Cover Page for Protocol and Statistical Analysis Plan

Sponsor name	Ferring Pharmaceuticals A/S
NCT Number	NCT05403476
Sponsor trial ID	000400
Official title of Study	A randomised, double-blind, placebo-controlled trial to assess the efficacy and safety of FE 999049 for treatment of men with idiopathic infertility
Document Date	04 July 2024

CLINICAL TRIAL PROTOCOL

A randomised, double-blind, placebo-controlled trial to assess the efficacy and safety of FE 999049 for treatment of men with idiopathic infertility

Trial 000400

ADAM
(Assessment of Follitropin Delta Efficacy and Safety for Treatment of Men with Idiopathic Infertility)

EU Clinical Trial Number:	2023-508430-34-00
IND Number:	155,804
UTN Number:	U1111-1268-6968
Investigational Medicinal Product:	FE 999049, recombinant human follicle-stimulating hormone (rFSH), solution for subcutaneous injection
Indication:	Treatment of men with idiopathic infertility
Phase:	2a
Name and Address of Sponsor:	Ferring Pharmaceuticals A/S Amager Strandvej 405 2770 Kastrup, Denmark Tel: (+45) 88 33 88 34
Version:	6.0 (Consolidated protocol; changes introduced with protocol amendment 03 implemented)
GCP Statement:	This trial will be performed in compliance with GCP.

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SYNOPSIS

TITLE OF TRIAL

A randomised, double-blind, placebo-controlled trial to assess the efficacy and safety of FE 999049 for treatment of men with idiopathic infertility

SIGNATORY INVESTIGATORS

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TRIAL SITES

Approximately 25 sites in approximately 7 countries across Europe and North America

PLANNED TRIAL PERIOD

First patient first visit (FPFV):	Q3 2022
Last patient first visit (LPFV):	Q3 2025
Last patient last visit (LPLV):	Q3 2026
Pregnancy follow-up completed:	Q2 2028

CLINICAL PHASE

2a

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

FE 999049 (follitropin delta) is a human recombinant follicle-stimulating hormone (rFSH) derived from a human cell line (PER.C6®). Ferring Pharmaceuticals received Marketing Authorisation from the European Commission for FE 999049 in December 2016. As of August 2021, FE 999049 is approved under the trade name REKOVELLE in more than 65 countries worldwide for the indication "Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle".

Apart from its indication in women, FE 999049 may also have therapeutic value in the treatment of infertile men as FSH is known to play a crucial role in spermatogenesis. A previous meta-analysis of controlled clinical trials of FSH treatment of men with idiopathic infertility indicated an improvement in pregnancy rates, both spontaneously and after ART. However, study heterogeneity, high risk of bias, and lack of precise criteria to select the population most

likely to respond to treatment highlighted the need for further research. A recent meta-analysis evaluating FSH treatment effects on sperm parameters concluded that high FSH doses (700-1050 IU/week) improved sperm concentration, total sperm count and progressive motility, whereas lower FSH doses (up to 262.5 IU/week) increased only sperm motility, and intermediate FSH doses (350-525 IU/week) improved sperm concentration with only a trend to increased sperm count and motility. In a dose-range trial including 354 men, it was demonstrated that men with idiopathic oligozoospermia treated with rFSH had a substantially increased sperm count when treated with at least 200 IU every other day, an improvement first observed at the beginning of the third month. Improvements in both sperm morphology and forward motility were also observed, beginning at the fifth month. Administration of 300 IU rFSH every other day for 5 months could substantially improve the spontaneous pregnancy rate as well as the ART pregnancy rate. Doses exceeding 300 IU rFSH every other day were not included in the study and may provide further improvements.

The primary purpose of this trial is to investigate whether men with idiopathic infertility, after being treated with a daily dose of 12 µg FE 999049 for 6 months, can improve the chance of spontaneous pregnancy observed in their female partners in comparison to placebo. A daily dose of 10 µg FE 999049 corresponds to 150 IU/day follitropin alfa, as shown in women. Therefore, a daily dose of 12 µg FE 999049 is anticipated to provide a 20% higher exposure level, i.e. approximately 180 IU/day. This dose will also result in smaller fluctuations in serum FSH levels than treatment with 300 IU rFSH every other day, a dosing regimen shown to be effective in men but not confirmed to be maximally effective. In men, supraphysiological FSH levels are believed to be safe and well-tolerated as FSH interacts only via the specific FSH receptor in the Sertoli cells of the testes.

OBJECTIVES

Primary Objective

- To investigate the effect of FE 999049 treatment of men with idiopathic infertility on the chance of spontaneous pregnancy in their female partners

Secondary Objectives

- To investigate the effect of FE 999049 on semen parameters and endocrine profiles in men with idiopathic infertility
- To evaluate the safety and immunogenicity of FE 999049 in men with idiopathic infertility

Exploratory Objective

- To characterise the genetic/ semen epigenetic profile of the trial population to identify determinants of conception and responsiveness to FE 999049

ENDPOINTS

Primary Endpoint

- Spontaneous pregnancy observed in female partner within 9 months after randomisation of male subject, where spontaneous pregnancy is defined as vital pregnancy (documentation of at least one intrauterine gestational sac with fetal heartbeat by ultrasound)

Secondary Endpoints

- Positive βhCG (positive urine βhCG test) observed in female partner after spontaneous conception
- Time from randomisation to spontaneous pregnancy observed in female partner in calendar time and number of menstrual cycles
- Changes in semen parameters (semen volume, sperm concentration, total count, motility, morphology, and DNA fragmentation) from pre-randomisation to 3, 6, and 9 months after randomisation
- Treatment responders defined by either spontaneous pregnancy observed in female partner, or increase of total sperm count or total motile sperm count to 50% over baseline at 6 and/or 9 months
- Changes in serum hormone concentrations (follicle-stimulating hormone [FSH], luteinising hormone [LH], inhibin B, testosterone, and estradiol) from randomisation to 3 and 6 months after randomisation
- Changes in free testosterone concentration from randomisation to 3 and 6 months after randomisation
- Treatment-induced anti-FSH antibodies, overall as well as with neutralising capacity
- Immune-related adverse events

PREGNANCY FOLLOW-UP

- Pregnancy losses
- Live birth
- Neonatal health, including minor/major congenital anomalies, at birth, 4 weeks, and 1 year after birth

METHODOLOGY

This is a randomised, double-blind, placebo-controlled, multiregional trial assessing the efficacy and safety of FE 999049 in men with idiopathic infertility. This proof-of-concept (PoC) trial has been designed to investigate whether men diagnosed with idiopathic infertility and treated with FE 999049 once daily for 6 months have an increased chance of achieving spontaneous pregnancy with their female partners compared to placebo treatment.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. Eligible subjects will be randomised in a 2:1 ratio to once daily subcutaneous administration of 12 µg FE 999049 or placebo. Following randomisation, each subject will be trained to self-administer FE 999049/placebo at home, but the first injection will be administered at the trial site under supervision of the trial staff. Each subject will use an electronic diary (eDiary) to report FE 999049/placebo injections (date and time) during the treatment period, intercourse during the trial, and injection site reactions during the first week of treatment. Following the first week, the occurrence of injection site reactions will be monitored by inquiry of subjects at their site visits. All subjects will return to the site at 1, 3, 6[a], 7[b] months after randomisation for assessment of serum hormones, sex hormone binding globulin (SHBG), and antibodies, and at 3, 6[a], and 9 months for collection of semen samples. In addition, subjects will attend a visit at 4 months after randomisation and receive a phone call at 2 weeks, 2 and 5 months after randomisation to be reminded of treatment compliance and to be inquired about the pregnancy status of their female partners. For any positive urine pregnancy test obtained by the subject's female partner during the trial, the subject will inform the site and provide documentation confirming vital pregnancy by ultrasound (to be conducted at the trial site or at the female partner's general practitioner or obstetrician/gynaecologist).

All randomised subjects will continue treatment for 6 months and remain in the trial for 9 months regardless of whether a spontaneous pregnancy is established at earlier time points. Should the couple experience a pregnancy loss, subjects will also remain in the trial.

Semen parameters will be analysed in local laboratories, with the exception of DNA fragmentation which will be analysed in a central laboratory. Since semen analysis is highly variable and observer-dependent, quality assurance measures will be implemented to standardise operations across local laboratories.

Exploratory Analyses

For subjects who have provided separate written informed consent, a blood sample for potential future genome characterisation will be collected at randomisation, and a semen sample for potential future epigenetic analysis will be collected at randomisation and at 6 months[a] after randomisation. Analyses will aim to identify novel relationships between subjects' genomic or

epigenomic variants and their responsiveness to FE 999049 treatment or associated outcome in conception.

Furthermore, in selected sites subjects will be provided with at-home sperm tests for monthly analysis of semen parameters, such as sperm concentration and total motile sperm count; data will be collected via smartphone app. These data will be used to explore the feasibility of at-home sperm tests in a clinical trial setting and they may provide additional information on the time course of changes in sperm parameters.

Finally, subjects who have provided separate written informed consent may be invited to a patient-experience interview after the end of treatment. Subjects will be invited from selected trial sites until approximately 60 subjects have completed the interview. The results will be used to obtain a better understanding of the patient perspective within this therapeutic area and to inform further patient-focused drug development, as per recommendations of the Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Pregnancy Follow-up

All cases of pregnancy of the female partner occurring within 9 months after the male subject's date of randomisation will be followed for the duration of the pregnancy to collect information on pregnancy losses and live births. Furthermore, data will be collected on minor/major congenital anomalies of neonates, at birth, 4 weeks, and 1 year after birth.

NUMBER OF SUBJECTS

It is planned to randomise approximately 240 subjects, of whom approximately 160 subjects will be randomised to FE 999049 treatment and approximately 80 subjects to placebo treatment. It is estimated that approximately 360 subjects should be screened to achieve 240 subjects eligible for randomisation. The dropout rate is assumed to be 25% and will be monitored continuously.

[a] End-of-treatment visit, which takes place at 6 months after randomisation for subjects who complete treatment but can be earlier for subjects who prematurely discontinue the treatment.

[b] Visit must be scheduled between 21-35 days after the last IMP dose. The time point of the visit will thus be around 7 months for subjects who complete 6 months of treatment but can be earlier for subjects who prematurely discontinue the treatment.

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

1. Subject informed consent form, signed and dated prior to any trial-related procedures.
2. Parental informed consent form, signed and dated prior to randomisation.
3. History of infertility with current partner at randomisation must be 12-60 months if current partner is aged <35 years or 6-60 months if current partner is aged 35-38 years.
4. Men between the ages of 18 and 50 years. The subject must be at least 18 years (including the 18th birthday) when he signs the informed consent forms and no more than 50 years (up to the day before the 51st birthday) at the time of randomisation.
5. Body mass index (BMI) ≤40 kg/m^2 at randomisation. Subjects with BMI >35 kg/m^2 must have serum estradiol levels of 10-50 pg/mL (measured at central laboratory) at screening.
6. Total sperm count 5-39 million at screening; confirmed by two samples taken ≥2 weeks apart before randomisation. If a semen sample has been taken within 3 months prior to screening and been analysed at an andrology laboratory, it can be included as the first of the two semen samples at screening.
7. Total sperm motility of ≥10% at screening; confirmed by two samples taken ≥2 weeks apart before randomisation. If a semen sample has been taken within 3 months prior to screening and been analysed at an andrology laboratory, it can be included as the first of the two semen samples at screening.
8. Semen volume ≥1.4 mL at screening; confirmed by two samples taken ≥2 weeks apart before randomisation. If a semen sample has been taken within 3 months prior to screening and been analysed at an andrology laboratory, it can be included as the first of the two semen samples at screening.
9. Serum follicle-stimulating hormone (FSH) levels of 2-12 IU/L (measured at central laboratory) at screening.
10. Serum luteinising hormone (LH) levels of 1.2-7.5 IU/L (measured at central laboratory) at screening.
11. Serum total testosterone levels of ≥300 ng/dL (equals ≥10.4 nmol/L; measured at central laboratory) at screening.
12. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV), and Human Immunodeficiency Virus (HIV) antibody tests within 12 months prior to randomisation.
13. In good general physical and mental health as judged by the investigator and willing to comply with the trial protocol.
14. Agree to have regular intercourse with current female partner with the intent of spontaneous conception within 9 months from randomisation.

15. Agree to provide information on female partner's positive urine pregnancy test(s) and documentation of ultrasound(s), delivery, and neonatal/infant health.
16. Agree not to obtain infertility treatment outside of this trial for 9 months from randomisation. However, after 6 months from randomisation, the subject's semen can be used in infertility treatment procedures of his partner.
17. Current partner fulfilling all the criteria below:
    a) Female partner informed consent form, signed and dated prior to randomisation of male subject.
    b) Parental informed consent form signed and dated prior to randomisation of male subject.
    c) Pre-menopausal woman between the ages of 18 and 38 years (both inclusive) at the time of randomisation of male subject.
    d) Regular menstrual cycles of 21-35 days (both inclusive).
    e) No history or current condition of pelvic inflammatory disease, endometriosis stage II-IV by definite or empirical diagnosis, or tubal ligation.
    f) No contraindications to pregnancy or known conditions, abnormalities, or medical history associated with a reduced chance of pregnancy.
    g) No pregnancy at the time of randomisation of the male subject (as documented by negative result of urine pregnancy test taken ≤72 hours before randomisation).
    h) Agree to have regular intercourse with current partner with the intent of spontaneous conception within 9 months from randomisation of male subject.
    i) Agree to provide information on positive urine pregnancy test(s) and documentation of ultrasound(s), delivery, and neonatal/infant health.
    j) Agree not to obtain infertility treatment outside of this trial for 6 months from randomisation of male subject.

Exclusion Criteria

1. Previous FSH treatment for ≥4 months not leading to conception.
2. Past or current use of finasteride within 3 months prior to screening.
3. Any history of anatomical disorder of the pituitary gland or testes.
4. Any structural abnormalities of the vas deferens (unilateral or bilateral) at screening.
5. Any known, clinically significant, systemic disease in addition to the trial indication that might negatively impact fertility.
6. Known history or presence of clinical varicocele (subclinical and Grade 1 varicocele are acceptable).
7. Known history of cryptorchidism, testicular torsion, or orchitis.

8. Known abnormal karyotype (including Y-chromosome microdeletion).
9. Current or past treatment of urogenital (kidney, bladder, testicular, or prostate) cancer as well as history of chemo- or radiotherapy that can have impact on testes.
10. Any known uncontrolled non-gonadal endocrinopathies (thyroid, adrenal, pituitary disorders).
11. Administration of hormonal preparations, agents known to impair testicular function or affect sex hormone secretion, and known or suspected teratogens within 3 months prior to screening. Administration of anabolic steroids within 12 months prior to screening.
12. Any abnormal finding of clinical chemistry, haematology, and vital signs at screening, which is judged clinically significant by the investigator.
13. History of drug abuse within 12 months prior to screening.
14. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.
15. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.

MEDICINAL PRODUCTS

Investigational Medicinal Products (IMPs)

IMP name	**Drug type**	**Active ingredient, route of administration, and concentration**	**Dose**
FE 999049 (follitropin delta)	rFSH	Pre-filled pen containing 72 µg FE 999049 in 2.16 mL solution, subcutaneous injection	Daily dose of 12 µg FE 999049 for 6 months
Placebo	Placebo	Pre-filled pen containing 2.16 mL solution, subcutaneous injection	Daily dose for 6 months

DURATION OF TREATMENT

Each randomised subject will be treated with FE 999049/placebo for 6 months with follow-up for an additional 3 months.

STATISTICAL METHODS

The full analysis set (FAS) includes all randomised and exposed subjects and will be analysed according to the planned treatment assignment. The safety analysis set comprises all randomised and exposed subjects and will be analysed according to the actual treatment received.

The analysis of efficacy will be performed for the FAS analysis set.

Sample Size Justification

The primary objective of this PoC trial is to investigate the effect of FE 999049 treatment of men with idiopathic infertility on the chance of spontaneous pregnancy in their female partners, compared to placebo treatment. The primary endpoint is spontaneous pregnancy observed in the female partners within 9 months after randomisation of the male subjects, where spontaneous pregnancy is defined as vital pregnancy (documentation of at least one intrauterine gestational sac with fetal heartbeat by ultrasound).

The trial is designed to provide 80% power to reject the null hypothesis,

$$H_0: \pi_{FE999049} \leq \pi_{Placebo}$$

where $\pi_{FE999049}$ and $\pi_{Placebo}$ are the 9-month spontaneous pregnancy rates in FE 999049 and placebo arms under the following conditions/assumptions:

- Two-sided significance level of 20%.
- 9-month spontaneous pregnancy rates in the FE 999049 and placebo arms are assumed to be 17.0% and 7.0%.
- Time to spontaneous pregnancy follows an exponential distribution.
- Time to withdrawal or experiencing an intercurrent event follows the same exponential distribution for both treatment arms. The cause-specific hazard of withdrawal/experiencing an intercurrent event corresponds to a 25% risk of withdrawal/experiencing an intercurrent event over the course of the 9-month trial period for subjects randomised to placebo.
- 10% of subjects whose female partner has not achieved a spontaneous pregnancy prior to the end of the treatment period will access additional infertility treatments during the 3-month follow-up period. This is in addition to the risk of withdrawal/experiencing an intercurrent event and is assumed to be the same for both treatment arms.

Primary Endpoint: Primary Analysis

The primary endpoint of the trial is spontaneous pregnancy observed in the female partner within 9 months after randomisation of the male subject, where spontaneous pregnancy is defined as vital pregnancy (documentation of at least one intrauterine gestational sac with fetal heartbeat by ultrasound). Interest lies in assessing the effect of once daily dosing of 12 µg of FE 999049 vs placebo with respect to the difference in spontaneous pregnancy rates, if all subjects remain on and in compliance with the randomised dosing regimen, continue to have sexual intercourse with their female partners, and do not have access to additional infertility treatments.

The primary endpoint will be analysed as a time-to-event endpoint. Subjects experiencing an intercurrent event (for example treatment discontinuation, lack of compliance to the randomised treatment regimen, lack of sexual intercourse, or additional infertility treatment) prior to their partner achieving a spontaneous pregnancy during the 9-month trial period will be censored. Subjects whose partner does not achieve a spontaneous pregnancy by the end of the 9-month trial period will be censored at the end of the trial period. Additionally, subjects prematurely withdrawing from the trial will be censored at the date of withdrawal.

The difference in 9-month spontaneous pregnancy rates between the FE 999049 and placebo arms will be estimated based on the Kaplan-Meier estimator, with standard errors calculated using Greenwood’s formula.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

List of Abbreviations

ART	assisted reproductive technologies
βhCG	beta human chorionic gonadotropin
BMI	body mass index
COVID-19	coronavirus disease 2019
CRO	contract research organisation
EDC	electronic data capture system
eDiary	electronic diary
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration, U.S.
FPFV	first patient first visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLMM	generalised linear mixed model
ICH	International Council for Harmonisation
ICSI	intracytoplasmic sperm injection
ID	identifier
IMP	investigational medicinal product
IND	investigational new drug (application)
IRT	interactive response technology system
ITT	intention-to-treat
IU	international unit
IVF	in vitro fertilisation
LH	luteinising hormone
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
NCU	neonatal care unit
NICU	neonatal intensive care unit
PCU	paediatric care unit

PoC	proof of concept
PP	per-protocol
rFSH	recombinant follicle-stimulating hormone
SAE	serious adverse event
SAP	statistical analysis plan
SHBG	sex hormone binding globulin
SMQ	Standardised MedDRA Queries
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
U.S.	United States
UTN	Universal Trial Number
WHO	World Health Organisation

Company Names

Ferring will be used as abbreviation for Ferring Pharmaceuticals.

Definition of Terms

Major congenital anomaly	A life-threatening structural anomaly or one likely to cause significant impairment of health or functional capacity and which needs medical or surgical treatment.
Minor congenital anomaly	Relatively frequent structural anomaly not likely to cause any medical or cosmetic problems.
Spontaneous pregnancy	A pregnancy conceived without the help of assisted reproductive technologies or other infertility treatment

1 INTRODUCTION

1.1 Background

FE 999049 (follitropin delta) is a human recombinant follicle-stimulating hormone (rFSH) belonging to the pharmaceutical class of gonadotropins. The current trial is intended to support the indication "Treatment of men with idiopathic infertility".

FE 999049 is derived 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.

Ferring received Marketing Authorisation from the European Commission for FE 999049 for the indication "Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle" in December 2016. As of August 2021, FE 999049 is approved for this indication under the trade name REKOVELLE in more than 65 countries worldwide.

Apart from its indication in women, FE 999049 may also have therapeutic value in the treatment of infertile men as FSH is known to play a crucial role in spermatogenesis. A previous meta-analysis of controlled clinical trials of FSH treatment of men with idiopathic infertility indicated an improvement of pregnancy rates, both spontaneously and after ART.[1] Similarly, a recent meta-analysis evaluating FSH treatment effects on sperm parameters concluded that high FSH doses (700-1050 IU/week) improved sperm concentration, total sperm count and progressive motility, whereas lower FSH doses (up to 262.5 IU/week) increased only sperm motility, and intermediate FSH doses (350-525 IU/week) improved sperm concentration with only a trend to increased sperm count and motility.[2] In a dose-range trial including 354 men[3], it was demonstrated that men with idiopathic oligozoospermia treated with rFSH had a substantially increased sperm count when treated with at least 200 IU every other day, an improvement first observed at the beginning of the third month. Improvements in both sperm morphology and forward motility were also observed, beginning at the fifth month. Administration of 300 IU rFSH every other day for 5 months could substantially improve the spontaneous pregnancy rate as well as the ART pregnancy rate. Doses exceeding 300 IU rFSH every other day were not included in the study and may add further improvements.

1.2 Scientific Justification for Conducting the Trial

In the management of male infertility, there is a need to explore alternative treatment options to the current standard approach, ICSI. As detailed in section 1.1, current data in the literature suggests a positive effect of FSH preparations for the treatment of male infertility. However, study heterogeneity, high risk of bias, and lack of precise criteria to select the population most likely to respond to treatment lead to the continued need for further research. The current proof-of-concept (PoC) trial therefore aims to investigate the effect of FE 999049 treatment in idiopathic male infertility.

The primary purpose of this trial is to investigate whether men with idiopathic infertility, after being treated with a daily dose of 12 µg FE 999049 for 6 months, can improve the chance of spontaneous pregnancy observed in their female partners in comparison to placebo. Additionally, it will be investigated whether FE 999049-treated men show improved semen parameters.

As detailed in section 1.1, treatment of oligozoospermic men with 300 IU FSH every other day has been shown to be effective but not confirmed to be optimal: Doses exceeding 300 IU every other day have not been tested and may provide additional benefit, since FSH has been shown to act in a dose-dependent manner and the highest dose tested to date, i.e. 300 IU FSH every other day for 5 months, did not seem to reach the maximum treatment effect.[3] Thus, doses exceeding 300 IU every other day for 5 months may further improve semen parameters and spontaneous pregnancy rate. In women, 150 IU/day follitropin alfa correspond to 10µg/day FE 999049.[4] The daily dose of 12 µg FE 999049 is therefore anticipated to provide a 20% higher exposure level, i.e. approximately 180 IU/day. This dose will also result in smaller fluctuations in serum FSH concentrations than treatment with 300 IU rFSH every other day. In men, supraphysiological FSH levels are believed to be safe and well-tolerated as FSH interacts only via the specific FSH receptor in the Sertoli cells of the testes.[5]

1.3 Benefit / Risk Aspects

Benefits

The treatment is provided to the participating subjects free of charge, as Ferring compensates the investigational sites for their expenses. Subjects participating in this trial might benefit in the form of an improvement in their semen parameters and by achieving pregnancy of their female partners.

Subjects who complete 6 months of treatment will be offered cryopreservation of semen samples for future use in ART and other infertility treatment, if permitted by local laws and regulations.

Risks

The risks associated with this clinical trial, including the risks of the investigational medicinal product (IMP), clinical and laboratory procedures, are explained to subjects as part of the

consenting process, prior to start of the trial.

Investigational Medicinal Product

The clinical development programme for FE 999049 for the suggested indication in men is in an early stage and therefore no male subjects have been exposed to FE 999049.

FE 999049 will be administered subcutaneously on a daily basis for 6 months, which might cause injection site reactions.

Immunogenicity in terms of development of anti-FSH antibodies is a potential risk of FE 999049 therapy.

For further information on FE 999049 for the indication "Treatment of men with idiopathic infertility", please refer to the Investigator's Brochure.[6]

Clinical and Laboratory Procedures

The main procedures in this trial are semen sampling and blood sampling, which are non-invasive or minimally invasive. The blood sampling might be associated with mild discomfort, bruising and a very rare risk of infection.

Benefits / Risks

Participation in this trial is not expected to have a negative influence on the subject's general physical wellbeing, semen parameters, or chance to achieve spontaneous pregnancy with his female partner.

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

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary Objective

- To investigate the effect of FE 999049 treatment of men with idiopathic infertility on the chance of spontaneous pregnancy in their female partners

Secondary Objectives

- To investigate the effect of FE 999049 on semen parameters and endocrine profiles in men with idiopathic infertility
- To evaluate the safety and immunogenicity of FE 999049 in men with idiopathic infertility

Exploratory Objective

- To characterise the genetic/ semen epigenetic profile of the trial population to identify determinants of conception and responsiveness to FE 999049

2.2 Endpoints

Primary Endpoint

- Spontaneous pregnancy observed in female partner within 9 months after randomisation of male subject, where spontaneous pregnancy is defined as vital pregnancy (documentation of at least one intrauterine gestational sac with fetal heartbeat by ultrasound)

Secondary Endpoints

- Positive βhCG (positive urine βhCG test) observed in female partner after spontaneous conception
- Time from randomisation to spontaneous pregnancy observed in female partner in calendar time and number of menstrual cycles
- Changes in semen parameters (semen volume, sperm concentration, total count, motility, morphology, and DNA fragmentation) from pre-randomisation to 3, 6, and 9 months after randomisation
- Treatment responders defined by either spontaneous pregnancy observed in female partner, or increase of total sperm count or total motile sperm count to 50% over baseline at 6 and/or 9 months

- Changes in serum hormone concentrations (follicle-stimulating hormone [FSH], luteinising hormone [LH], inhibin B, testosterone, and estradiol) from randomisation to 3 and 6 months after randomisation
- Changes in free testosterone concentration from randomisation to 3 and 6 months after randomisation
- Treatment-induced anti-FSH antibodies, overall as well as with neutralising capacity
- Immune-related adverse events

Pregnancy Follow-up

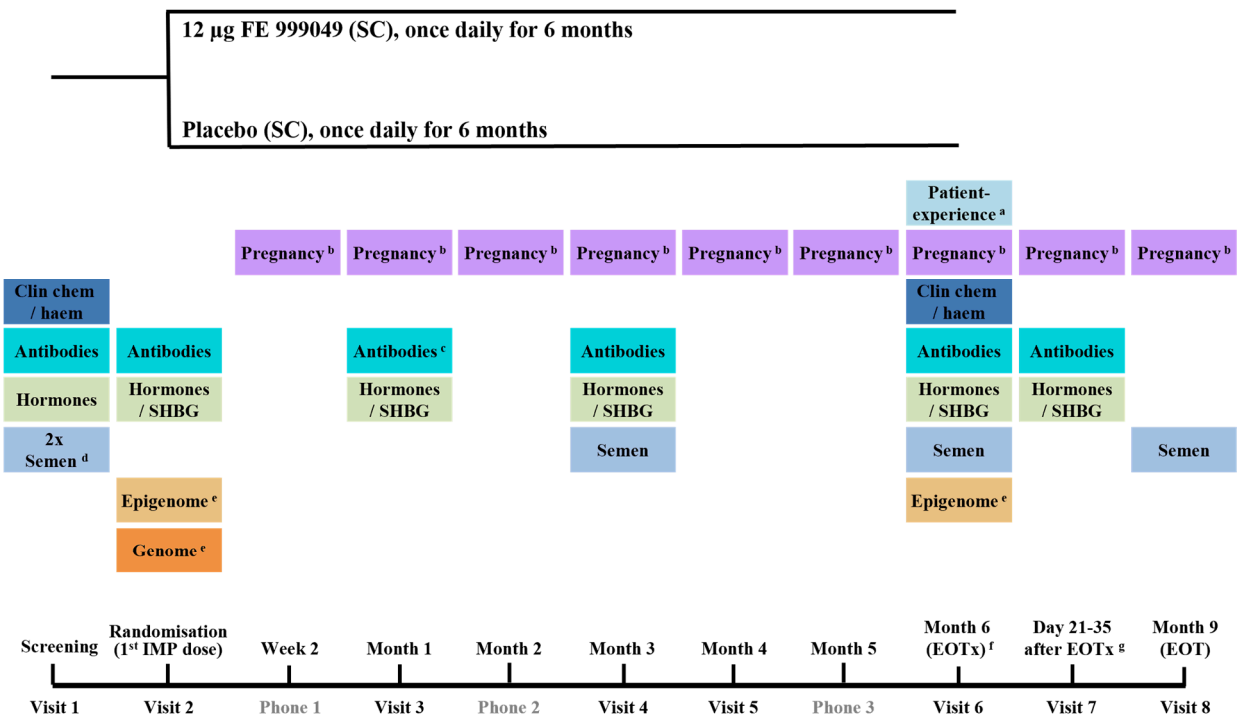
- Pregnancy losses
- Live birth
- Neonatal health, including minor/major congenital anomalies, at birth, 4 weeks, and 1 year after birth

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. Optional patient-experience interview for subjects who have provided separate written informed consent. Scheduled shortly (few days to weeks) after EoTx.
b. Subject will be inquired about the pregnancy status of his female partner (βhCG test results, and pregnancy ultrasound, if applicable).
c. Sample for assessment of early-drug antibody development; stored and only analysed if subsequent samples prove to be positive for FSH-antibodies.
d. Two samples, taken at least two weeks apart. If a semen sample has been taken within 3 months prior to screening, it can be included as the first of the two samples at screening.
e. Optional sampling for potential future exploratory analyses for subjects who have provided separate written informed consent.
f. End-of-treatment visit, which takes place at 6 months after randomisation for subjects who complete treatment but can be earlier for subjects who prematurely discontinue the treatment
g. Visit must be scheduled between 21-35 days after last IMP dose and will thus be around 7 months for subjects who complete 6 months of treatment, but can be earlier for subjects who prematurely discontinue the treatment.

EOT: end-of-trial; EOTx: end-of-treatment; FSH: follicle-stimulating hormone; IMP: investigational medicinal product; SC: subcutaneous; SHBG: sex hormone binding globulin

Figure 3-1 Trial Diagram – Trial Period

3.1.2 Overall Design and Control Methods

Trial Period

This will be a randomised, double-blind, placebo-controlled, multiregional trial assessing the efficacy and safety of the rFSH preparation FE 999049 in men with idiopathic infertility. The primary endpoint is spontaneous pregnancy observed in the female partner within 9 months after randomisation of the male subject, where spontaneous pregnancy is defined as vital pregnancy (documentation of at least one intrauterine gestational sac with fetal heartbeat by ultrasound). Secondary endpoints include positive βhCG after spontaneous conception in the female partner, changes in semen parameters, as well as pharmacodynamic parameters of FSH action related to efficacy and safety of treatment.

Subjects will be screened within 90 days prior to randomisation for compliance with the inclusion and exclusion criteria. Eligible subjects will be randomised in a 2:1 ratio to once daily administration of FE 999049 or placebo.

Each randomised subject will be trained to self-administer FE 999049/placebo at home using a pre-filled injection pen, but the first injection will be administered at the trial site under supervision of the trial staff. Subjects assigned to treatment with FE 999049 will receive a fixed dose of 12 µg daily for 6 months. Subjects assigned to placebo will have the injection pen dialled to the same value (dose) as if administering FE 999049.

Throughout the treatment period, subjects will be monitored for treatment compliance during their site visits at 1, 3, 4, and 6[c] months after randomisation, as well as during phone calls at 2 weeks, 2 and 5 months after randomisation. IMP injections (date and time) and intercourse will be reported by subjects in an electronic diary (eDiary). In this eDiary, subjects will also report injection site reactions after IMP administration during the first week of treatment. Following the first week, subjects will be inquired about the occurrence of any injection site reactions at their site visits.

The pregnancy status of the female partner will be assessed by inquiry of the male subject during his site visits at 1, 3, 4, 6[c], 7[d], and 9 months after randomisation, as well as during phone calls at 2 weeks, 2 and 5 months after randomisation. Any positive urine pregnancy test obtained by the subject's female partner during the trial will be documented, as will the confirmation of a vital pregnancy by ultrasound which can be conducted at the trial site or by the female partner's general practitioner or obstetrician/gynaecologist.

[c] End-of-treatment visit, which takes place at 6 months after randomisation for subjects who complete treatment but can be earlier for subjects who prematurely discontinue the treatment.

[d] Visit must be scheduled between 21-35 days after the last IMP dose. The time point of the visit will thus be around 7 months for subjects who complete 6 months of treatment but can be earlier for subjects who prematurely discontinue the treatment.

Semen samples will be collected for the evaluation of semen parameters during the screening period and during site visits at 3, 6[c], and 9 months after randomisation. During the screening period, two semen samples will be taken with a time interval of at least 2 weeks in order to determine the subject's eligibility to participate in the trial (one semen sample can be re-taken, in case the limits specified in the inclusion criteria are not met). If a semen sample has been taken within 3 months prior to screening and been analysed at an andrology laboratory, semen parameters for subject eligibility can be evaluated based on this pre-screening sample and a semen sample taken during the screening period at least two weeks later. Semen parameter analyses at 3, 6[e] and 9 months after randomisation will be based on the assessment of one semen sample each.

Blood samples will be collected for the purpose of evaluating serum hormone concentrations, sex hormone binding globulin (SHBG) concentrations, clinical chemistry and haematology parameters as well as anti-FSH antibodies. Serum hormone concentrations will be assessed at screening, randomisation, at 1, 3 and 6[e] months after randomisation, and 21-35 days after the last IMP dose. SHBG concentrations will be assessed at randomisation, at 1, 3 and 6[g] months after randomisation, and 21-35 days after the last IMP dose. Clinical chemistry and haematology will be assessed at screening and 6[e] months after randomisation. Samples for anti-FSH antibodies will be collected on six occasions. The first sample will be taken at the screening visit and will be used to re-establish the anti-drug antibody analytical assays. The subsequent five samples will be used for analysis of anti-FSH antibodies in individual subjects in the trial, and taken prior to dosing at the randomisation visit, as well as post-dosing at 1, 3 and 6[e] months after randomisation, and 21-35 days after the last IMP dose. Subjects with a treatment-induced anti-FSH antibody response will be followed until the response has become negative, returned to the pre-dosing level, or for a maximum of 1 year after the last IMP dose. These subjects will be called in for assessments 2 months after the last post-dosing anti-FSH antibody sampling, i.e. 3 months after the last IMP dose. If required, further assessments will be made at 5, 7, 9 and 12 months after the last IMP dose.

All randomised subjects will continue treatment for 6 months and remain in the trial for 9 months regardless of whether a pregnancy is established at earlier time points. Should the couple experience a pregnancy loss, subjects will also remain in the trial.

Pregnancy Follow-up

All cases of pregnancy of the female partner occurring within 9 months after the male subject's date of randomisation will be followed until delivery to collect information on pregnancy losses and live births. Furthermore, data will be collected on neonatal health, including minor/major congenital anomalies, at birth, 4 weeks, and 1 year after birth.

[e] End-of-treatment visit, which takes place at 6 months after randomisation for subjects who complete treatment but can be earlier for subjects who prematurely discontinue the treatment.

Exploratory Analyses

For subjects who have provided separate written informed consent, a blood sample for potential future genome characterisation will be collected at randomisation, and a semen sample for potential future epigenetic analysis will be collected at randomisation and at 6 months[e] after randomisation. Analyses will aim to identify novel relationships between subjects' genomic or epigenomic variants and their responsiveness to FE 999049 treatment or associated outcome in conception.

Furthermore, in selected sites subjects will be provided with at-home sperm tests for monthly analysis of semen parameters, such as sperm concentration and total motile sperm count; data will be collected via smartphone app. These data will be used to explore the feasibility of at-home sperm tests in a clinical trial setting and they may provide additional information on the time course of changes in sperm parameters.

Finally, subjects from selected trial sites will be contacted for a patient-experience interview within a few days to weeks after the end of treatment. Participation in the patient-experience interview is optional, and separate written informed consent must have been obtained, as appropriate, before participation. The patient-experience interview is designed to examine the impact of following the treatment regimen with daily injections on the subjects' self-reported quality of life, as well as their treatment expectations and satisfaction. The interview will be conducted by a third-party contract research organisation (CRO). Once approximately 60 subjects have completed the patient-experience interview, this part of the trial will be terminated and reported separately. The results will be used to obtain a better understanding of the patient perspective within this therapeutic area and to inform further patient-focused drug development, as per recommendations of the Food and Drug Administration (FDA) and European Medicines Agency (EMA).[7,8]

3.1.3 Trial Schedule

First patient first visit (FPFV):	Q3 2022
Last patient first visit (LPFV):	Q3 2025
Last patient last visit (LPLV):	Q3 2026
Pregnancy follow-up completed:	Q2 2028

3.2 Planned Number of Trial Sites and Subjects

It is planned to randomise approximately 240 subjects from approximately 25 sites in approximately 7 countries across Europe and North America.

It is estimated that approximately 360 subjects should be screened to achieve 240 subjects eligible for randomisation. The dropout rate is assumed to be 25% and will be monitored continuously.

3.3 Interim Analysis

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

3.4 Data Monitoring Committee

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

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

This trial is designed to investigate the effect of FE 999049 treatment of men with idiopathic infertility on the chance of spontaneous pregnancy in their female partners.

The trial is a randomised, double-blind, placebo-controlled trial. Randomised, double-blind, placebo-controlled clinical trials have a long history as the standard for investigations of new drugs, including those for the treatment of infertility. The randomised, double-blind design will ensure minimised bias in treatment allocation and treatment evaluation throughout the trial, including the pregnancy follow-up period. A placebo solution has been manufactured for the purpose of this trial; it is indistinguishable from the active FE 999049 solution and is provided in identical pre-filled injection pens.

The trial will be a multi-centre trial. This setup ensures that the required number of subjects can be recruited within a reasonable time and should facilitate subsequent generalisation of the results.

3.5.2 Selection of Endpoints

The primary endpoint of this trial, spontaneous pregnancy observed in the female partner within 9 months after randomisation of the male subject (documentation of at least one intrauterine gestational sac with fetal heartbeat by ultrasound), can be objectively assessed regarding its outcome and captures the clinical outcome that is most relevant for subjects.

The primary endpoint is complemented by secondary endpoints measuring the effect of FE 999049 treatment on the chance of spontaneous pregnancy, such as positive urine βhCG of the female partner and time to spontaneous pregnancy. Other secondary efficacy endpoints include changes in semen parameters, changes in serum hormone concentrations, and changes in free testosterone concentration, objectively measuring the effect of FE 999049 treatment on male subjects.

Safety endpoints cover immunogenicity and immune-related adverse events of FSH-treatment.

In conclusion, the primary and secondary endpoints are appropriate to document the efficacy and safety FE 999049 for the treatment of men with idiopathic infertility, in order to establish PoC for

this treatment.

3.5.3 Blinding

The randomised, placebo-controlled, double-blind trial design will ensure random allocation of eligible subjects to the FE 999049 and placebo treatment groups. It will also allow for unbiased evaluation by the subject, the investigator and other trial staff at site.

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

The pre-filled injection pens of FE 999049 and placebo will be identical in appearance to maintain the blinding. Central laboratory analysis results of serum hormone and SHBG concentrations from blood samples drawn post-dosing will not be available to subject, site or sponsor staff until after unblinding of the trial and local laboratory analysis of serum FSH is prohibited. Laboratory analysis results of semen samples will not be available to the subject until after unblinding of the trial, to prevent any unwarranted speculation by the subject as to treatment allocation.

The blind will be broken when the trial database is declared clean and locked.

3.5.4 Selection of Doses in the Trial

Dosing Regimen

A daily dosage of 12 µg FE 999049 has been selected for this trial based upon a previous study in which the treatment of oligozoospermic men with 300 IU FSH every other day correlated with improved semen parameters and increased spontaneous pregnancy rates. A dose of 300 IU FSH every other day has, however, not been confirmed to be optimal: Doses exceeding 300 IU every other day have not been tested and may provide increased benefit, since FSH has been shown to act in a dose-dependent manner and the highest dose tested to date, i.e. 300 IU FSH every other day for 5 months, did not seem to reach the maximum treatment effect.[3] Thus doses exceeding 300 IU every other day for 5 months may further improve semen parameters and spontaneous pregnancy rate.

In women, 150 IU/day follitropin alfa correspond to 10µg/day FE 999049[4] and the selected daily dose of 12 µg FE 999049 is therefore anticipated to provide a 20% higher exposure level, i.e. approximately 180 IU/day. This dose will also result in smaller fluctuations in serum FSH concentrations than treatment with 300 IU rFSH every other day. The higher dose ensures complete

[f] This excludes the representative from Clinical Trial Supply, and representatives from Global Quality Assurance during audits. Furthermore, it may be necessary for representatives from Global Safety to unblind an individual subject's treatment during the trial for the purpose of expedited reporting.

coverage of the expected therapeutic window of FE 999049 in this PoC trial. In men, supraphysiological FSH levels are believed to be safe and well-tolerated as FSH interacts only via the specific FSH receptor in the Sertoli cells of the testes.[5]

Duration of Treatment

In humans, the entire spermatogenic cycle has been described to vary between 42 and 76 days.[9,10,11] Consequently, a treatment duration of 6 months has been selected to ensure subject exposure during at least two complete spermatogenic cycles, to allow for a thorough assessment of the therapeutic potential of FE 999049.

Additionally, FSH treatment of men with idiopathic oligozoospermia has been described to cause gradual improvement of sperm concentration over a 5-month treatment period and the treatment effect appeared to persist for at least 3 months after treatment cessation. For this reason, outcomes will be followed in the present trial for 3 months after the end of treatment.

The relatively long trial schedule requiring 9 months overall participation might make it challenging for some subjects to remain adherent to protocol requirements. Close patient-counselling throughout the trial period will help ensure treatment compliance and minimise instances of missing data.

3.5.5 Selection of the Trial Population

This trial will include subjects aged 18-50 years with a body mass index (BMI) ≤40 kg/m^2 (if BMI >35 kg/m^2, concomitant estradiol levels of 10-50 pg/mL are required), who have a history of infertility with their current partner (12-60 months if partner is aged <35 years or 6-60 months if partner is aged 35-38 years), and who have idiopathic infertility (i.e. testosterone ≥300 ng/dL and absence of all of the following: anatomical abnormalities of pituitary or testes, clinical varicocele, cryptorchidism, testicular torsion, orchitis, or abnormal karyotype). Their current partner must be a pre-menopausal woman aged 18-38 years with no contraindications to pregnancy.

An age cut-off at 50 years was selected to limit possible confounding effects of subject age, since sperm motility and other important semen parameters (indicative of epididymal, prostatic, and seminal vesicle function) have been shown to be lower in men aged ≥50 years than in men aged 21-30 years.[12] A BMI cut-off at 40 kg/m^2, combined with specific estradiol level requirements in subjects with BMI >35 kg/m^2, was introduced to reduce the likelihood that an efficacy signal could be obscured by aromatisation of testosterone to estradiol in subjects with obesity.

Consistent with the current World Health Organisation (WHO) definitions, this trial will recruit men with a normal semen volume of ≥1.4 mL but a total sperm count below the lower WHO reference limit of 39 million[13], meeting the criteria for oligozoospermia.

This PoC trial will be restricted to patients with a baseline serum FSH of 2-12 IU/L. Serum FSH levels below 2 IU/L, particularly when accompanied by an LH lower than 1.2 IU/L, suggest a diagnosis of hypogonadotropic hypogonadism; FSH treatment alone is not expected to benefit this population. On the other end, patients with a serum FSH concentration ≥12 IU/L may have a reduced therapeutic window for administration of exogenous FSH.

3.5.6 Follow-up Procedures

Pregnancy Follow-up

Follow-up activities cover pregnancy and neonatal health follow-up at birth, 4 weeks, and 1 year after birth, including the documentation of minor/major congenital anomalies.

This follow-up might pose challenges due to the need of data collection after the end-of-trial visit. Parental consent to data collection on the neonate will be obtained prior to randomisation and effort will be made to capture the follow-up information described in the protocol by use of contact logs and other measures, but instances of missing data cannot be ruled out.

Immunogenicity Follow-up

As a safety precaution, subjects with treatment-induced anti-FSH antibody response will be followed until the response has become negative or returned to the pre-dosing level, or for a maximum of 1 year after the last IMP dose.

Access to Therapy after End-of-trial

FE 999049 is currently under clinical development for the present indication in men and cannot be offered to subjects after participation in this clinical trial.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

1. Subject informed consent form, signed and dated prior to any trial-related procedures.
2. Parental informed consent form, signed and dated prior to randomisation.
3. History of infertility with current partner at randomisation must be 12-60 months if current partner is aged <35 years or 6-60 months if current partner is aged 35-38 years.
4. Men between the ages of 18 and 50 years. The subject must be at least 18 years (including the 18th birthday) when he signs the informed consent forms and no more than 50 years (up to the day before the 51st birthday) at the time of randomisation.
5. Body mass index (BMI) ≤40 kg/m^2 at randomisation. Subjects with BMI >35 kg/m^2 must have serum estradiol levels of 10-50 pg/mL (measured at central laboratory) at screening.
6. Total sperm count 5-39 million at screening; confirmed by two samples taken ≥2 weeks apart before randomisation. If a semen sample has been taken within 3 months prior to screening and been analysed at an andrology laboratory, it can be included as the first of the two semen samples at screening.
7. Total sperm motility of ≥10% at screening; confirmed by two samples taken ≥2 weeks apart before randomisation. If a semen sample has been taken within 3 months prior to screening and been analysed at an andrology laboratory, it can be included as the first of the two semen samples at screening.
8. Semen volume ≥1.4 mL at screening; confirmed by two samples taken ≥2 weeks apart before randomisation. If a semen sample has been taken within 3 months prior to screening and been analysed at an andrology laboratory, it can be included as the first of the two semen samples at screening.
9. Serum follicle-stimulating hormone (FSH) levels of 2-12 IU/L (measured at central laboratory) at screening.
10. Serum luteinising hormone (LH) levels of 1.2-7.5 IU/L (measured at central laboratory) at screening.
11. Serum total testosterone levels of ≥300 ng/dL (equals ≥10.4 nmol/L; measured at central laboratory) at screening.
12. Negative serum Hepatitis B Surface Antigen (HBsAg), Hepatitis C Virus (HCV), and Human Immunodeficiency Virus (HIV) antibody tests within 12 months prior to randomisation.
13. In good general physical and mental health as judged by the investigator and willing to comply with the trial protocol.
14. Agree to have regular intercourse with current female partner with the intent of spontaneous conception within 9 months from randomisation.

15. Agree to provide information on female partner's positive urine pregnancy test(s) and documentation of ultrasound(s), delivery, and neonatal/infant health.
16. Agree not to obtain infertility treatment outside of this trial for 9 months from randomisation. However, after 6 months from randomisation, the subject's semen can be used in infertility treatment procedures of his partner.
17. Current partner fulfilling all the criteria below:
    a) Female partner informed consent form, signed and dated prior to randomisation of male subject.
    b) Parental informed consent form, signed and dated prior to randomisation of male subject.
    c) Pre-menopausal woman between the ages of 18 and 38 years (both inclusive) at the time of randomisation of male subject.
    d) Regular menstrual cycles of 21-35 days (both inclusive).
    e) No history or current condition of pelvic inflammatory disease, endometriosis stage II-IV by definite or empirical diagnosis, or tubal ligation.
    f) No contraindications to pregnancy or known conditions, abnormalities, or medical history associated with a reduced chance of pregnancy.
    g) No pregnancy at the time of randomisation of the male subject (as documented by negative result of urine pregnancy test taken ≤72 hours before randomisation).
    h) Agree to have regular intercourse with current partner with the intent of spontaneous conception within 9 months from randomisation of male subject.
    i) Agree to provide information on positive urine pregnancy test(s) and documentation of ultrasound(s), delivery, and neonatal/infant health.
    j) Agree not to obtain infertility treatment outside of this trial for 6 months from randomisation of male subject.

4.1.2 Exclusion Criteria

1. Previous FSH treatment for ≥4 months not leading to conception.
2. Past or current use of finasteride within 3 months prior to screening.
3. Any history of anatomical disorder of the pituitary gland or testes.
4. Any structural abnormalities of the vas deferens (unilateral or bilateral) at screening.
5. Any known, clinically significant, systemic disease in addition to the trial indication that might negatively impact fertility.
6. Known history or presence of clinical varicocele (subclinical and Grade 1 varicocele are acceptable).
7. Known history of cryptorchidism, testicular torsion, or orchitis.

8. Known abnormal karyotype (including Y-chromosome microdeletion).
9. Current or past treatment of urogenital (kidney, bladder, testicular, or prostate) cancer as well as history of chemo- or radiotherapy that can have impact on testes.
10. Any known uncontrolled non-gonadal endocrinopathies (thyroid, adrenal, pituitary disorders).
11. Administration of hormonal preparations, agents known to impair testicular function or affect sex hormone secretion, and known or suspected teratogens within 3 months prior to screening. Administration of anabolic steroids within 12 months prior to screening.
12. Any abnormal finding of clinical chemistry, haematology, and vital signs at screening, which is judged clinically significant by the investigator.
13. History of drug abuse within 12 months prior to screening.
14. Use of any non-registered investigational drugs during the last 3 months prior to randomisation.
15. Hypersensitivity to any active ingredient or excipients in the medicinal products used in the trial.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

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

A screening number is allocated to each subject who has signed the subject informed consent form. A subject must always be assigned to the lowest available screening number. A subject screening / enrolment log for all screened subjects must be maintained by the investigator.

4.2.2 Randomisation

Subjects will be randomised in a 2:1 ratio to FE 999049 or placebo.

Randomisation is performed centrally through the interactive response technology system (IRT). When a subject is randomised to the trial, he will always be assigned to the lowest available randomisation number. An independent statistician will prepare a computer-generated randomisation list and randomisation will be performed in blocks to distribute placebo subjects randomly over the trial enrolment period. Blocks will be maintained within trial sites, i.e. the randomisation will be stratified by trial site. The block size will only be revealed when the trial

[g]The term “ethics committee” covers the Independent Ethics Committees (IECs) in Europe and the Institutional Review Boards (IRBs) in the United States. This is applicable throughout the document.

database is declared clean and locked.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

The subjects must not have used hormonal preparations, agents known to impair testicular function or affect sex hormone secretion, or known/suspected teratogens within 3 months prior to screening. Subjects must not have administered anabolic steroids within 12 months prior to screening. Subjects must not have used any non-registered investigational drug during the last 3 months prior to randomisation.

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

4.3.2 Prohibited Therapy

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

Use of infertility treatments other than the trial medication (e.g. intrauterine insemination, controlled ovarian stimulation, ART, clomiphene citrate or aromatase inhibitors) is not permitted from randomisation until 6 months after randomisation for the trial subject or his female partner. From 6 months after randomisation of the subject, the female partner is allowed to undergo infertility treatment. The type, medication, timing, and outcome of the treatment will be recorded. The subject is not permitted to undergo infertility treatment outside of this trial for the entire trial duration, but his semen can be used for infertility treatment procedures (including intrauterine insemination or IVF/ICSI) for his female partner.

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

4.4 Discontinuation and Withdrawal Criteria

Discontinuation of Treatment

The subjects have the right to discontinue treatment at any time for any reason, without the need to justify their decision. However, the investigator should record the reason for the subject's discontinuation, if possible. Subjects that discontinue treatment prematurely will be asked to remain in the trial. Subjects will attend the end-of-treatment visit, the visit 21-35 days after

end-of-treatment, and the end-of-trial visit, which will include all procedures outlined in sections 6.10, 6.11, and 6.12. This includes eDiary completion for recording of intercourse.

The investigator also has the right to discontinue the subject's treatment due to:

- Medical or safety reasons, including but not limited to any adverse event indicating that continued treatment endangers the safety of the subject

The subject must discontinue treatment if he experiences any of the following:

- Life-threatening treatment-emergent serious adverse event (SAE)
- Formation of treatment induced neutralising antibodies to FSH

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

Withdrawal from Trial

The subjects have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the investigator should record the reason for the subject's withdrawal, if possible. If, at the time of withdrawal, subjects have already been exposed to IMP they will be asked to attend the end-of-treatment visit, which will include all procedures outlined in section 6.10.

The investigator also has the right to withdraw subjects from the trial due to:

- Medical or safety reasons, including but not limited to any adverse event indicating that continued participation endangers the safety of the subject
- Significant non-compliance with trial procedures, as judged by the investigator

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

Withdrawal of Consent

If the subject withdraws his consent, data collected up to withdrawal will remain in the database, but no further data will be collected. Samples and recordings obtained before withdrawal may be analysed. This will be described in the subject informed consent form. The subject can request destruction of samples which would otherwise have been kept in storage.

If the subject's female partner withdraws her consent, data collected up to withdrawal will remain in the database, but no further data on her will be collected. Recordings obtained before withdrawal

may be analysed. This will be described in the female partner informed consent form. Correspondingly, for any pregnancy during the trial leading to the birth of a baby, if one of the child-custody holders withdraws his/her consent to data collection on the neonate, pregnancy follow-up data collected up to withdrawal will remain in the database, but no further data on the neonate will be collected. Recordings obtained before withdrawal may be analysed. This will be described in the parental informed consent form.

4.5 Subject Replacement

Generally, a subject can only be assigned one screening number and one randomisation number, i.e. re-screening is not allowed, with one exception: subjects who did not meet the eligibility criteria defined in protocol version 4.0 can be re-screened once for eligibility according to protocol version 5.0.

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

4.6 Trial Stopping Criteria

Occurrence of the following may warrant consideration of trial termination:

- Life-threatening SAEs with suspected causality to the IMP
- Formation of treatment-induced neutralising antibodies to FSH

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

In addition to the trial-specific trial stopping criteria listed in this section, please see section 12.4 for trial stopping criteria related to the conduct of clinical trials in general.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Products (IMPs)

Subjects will be randomised in a 2:1 ratio to once daily subcutaneous administration of 12 µg FE 999049 (follitropin delta) or placebo, for a treatment duration of 6 months. Table 5-1 shows an overview of the dosing regimen.

Table 5-1 FE 999049 and Placebo Dosing Regimen

IMP	Dosing Regimen
FE 999049	Daily subcutaneous injection of 12 µg.
Placebo	Daily subcutaneous injection. Injection pen will be dialled to the same value (dose) as if administering FE 999049.

The IMPs will be self-administered by the subject as a daily subcutaneous injection in the lower part of the abdomen using a pre-filled injection pen. The date and time of each IMP injection will be recorded by the subject in an eDiary. To minimise local injection site reactions, it is advisable to change the injection site regularly, i.e. between the right and left lower part of the abdomen.

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. Table 5-2 provides an overview of the presentation of each medicinal product.

Table 5-2 Characteristics of Medicinal Products

IMP	Presentation	Manufacturer
FE 999049	Pre-filled pen containing 72 µg of FSH in 2.16 mL.	Ferring Pharmaceuticals
Placebo	Pre-filled pen containing 2.16 mL of placebo.	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 Good Manufacturing Practice and

national regulatory requirements. Details on the packaging and labelling of each medicinal product are provided in the Trial Supply Manual.

5.4 Conditions for Storage and Use

The investigator will ensure that the medicinal products will be stored under appropriate conditions in a secure location with controlled access. The storage compartment shall be monitored regularly, and the temperature shall be documented as instructed in the Trial Supply Manual.

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

For information on warnings, precautions and treatment of overdose, please refer to the Investigator's Brochure for FE 999049 for indication "Treatment of men with idiopathic infertility".[6]

5.5 Blinding / Unblinding

5.5.1 Blinding

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

The IMP will be packaged according to a computer-generated randomisation list prepared for all trial sites. The randomisation list will not be available to any person involved in the conduct and evaluation of the trial until the trial database is declared clean and locked. Likewise, the treatment allocation information in the EDC or IRT will not be accessible to investigators, other trial staff at site, laboratory personnel, or sponsor staff[h] during the trial.

5.5.2 Unblinding of Individual Subject Treatment

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

It is the investigator's responsibility to decide whether it is medically necessary to know which IMP the subject has received (i.e. unblinding), to ensure the subject's welfare and safety. Breaking of the blind for individual subjects in emergency situations could be required in case of suspected unexpected serious adverse events (SUSARs) or in case of other important adverse events when the knowledge of the IMP in question is required for therapeutic decisions for the management of the subject.

[h] This excludes the representative from Clinical Trial Supply, and representatives from Global Quality Assurance during audits. Furthermore, it may be necessary for representatives from Global Safety to unblind an individual subject's treatment during the trial for the purpose of expedited reporting.

The investigator who unblinds a treatment will use the IRT and is required to enter a password before the treatment code can be broken. The IRT records when, and by whom, the code was broken. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided. The investigator should notify the ethics committee about the circumstances for unblinding in accordance with local requirements.

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

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

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

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

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

The IMP will only be dispensed to subjects who meet the eligibility criteria and are randomised to a treatment group in the trial.

An IRT will be used to assign and dispense the medicinal products to the subject. The investigator (or his/her designated trial staff) will maintain subject dispensing logs, detailing the dates, quantities and batch numbers of dispensed and returned medicinal products for each subject in the IRT to manage the overall drug accountability. The monitor will verify the drug accountability during the trial and if applicable document any discrepancies.

5.6.2 Assessment of Compliance

In order to monitor compliance, the subjects are to return empty, partially used, and unused pre-filled pens, and are to report all IMP injections in an eDiary. The investigator (or his/her designated trial staff) will review the eDiary entries and will reconcile and document the return on the drug accountability log. Any discrepancies should be discussed with the subject at the time of the return.

5.6.3 IMP Medication errors

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

5.7 Return and Destruction of Medicinal Products

All used and unused (non-dispensed / non-allocated) trial medication will be disposed as instructed in the Trial Supply Manual, after drug accountability has been finalised and verified by the monitor.

5.8 Auxiliary Supplies

Ferring will supply safety containers for the collection of used needles, etc.

6 TRIAL PROCEDURES

The flow of trial procedures for the subjects, as well as for their female partners, are shown in Table 6-1.

6.1 Trial Flow Chart

Table 6-1 Trial Flow Chart – Subject Procedures

	Screening	Treatment period								Follow-up	
Visit/Phone call No.	V1	V2	P1	V3	P2	V4	V5	P3	V6	V7	V8
Timing	<90 days before V2	Ran-dom-isation	Week 2	Month 1	Month 2	Month 3	Month 4	Month 5	EOTx/ Month 6[a)]	Day 21-35 after EOTx[b)]	EOT/ Month 9
Written informed consents [c)]	X	X [d)]									
Inclusion/exclusion criteria [c)]	X	X [d)]									
Demographics [c)]	X										
Medical history [c)]	X										
Body weight and height [c)]	X										
Physical examination [c)]	X					X			X		
Infertility history	X										
Reproductive history	X										
Urological examination	X										
Vital signs	X								X		
Semen collection	X [e)]					X			X		X
Blood collection, clin chem/haem	X								X		
Blood collection, hormones/ SHBG	X [f)]	X [g) h)]		X [h)]		X [h)]			X [h)]	X [h)]	
Blood collection, antibodies [i)]	X [j)]	X [g)]		X [k)]		X			X	X	
Blood collection, genome [l)]		X [g)]									
Semen epigenome [l)]		X [g)]							X		
Randomisation		X									
IMP dispensing/ administration		X [m)]		X		X	X				
Urine pregnancy test dispensing	X [n)]	X		X		X	X		X	X	
Pregnancy status [o)]			X	X	X	X	X	X	X	X	X
At-home sperm test dispensing [p)]		X		X		X	X		X	X	
Drug accountability				X		X	X		X		
Concomitant medication [q)]	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Injection site reaction inquiry				X		X	X		X		
eDiary review [r)]				X		X	X		X	X	X
Patient-experience interview [s)]									X [t)]		

a) Visit must be scheduled within 5 days after end-of-treatment. The visit will thus be around 6 months for subjects who complete treatment but can be earlier for subjects who prematurely discontinue IMP administration.
b) Visit must be scheduled between 21-35 days after last IMP dose and will thus be around 7 months for subjects who complete 6 months of treatment but can be earlier for subjects who prematurely discontinue IMP administration.
c) Performed in male subjects, and performed in female partners at screening. All other procedures are performed in male subjects only. Procedures for female partners can be performed at their general practitioner/obstetrician/gynaecologist, or at the trial site, except informed consent, which will be obtained at the trial site. Only one site visit is required for female partners; this visit must occur before randomisation of male subject.
d) Performed before randomisation.
e) Two semen samples taken at least 2 weeks apart. If a semen sample has been taken within 3 months prior to screening and been analysed at an andrology laboratory, it can be included as the first of the two semen samples at screening.
f) Serum hormones include FSH, LH, testosterone, and estradiol (central laboratory). SHBG is not analysed at screening.
g) Performed before IMP administration.
h) Serum hormones include FSH, LH, inhibin B, testosterone, and estradiol; additionally, SHBG is analysed (central laboratory).
i) Subjects with treatment-induced antibody response will be followed until the response is negative or has returned to pre-dosing level or until a maximum of 1 year from last IMP dose.
j) Sample used to re-establish the anti-drug antibody analytical assays.
k) Sample for assessment of early anti-drug antibody development; stored and only analysed if subsequent samples prove to be positive for FSH antibodies.
l) Optional sampling for potential future exploratory analyses for subjects who have provided separate written informed consent.
m) First dose of IMP is self-administered at the site under supervision of trial staff. Remaining doses will be self-administered daily at home for 6 months.
n) Urine pregnancy test to be used for documentation of negative pregnancy status of female partner ≤72 hours before randomisation of male subject; as required by inclusion criteria. Test can be taken at home.
o) Subjects will be inquired about the pregnancy status of their female partner (βhCG test results, and pregnancy ultrasound if applicable). A patient form for documentation of vital pregnancy by ultrasound will be handed out at each site visit from randomisation onwards, as applicable. Alternatively, instead of filling in the patient form, vital pregnancy can be documented by providing a verified medical record.
p) In selected sites, subjects will be provided with at-home sperm tests for monthly analysis of semen parameters.
q) During site visits, subjects are additionally asked whether their partner has received any infertility treatment during the trial period (infertility treatment for the partner only allowed from 6 months after randomisation). Recording of treatment type, medication, timing, treatment outcome, if any.
r) Between site visits, eDiary entries will additionally be reviewed, as applicable (by the trial site staff via the EDC).
s) Interview conducted for approximately 60 subjects from selected sites; subjects must have provided separate written informed consent.
t) Interview will be conducted by phone within a few days to weeks after end-of-treatment.

βhCG: beta-human chorionic gonadotropin; EOT: end-of-trial; EOTx: end-of-treatment; FSH: follicle-stimulating hormone; IMP: investigational medicinal product, LH: luteinising hormone; P: phone call to subject; SHBG: sex hormone binding globulin; V: visit at trial site.

6.2 Screening (Visit 1)

Potential subjects will be scheduled to come to the site 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 subject informed consent form, obtained prior to any trial-related procedures.
  This includes consent for participation in the trial, separate consent for exploratory analyses (*optional*) covering potential future genome sequencing and semen epigenome sequencing, as well as separate consent for potential participation in a patient-experience interview (*optional*)
- Signed and dated written parental informed consent form for data collection on the neonate, obtained prior to randomisation
- Allocation of a screening number
- Check of inclusion and exclusion criteria (those which are possible to check at screening)
- Dispense urine pregnancy test (to be used for documentation of negative pregnancy status of female partner ≤72 hours prior to randomisation of male subject. Test can be taken at home.)
- Demographics (age, ethnicity, race)
- Collection of the following data:
  - Medical history
  - Infertility history
  - Reproductive history
- Body measurements (body weight, height) [*note*: these are used for calculation of BMI]
- Physical examination
- Urological examination
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Semen collection (2 samples taken ≥2 weeks apart) for semen parameter analysis (in local and central laboratories)
  [*note*: local laboratory analyses results of both semen samples must be available prior to randomisation and both must conform with the limits specified in the inclusion criteria. If results of one of the two semen samples do not meet the inclusion criteria, this semen sample and analysis can be repeated. If a semen sample has been taken within 3 months prior to screening and been analysed at an andrology laboratory, it can be included for eligibility assessment instead of the first of the two semen samples at screening. Laboratory

procedures regarding handling and evaluation of semen samples will be described in a trial-specific manual provided to participating sites and will follow WHO standards[13].]

- Blood collection for central laboratory analysis of:
  - Clinical chemistry and haematology parameters [*note*: the results must be available prior to randomisation]
  - Serum hormone concentrations (screening panel: FSH, LH, testosterone, and estradiol) [*note*: the results must be available prior to randomisation]
  - Anti-FSH antibodies (used to re-establish the anti-drug antibody analytical assays)
- Recording of use of any concomitant medication (within the last 3 months prior to the date of signed subject informed consent form)
- Recording of adverse events (from the date of signed subject informed consent form)

Female partners of potential subjects will attend the site for informed consent. All other procedures can be performed at the trial site or at their general practitioner or obstetrician/gynaecologist. The following procedures for female partners must take place during the screening period of the male subjects:

- Signed and dated written female partner informed consent form for collection of her data, obtained prior to any trial-related procedures in the female and prior to randomisation of male subject
- Signed and dated written parental informed consent form for data collection on the neonate, obtained prior to randomisation of male subject
- Check of inclusion criteria for subject's female partner (those which are possible to check at screening)
- Demographics (age, ethnicity, race)
- Collection of the following data:
  - Medical history, including menstrual history
- Body measurements (body weight, height) [*note*: these are used for calculation of BMI]
- Physical examination

Subjects considered eligible for the trial based on the inclusion and exclusion criteria at screening may proceed to randomisation, which may take place as soon as all eligibility criteria are met but within 90 days from the first screening visit.

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

6.3 Randomisation (Visit 2)

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
- Obtain signed and dated written parental informed consent form for collection of data on the neonate, if not obtained at screening

If the subject and his partner are deemed eligible based on all inclusion and exclusion criteria, the subject will proceed to randomisation:

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

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

- Blood collection for central laboratory analysis of:
  - Serum hormone concentrations (FSH, LH, inhibin B, testosterone, and estradiol)
  - Serum SHBG concentration
  - Anti-FSH antibodies
- Blood collection for potential future genome sequencing *(applicable for subjects who have provided separate informed consent)*
- Semen collection for potential future epigenome sequencing *(applicable for subjects who have provided separate informed consent)*

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

- The subject must be instructed on how to complete the eDiary for recording of IMP injections, intercourse, and injection site reactions. This includes handing out of the eDiary subject manual with written instructions for the subjects.
  The first evaluation of injection site reactions is done immediately after the IMP administration at the site, followed by a second evaluation 30 minutes after IMP

administration, and a third evaluation 24 hours after IMP administration (before the next day's injection of IMP).

- Dispense IMP according to randomisation (i.e. as instructed by the IRT) and instruct the subject on self-administration of the IMP. IMP will be self-administered as a subcutaneous injection in the lower part of the abdomen. The first dose of IMP will be self-administered at the site under supervision of the trial staff.
- Dispense urine pregnancy tests
- Hand out patient form for documentation of vital pregnancy by ultrasound
- Dispense at-home sperm tests and instruct the subject on how to use the smartphone app used for data collection [*note:* in selected trial sites only]

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

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

The IMP should preferably be administered at the same time each day (with the possible exception of the administration during the site visit for randomisation; Visit 2).

Between site visits, eDiary entries are reviewed by the trial site staff via the EDC, as applicable.

6.4 Week 2 (Phone Call 1)

The following must take place during the phone call at 2 weeks (14±3 days) after randomisation:

- Inquiry of male subject about the pregnancy status of his female partner; documentation of positive βhCG test result, if applicable
- Recording of use of any concomitant medication
- Recording of adverse events
- Remind subject to record IMP administration and intercourse in eDiary

6.5 Month 1 (Visit 3)

The following must take place 1 month (30±5 days) after randomisation:

- Blood collection for central laboratory analysis of:
  - Serum hormone concentrations (FSH, LH, inhibin B, testosterone, and estradiol)
  - Serum SHBG concentration

- Anti-FSH antibodies[i]

- Dispensing of IMP
- Dispensing of urine pregnancy tests, as applicable
- Hand out patient form for documentation of vital pregnancy by ultrasound, as applicable
- Inquiry of male subject about the pregnancy status of his female partner; documentation of positive βhCG test result, if applicable
- Dispensing of at-home sperm tests [*note:* in selected trial sites only]
- Drug accountability of IMP
- Recording of use of any concomitant medication [*note:* this includes verification that the subject's female partner has not received any infertility treatment during the treatment period; recording of treatment type, medication, timing, and treatment outcome, if any]
- Recording of adverse events
- Recording of occurrence of any injection site reactions

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

- Review eDiary (data on IMP administration, intercourse, and data on injection site reactions during first week of treatment)
- Remind subject to record IMP administration and intercourse in eDiary

Between site visits, eDiary entries are reviewed by the trial site staff via the EDC, as applicable.

6.6 Month 2 (Phone Call 2)

The following must take place during the phone call at 2 months (60±5 days) after randomisation:

- Inquiry of male subject about the pregnancy status of his female partner; documentation of positive βhCG test result and pregnancy ultrasound, if applicable
- Recording of use of any concomitant medication
- Recording of adverse events
- Remind subject to record IMP administration and intercourse in eDiary

[i] Sample for assessment of early anti-drug antibody development; stored and only analysed if subsequent samples prove to be positive for anti-FSH antibodies

6.7 Month 3 (Visit 4)

The following must take place 3 months (90±5 days) after randomisation:

- Physical examination
- Semen collection for local and central laboratory analysis of semen parameters
- Blood collection for central laboratory analysis of:
  - Serum hormone concentrations (FSH, LH, inhibin B, testosterone, and estradiol)
  - Serum SHBG concentration
  - Anti-FSH antibodies
- Dispensing of IMP
- Dispensing of urine pregnancy tests, as applicable
- Hand out patient form for documentation of vital pregnancy by ultrasound, as applicable
- Inquiry of male subject about the pregnancy status of his female partner; documentation of positive βhCG test result and pregnancy ultrasound, if applicable
- Dispensing of at-home sperm tests [*note:* in selected trial sites only]
- Drug accountability of IMP
- Recording of use of any concomitant medication [*note:* this includes verification that the subject's female partner has not received any infertility treatment during the treatment period; recording of treatment type, medication, timing, treatment outcome, if any]
- Recording of adverse events
- Recording of occurrence of any injection site reactions

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

- Review eDiary (data on IMP administration and intercourse)
- Remind subject to record IMP administration and intercourse in eDiary

Between site visits, eDiary entries are reviewed by the trial site staff via the EDC, as applicable.

6.8 Month 4 (Visit 5)

The following must take place 4 months (120±5 days) after randomisation:

- Dispensing of IMP

- Dispensing of urine pregnancy tests, as applicable
- Hand out patient form for documentation of vital pregnancy by ultrasound, as applicable
- Inquiry of male subject about the pregnancy status of his female partner; documentation of positive βhCG test result and pregnancy ultrasound, if applicable
- Dispensing of at-home sperm tests [*note:* in selected trial sites only]
- Drug accountability of IMP
- Recording of use of any concomitant medication [*note:* this includes verification that the subject's female partner has not received any infertility treatment during the treatment period; recording of treatment type, medication, timing, treatment outcome, if any]
- Recording of adverse events
- Recording of occurrence of any injection site reactions

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

- Review eDiary (data on IMP administration and intercourse)
- Remind subject to record IMP administration and intercourse in eDiary

Between site visits, eDiary entries are reviewed by the trial site staff via the EDC, as applicable.

6.9 Month 5 (Phone Call 3)

The following must take place during the phone call at 5 months (150±5 days) after randomisation:

- Inquiry of male subject about the pregnancy status of his female partner; documentation of positive βhCG test results and pregnancy ultrasound, if applicable
- Recording of use of any concomitant medication
- Recording of adverse events
- Remind subject to record IMP administration and intercourse in eDiary

6.10 Month 6: End-of-Treatment (Visit 6)

This visit must be scheduled within 5 days after end-of-treatment. The visit will thus be at 6 months (180+5 days) for subjects who complete treatment, but can be earlier for subjects who prematurely discontinue IMP administration.

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

- Physical examination
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Semen collection for local and central laboratory analysis of semen parameters
- Blood collection for central laboratory analysis of:
  - Clinical chemistry and haematology parameters
  - Serum hormone concentrations (FSH, LH, inhibin B, testosterone, and estradiol)
  - Serum SHBG concentration
  - Anti-FSH antibodies
- Semen collection for potential future epigenome sequencing *(applicable for subjects who have provided separate informed consent)*
- Dispensing of urine pregnancy tests, as applicable
- Hand out patient form for documentation of vital pregnancy by ultrasound, as applicable
- Inquiry of male subject about the pregnancy status of his female partner; documentation of positive βhCG test result and pregnancy ultrasound, if applicable
- Dispensing of at-home sperm tests [*note:* in selected trial sites only]
- Drug accountability of IMP
- Recording of use of any concomitant medication [*note:* this includes verification that the subject's female partner has not received any infertility treatment during the treatment period; recording of treatment type, medication, timing, treatment outcome, if any]
- Recording of adverse events
- Recording of occurrence of any injection site reactions

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

- Review eDiary (data on IMP administration and intercourse)
- Remind subject to record intercourse in eDiary

Between site visits, eDiary entries are reviewed by the trial site staff via the EDC, as applicable.

Subjects might be contacted for a patient experience interview via phone within a few days to weeks after this site visit [*note*: only in selected sites and for subjects who have provided separate written informed consent].

6.11 Day 21-35 after End-of-Treatment (Visit 7)

This visit must be scheduled between 21-35 days after administration of the last IMP dose. The time point of the visit will thus be around 7 months after randomisation for subjects who complete 6 months of treatment but can be earlier for subjects who prematurely discontinue IMP administration.

The following must take place between 21-35 days after the last IMP dose:

- Blood collection for central laboratory analysis of:
  - Serum hormone concentrations (FSH, LH, inhibin B, testosterone, and estradiol)
  - Serum SHBG concentration
  - Anti-FSH antibodies
- Dispensing of urine pregnancy tests, as applicable
- Hand out patient form for documentation of vital pregnancy by ultrasound, as applicable
- Inquiry of male subject about the pregnancy status of his female partner; documentation of positive βhCG test result and pregnancy ultrasound, if applicable
- Dispensing of at-home sperm tests [*note:* in selected trial sites only]
- Recording of use of any concomitant medication [*note:* this includes recording of any infertility treatment the subject's female partner may have received outside of the trial; recording of treatment type, medication, timing, treatment outcome, if any]
- Recording of adverse events
- Review eDiary (data on intercourse)
- Remind subjects to record intercourse in eDiary

Between site visits, eDiary entries are reviewed by the trial site staff via the EDC, as applicable.

6.12 Month 9: End-of-Trial (Visit 8)

The following must take place at the end-of-trial visit 9 months (270±5 days) after randomisation:

- Semen collection for local and central laboratory analysis of semen parameters
- Inquiry of male subject about the pregnancy status of his female partner; documentation of positive βhCG test result and pregnancy ultrasound, if applicable
- Recording of use of any concomitant medication [*note:* this includes recording of any infertility treatment the subject's female partner may have received outside of the trial; recording of treatment type, medication, timing, treatment outcome, if any]

- Recording of adverse events

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

- Review eDiary (data on intercourse)

6.13 Pregnancy Follow-up

All couples with a pregnancy during the trial period (spontaneous pregnancy or pregnancy following infertility treatment of the female partner, which is allowed from 6 months after the subject's randomisation) will be followed until delivery to collect information on pregnancy losses and live births. Furthermore, data on neonatal health, including minor/major congenital anomalies, will be collected at birth, 4 weeks, and 1 year after birth. These follow-up data can be obtained from the subject, unless medical judgement is required. The subject will be contacted by phone and a contact log will be maintained at the trial site. These data will be reported separately.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Primary Endpoint

7.1.1 Spontaneous Pregnancy Observed in Female Partner

Spontaneous pregnancy will be documented by transvaginal or abdominal ultrasound in the subject's female partner and is defined as vital pregnancy, i.e. the observation of at least one intrauterine gestational sac with fetal heartbeat. Ultrasounds will be performed at the trial site or by the female partner's general practitioner or obstetrician/gynaecologist. Ultrasound results will be documented in a pre-specified patient form that is provided to the subjects or in a verified medical record.

7.2 Assessments Related to Secondary Efficacy Endpoints

7.2.1 Positive βhCG Observed in Female Partner after Spontaneous Conception

Urine pregnancy (βhCG) tests will be performed by the subjects' female partners and any positive result reported to trial sites.

7.2.2 Time to Spontaneous Pregnancy

Based on the recordings of the date of subject randomisation and confirmation of spontaneous pregnancy by ultrasound (date), the time to spontaneous pregnancy will be calculated in calendar time and in number of menstrual cycles.

7.2.3 Semen Parameters

Semen samples will be obtained during the subjects' site visits and assessed regarding semen volume, sperm concentration, total sperm count, total motile sperm count, sperm morphology, and DNA fragmentation. Samples will generally be analysed in local laboratories, except for DNA fragmentation which will be assessed in a central laboratory. Samples will be analysed according to WHO standards. Laboratory procedures regarding handling and evaluation of semen samples will be described in a trial-specific manual provided to participating sites to ensure standardisation across local laboratories.

During the trial, the laboratory analysis results of semen samples taken at 3, 6[j], and 9 months after randomisation will not be made available to the subject, to prevent any unwarranted speculation by the subject as to treatment allocation.

[j] End-of-treatment visit, which takes place at 6 months after randomisation for subjects who complete treatment but can be earlier for subjects who prematurely discontinue the treatment.

7.2.4 Treatment Responders

Subjects will be regarded as treatment responders if their female partner achieved spontaneous pregnancy (documentation of at least one intrauterine gestational sac with fetal heartbeat by ultrasound) during the trial period and/or if subjects show an increase in total sperm count or total motile sperm count to 50% over baseline at 6 and/or 9 months after randomisation. The percentage of treatment responders will be calculated based on the recordings regarding spontaneous pregnancy and semen parameters.

7.2.5 Serum Hormone Concentrations

Concentrations of the following serum hormones will be evaluated: FSH, LH, inhibin B, testosterone, and estradiol.

Blood samples will be drawn at randomisation, months 1, 3 and 6[k], and day 21-35 after the last IMP dose. The sample at randomisation (baseline) will be collected prior to the first dose of IMP. The samples will be analysed at a central laboratory.

The serum hormone concentrations include pharmacokinetic and pharmacodynamic markers of FSH therapy, and therefore to maintain blinding of treatment allocation the laboratory results from samples drawn at 1, 3 and 6[k] months, as well as 21-35 days after the last IMP dose will not be made available to the subject, investigator, other trial staff at site, or sponsor staff during the trial.

7.2.6 Free Testosterone Concentration

Blood samples for assessment of SHBG concentrations will be drawn at randomisation, months 1, 3 and 6[k], and day 21-35 after the last IMP dose in order to calculate free testosterone concentrations. The samples will be analysed at a central laboratory.

To prevent any risk of unblinding of treatment allocation, the laboratory results from samples drawn at 1, 3 and 6[k] months, as well as 21-35 days after the last IMP dose will not be made available to the subject, investigator, other trial staff at site, or sponsor staff during the trial.

7.3 Assessments Related to Secondary Safety Endpoints

7.3.1 Anti-FSH Antibodies

Blood samples for assessment of anti-FSH antibodies in the individual subjects in the trial will be drawn before, during, and after the IMP treatment period:

[k] End-of-treatment visit, which takes place at 6 months after randomisation for subjects who complete treatment but can be earlier for subjects who prematurely discontinue the treatment.

- Screening [*note*: this sample is used to re-establish the anti-drug antibody analytical assays, and will not be reported as part of the subject's analysis results[l]]
- Randomisation (Visit 2), prior to dosing (baseline)
- Month 1 after randomisation (Visit 3) [*note:* sample for assessment of early-drug antibody development; stored and only analysed if subsequent samples prove to be positive for anti-FSH antibodies]
- Month 3 after randomisation (Visit 4)
- Month 6[k] after randomisation (end-of-treatment, Visit 6)
- Day 21-35 after the last IMP dose (Visit 7)
  This will be around 7 months after randomisation for subjects who complete 6 months of treatment but can be earlier for subjects who prematurely discontinue IMP administration.

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

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

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

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

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

Assay 5 A confirmatory assay based on native FSH, in order to assess cross-reactivity with native FSH of any anti-FSH antibodies confirmed to be specific towards exogenous FSH in assay 2, using a cut-point approach with a 1% false positive rate.

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

[1] In the exceptional case that any other pre-dose blood sample is lost, the blood sample taken at screening may be used as backup sample.

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

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

Subjects with a treatment-induced anti-FSH antibody response (based on outcome of assay 2) will be followed until the response is negative or has returned to pre-dosing level or after a maximum of 1 year after the last IMP dose. These subjects will be called in for assessments 2 months after the last post-dosing anti-FSH antibody sampling, i.e. 3 months after the last IMP dose. If required, further assessments will be made at 5, 7, 9 and 12 months after the last IMP dose. The assessments will be terminated when two consecutive assessments are negative or indicate that the pre-dosing level has been reached, or after a maximum of 1 year.

7.3.2 Immune-related Adverse Events

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

7.4 Other Assessments − Subject

7.4.1 Demographics

Demographic information will be obtained during the screening period, including age, 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), according to local

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

regulation.

7.4.2 Medical History

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

7.4.3 Infertility History

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

7.4.4 Reproductive History

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

7.4.5 Body Measurements

Body weight and height will be measured during the screening period (this can be at the screening visit or prior to randomisation at visit 2, if up-to-date data are needed to determine eligibility) and will be used to calculate BMI. Body weight and height will be measured without shoes and coat.

7.4.6 Physical Examination

A complete physical examination will be performed during the screening period, at 3 months after randomisation, and end-of-treatment (i.e. 6 months after randomisation for subjects who complete treatment). Information will be recorded for general appearance, central and peripheral nervous system, head and neck (including ears, eyes, nose, mouth and throat), respiratory system, cardiovascular system, gastrointestinal system, lymphatic system, urinary system, musculoskeletal system and skin.

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

7.4.7 Urological Examination

A complete urological examination will be performed during the screening period. This will include a genital exam, as well as imaging studies of kidney and prostate as deemed necessary by the

investigator's assessment of medical history.

7.4.8 Vital Signs

Systolic and diastolic blood pressure as well as pulse will be measured during the screening period and at end-of-treatment (i.e. 6 months after randomisation for subjects who complete treatment). All assessments of vital signs will be done while the subject is in supine position after resting for 3 minutes.

7.4.9 Serum Hormone Concentrations at Screening

At screening, the concentrations of the following serum hormones will be evaluated: FSH, LH, testosterone, and estradiol. The sample will be analysed at a central laboratory.

The results must be made available prior to randomisation. The investigator will review and evaluate the laboratory results. The laboratory report will be signed and dated by the investigator.

7.4.10 Clinical Chemistry and Haematology Parameters

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

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

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

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

7.4.11 Concomitant Medication

The use of any concomitant medication within the last 3 months prior to screening, i.e. the date of signed subject informed consent form, and throughout the trial will be recorded (except medication used in previous infertility treatment which will be recorded as part of the infertility history).

Recording of concomitant medication will be performed at all visits. Any changes in concomitant medications or treatments must be recorded at each visit and phone call.

Subjects will additionally be asked to verify that their female partner has not received any infertility treatment during the subject's treatment period of 6 months. Subjects will also be asked whether their female partner has received any infertility treatment between the subject's end-of-treatment at 6 months and the end-of-trial. If any treatment occurred throughout the trial period, the type, medication, timing, and outcome of treatment will be recorded.

7.4.12 Drug Dispensing and Accountability

Subjects will record dates and time of IMP administration in their eDiary. Details on drug dispensing and accountability are provided in section 5.6.1.

7.4.13 Intercourse Frequency

Once per week, subjects will record the number of intercourses with their partner during the last 7 days in their eDiary.

7.4.14 Injection Site Reactions

During the first week of IMP administration, subjects will assess the local tolerability of subcutaneous injections of FE 999049 and placebo at three time points relative to each daily administration: immediately after the injection, 30 minutes after the injection, and 24 hours after the injection. The following injection site reactions will be assessed: redness, pain, itching, swelling and bruising. The presence and intensity of each injection site reaction will be rated as one of the following: none, mild, moderate or severe. The subject will record the assessments in an eDiary.

In addition, subjects will be asked regarding the occurrence of injection site reactions during each site visit, to account for reactions occurring after the first week of treatment.

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

7.5 Other Assessments - Female Partner

7.5.1 Demographics

Demographic information will be obtained during the screening period, including age, 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), according to local regulation.

7.5.2 Medical History

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

7.5.3 Body Measurements

Body weight and height will be measured during the screening period and will be used to calculate BMI. Body weight and height will be measured without shoes and coat.

7.5.4 Physical Examination

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

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

7.6 Assessments Related to Pregnancy Follow-up

For couples with a pregnancy during the trial period (spontaneous pregnancy or pregnancy following infertility treatment of the female partner, which is allowed from 6 months after the subject's randomisation), information on the pregnancy period, including any relevant interventions performed and incidence of pregnancy loss, as well as the pregnancy outcome, e.g. live birth, will be gathered. Further, neonatal health data will be collected at birth, 4 weeks, and 1 year after birth for all children born. At birth, the data collected will include gender, birth weight and length, way of delivery, position of neonate and Apgar score, as well as information on minor/major congenital anomalies, admission to neonatal intensive care unit (NICU) or neonatal care unit (NCU), or any other relevant medical event. At 4 weeks and at 1 year after birth, the data collected will include information on minor/major congenital anomalies, admission to NICU, NCU, or paediatric care units (PCU), death of neonate/infant and any other relevant medical event. These follow-up data can be obtained from the subject, unless medical judgement is required. These data will be reported separately.

7.7 Exploratory Analyses

7.7.1 Genome Sequencing (*Optional*)

For subjects who have provided separate informed consent, a blood sample for potential future genome sequencing will be collected at randomisation. The separate informed consent for this

optional exploratory analysis must have been obtained through the subject informed consent form for the trial, as appropriate, prior to the sampling.

Resultant sequence data may be used in exploratory pharmacogenomic analyses aimed at identifying novel relationships between responsiveness to FE 999049/ associated outcome in conception and subjects' genomic variants.

Results of these potential future exploratory analyses will not be provided to trial sites or subjects.

7.7.2 Semen Epigenome Sequencing (*Optional*)

For subjects who have provided separate informed consent, a semen sample for potential future epigenome sequencing will be collected at randomisation and end-of-treatment visit. The separate informed consent for this optional exploratory analysis must have been obtained through the subject informed consent form for the trial, as appropriate, prior to the sampling.

Resultant data may be used in exploratory pharmacogenomic analyses aimed at identifying novel relationships between responsiveness to FE 999049/ associated outcome in conception and subjects' epigenomic variants.

Results of this potential future exploratory analysis will not be provided to trial sites or subjects.

7.7.3 At-home Semen Analysis

In selected trial sites, subjects will be provided at-home sperm tests for monthly analysis of semen parameters, including sperm concentration and total motile sperm count. Data will be collected via smartphone app. Subjects will be instructed by the trial site staff on how to use the app for data collection.

Resultant data will be used to explore the feasibility of at-home sperm tests in a clinical trial setting and may provide additional information on the time course of changes in semen parameters.

The data will not be made available to the subject, investigator, other site staff, or sponsor staff during the trial.

7.7.4 Patient-experience Interview (*Optional*)

Patient-experience interviews will be conducted for approximately 60 subjects in the trial. All subjects from selected sites in the U.S. and Europe will be invited to participate in the interview. Participation in the patient-experience interview is voluntary and separate written informed consent must have been obtained through the subject informed consent form for the trial, as appropriate, before participation.

Both, subjects who completed 6 months of treatment and subjects who discontinued treatment prematurely, will be contacted via phone by a third-party CRO for the patient-experience interview within a few days to weeks after end-of-treatment or as soon as the CRO becomes aware of the discontinuation of treatment.

The patient-experience interview is designed to examine the patient perspective on the treatment regimen in relation to their quality of life, and understand the patient experience, expectations and satisfaction with the treatment and the daily injection schedule. The interviewer will be blinded to treatment. Once approximately 60 subjects have completed the patient experience interviews, this part of the trial will be terminated. The results will be used to obtain a better understanding of the patient perspective within this therapy area and to inform further patient-focused drug development, which is in line with recommendations of FDA and EMA.[7,8]

A detailed description of the patient-experience interview is provided in the separate patient-experience interview protocol.

All patient-experience interviews will be conducted over the phone, in local language, by a trained interviewer from a third-party CRO.

7.8 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, semen) in this trial.

Blood samples will be analysed at central laboratories and may be maintained in storage after the end-of-trial. Destruction will take place within 2 years after reporting of the trial. Exceptions are blood samples for which methods / results have not been adequately validated and blood samples collected for potential future genome sequencing; these will be stored for a maximum of 10 years after reporting of the trial prior to destruction in line with local regulations.

Semen samples will be analysed at local laboratories and will be destroyed after analysis. Exceptions are semen samples collected for DNA fragmentation analysis, which will be analysed at a central laboratory and may be maintained in storage after the end-of-trial. Destruction will take place within 2 years after reporting of the trial, except samples for which methods / results have not been adequately validated and semen samples collected for potential future epigenome sequencing; these will be stored for a maximum of 10 years after reporting of the trial prior to destruction in line with local regulations.

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

7.9 Implications of COVID-19 Pandemic

The following considerations must be taken into account due to the current coronavirus disease 2019 (COVID-19) pandemic:

- Vaccination against COVID-19
  Vaccination against COVID-19 will be recorded at screening as part of the subject's medical history and/or throughout the trial as concomitant medication, and should be reported using the term "COVID-19 immunisation". Based on the currently available information and the ESHRE position on COVID-19 vaccination and assisted reproduction[14], Ferring's risk assessment is that there will be no protocol-specific requirements on COVID-19 vaccination.

- Medical history related to COVID-19
  Past or ongoing occurrence of COVID-19 will be recorded at screening as part of the subject's medical history, and should be reported using the term "COVID-19".

- Adverse events related to COVID-19
  In case of confirmed COVID-19 by a SARS-CoV-2 positive test, the term "COVID-19" should be used to report the adverse event irrespective of the type of test. In case of suspected COVID-19 infection, the term "Suspected COVID-19" should be used to report the adverse event. In case of recording concomitant medication against COVID-19, the indication should be "COVID-19" irrespective of the treatment.

- Missing visits / missing data
  In case subjects are prevented from attending scheduled visits due to the COVID-19 pandemic, the investigator (or designee) will attempt to contact the subject by phone or other ways to inquire about potential adverse events and changes to concomitant medication. In case not attending scheduled visits due to the COVID-19 pandemic may have any implications in the drug accountability of IMP, it should be documented by the trial site staff.

- Protocol deviations due to COVID-19 illness and/or COVID-19 control measures
  Protocol deviations should be avoided whenever possible except when necessary to eliminate an immediate hazard to the subject. If deviations occur they will be documented as per standard practice, with additional specification whether they were related to the COVID-19 pandemic.

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 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 using the Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version will be documented.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

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

The sources of adverse events cover:

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

8.2.2 Recording of Adverse Events

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

- Adverse event description

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

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

Adverse Event Description

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

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

Note the following: 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.

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

Intensity

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

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

Moderate: Disruption of usual activities (disturbing).

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

Causal Relationship to IMP

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

Reasonable possibility:

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

Examples:

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

No reasonable possibility:

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

Examples:

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

Action Taken to IMP

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

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

- Discontinued
- Interrupted
- Dose reduced
- Dose increased

Other Action Taken

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

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

End Date and Time

The date and time 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 Events Requiring Special Handling

8.3.1 Injection Site Reactions

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

8.3.2 Treatment-induced Anti-FSH Antibodies

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

8.4 Serious Adverse Events

8.4.1 Serious Adverse Event Definition

Serious Adverse Events during the Trial

An event is defined as a serious adverse event if it:	Guidance
results in **death**	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 an SAE. Hospital admissions and/or surgical operations planned before trial inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability/incapacity**	Disability / incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgement by the investigator.
is an **important medical event**	Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or 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

An event is defined as a serious adverse event if it:	Guidance
	allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Serious Adverse Events during Pregnancy Follow-up

The following untoward medical occurrences reported as part of the pregnancy outcome and neonatal health data collection will be recorded as SAEs. Data will be collected at birth, 4 weeks, and 1 year after birth.

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

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

Congenital anomalies will be coded by Ferring using both MedDRA and ICD-10 and classified as minor or major.[p,15,16]

8.4.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

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

[o] Stillbirth: gestational age ≥24 weeks + 0 days, calculated from the first day of last menstrual period

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

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

The same timelines and requirements apply for both the SAE Report Form and any follow-up with additional information regarding the SAE, i.e. 24 hours within obtaining knowledge of the follow-up information and 3 calendar days for providing the fullest possible details.

SAE Report Form

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

Global Safety, Ferring Pharmaceuticals A/S
E-mail: Safety.Mailbox@ferring.com

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

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

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

Expedited Reporting by Ferring

Ferring will report all adverse events, including SUSARs, according to local regulations.

8.5 Follow-up of Adverse Events and Serious Adverse Events

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

During the trial, the investigator must follow-up on each adverse event until the subject's last visit.

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

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

If an investigator becomes aware of an SAE after the subject's last visit in the trial, and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring, regardless how long after the end of the trial this takes place.

8.6 Pregnancy and Pregnancy Outcome in a Female Partner not Participating in the Trial

If an investigator becomes aware that a fetus in a female partner who is not participating in this trial may have been exposed through transmission of the IMP via semen following paternal exposure, the pregnancy must be reported to Global Safety at Ferring via Safety.Mailbox@ferring.com including the pregnancy outcome. If the pregnancy results in an abnormal outcome (birth defect/congenital anomaly) this must be reported as a serious adverse event to Global Safety at Ferring via Safety.Mailbox@ferring.com. Any information can be reported as blinded information, in case the investigator cannot obtain consent from the child custody holder(s).

8.7 Technical Complaints

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

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

9 STATISTICAL METHODS

This section details the planned statistical analyses for the primary endpoint and outlines the analysis plan for the secondary endpoints. All analyses and further descriptions of the statistical methodology for the primary and secondary endpoints will be described in a statistical analysis plan (SAP). The analyses and statistical methodology for pregnancy follow-up information will be covered in the same or a separate SAP.

9.1 Determination of Sample Size

The primary objective of this PoC trial is to evaluate the effect of FE 999049 treatment of men with idiopathic infertility, compared to placebo, on the spontaneous pregnancy outcomes in their female partners. The primary endpoint is spontaneous pregnancy observed in the female partners within 9 months after randomisation of the male subjects, where spontaneous pregnancy is defined as vital pregnancy (documentation of at least one intrauterine gestational sac with fetal heartbeat by ultrasound).

The trial is designed to provide 80% power to reject the null hypothesis,

$$H_0: \pi_{FE999049} \leq \pi_{Placebo}$$

where $\pi_{FE999049}$ and $\pi_{Placebo}$ are the 9-month spontaneous pregnancy rates in FE 999049 and placebo arms under the following conditions/assumptions:

- Two-sided significance level of 20%.
- 9-month spontaneous pregnancy rates in the FE 999049 and placebo arms are assumed to be 17.0% and 7.0%.
- Time to spontaneous pregnancy follows an exponential distribution.
- Time to withdrawal or experiencing an intercurrent event follows the same exponential distribution for both treatment arms. The cause-specific hazard of withdrawal/experiencing an intercurrent event corresponds to a 25% risk of withdrawal/experiencing an intercurrent event over the course of the 9-month trial period for subjects randomised to placebo.
- 10% of subjects whose female partner has not achieved a spontaneous pregnancy prior to the end of the treatment period will access additional infertility treatments during the 3-month follow-up period. This is in addition to the risk of withdrawal/experiencing an intercurrent event and is assumed to be the same for both treatment arms.

9.2 Subject Disposition

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

Subject disposition with respect to analysis sets will be tabulated. A separate table will summarise the subject disposition with respect to analysis sets by trial site. Subject attendance at selected trial visits and adherence to selected trial procedures will be tabulated. The number of subjects randomly assigned to receive FE 999049 or placebo, completing the treatment period, and completing the trial will be summarised by treatment group and analysis sets. Reasons for discontinuation of treatment and withdrawal from trial will be tabulated.

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

9.3 Protocol Deviations

Important protocol deviations will be summarised. The impact of important protocol deviations on the trial results may be addressed in additional supplementary analyses.

9.4 Analysis Sets

Intention-to-Treat Analysis Set

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

Full Analysis Set

The full analysis set (FAS) comprises all randomised and exposed subjects, i.e. subjects who received at least 1 dose of IMP (FE 999049 or placebo). Subjects will be analysed according to the planned treatment.

Safety Analysis Set

The safety analysis set comprises all randomised and exposed subjects, i.e. subjects who received at least 1 dose of IMP (FE 999049 or placebo). Subjects will be analysed according to the actual treatment received.

9.5 Trial Population

9.5.1 General Considerations

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

Listings will only be produced for the FAS.

Unless otherwise noted, missing data will not be imputed.

9.5.2 Trial Population Parameters

Demographics and other Baseline Characteristics

Demographics and other baseline characteristics (body measurements, vital signs, serum hormone concentrations, SHBG, free testosterone concentration, semen parameters) obtained before first exposure to IMP will be presented in summary tables by treatment group.

Medical History

All medical history will be coded using MedDRA. The version of MedDRA will be documented. Medical history will be summarised by treatment group for each medical item.

Infertility History and Reproductive History

Infertility history and reproductive history will be presented in summary tables.

Physical Examination and Urological Examination

Physical examination and urological examination performed during the screening period will be summarised per category.

Clinical Chemistry and Haematology Parameters

Clinical chemistry and haematology parameters analysed during the screening period will be summarised.

Concomitant Medication

Concomitant medications will be coded using the WHO Drug Reference List. Prior and concomitant medication will be summarised by Anatomical Therapeutic Chemical classification 1st level (alphabetically) and Anatomical Therapeutic Chemical 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 trial period (i.e. medication that is ongoing at the start of the 1st IMP administration, or initiated on or after the start date/time of 1st IMP administration and up to the end-of-trial)

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 summarised by treatment group.

9.5.3 Parameters in the Female Partner

Demographics and other Baseline Characteristics

Demographics and body measurements of the female partner obtained during the screening period will be summarised.

Medical History

The medical history, including menstrual history, will be obtained during the screening period and will be coded using MedDRA. The version of MedDRA will be documented. Medical history of the female partner will be summarised by treatment group for each medical item.

Physical Examination

The physical examination performed during the screening period will be summarised per category.

9.6 Extent of Exposure and Treatment Compliance

Treatment duration will be defined as the number of days from first exposure to the day of last exposure (both inclusive). Summary statistics will be produced by treatment groups for FAS.

Treatment compliance will be defined as the percentage of days on which treatment was received, i.e. total number of days with treatment received in relation to the treatment duration. Compliance will be summarised by treatment group.

9.7 Endpoint Assessments

9.7.1 General Considerations

Analysis and Presentation of Primary and Secondary Endpoints

Summary tables and results for the primary endpoint and secondary efficacy endpoints will be presented for the FAS. Secondary safety endpoints will be reported using the safety analysis set.

All tabulations will be presented by treatment group. Continuous variables will be summarised using the number of subjects, mean, standard deviation, median, inter-quartile range, minimum, and maximum. Categorical variables will be summarised using frequency counts and percentages within each specific category. All primary and secondary efficacy endpoints will be presented in data listings for the FAS.

For exploratory and supportive purposes, treatment differences will (where appropriate) be presented with two-sided 80% confidence intervals and p-values corresponding to the statistical test of the hypothesis “equal effect” against the alternative “different effect”. All statistical tests will be performed using a two-sided test at a 20% significance level, unless otherwise stated.

Multiplicity

No formal adjustment for multiplicity will be utilised. Statistically significant results will be interpreted cautiously.

Handling of Intercurrent Events

Intercurrent events are events that occur after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.[17]

Relevant intercurrent events for this trial include treatment discontinuation, lack of compliance to the randomised treatment regimen, lack of sexual intercourse, and the initiation of additional infertility treatments. In this context, treatment discontinuation refers to subjects who prematurely discontinue from treatment but remain in the trial, providing additional data after discontinuation.

Working definitions for what constitutes a lack of compliance to the randomised treatment regimen or intercourse will be provided in the SAP.

The general clinical principle for handling the above intercurrent events will be through the specification of a hypothetical strategy. Specifically, interest lies in assessing the effect of once daily dosing of 12 µg of FE 999049 vs placebo, among men with idiopathic infertility, in a trial setting where subjects remain on and are compliant to the randomised dosing regimen, continue to have sexual intercourse with their female partners, and do not have access to additional infertility treatments.

The occurrence of intercurrent events not considered above, will in general be handled through the implementation of the treatment policy strategy, unless otherwise specified in the SAP.

9.7.2 Primary Endpoint

The primary endpoint of the trial is spontaneous pregnancy observed in the female partner within 9 months after randomisation of the male subject, where spontaneous pregnancy is defined as vital pregnancy (documentation of at least one intrauterine gestational sac with fetal heartbeat by ultrasound).

The primary endpoint will be analysed as a time-to-event endpoint. Subjects prematurely withdrawing from the trial or experiencing one of the above identified intercurrent events prior to their partner achieving a spontaneous pregnancy, will have their time to spontaneous pregnancy censored.

The difference in the 9-month spontaneous pregnancy rates between the FE 999049 and placebo arms will be estimated using the Kaplan-Meier estimator. Under the independent censoring assumption, the Kaplan-Meier estimator is an unbiased estimator for the treatment effect of interest. Standard errors for the estimated within-arm 9-month spontaneous pregnancy rates will be based on Greenwood's formula.

Sensitivity Analysis

Sensitivity analyses will be defined in the SAP to explore the robustness of the primary analysis results to the assumption of independent censoring.

Supplementary Analysis

Subjects prematurely withdrawing from the trial or experiencing one of the above identified intercurrent events prior to their partner achieving a spontaneous pregnancy, will have their partner's spontaneous pregnancy status at the end of the 9-month trial period imputed. The imputation model will impute the time to spontaneous pregnancy, given that the subject's partner had not achieved a spontaneous pregnancy at the time of withdrawal/occurrence of an intercurrent

event. Details pertaining to the multiple imputation procedure, including the seed, number of imputations, imputation models, etc, will be specified in the SAP.

The completed data sets will be analysed based on the g-computation estimator referenced in the FDA guidance document on adjusting for covariates in randomised clinical trials.[18] The working model used to implement the g-computation estimator will be based on a logistic regression model with a logit link function, including treatment as a factor variable, and adjusting for relevant baseline sperm parameters which will be specified in the SAP. The variance estimator will be described in the SAP.

The pooled estimate of the difference in the spontaneous pregnancy rates, along with the associated 95% CIs and nominal p-value will be presented based on applying Rubin's rules to the estimates and standard errors from the analysis of the imputed data sets.

9.7.3 Secondary Efficacy Endpoints

9.7.3.1 Positive βhCG Observed in Female Partner after Spontaneous Conception

The endpoint, positive βhCG test observed in the female partner will be analysed in accordance with the analysis of the primary endpoint.

Sensitivity Analysis

Sensitivity analyses will be defined in the SAP to explore the robustness of the primary analysis results to the assumption of independent censoring.

9.7.3.2 Time to Spontaneous Pregnancy

The analysis of the time to spontaneous pregnancy will follow the censoring rules specified for the analysis of the primary endpoint. Time to spontaneous pregnancy will be analysed using the Kaplan-Meier method and the reported p-value will be based on the log-rank test.

Sensitivity Analysis

Sensitivity analyses will be defined in the SAP to explore the robustness of the primary analysis results to the assumption of independent censoring.

Supplementary Analysis

The time to spontaneous pregnancy will also be analysed using the number of menstrual cycles as a discrete time scale. The number of menstrual cycles will be estimated using the average menstrual cycle duration of the female partner based on information obtained at her screening assessment. The analysis will be based on fitting a logistic regression model. Details pertaining to the specification of the regression model and the data set to be used in the analysis will be provided in the SAP. Note that an individual subject will contribute one row to the data set for every cycle in which they're

observed prior to experiencing any of the above identified intercurrent events.

9.7.3.3 Changes in Semen Parameters

Semen parameters (semen volume, sperm concentration, total sperm count, total motile sperm count, sperm morphology, and DNA fragmentation) measured at each of the visits at 3, 6, and 9 months after randomisation, as well as changes from pre-randomisation to 3, 6, and 9 months after randomisation will be summarised by treatment groups and visit.

Missing values, either non-monotone (due to missed intermediate assessments) or monotone (due to withdrawal or through the implementation of the proposed hypothetical strategy to handle the occurrence of an intercurrent event), for semen parameters will be imputed as a part of the supplementary analysis of the primary endpoint.

The imputed data sets will be analysed by timepoint, i.e. at 3, 6, and 9 months, based on the specification of relevant generalised linear models to be detailed in the SAP. The pooled estimates, along with associated 95% CIs and nominal p-values will be presented based on applying Rubin's rules to the estimates and standard errors from the analysis of the imputed data sets.

9.7.3.4 Treatment Responders

The analysis of the treatment responder endpoint will be based on the imputed data sets obtained as a part of the supplementary analysis of the primary endpoint. Based on the imputed data sets, subjects will be defined as treatment responders if their female partner achieves a spontaneous pregnancy during the trial period or if subjects show a 50% increase (compared to baseline) in total sperm count or total motile sperm count at 6 and/or 9 months after randomisation.

The difference in the treatment response rates between the two treatment groups will be estimated for each imputed data set using a similar g-computation estimator to the one described for the supplementary analysis of the primary endpoint. The pooled estimate of the difference in the treatment response rates, along with the associated 95% CIs and nominal p-value will be presented based on applying Rubin's rules to the estimates and standard errors from the analysis of the imputed data sets.

9.7.3.5 Serum Hormone Concentrations

Serum hormone concentrations (FSH, LH, inhibin B, testosterone, and estradiol) measured at each visit as well as changes in serum hormone concentrations from randomisation to 3 and 6 months after randomisation will be summarised by treatment groups and visit. For each parameter, the concentrations at 3 and 6 months after randomisation will be compared between treatment groups in separate analyses using log-normal accelerated failure time models. Details regarding the

specification of the log-normal accelerated failure time models will be provided in the SAP.

9.7.3.6 Free Testosterone Concentration

Free testosterone concentration will be calculated based on measured serum SHBG and testosterone concentrations. The free testosterone concentration at each visit as well as changes in free testosterone concentration from randomisation to 3 and 6 months after randomisation will be summarised by treatment groups and visit. The concentrations at 3 and 6 months after randomisation will be compared between treatment groups in separate analyses using log-normal accelerated failure time models. Details regarding the specification of the log-normal accelerated failure time models will be provided in the SAP.

9.7.4 Secondary Safety Endpoints

Secondary safety endpoints will be reported using the safety analysis set.

9.7.4.1 Treatment-induced Anti-FSH Antibodies

The proportion of subjects with treatment-induced anti-FSH antibodies as well as the proportion of subjects with treatment-induced anti-FSH antibodies with neutralising capacity will be tabulated. A Fisher's exact test will be used to compare the percentage of such subjects between the treatment groups.

9.7.4.2 Immune-related Adverse Events

Potential immune-related adverse events will be tabulated using SMQs, MedDRA preferred terms, and MedDRA high level terms as stated in section 7.3.2.

9.8 Additional Safety Evaluations

9.8.1 General Considerations

Additional safety parameters will be evaluated for the safety analysis set. Data will be presented by summary tables.

9.8.2 Adverse Events

All adverse events recorded for subjects will be coded using MedDRA. The version of MedDRA will be documented. Adverse events will be grouped as follows:

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

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

TEAEs[q] and adverse events will be presented in summary tables and listings. Pre-treatment adverse events will be presented in a listing only.

A TEAE overview summary table will be prepared including the number of subjects reporting a TEAE, the percentage of subjects with a TEAE, and the number of events reported. Summary tables will be prepared for the following categories:

- All TEAEs
- TEAEs by causality (related / unrelated)
- TEAEs leading to discontinuation of treatment / withdrawal from trial
- TEAEs leading to death
- TEAEs by intensity
- Treatment-emergent adverse drug reactions[r] by intensity
- Treatment-emergent serious adverse events

TEAEs will be tabulated by system organ class alphabetically and by MedDRA preferred term in decreasing order of frequency. The table will display the total number of subjects reporting an adverse event, the percentage of subjects with an adverse event, and the number of events reported. Summary tables will be prepared for the following:

- All treatment-emergent adverse events
- TEAEs by causality (reasonable possibility / no reasonable possibility)
- TEAEs leading to death
- TEAEs by intensity
- Treatment-emergent adverse drug reactions[s] by intensity

q A treatment-emergent adverse event is any adverse event occurring after start of IMP and until the end-of-trial visit, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of IMP and until the end-of-trial visit.

r Adverse drug reactions are adverse events judged by the investigator as being related to IMP with reasonable possibility.

s Adverse drug reactions are adverse events judged by the investigator as being related to IMP with reasonable possibility

- Treatment-emergent serious adverse events
- TEAEs with an incidence of ≥5% in any treatment group
- Non-serious treatment-emergent adverse events with an incidence of ≥5% in any treatment group
- TEAEs leading to discontinuation of treatment / withdrawal from trial

Missing Data for Adverse Events

In case of missing data for adverse events, a worst-case approach or the most conservative approach will be used. If the intensity of adverse event is missing, the adverse event will be regarded as "severe"; if the causal relationship to IMP is missing, the adverse event will be regarded as "reasonable possibility"; if seriousness is missing, the adverse event will be regarded as serious; if outcome is missing, and no date of outcome is present, the outcome is regarded as "Not recovered".

9.8.3 Clinical Chemistry and Haematology Parameters

Laboratory variables will be grouped as "Haematology" and "Clinical Chemistry". Blood samples for haematology and clinical chemistry parameters will be drawn at screening and at the end-of-treatment visit.

For each laboratory parameter, a summary table will be prepared. Descriptive statistics (the number of subjects with data, mean, standard deviation, median, minimum, and maximum values) will be presented for observed values, absolute change, and percentage (%) change from screening to the end-of-treatment visit for each laboratory variable.

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

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

9.8.4 Vital Signs

Vital signs and their mean change and mean percentage (%) change from screening (baseline) to the end-of-treatment visit will be presented for each vital sign variable (systolic blood pressure, diastolic blood pressure, and pulse rate). Summary statistics for observed values and change from baseline to end-of-treatment visit will be provided. All vital signs values will be listed per subject, treatment group, and visit.

9.8.5 Physical Examination

Summary tables will be prepared displaying the number and percentage of subjects with abnormal physical examination at screening, at 3 months after randomisation, and at the end-of-treatment. Number and percentage of subjects changing from Normal at screening to Abnormal at 3 months or end-of-treatment will be summarised in a table for each physical examination variable. All subjects with any abnormal finding will be listed per subject.

9.8.6 Injection Site Reactions

Frequency and intensity of injection site reactions after IMP administration during the first week of treatment will be summarised. For each injection site reaction (redness, pain, itching, swelling, and bruising), the number of events and the number of subjects experiencing those events will be tabulated by time (immediately, 30 minutes, and 24 hours after the injection), reaction type, and intensity (none, mild, moderate, severe).

After the first week of treatment, the occurrence of injection site reactions will be recorded during each site visit, and will be evaluated and summarised.

9.9 Pregnancy Follow-up

As part of the pregnancy follow-up, the live birth rate based on the total number of subjects in the treatment groups will be calculated. Subjects with no information on live birth given by their female partners will be defaulted to a negative response. Descriptive statistics will be presented by treatment group.

Gender, birth weight and length, and Apgar score will be tabulated. The rate of minor/major congenital anomalies at birth, 4 weeks, and 1 year after birth will be calculated. Descriptive statistics will be presented by treatment group.

9.10 Exploratory Analyses

Results on the potential future genome sequencing and semen epigenome sequencing and outcomes of the patient-experience interview will be reported separately from the clinical trial report.

9.11 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 subject's medical record that the subject participates in this trial, and will record at least the following information, if applicable:

- Existence of subject (initials, date of birth)
- Confirmation of participation in trial (trial identifier [ID], subject ID)
- Informed consent (date and time of oral information, date and time of handing out of informed consent forms, date and time of obtaining written informed consents)
- Eligibility for participation in the trial (documenting all inclusion/exclusion criteria)
- Relevant medical history, infertility history and reproductive history
- Body weight and height at screening
- Results of physical examinations
- Results of urological examination
- Vital signs
- Visit dates
- Phone call dates
- Dates and daily dose of concomitant medication

- Adverse events (description as well as start/stop date and time)
- Event of unblinding, including the reason for unblinding
- Follow-up on treatment-induced anti-FSH antibody response
- Date(s) and result(s) of positive βhCG test(s) of female partner
- Any infertility treatment of female partner during the trial period, including treatment type, medication, timing, treatment outcome
- Pregnancy outcome of female partner, i.e. live birth or pregnancy loss, and neonatal health at birth, 4 weeks, and 1 year after birth
- Reason for subject's discontinuation from treatment / withdrawal from the trial (if applicable)

In addition, each subject will complete an eDiary to record the following:

- Dates and times of IMP administration
- Weekly intercourse count
- Injection site reactions after IMP administration during the first week of treatment

The eDiary is a subject interface to the EDC which means eDiary entries are made directly into the EDC. The service provider database is considered source data and will be available at the EDC vendor. The eDiary entries will be reviewed by the trial site staff via the EDC throughout the trial, i.e. at the site visits, and between site visits, as applicable.

Generally, no specific protocol data can be recorded directly in the EDC without prior written or electronic record (with the exception of the subjects' eDiary entries, as described above). The data entered in the EDC that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

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

The following documents collected during the trial must be stored and archived together with the subject's hospital/medical records or in the investigator file as agreed upon prior to trial start:

- Laboratory reports from central and local laboratories
- Documentation of pregnancy ultrasound(s) of female partner, including date(s) and result(s)
- Documentation of results of any semen sample taken within 3 months prior to screening that has been included for subject eligibility assessment (if applicable)
- Drug dispensing logs

- Relevant records for collection of laboratory samples

The source data for serum hormone and SHBG concentrations, clinical chemistry and haematology parameters as well as anti-FSH antibodies will be available at the central laboratory. Laboratory reports will be available at the sites for serum hormone concentrations at screening, and clinical chemistry and haematology parameters.

The source data for semen parameters will be available at the local laboratories, except for DNA fragmentation, for which source records will be available at the central laboratory. Laboratory reports for semen parameters analysed at local laboratories will be available at the sites.

10.2 EDC

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

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

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

The EDC 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 EDC is revoked.

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

10.3 Data Management

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

The data management plan will include information about the intended use of computerised systems, a description of the security measures employed to protect the data, and a description of

the electronic data flow.

10.4 Provision of Additional Information

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

11 MONITORING PROCEDURES

11.1 Monitoring

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

The investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The investigator will co-operate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits. In addition to on-site monitoring visits, remote monitoring is also an option. Remote monitoring is conducted off-site and may include video conference, telephone contact, and remote review of trial systems.

When the first subject is randomised at the trial site a monitoring visit will take place shortly afterwards. For this trial, the frequency of the monitoring visits per site will be determined through a risk-based approach, depending on e.g. recruitment rate, observed data quality, and overall site performance and will be detailed in the Monitoring Plan.

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

11.2 Audit and Inspection

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

The main purposes of an audit or inspection are to evaluate trial conduct and compliance with the trial protocol, ICH-GCP, the applicable regulatory requirements, and standard operating procedures.

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

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

11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the EDC 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 form, will be maintained by the investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

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

12.2 Deviations from the Protocol

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

12.3 Serious Breaches

Serious breaches will be reported in accordance with Regulation (EU) No. 536/2014. If an investigator becomes aware of the occurrence of a (suspected) serious breach, he/she must inform the sponsor without delay. Investigators will be trained regarding identification and reporting of serious breaches, including details on what, when, and how to report. Details on reporting procedures will be provided in a separate document.

12.4 Premature Trial Termination

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

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

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

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

For a list of additional trial-specific trial stopping criteria, please see section 4.6.

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 investigators. Furthermore, the data and information collected during the pregnancy follow-up period will be reported in clinical trial report addendums, including pregnancy losses, live births, neonatal health at birth, 4 weeks, and 1 year after birth.

13.2 Confidentiality and Ownership of Trial Data

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

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

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

In addition, the following requirements must be adhered to:

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

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

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

Authorship is granted based on the ICMJE criteria (see current official version: http://www.ICMJE.org). The total number of authors is based on the guideline from the relevant

journal or congress. In the event of any disagreement in the content of a publication, both the investigator's and Ferring's opinion will be fairly and sufficiently represented in the publication.

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

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. It is the responsibility of Ferring to register the trial in an appropriate public registry, e.g. www.clinicaltrials.gov; a website maintained by the National Library of Medicine (NLM) at the U.S. National Institutes of Health (NIH). The trial will also be made publicly available at the EU Clinical Trials Information System (CTIS) at https://euclinicaltrials.eu/search-for-clinical-trials. Trial registration may occur in other registries in accordance with local regulatory requirements. Trial results will be made publicly available in accordance with applicable regulatory requirements. The reporting of results in EU will occur within 12 months of the end of the trial (i.e. the global end of the trial, not the end of trial within the EU), to avoid premature unblinding which would jeopardize the scientific integrity of the trial.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Ethics Committee

An ethics committee will review the protocol and any amendments and advertisements used for recruitment. The ethics committee will review the informed consent forms, their updates (if any), and any written materials given to the subjects. A list of all ethics committees 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 Start-of-Trial, End-of-Trial and End-of-Trial Notification

The start of the trial is defined as the date of FPFV.

The end of the trial is defined as the date of LPLV, i.e. when the last subject globally completes the end-of-trial visit for follow-up at 9 months after his randomisation. This date is also the primary completion date.

Pregnancy follow-up will cover the period from LPLV until completion of the neonatal health follow-up 1 year after birth.

The regulatory authorities and the concerned ethics committees in the participating countries will be notified about the end of the trial and about the completion of the pregnancy follow-up according to local legislation.

In case of early termination, Ferring must notify the relevant regulatory authorities and ethics committees about the termination of the trial as soon as possible and in line with local regulations, clearly explain the reasons, and describe follow-up measures, if any, taken for safety reasons.

Within one year of the end of the trial (LPLV globally), Ferring shall send a summary of the final clinical trial report to the concerned ethics committees and the national regulatory authorities (if applicable according to local regulation).

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki[19], in compliance with the approved protocol, ICH-GCP and applicable regulatory requirements.

14.5 Subject Information and Consent

This trial will use three informed consent forms: one subject informed consent form, one female partner informed consent form, and one parental informed consent form. The latter two documents will describe the aspects relevant to the female partner's trial participation and to the data collection on the neonate, respectively, and should be read in conjunction with the subject informed consent form.

Subject Informed Consent Form

The subject informed consent form will cover: general consent for trial participation, separate consent for a patient-experience interview, and separate consent for potential future exploratory genome sequencing and semen epigenome sequencing. Participation in the patient-experience interview and in the potential future exploratory analyses are both optional.

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

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

The subject should receive a copy of his signed and dated informed consent form before any trial-related procedure.

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

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

compliance with applicable regulations.

Female Partner Informed Consent Form

The female partner informed consent form will cover her participation in the trial.

The investigator (or the person delegated by the investigator) will obtain a freely given written consent from each subject's female partner after an appropriate explanation of the aims, methods, sources of funding, any possible conflicts of interest, anticipated benefits, potential risks of the trial and the discomfort it may entail, post-study provisions and any other aspects of the trial which are relevant to the female partner's decision to participate. The female partner must be given ample time to consider her participation in the trial, before the consent is obtained. The informed consent form must be signed and dated by the female partner and the investigator who has provided information to the female partner regarding the trial before the female partner is exposed to any trial-related procedure, including recording of information during the screening period for assessment of eligibility, and prior to randomisation of the male subject.

The investigator (or the person delegated by the investigator) will explain that the female partner is completely free to refuse to participate in 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 female partner should receive a copy of her signed and dated informed consent form before any trial-related procedure.

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

Parental Informed Consent Form

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

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

The child-custody holders will receive a copy of their signed and dated parental informed consent forms.

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 applicable regulations.

14.6 Subject Participation Card

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

- That he is participating in a clinical trial (including trial code).
- That he is treated with FE 999049 or placebo.
- The name and phone number of the investigator.
- The name, address and phone number of Ferring contact (as required by local regulations).

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

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

14.7 Checklist for Pregnancy Follow-up

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

<u>At delivery:</u>

- Date of delivery
- Way of delivery (vaginal / vacuum extraction / forceps / caesarean section)
- Position of neonate (head / breech / transverse / other – please specify)
- Gender
- Birth weight
- Birth length

- Apgar score after 1 and 5 minutes
- Admission to NICU regardless of duration
- Admission to NCU for more than 2 hours
- Congenital anomaly
- Neonatal death
- Any medically important event in the neonate

4 weeks after delivery:

Relevant important conditions since delivery:

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

1 year after delivery:

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

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

14.8 Compliance Reference Documents

The Declaration of Helsinki, the consolidated ICH-GCP, Regulation (EU) No. 536/2014, 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, including being responsible for all trial-related medical decisions, for dispensing the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

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

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records that enable the conduct of the trial at the site to be fully understood, and for maintaining a record of the location of their essential documents including source documents, in accordance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 25 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 EDC data for Ferring. The investigator must arrange for the retention of this Subject Identification Log and signed informed consent forms for at least 25 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 Santi D, Granata AR, Simoni M. FSH treatment of male idiopathic infertility improves pregnancy rate: a meta-analysis. Endocr Connect. 2015; 4: R46-58.

2 Canarella R, La Vignera S, Condorelli RA, Mongioì LM, Calogero AE. FSH dosage effect on conventional sperm parameters: a meta-analysis of randomized controlled studies. Asian J Androl. 2020; 22: 309-16.

3 Ding YM, Zhang XJ, Li JP, Chen SS, Zhang RT, Tan WL, Shi XJ. Treatment of idiopathic oligozoospermia with recombinant human follicle-stimulating hormone: a prospective, randomized, double-blind, placebo-controlled clinical study in Chinese population. Clin Endocrinol. 2015; 83: 866-71.

4 Arce J-C, Larsson P, García-Velasco JA. Establishing the dose that provides a comparable ovarian response to 150 IU/day follitropin alfa. RBMO. 2020; 41(4): 616-22

5 Simoni M and Santi D. FSH treatment of male idiopathic infertility: Time for a paradigm change. Andrology 2020; 8(3): 535-44.

6 FE 999049 Investigator's Brochure for the indication "Treatment of men with idiopathic infertility", Ferring Pharmaceuticals, current edition.

7 FDA. Patient-Focused Drug Development: Methods to Identify What Is Important to Patients. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. October 2019

8 EMA. Reinforce patient relevance in evidence generation. EMA's Regulatory Science Strategy to 2025 – Human Stakeholder Workshop. Available at: https://www.ema.europa.eu/en/documents/presentation/presentation-ema-regulatory-science-2025-reinforce-patient-relevance-evidence-generation_en.pdf (Accessed on 01 September 2021)

9 Heller CH, Clermont Y. Spermatogenesis in Man: An Estimate of its Duration. Science 1963; 140(3563):184-6.

10 Heller CH, Clermont Y. Kinetics of the germinal epithelium in man. Recent Prog Horm Res. 1964; 20: 545-75.

11 Misell LM, Holochwost D, Boban D, Santi N, Shefi S, et al. A stable isotope-mass spectrometric method for measuring human spermatogenesis kinetics in vivo. J Urol. 2006; 175(1): 242-6.

12 Elzanaty S. Association between age and epididymal and accessory sex gland function and their relation to sperm motility. Arch Androl. 2007; 53(3): 149-56.

13 World Health Organization (WHO). WHO laboratory manual for the examination and processing of human semen. Sixth edition, 2021.

14 European Society of Human Reproduction and Embryology (ESHRE) statement on COVID-19 vaccination and medically assisted reproduction. https://www.eshre.eu/Europe/Position-statements/COVID19/vaccination (Accessed on 01 September 2021)

[15] European Medicines Agency (EMA). Committee for medicinal products for human use (CHMP). Guideline on the exposure to medicinal products during pregnancy: need for postauthorisation data. EMEA/CHMP/313666/2005.

[16] 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.

[17] European Medicines Agency (EMA). Committee for medicinal products for human use (CHMP). ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. EMA/CHMP/ICH/436221/2017.

[18] Food and Drug Administration (FDA). Guidance for Industry: Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products (Docket number: FDA-2019-D-0934).

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