weeks after transfer divided by the number of blastocysts transferred.

Ongoing implantation rate will be calculated as the number of intrauterine viable fetuses 10-11 weeks after transfer divided by the number of blastocysts transferred.

The implantation rate and the ongoing implantation rate will be described for each of the two protocols and for subgroups based on age strata and AMH at screening.

Proportion of Subjects with Early OHSS (including OHSS of Moderate/Severe grade)

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

Proportion of Subjects with Late OHSS (including OHSS of Moderate/Severe grade)

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

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 FE 999049 as follows:

- Pre-treatment adverse event, i.e. any adverse event occurring after signed informed consent and before start of FE 999049 treatment, or a pre-existing medical condition that worsens in intensity after signed informed consent but before start of FE 999049 treatment.
- Treatment-emergent adverse event, i.e. any adverse event occurring after start of FE 999049 treatment and before the end-of-trial visit, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of FE 999049 treatment and before the end-of-trial visit.

Treatment-emergent adverse events will be presented in summary tables and listings. Pre-treatment adverse events will be presented in a listing only. Treatment-emergent adverse events will be summarised overall and tabulated by System Organ Class (SOC) and PT in decreasing order of frequency. The total number of subjects reporting an adverse event, the percentage of subjects with an adverse event, and the number of events reported will be presented.

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

Technical Malfunctions of the Pre-filled Injection Pen

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

Post-trial Information

Live birth rate and neonatal health, including minor / major congenital anomalies, at birth and at 4 weeks after birth will be described. These data will be reported separately.

9.7 Interim Analyses

No interim analysis is planned.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – ICH Definition

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

Source Documents - ICH Definition

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

Trial-specific Source Data Requirements – Ferring

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

- Existence of subject (initials, date of birth or age at screening and randomisation, as applicable)
- Confirmation of participation in trial (trial ID, subject ID)
- Informed consent(s) (date and time of obtaining written informed consent(s))
- Eligibility for participation in the trial (documenting all inclusion / exclusion criteria, and successful pituitary down-regulation, if applicable)
- Continuous eligibility for participation in the trial (documenting that none of the withdrawal criteria are met)
- Relevant medical history, infertility history, menstrual history and reproductive history
- Body weight measurements
- Visit dates
- Dates and time of IMP, GnRH antagonist and hCG administration
- Daily dose of IMP administered
- Dates of first day and last day of GnRH agonist and progesterone administration

- Dates and daily doses of concomitant medication
- Date of oocyte retrieval and number of oocytes retrieved
- Date of transfer and number and quality of blastocysts transferred
- Results of βhCG test and ultrasound at clinical and ongoing pregnancy visits
- Pregnancy outcome, i.e. live birth or pregnancy loss, and neonatal health at birth and 4 weeks after birth
- Adverse events (description as well as start/stop date and time)
- OHSS symptoms, preventive intervention (i.e. cycle cancellation), investigations and treatments
- Reason for discontinuation / withdrawal

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

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

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

10.2 e-CRF

An e-CRF system provided by an independent third-party contract research organisation (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.

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

The investigator will approve / authorise the e-CRF entries for each subject with an electronic signature which is equivalent to a handwritten signature.

The e-CRF 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 e-CRF is revoked.

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

10.3 Use of Patient Reported Outcome

All medication will be dispensed at the trial site and the subject will enter dates and time of IMP, GnRH antagonist and hCG administration, dose of IMP administered, and date of first and last GnRH agonist and progesterone administration in a trial specific diary. For each day between first and last GnRH agonist administration and between first and last progesterone administration, information about whether the drug was administered will also be entered in the trial specific diary. This will later be entered into the e-CRF by delegated and trained trial staff (*for GnRH agonist and progesterone administration between first day and last day of administration, summary information will be entered into the e-CRF*). If progesterone is continued after the positive βhCG test is obtained, information about progesterone administration hereafter will not be recorded in the trial specific diary but will be entered on the concomitant medication form in the e-CRF. In case the subject has taken an incorrect IMP dose, this will be captured in the e-CRF as a medication error.

10.4 Health Economics

Not applicable.

10.5 Data Management

A data management plan will be created under the responsibility of the Global Biometrics Department of Ferring Pharmaceuticals A/S. 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 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.

10.6 Provision of Additional Information

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

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Conference of Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of e-CRF entries compared to source data, verification of drug accountability and compliance to safety reporting instructions.

The investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The investigator will co-operate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits.

When the first subject is randomised at the trial site, a monitoring visit will take place shortly thereafter. For this trial, the frequency of monitoring visits per site will be determined through a risk-based approach depending on recruitment rate, observed data quality, and overall site performance. The source data verification process and definition of key variables to be monitored will be described in detail in the Monitoring Plan for the trial.

For the pregnancy follow-up data, accuracy and verifiability of the e-CRF entries compared to the reports obtained from the subject's gynaecologist / obstetrician / paediatrician or information by the subject herself, or other sources, as applicable, will be ensured.

11.2 Audit and Inspection

The investigator will make all the trial-related source data and records available at any time to quality assurance auditor(s) mandated by Ferring, or to domestic / foreign regulatory inspectors or representatives from IECs 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[26] and all other relevant regulations.

The subjects must be informed by the investigator and in the Informed Consent Form that authorised Ferring representatives and representatives from regulatory authorities and IECs may wish to inspect their medical records. During audits / inspections the auditors / inspectors may copy relevant parts of the medical records. No personal identification apart from the screening / randomisation number will appear on these copies.

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

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the e-CRF or any other documents submitted to Ferring, the subjects will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to Ferring, e.g. the confidential subject identification code and the signed Informed Consent Forms, will be maintained by the investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

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

12.2 Deviations from the Protocol

Deviations from the protocol should not occur. If deviations occur, the investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and filed in the Trial Master File at the end of the trial.

12.3 Premature Trial Termination

Both the investigator (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, Ferring and the investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and IEC(s) will be informed.

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

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring and submitted for comments and signature to the signatory investigator.

13.2 Confidentiality and Ownership of Trial Data

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

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the investigator(s) offered authorship and Ferring. In a multi-site trial based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multi-site trials must be reported in entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the International Committee of Medical Journal Editors (ICMJE) criteria.[27] The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the investigator's and Ferring's opinion will be fairly and sufficiently represented in the publication.

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

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

13.3.2 Public Disclosure Policy

ICMJE member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is

the responsibility of Ferring to register the trial in an appropriate public registry, i.e. www.ClinicalTrials.gov; a website maintained by the National Library of Medicine (NLM) at the U.S. National Institutes of Health (NIH). The trial will also be made publicly available at the EU Clinical Trials Register at www.clinicaltrialsregister.eu. Trial registration may occur in other registries in accordance with local regulatory requirements. A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Independent Ethics Committee

An IEC will review the protocol and any amendments and advertisements used for recruitment. The IEC 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 IECs 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 Authorities Authorisation / Approval / Notification

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

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

The end of the trial is defined as the date of LPLV.

The primary completion date is when the last subject undergoes oocyte retrieval.

The sponsor shall make an end-of-trial declaration to the regulatory authorities and the concerned ethics committees in the participating countries, when the last data in the post-trial follow-up period has been collected in all Member States / third countries concerned (global end-of-trial).

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

14.4 Ethical Conduct of the Trial

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

14.5 Subject Information and Consent

Informed Consent regarding Participation in the Trial – Subject

The investigator will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the subject's decision to participate. The trial subject must be given ample time to consider participation in the trial, before the consent is obtained. The Informed Consent Form must be signed and dated by the subject and the investigator who has provided information to the subject regarding the trial before the subject is exposed to any trial-related procedure, including screening tests for eligibility.

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

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

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

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

Informed Consent regarding Data Collection on the Neonate – Child-custody Holders

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

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

The child-custody holders will receive a copy of the 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 regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review the neonate's source records and data. Data protection will be handled in compliance with national / local regulations.

Informed Consent regarding Participation in the Trial – Partner

For countries where a separate information and informed consent form is required in order to collect data on the partner and use the partner's sperm for IVF or ICSI, the investigator will obtain a freely given written consent from the partner. The partner must be given ample time before the consent is obtained. The Informed Consent Form must be signed and dated by the partner and the investigator who has provided information to the partner. Written consent by the partner must be obtained before the subject is randomised and preferably at the time of obtaining written consent by the subject regarding participation in the trial.

The investigator will explain that the partner is completely free to refuse to consent to this data collection or to withdraw consent at any time without the need to justify the decision.

The partner will receive a copy of the Informed Consent Form.

The partner will be informed that the monitor(s), quality assurance auditor(s) mandated by Ferring, ethics committee representatives or regulatory authority inspector(s), in accordance with applicable regulatory requirements, will review the partner's source records and data. Data protection will be handled in compliance with national / local 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 (incl. trial code)
- That the trial involves controlled ovarian stimulation with recombinant FSH
- The name and phone number of the investigator
- Ferring Pharmaceuticals A/S, Kay Fiskers Plads 11, 2300 Copenhagen S, Denmark [*note*: this statement is only to be included on the Subject Information Card if required by local regulations]

The subject will be asked to keep the Subject Participation Card in her possession at all times during the trial and to return it at the last trial visit, if applicable.

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

14.7 Delivery Data Checklist

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

At delivery:

- Date of delivery
- Type of delivery (vaginal / vacuum extraction / forceps / caesarean section)
- Fetal presentation (head / breech / transverse / other – please specify)
- Gender
- Birth weight
- Birth length
- Apgar score after 1, 5 and 10 minutes
- Admission to NICU/PICU regardless of duration
- Admission to NCU/PCU for at least 2 hours
- Any medically important event requiring treatment
- Congenital anomaly
- Neonatal death

4 weeks after delivery:

Relevant important conditions since birth:

- Admission to NICU/PICU regardless of duration
- Admission to NCU/PCU for at least 2 hours
- Any medically important event requiring treatment
- Any congenital anomaly discovered since birth
- Neonatal death

14.8 Compliance Reference Documents

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

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

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

15.2 Liabilities and Insurance

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

16 ARCHIVING

16.1 Investigator File

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

The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and anonymous e-CRF data for Ferring. The investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Forms 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.

17 REFERENCES

1 European Medicines Agency (EMA). Committee for medicinal products for human use (CHMP). Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data. EMEA/CHMP/313666/2005.

2 Food and Drug Administration (FDA). Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). Reviewer Guidance: Evaluating the risk of drug exposure in human pregnancies. April 2005.

3 Nyboe Andersen A, Nelson SM, Fauser BCJM, Garcia-Velasco JA, Klein BM, Arce J-C on behalf of the ESTHER-1 study group. Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicentre, randomized, controlled, assessor-blinded, phase 3 noninferiority trial. Fertil Steril 2017; 107: 387-396.

4 REKOVELLE Summary of Product Characteristics. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003994/WC500220235.pdf

5 European Orgalutran Study Group, Borm G, Mannaerts B. Treatment with the gonadotrophin releasing hormone antagonist ganirelix in women undergoing ovarian stimulation with recombinant follicle stimulating hormone is effective, safe and convenient: results of a controlled, randomized, multicenter trial. Hum Reprod 2000; 15: 1490-1498.

6 Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonist for assisted conception: a Cochrane Review. RBMOnline 2007; 14: 640-649.

7 Coelingh Bennink HJT, Fauser BCJM, Out HJ. Recombinant follicle-stimulating hormone (FSH; Puregon) is more efficient than urinary FSH (Metrodin) in women with clomiphene citrate-resistant, normogonadotropic, chronic anovulation: a prospective, multicenter, assessor-blind, randomized, clinical trial. Fertil Steril 1998; 69: 19-25.

8 Recombinant Human FSH Study Group. Clinical assessment of recombinant human follicle-stimulating hormone in stimulating ovarian follicular development before in vitro fertilization. Fertil Steril 1995; 63: 77-86.

9 Out HJ, Mannaerts BMJL, Driessen SGAJ, Coelingh Bennink HJT. A prospective, randomized, assessor-blind, multicentre study comparing recombinant and urinary follicle stimulating hormone (Puregon versus Metrodin) in in-vitro fertilization. Hum Reprod 1995; 10: 2534-2540.

10 Wadhwa M, Thorpe R. Unwanted immunogenicity: implications for follow-on biologicals. Drug Information Journal 2007; 41: 1-10.

11 Buur Rasmussen B, Mannaerts B, Klein BM, Helmgaard L, Arce J-C on behalf of the ESTHER-1 and ESTHER-2 trial group. Low immunogenicity potential of follitropin delta, a recombinant FSH preparation produced from a human cell line: Results from phase 3 trials (ESTHER-1 and ESTHER-2). Poster presented at the 32nd Annual Meeting of ESHRE; 2016 Jul 3-6; Helsinki, Finland.

12 European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP). Assessment Report for Elonva (corifollitropin alfa). EMA/CHMP/802299/2009.

[13] Norman RJ, Zegers-Hochschild F, Salle BS, Elbers J, Heijnen E, Marintcheva-Petrova M, Mannaerts B on behalf of the Trust Investigators. Repeated ovarian stimulation with corifollitropin alfa in patients in a GnRH antagonist protocol: no concern for immunogenicity. Hum Reprod 2011; 26: 2200-2208.

[14] Blake DA, Proctor M, Johnson NP. The merits of blastocyst versus cleavage stage embryo transfer: a Cochrane review. Hum Reprod 2004; 19: 795-807.

[15] Papanikolaou EG, Kolibianakis EM, Tournaye H, Venetis CA, Fatemi H, Tarlatzis B, Devroey P. Live birth rates after transfer of equal number of blastocysts or cleavage-stage embryos in IVF. A systematic review and meta-analysis. Hum Reprod 2008; 23: 91-99.

[16] Csokmay JM, Hill MJ, Chason RJ, Hennessy S, James AN, Cohen J, DeCherney AH, Segars JH, Payson MD. Experience with a patient-friendly, mandatory, single-blastocyst transfer policy: the power of one. Fertil Steril 2011; 96: 580-584.

[17] Kresowik JD, Stegmann BJ, Sparks AE, Ryan GL, van Voorhis BJ. Five-years of a mandatory single-embryo transfer (mSET) policy dramatically reduces twinning rate without lowering pregnancy rates. Fertil Steril 2011; 96: 1367-1369.

[18] Practice Committee of Society for Assisted Reproductive Technology and Practice Committee of the American Society for Reproductive Medicine. Elective single-embryo transfer. Fertil Steril 2012; 97: 835-842.

[19] Rehman KS, Bukulmez O, Langley M, Carr BR, Nackley AC, Doody KM, Doody KJ. Late stages of embryo progression are a much better predictor of clinical pregnancy than early cleavage in intracytoplasmic sperm injection and in vitro fertilization cycles with blastocyst-stage transfer. Fertil Steril 2007; 87: 1041-1052.

[20] Al-Inany HG, Youssef MA, Ayeleke RO, Brown J, Lam WS, Broekmans FJ. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology (Review). Cochrane Database Syst Rev 2016; 4: CD001750.

[21] European Society of Human Reproduction and Embryology (ESHRE). ART fact sheet. https://www.eshre.eu/Guidelines/ART-fact-sheet_vFebr18_VG.pdf
Accessed on 29th May 2018.

[22] American Society for Reproductive Medicine. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 1997; 67: 817-821.

[23] Gardner DK, Schoolcraft WB. In vitro culture of human blastocysts. In: Towards reproductive certainty (Eds Jansen R & Mortimer D). The plenary proceedings of the 11th world congress on in vitro fertilization and human reproductive genetics. The Parthenon Publishing Group. 1999. Pp 378-388.

[24] Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, Rienzi L, Sunde A, Schmidt L, Cooke ID, Simpson JL, van der Poel S. The international glossary on infertility and fertility care. Hum Reprod 2017; 32: 1786-1801.

[25] Golan A, Ron-El R, Herman A, Soffer Y, Weinraub Z, Caspi E. Ovarian hyperstimulation syndrome: an update review. Obstet Gynecol Survey 1989; 44: 430-440.

[26] World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

[27] International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: ethical considerations in the conduct and reporting of research: authorship and contributorship. Downloaded from www.ICMJE.org on May 14th 2018.