FERRING
PHARMACEUTICALS

# Protocol

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|---|
| **Title of trial**<br>An open-label trial investigating the pharmacokinetics of FE 999049 given as a single subcutaneous dose in gonadotropin down-regulated healthy Chinese women |
| **NCT number:**<br>NCT04150861 |
| **Sponsor trial code:**<br>000152 |
| **Date:**<br>20 Sep 2018 |

# CLINICAL TRIAL PROTOCOL

# An open-label trial investigating the pharmacokinetics of FE 999049 given as a single subcutaneous dose in gonadotropin down-regulated healthy Chinese women

# 000152

| | |
|---|---|
| **EudraCT Number:** | Not applicable |
| **IND Number:** | |
| **Investigational Medicinal Product:** | FE 999049 |
| **Indication:** | Controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle |
| **Phase:** | 1 |
| **Name and Address of Global Sponsor:** | Ferring Pharmaceuticals<br>Global Clinical R&D<br>International PharmaScience Center<br>Kay Fiskers Plads 11<br>DK-2300 Copenhagen S<br>Denmark<br>Tel: +45 88 33 88 34<br>Fax: +45 88 33 88 80 |
| **Local Sponsor** | Ferring Pharmaceuticals (Asia) Company Limited<br>19/F Century Link Tower One<br>1198 Century Avenue, Shanghai<br>China 200122<br>Tel: +86-21-80303001<br>Fax: +86-21-80303010 |
| **GCP Statement:** | This trial will be performed in compliance with GCP. |

# SYNOPSIS

**TITLE OF TRIAL**

An open-label trial investigating the pharmacokinetics of FE 999049 given as a single subcutaneous dose in gonadotropin down-regulated healthy Chinese women

**SIGNATORY INVESTIGATOR**

[redacted]

**TRIAL SITE**

One trial site in China.

| PLANNED TRIAL PERIOD | CLINICAL PHASE |
|---|---|
| The first subject is expected to be enrolled in 2019 with a total duration of the trial of approximately 7 months. | 1 |

**BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL**

FE 999049 is a gonadotropin preparation containing recombinant human follicle stimulating hormone (rhFSH) under development by Ferring Pharmaceuticals for controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle. In previous trials the exposure to and dose proportionality of FE 999049 in a clinically relevant dose range in Caucasian and Japanese healthy women have been shown to be very similar.This is a trial in healthy Chinese women investigating the pharmacokinetics, safety, and tolerability of a single subcutaneous dose of FE 999049.

**OBJECTIVES**

The objectives of the trial are to:

- Investigate the single-dose pharmacokinetics of FE 999049 administered as a subcutaneous abdominal injection in healthy Chinese women
- Investigate the safety and tolerability of a single dose of FE 999049 administered as a subcutaneous abdominal injection in healthy Chinese women

**METHODOLOGY**

This is an open-label, randomised parallel group trial investigating the pharmacokinetics of FE 999049 after a single subcutaneous abdominal injection of 12, 18, or 24 µg, with 8 healthy Chinese women in each dose group.

Blood samples for analysis of FE 999049 concentration will be collected during 10 days.

Premenopausal women are chosen as trial population to mimic the target patient population. In order to minimise the interference by endogenous FSH with the pharmacokinetic assessment of the recombinant FSH, a gonadotropin releasing hormone (GnRH) receptor agonist, DECAPEPTYL Depot, will be administered throughout the trial period to suppress the endogenous release of FSH.

The doses in the trial are chosen to cover a possible range of clinical dosing of FSH in the targeted indications, however restricted at the lower end due to analytical constraints.

**NUMBER OF SUBJECTS**

24 healthy Chinese women will be included and dosed.

**CRITERIA FOR INCLUSION / EXCLUSION**

Healthy Chinese women, 21-40 years of age with a normal menstrual cycle (24-35 days), may be included in this trial. The complete list of inclusion and exclusion criteria is provided below.

**Inclusion Criteria**

1. Signed written Informed Consent Form
2. Female of Chinese origin, with two ethnic Chinese parents and four ethnic Chinese grandparents
3. 21–40 years of age (both inclusive)
4. Willing to stop using combined oral contraceptives (COC) in relation to the first DECAPEPTYL Depot administration on Day -28
5. Agrees to use a double barrier method of contraception between Day -63 and Day 28, if not abstinent. A double barrier method of contraception should also be used after Day 28 until menses resumes or until another contraceptive method has been established
6. Normal menstrual cycles with a range of 24-35 days in the absence of oral contraceptives
7. Serum follicle-stimulating hormone (FSH) ≤5 IU/L on Day -3 and Day -1
8. Body mass index (BMI) of 18.5 -25 $kg/m^2$ (both inclusive)
9. Negative serology for human immunodeficiency virus (HIV) antibody, hepatitis B (surface antigen), hepatitis C antibody, and syphilis bacteria
10. Healthy according to medical history, physical examination, gynaecological examination, electrocardiogram (ECG), blood pressure, and laboratory profile of blood and urine
11. Negative urine drug screen and alcohol breath test at screening and on Day -1
12. Non-smoker or light smoker (≤ 5 cigarettes/day) for at least 6 months prior to trial start

**Exclusion Criteria**

1. Presence or a history of clinically significant diseases of the renal, hepatic, gastrointestinal, cardiovascular, or musculoskeletal systems, or presence or history of clinically significant reproductive, psychiatric, immunological, endocrine or metabolic diseases
2. Cancer within the last 5 years except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin
3. Pregnancy or breastfeeding
4. Current or a history of endocrine abnormalities such as hyperprolactinaemia, polycystic ovary syndrome or other ovarian dysfunction, tumours of the pituitary gland or hypothalamus, thyroid or adrenal disease
5. Clinically significant findings on the trans-vaginal ultrasound, cytology, gynaecological or breast examination at screening or on Day –1 including ovarian cysts or tumours of the ovaries or uterus
6. Contraindications for the use of gonadotropins and gonadotropin-releasing hormone (GnRH) agonists
7. Previously treated with gonadotropins within the last 6 months prior to screening
8. History within the last two years or current abuse of alcohol or drugs
9. Presence or history of severe allergy or anaphylactic reactions
10. Intake of prescribed medication, over-the-counter (OTC) medication, or herbal medicines, with the exceptions of COC, cromoglycate, and paracetamol according to the labelling, within 2 weeks or 5 half-lives of the drug, whichever is longer, prior to first dose of DECAPEPTYL Depot. Topical treatments of bacterial or fungal infection are allowed if stopped before first dose of IMP.
11. Intake of any non-registered investigational drug within the last 12 weeks preceding screening, or longer if judged by the investigator to possibly influence the outcome of the current trial
12. High daily consumption of caffeine-containing beverages (e.g. more than five cups of coffee or equivalent) with a risk of withdrawal symptoms arising during the trial that may confound the safety evaluation
13. Blood donation or major blood loss (≥500 mL) within the last 8 weeks, or plasma donation with the last 4 weeks preceding the first day of IMP dosing
14. Current non-smokers or light smoker with a history of long-term, heavy smoking (>10 pack-years)
15. Previously dosed in this trial
16. Mental incapacity or language barrier precluding adequate understanding or co-operation

17. Considered by the investigator to be unsuitable to participate in the trial for any other reason

**MEDICINAL PRODUCTS**

Investigational medicinal product

- FE 999049 is provided as a cartridge with 72 µg rhFSH in 2.16 mL and an injection pen

Non-investigational product

- DECAPEPTYL Depot 3.75 mg

**DURATION OF TREATMENT**

Each subject is planned to receive a single injection of FE 999049. For each subject, the duration of the trial including screening and follow-up visits will not exceed 13 weeks.

**ENDPOINTS**

- Pharmacokinetics (AUC, $AUC_t$, $C_{max}$, $t_{max}$, CL/F, $V_z$/F, $t_{½}$)
- Safety (ECG, vital signs, laboratory parameters, adverse events)
- Injection site reactions
- Presence of anti-FSH antibodies

**TRIAL PROCEDURES / ASSESSMENTS**

Before inclusion into the trial, all subjects will undergo a general physical and a gynaecological examination, including vital signs, ECG, transvaginal ultrasonography and cytology as well as laboratory assessments including haematology, clinical chemistry, and urinalysis.

The subjects will receive two administrations of a 1-month depot formulation of DECAPEPTYL Depot 3.75 mg to down-regulate endogenous release of FSH during the trial. The first DECAPEPTYL Depot administration will be given 28±1 days prior to the first dose of IMP. In women not receiving hormonal contraceptives, the first DECAPEPTYL Depot administration should take place in the time interval 7 days before to 3 days after the expected start of menstruation. In women discontinuing combined oral contraceptives, the first DECAPEPTYL Depot administration should take place after the subjects have discontinued the hormonal contraception and within 5 days of commencement of bleeding. A second administration will be given 10±1 days prior to the first IMP administration.

To verify low stable endogenous hormones, serum FSH will be measured at Day -3 and Day -1. If any of the measurements is >5 mIU/mL, the subject will be excluded.

Subjects will come for a residential stay, lasting between Day -1 and Day 3, and ambulatory visits or, if agreed between investigator and subject, a residential stay from Day 4 to Day 10. A follow-up visit will be performed on Day 11. Blood samples for pharmacokinetic (PK) analysis of FE 999049 will be collected from Day 1 to Day 10, every 4 hours during the first 48 hours and then once daily.

Safety and tolerability will be assessed in terms of AEs, vital signs, ECG, and safety laboratory parameters up to and including Day 11. On Day 1, Day 7 and Day 28, assessment of the presence of anti-FSH antibodies will be performed.

**STATISTICAL METHODS**

Pharmacokinetic analysis

Pharmacokinetic parameters will be calculated using non-compartmental methods and evaluated using descriptive statistics. Dose proportionality will be investigated for AUC and $C_{max}$.

Safety

Safety endpoints will be evaluated by data listings and descriptive statistics.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| AMH | anti-Müllerian hormone |
| ANOVA | analysis of variance |
| ART | assisted reproductive technology(ies) |
| ATC | anatomical therapeutic chemical classification system |
| βhCG | beta unit of human chorionic gonadotropin |
| BMI | body mass index |
| CFDA | China Food and Drug Administration |
| CHO | Chinese hamster ovary |
| COC | combined oral contraceptive |
| COS | controlled ovarian stimulation |
| CRO | clinical research organisation |
| CV | coefficient of variation |
| ECG | electrocardiogram |
| e-CRF | electronic case report form |
| FAS | full analysis set |
| FDA | Food and Drug Administration, USA |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| GnRH | gonadotropin-releasing hormone |
| HIV | human immunodeficiency virus |
| ICH | International Conference on Harmonisation |
| ICSI | intracytoplasmic sperm injection |
| IEC | independent ethics committee |
| IMP | investigational medicinal product |
| IRB | institutional review board |
| IVF | in vitro fertilisation |
| LLQ | lower limit of quantification |
| MCH | mean corpuscular haemoglobin content |
| MCHC | mean corpuscular haemoglobin concentration |
| MCV | mean cellular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCA | non-compartmental analysis |
| NIMP | non-investigational medicinal product |
| OHSS | ovarian hyperstimulation syndrome |
| OTC | over-the-counter |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| PP | per protocol |

| | |
|---|---|
| rhFSH | recombinant human follicle stimulating hormone |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | system organ class |
| WHO | World Health Organization |

# DEFINITION OF TERMS

## Definition of general terms

| | |
|---|---|
| Enrolled | When subject and investigator have signed the Informed Consent Form |
| Included | When the subject has been dosed with investigational medicinal product (IMP) |
| Pre-dose | Before dosing on the day of IMP dosing |
| Treatment period | Time from administration of the IMP until discharge from the clinic at Visit 12 |
| End-of-trial | The last visit (Visit 14) for the last subject |

## Pharmacokinetic terms and definitions

| | |
|---|---|
| AUC | Area under the concentration-time curve from dosing to infinity |
| $AUC_t$ | Area under the concentration-time curve from dosing up to time t, where t is the last time point at which the concentration is above the lower limit of quantification. |
| % Extrap AUC | Percentage of AUC that is due to extrapolation from the last measurable concentration |
| CL/F | Apparent total systemic clearance |
| $C_{max}$ | Maximum concentration observed |
| $\lambda_z$ | First-order rate constant associated with the terminal (log-linear) portion of the concentration-time curve |
| NCA | Non-compartmental analysis |
| $t_{½}$ | Terminal elimination half-life |
| $t_{max}$ | Time of maximum observed concentration ($C_{max}$) |
| $V_z/F$ | Apparent volume of distribution associated with the terminal phase |

# 1 INTRODUCTION

## 1.1 Background

FE 999049 is a gonadotropin preparation containing recombinant human follicle-stimulating hormone (rhFSH) under development by Ferring Pharmaceuticals. It is intended for controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technologies (ART) such as an in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) cycle.

FE 999049 is developed from a human cell line, in contrast to the commercially available rFSH products that are derived from Chinese hamster ovary (CHO) cell lines. In December 2016, Ferring received Marketing Authorisation approval from the European Commission for FE 999049 under the trade name REKOVELLE. During 2017, FE 999049 was approved in Australia, Brazil, Israel, and Switzerland, and in 2018, also in Mexico and Canada.

Before the current trial, Ferring has completed four phase 1 trials (CS01, CS02, CS03 and 000020, all conducted in US), two phase 2 dose-response trials (000009 conducted in EU and 000124 conducted in Japan) and two phase 3 trials (000004 and 000071 conducted in Europe and Rest of World) as part of the clinical development programme for FE 999049. A total of 1,927 subjects have been included in the completed clinical trials, of whom 1,112 subjects were exposed to FE 999049. Momentarily, two phase 3 trials are ongoing (a Pan-Asian trial conducted in China, Taiwan, South Korea, and Vietnam and one conducted in Japan) including approximately 1,328 subjects in total of whom approximately 664 subjects will be randomised to treatment with FE 999049.

Of the four previous phase 1 trials, CS01, CS03, and 000020 were single dose trials conducted in healthy female subjects.[1,2,3] These trials showed that FE 999049 is absorbed slowly after single subcutaneous administration, with the median $t_{max}$ ranging from 10 to 24 hours. Mean absolute bioavailability of FE 999049 given subcutaneously was determined to be 64%.[3] Single subcutaneous administration of increasing doses to healthy female subjects indicated dose proportionality of $C_{max}$ and AUC over a wide dose range of 8.8 to 26.3 µg (based on conversion from IU to µg for the specific batch used).[1] Thus, the data demonstrated that the exposure to FE 999049 increased proportionally with doses across the whole therapeutic dose range up to 24 µg FE 999049 (24 µg being the maximum dose in the phase 3 programme and in the proposed posology for repeated cycles). The fraction of FE 999049 excreted unchanged in urine was approximately 11%.[3] Comparisons between Japanese and Caucasian women following administration of 450 IU FE 999049 demonstrated similar exposure by means of AUC and $C_{max}$.[2] Also the PK parameters $t_{max}$, $t_{½}$, CL/F, and $V_z$/F were similar for the Japanese and Caucasian women. Single dose administration of FE 999049 was safe and well tolerated as assessed by AEs, vital signs, ECG, clinical laboratory measurements, and physical examination. There were no signs of any anti-FSH antibody formation or allergic reactions. No serious adverse event or death occurred during the trials.

One previous phase 1 trial, CS02, evaluated daily subcutaneous administration of 225 IU FE 999049 in healthy female subjects.[4] This trial showed that a steady-state level of FSH was reached on treatment day 6-7 at which time the $C_{max}$ concentrations were 2.5- to 3-fold higher than those obtained after a single dose. The terminal half-life of FE 999049 was 28 hours after multiple subcutaneous administrations, which was shorter than the average of 40 hours after single subcutaneous administration. The time to maximal concentration was also shorter after multiple compared to single subcutaneous administration, with medians of 10 hours versus 24 hours, respectively.[1,2,3,4] The reason for this is as yet unknown, but these differences have also been observed for other FSH preparations.[5]

The two phase 2 trials 000009 and 000124 were randomised, controlled, assessor-blind, multi-centre dose-response trials in which randomisation was stratified according to the subject's anti-Müllerian hormone (AMH) level at screening. In both trials, a statistically significant dose-response relationship for FE 999049 with respect to the number of oocytes retrieved was observed. Furthermore, the dose-response relationship observed in Japanese and European subjects was similar. The similarity of the dose-response relationship between Japanese and European subjects supported the pharmacological rationale of the individualised treatment regimen.[6,7]

During the two phase 3 trials 000004 and 000071, 665 IVF/ICSI subjects were treated with FE 999049 in 1,012 treatment cycles. The two trials supported the efficacy and safety of FE 999049 in the proposed indication with the individualised FE 999049 dosing regimen based on AMH level (measured by Elecsys® AMH Immunoassay, Roche Diagnostics) and body weight.[8,9]

The ongoing phase 3 trial in Pan Asia is a randomised, controlled, assessor-blind, parallel groups, multicentre, non-inferiority trial comparing the efficacy and safety of FE 999049 and GONAL-F.

The ongoing phase 3 trial in Japan is a randomised, controlled, assessor-blind, parallel groups, multicentre, non-inferiority trial assessing the efficacy and safety of FE 999049 versus FOLLISTIM.

### 1.2 Scientific Justification for Conducting the Trial

This is a trial with the overall objective to obtain data on the pharmacokinetics of FE 999049 in healthy Chinese women. The trial will support the registration of FE 999049 in China.

### 1.3 Benefit / Risk Aspects

This is a phase 1 trial in healthy subjects and does not entail any medical benefit for the trial participants.

FE 999049 is a recombinant human FSH, and it is expected that the pharmacological effects and side effects of FE 999049 resemble those reported for other FSH products. The most frequently reported AEs in a previous single dose trial with FE 999049 in Caucasian women at doses ranging from 37.5 IU to 450 IU were headache and injection site reactions, the latter of short duration and possibly related to the volume administered.[1] In another previous single dose trial with FE 999049 in Japanese and Caucasian women at doses ranging from 75 IU to 450 IU, the most frequently reported AEs were lower abdominal pain, vaginal haemorrhage and injection site reactions.[2] In both trials a limited number of other AEs were sporadically reported in all treatment groups, including the placebo groups, and FE 999049 was regarded well tolerated. In the third previous single dose trial with FE 999049 in Caucasian women receiving 450 IU, the most frequently reported AEs were headache, breast tenderness and pelvic discomfort.[3] Common side effects reported for other FSH products are ovarian enlargement, breast complaints, abdominal pain, pelvic pain, headache, gastrointestinal symptoms, injection site reactions (swelling, pain, redness), hypersensitivity reactions, and ovarian cysts. Cases of ovarian hyperstimulation syndrome (OHSS), characterised by large ovarian cysts, abdominal pain, abdominal distension, vascular leakage, and rarely associated with thromboembolic events, have occurred in multiple dose trials with other FSH products, but no signs of OHSS were observed in the previous phase 1 trials.[1,2,3,4]

Adverse drug reactions following treatment with GnRH agonists such as DECAPEPTYL Depot include, but are not restricted to, hot flushes, decreased libido, mood changes, headache, abdominal pain and menstrual disorders that may be related to the induced transient oestrogen deficiency. Functional follicular cysts may occur upon treatment with GnRH agonists, the incidence being up to 9.3 %.[10] In this trial, the subjects will undergo an ultrasound examination prior to the administration of the investigational medicinal product (IMP), and those who have developed cysts will be withdrawn from the trial. Without gonadotropin stimulation, these cysts have virtually no clinical significance in a healthy woman.

Overall, the risks posed to the subjects participating in the trial are deemed low and ethically justifiable. For more detailed information on FE 999049 please refer to the Investigator's Brochure.[11]

# 2 TRIAL OBJECTIVES AND ENDPOINTS

## 2.1 Objectives

The objectives of the trial are to:

- Investigate the single-dose pharmacokinetics of FE 999049 administered as a subcutaneous abdominal injection in healthy Chinese women
- Investigate the safety and tolerability of a single dose of FE 999049 administered as a subcutaneous abdominal injection in healthy Chinese women

## 2.2 Endpoints

- Pharmacokinetics (AUC, AUCt, $C_{max}$, $t_{max}$, CL/F, Vz/F, t½)
- Safety (ECG, vital signs, laboratory parameters, adverse events)
- Injection site reactions
- Presence of anti-FSH antibodies

# 3 INVESTIGATIONAL PLAN

## 3.1 Overall Trial Design

### 3.1.1 Trial Design Diagram

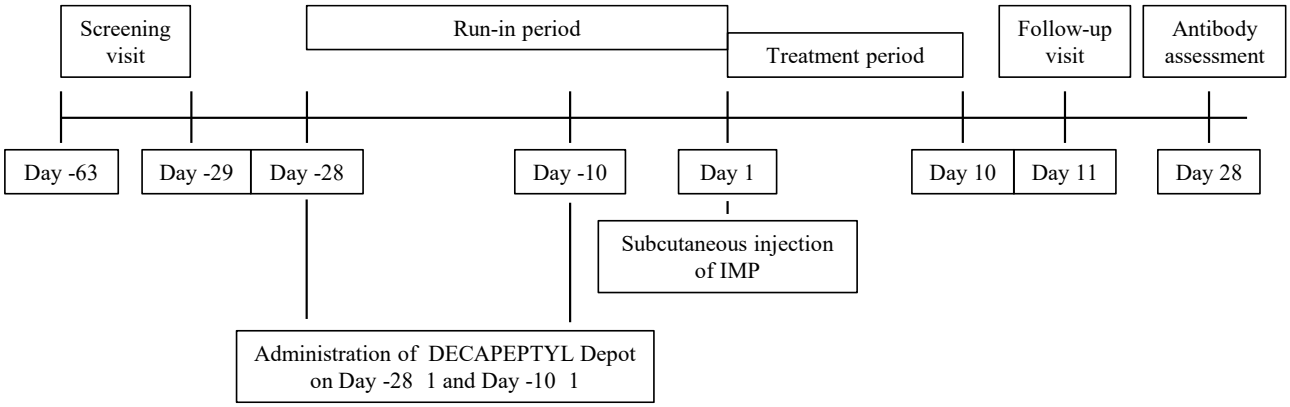


**Figure 1 Overall trial design: sequence and timing of trial events for each subject**

### 3.1.2 Overall Design and Control Methods

This is an open-label, randomised parallel group trial investigating the pharmacokinetics of a single subcutaneous abdominal injection of FE 999049. There will be 3 dose panels with 8 healthy Chinese women in each dose panel.

After testing negative in pregnancy tests, the subjects will receive two subcutaneous administrations of a 1-month depot formulation of the GnRH agonist DECAPEPTYL Depot 3.75 mg to down-regulate endogenous release of FSH during the trial. The first DECAPEPTYL Depot administration will be given 28±1 days prior to the first dose of IMP. In women not receiving hormonal contraceptives, the first DECAPEPTYL Depot administration should take place in the time interval 7 days before to 3 days after the expected start of menstruation. In women discontinuing combined oral contraceptives, the first DECAPEPTYL Depot administration should take place after the subjects have discontinued the hormonal contraception and within 5 days of commencement of bleeding. A second administration will be given 10±1 days prior to the first IMP administration.

To verify low stable endogenous hormones, serum FSH will be measured at Day -3 and Day -1. If any of the measurements is >5 mIU/mL, the subject will be excluded.

The doses to be administered are 12, 18, and 24 µg at a concentration of 33.3 µg/mL.

For each subject the treatment period is 10 days, and the total duration of the trial from screening to the last follow-up visit after treatment will not exceed 13 weeks.

### 3.1.3 Trial Schedule

The first subject is expected to be enrolled in 2019 with a total duration of the trial of approximately 7 months. The end of the trial is defined as the last visit (Visit 14, Day 28) for the last subject.

## 3.2 Planned Number of Trial Sites and Subjects

The trial will be conducted at a single site, including 24 healthy women receiving active treatment.

## 3.3 Interim Analysis

No interim analysis is planned.

## 3.4 Data Monitoring Committee

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

## 3.5 Discussion of Overall Trial Design and Choice of Control Groups

### 3.5.1 Trial Design

Premenopausal women are chosen as trial population to mimic the target patient population. These women have endogenous biosynthesis and release of gonadotropin hormones. In order to minimise the interference of the endogenous FSH with the PK assessment of FE 999049, the GnRH agonist DECAPEPTYL Depot will be administered throughout the trial.

Subcutaneous injection has been selected as the route of administration for the trial since this is the intended route of administration in the clinical setting. The duration of the treatment period is governed by the expected half-life of FE 999049, which after a single subcutaneous administration is reported to be 40-44 hours.[1] Thus, more than five half-lives, which is generally considered to be sufficient for a drug to be regarded as eliminated, are likely to have elapsed at the follow-up visit.

### 3.5.2 Selection of Endpoints

The selected endpoints focus on evaluating the PK, safety, and tolerability of FE 999049 in Chinese women.

### 3.5.3 Blinding

This is an open-label trial.

### 3.5.4 Selection of Doses in the Trial

The selection of doses is governed by the anticipated doses that may be considered in the clinical setting. The trial will include 3 dose groups of 12, 18, and 24 µg FE 999049. The doses will enable the single dose PK determination of FE 999049 at each dose level and investigate dose proportionality in Chinese women. The lowest dose of 12 µg FE 999049 will be the daily administered dose in any phase 3 trial for IVF patients with an AMH level < 15 pmol/L. The 18 and 24 µg FE 999049 are the doses applied in a phase 3 safety trial in patients that require a higher FE 999049 dose in their second or third treatment cycle. The 24 µg dose will be the highest dose of FE 999049 applied for controlled ovarian stimulation (COS) prior to ART.

### 3.5.5 Selection and Timing of Dose for Each Subject

All subjects will be dosed in the morning not less than 2 hours subsequent to a light standardised breakfast. This is assumed to minimise the possible analysis interference and variance caused by the intake of food just prior to sampling.

### 3.5.6 Withdrawal Criteria

In order to ensure down-regulation and minimise any interference from endogenous FSH, any subject that does not have a FSH concentration ≤5 IU/L on Day -3 and Day -1 will be withdrawn from the trial before randomisation. The Day -3 assessment may be repeated up to 5 days later if the first FSH measurement is >5 IU/L (subsequent visits will be postponed accordingly). The second assessment and the Day -1 assessment must be within acceptable ranges. No other specific withdrawal criteria are defined.

Since this trial comprises a single subcutaneous injection, no specific withdrawal criteria are defined that will arrest the treatment.

# 4 SELECTION OF TRIAL POPULATION

## 4.1 Trial Population

Healthy Chinese women, 21-40 years of age and with a body mass index (BMI) of 18.5-25 kg/m$^2$, with a normal menstrual cycle, may be included in this trial.

### 4.1.1 Inclusion Criteria

All of the following inclusion criteria must be met before the subject can enter into the trial:

1. Signed written Informed Consent Form
2. Female of Chinese origin, with two ethnic Chinese parents and four ethnic Chinese grandparents
3. 21–40 years of age (both inclusive)
4. Willing to stop using combined oral contraceptives (COC) in relation to the first DECAPEPTYL Depot administration on Day -28
5. Agrees to use a double barrier method of contraception between Day -63 and Day 28, if not abstinent. A double barrier method of contraception should also be used after Day 28 until menses resumes or until another contraceptive method has been established
6. Normal menstrual cycles with a range of 24-35 days in the absence of oral contraceptives
7. Serum follicle-stimulating hormone (FSH) ≤5 IU/L on Day -3 and Day -1
8. Body mass index (BMI) of 18.5 -25 kg/m$^2$ (both inclusive)
9. Negative serology for human immunodeficiency virus (HIV) antibody, hepatitis B (surface antigen), hepatitis C antibody, and syphilis bacteria
10. Healthy according to medical history, physical examination, gynaecological examination, electrocardiogram (ECG), blood pressure, and laboratory profile of blood and urine
11. Negative urine drug screen and alcohol breath test at screening and on Day -1
12. Non-smoker or light smoker (≤5 cigarettes/day) for at least 6 months prior to trial start

### 4.1.2 Exclusion Criteria

Any subject meeting one or more of the following exclusion criteria cannot be included in the trial and will be withdrawn if occurring during the trial:

1. Presence or a history of clinically significant diseases of the renal, hepatic, gastrointestinal, cardiovascular, or musculoskeletal systems, or presence or history of clinically significant reproductive, psychiatric, immunological, endocrine or metabolic diseases
2. Cancer within the last 5 years except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin
3. Pregnancy or breastfeeding

4. Current or a history of endocrine abnormalities such as hyperprolactinaemia, polycystic ovary syndrome or other ovarian dysfunction, tumours of the pituitary gland or hypothalamus, thyroid or adrenal disease
5. Clinically significant findings on the trans-vaginal ultrasound, cytology, gynaecological or breast examination at screening or on Day –1 including ovarian cysts or tumours of the ovaries or uterus
6. Contraindications for the use of gonadotropins and gonadotropin-releasing hormone (GnRH) agonists
7. Previously treated with gonadotropins within the last 6 months prior to screening
8. History within the last two years or current abuse of alcohol or drugs
9. Presence or history of severe allergy or anaphylactic reactions
10. Intake of prescribed medication, over-the-counter (OTC) medication, or herbal medicines, with the exceptions of COC, cromoglycate, and paracetamol according to the labelling, within 2 weeks or 5 half-lives of the drug, whichever is longer, prior to first dose of DECAPEPTYL Depot. Topical treatments of bacterial or fungal infection are allowed if stopped before first dose of IMP.
11. Intake of any non-registered investigational drug within the last 12 weeks preceding screening, or longer if judged by the investigator to possibly influence the outcome of the current trial
12. High daily consumption of caffeine-containing beverages (e.g. more than five cups of coffee or equivalent) with a risk of withdrawal symptoms arising during the trial that may confound the safety evaluation
13. Blood donation or major blood loss (≥500 mL) within the last 8 weeks, or plasma donation with the last 4 weeks preceding the first day of IMP dosing
14. Current non-smokers or light smoker with a history of long-term, heavy smoking (>10 pack-years)
15. Previously dosed in this trial
16. Mental incapacity or language barrier precluding adequate understanding or co-operation
17. Considered by the investigator to be unsuitable to participate in the trial for any other reason

## 4.2 Method of Assigning Subjects to Treatment Groups

### 4.2.1 Recruitment

The subjects will be recruited from the healthy subject database of the clinical site conducting the trial, and by advertising.

### 4.2.2 Randomisation

The subjects will be randomised into three dose groups (12, 18, and 24 µg) according to a computer-generated randomisation list provided by Global Biometrics, Ferring Pharmaceuticals. Randomisation will be carried out in the morning of the administration day. In case a withdrawn subject is replaced, she will receive the same dose as the subject she is replacing.

## 4.3 Restrictions

### 4.3.1 Prior and Concomitant Therapies

No concomitant medication, including Chinese herbs, is allowed, except for treatment of AEs when necessary, cromoglycate, and paracetamol according to label. Combined oral contraceptives should be stopped prior to first dose of DECAPEPTYL Depot; this will be administered on Day -28 and within 5 days of commencement of bleeding, and may not be used during the trial. Topical treatment of bacterial or fungal infection is allowed if stopped before IMP administration. Any concomitant medication will be recorded in the electronic case report form (e-CRF), together with the main reason for its prescription. Also the dose and dosage regimen will be documented in the e-CRF.

### 4.3.2 Other Restrictions

Subjects should abstain from drinking alcoholic beverages for 72 hours before the screening and all subsequent visits to the clinical investigation unit. In addition, subjects should abstain from drinking coffee and alcoholic beverages during the residential session in the treatment period.

Intake of products containing poppy seeds (e.g. poppy cake) should be avoided for a period of at least 48 hours before screening and admission to the clinic in order to avoid analytical interference with the drug screen for opiates.

The subjects should abstain from strenuous physical activity that is not within the subject's normal weekly routine for 48 hours prior to screening, and from 48 hours prior to admission until the last safety examination.

### 4.3.3 Subsequent Therapy

Since the trial population comprises healthy subjects only, no subsequent therapy is planned.

## 4.4 Withdrawal Criteria

Since this is a single injection trial no specific withdrawal criteria are defined. The subject will be withdrawn from the trial if any of the inclusion or exclusion criteria during the conduct of the trial is violated in a way that invalidate subsequent assessments. The sponsor, and the investigator in agreement with the sponsor, reserves the right to discontinue the trial at any time for safety reasons or other reasons jeopardising the justification of the trial. Such a termination will be implemented in a time frame that is compatible with the subject's well-being. If the trial is prematurely terminated or suspended, the investigator should promptly inform the subjects and assure appropriate follow-up and treatment if required. Ferring Pharmaceuticals will notify the regulatory authorities of any plans to terminate the trial, and the investigator will notify the independent ethics committee (IEC)/institutional review board (IRB).

The subjects have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. For any discontinuation, the investigator will obtain all the required details and document the date of the premature termination and the main reason in the e-CRF.

## 4.5 Subject Replacement

Subjects that are withdrawn may be replaced to reach 8 completed subjects at each dose level.

# 5 TREATMENTS

## 5.1 Treatments Administered

### Investigational Medicinal Product

The subjects will receive a single subcutaneous abdominal injection of FE 999049 (follitropin delta). The doses administered will be 12, 18, and 24 µg according to randomisation.

### Non-investigational Medicinal Product

The subjects will receive two subcutaneous abdominal injections of a 1-month depot formulation of the GnRH agonist DECAPEPTYL Depot 3.75 mg (Triptorelin).

## 5.2 Medicinal Products

### 5.2.1 Characteristics and Source of Supply

Ferring Pharmaceuticals will provide the clinical site conducting the trial with FE 999049 and DECAPEPTYL Depot 3.75 mg in amounts sufficient for the trial. FE 999049 will be provided as cartridges with an isotonic phosphate buffered solution of pH 6.5 containing 33.3 µg/mL rhFSH (72 µg in 2.16 mL) and an injection pen. DECAPEPTYL Depot 3.75 mg will be provided as powder and solvent for suspension for injection.

### 5.2.2 Packaging and Labelling

Packaging and labelling of the IMP and non-investigational medicinal product (NIMP) will be carried out under the responsibility of the Clinical Trial Supply (CTS) Department, Ferring Pharmaceuticals, Copenhagen, Denmark. The IMP and NIMP will be packed and labelled according to Good Manufacturing Practice (GMP), as well as any national regulatory requirements. All medicinal products will be labelled with trial specific labels, which contain a self- adhesive tear off portion to be affixed to the subject dispensing log maintained at trial site.

### 5.2.3 Conditions for Storage and Use

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

In case of technical malfunction of an administration pen, all relevant details (including time, date, a description of the malfunction and whether dosing was affected) of the incidence should be reported in the e-CRF, the pen should be replaced and the treatment continued. Human errors such as misunderstanding of instructions or incorrect handling of the device should not be regarded as technical malfunctions. In case of adverse events caused by malfunction of the administration pen, these will be identified and described.

## 5.3 Blinding/Unblinding

This is an open-label trial.

## 5.4 Treatment Compliance, 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.

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

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

The IMP and NIMP will be administered by authorised staff at the clinical investigation unit. Compliance is assessed by recording the amount administered.

## 5.5 Return and Destruction of Medicinal Products and Auxiliary Supplies

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

Any non-dispensed IMP and NIMP must be returned for destruction, as instructed by the Ferring CTS Department, after the drug accountability has been finalised and verified by the monitor.

# 6 TRIAL PROCEDURES

The trial comprises 14 visits, 1 of which is the residential treatment visit. The duration of the trial including the screening period and the follow-up visits will not exceed 13 weeks.

Assessments of AEs and concomitant medication will be performed throughout the trial.

### Visit 1 (Screening, Day -63 to Day -29)

At the screening visit each subject will be informed about the trial and after signing the Informed Consent Form, assessments for eligibility will commence. The eligibility evaluation includes adherence to inclusion and exclusion criteria, collection of demographic data and medical history, physical examination, gynaecological examination with PAP smear (unless done within 6 months prior to screening) and transvaginal ultrasound, urine drug screen and alcohol breath test, assessment of vital signs, 12-lead ECG, blood sampling for clinical chemistry, haematology, serology, and pregnancy test, and urine sampling for urinalysis.

### Visit 2 (Run-in Period, Day -28)

All subjects found eligible at the screening will be asked to return for the run-in period Visit 2. On Day -28±1, the subject will do a urinary pregnancy test, and if negative, receive an administration of DECAPEPTYL Depot 3.75 mg. In women not receiving hormonal contraceptives the first DECAPEPTYL Depot administration should take place in the time interval 7 days before to 3 days after the expected start of menstruation. In women discontinuing combined oral contraceptives, the first DECAPEPTYL Depot administration should take place after the subjects have discontinued the hormonal contraception and within 5 days of commencement of bleeding.

### Visit 3 (Run-in Period, Day -10)

A urinary pregnancy test will be repeated on Day -10±1, and if negative, the subject will receive a second administration of DECAPEPTYL Depot 3.75 mg.

### Visit 4 (Run-in Period, Day -3)

On Day -3 a blood sample will be collected for analysis and eligibility check of the FSH concentration. The Day -3 assessment may be repeated up to 5 days later if the first FSH measurement is >5 IU/L (subsequent visits will be postponed accordingly). A gynaecological examination and transvaginal ultrasound may be performed.

### Visit 5 (Run-in Period and Treatment, Day -1 to Day 3)

All subjects still found eligible after the FSH analysis will be asked to return for a treatment visit (residential stay). At the arrival to the clinic on the day before the administration day (Day -1 in the run-in period), blood sampling for analysis and eligibility check of the FSH concentration, clinical chemistry, haematology, and pregnancy test, and urine sampling for urinalysis will be performed. A limited general eligibility check (inclusion/exclusion criteria), urine drug screen, alcohol breath test, vital signs, and 12-lead ECG will also be performed. A gynaecological examination and transvaginal ultrasound will be performed if not done on Days -3 or -2.

The next day (Day 1), a blood sample for assessment of the presence of anti-FSH antibodies will be collected prior to administration of FE 999049. The subject will then be randomised to and receive an abdominal subcutaneous injection of either 12, 18, or 24 µg FE 999049. Safety assessments will be performed, injection site reactions assessed, and blood samples for PK analysis collected at predetermined time-points (Table 1). On Day 3, subsequent to the 48-hour PK sampling, the blood sampling for assessment of clinical chemistry, haematology, urine sampling for urinalysis, and assessment of vital signs and ECG, the subjects will be discharged from the clinic.

**Visits 6 - 12 (Assessment, Day 4 to Day 10)**

The subjects will visit the clinic each day in the morning or, if agreed between investigator and subject, have a residential stay from Day 4 to Day 10 for assessment of serum concentration of FE 999049. Additionally, at Visit 9 (Day 7) a blood sample for assessment of the presence of anti-FSH antibodies will be collected.

**Visit 13 (Follow-up, Day 11)**

A follow-up visit will be scheduled on Day 11, the day after the last assessment day. Blood samples for analysis of clinical chemistry and haematology and for a pregnancy test will be collected as well as urine samples for urinalysis. Physical examination, 12-lead ECG and vital signs will be assessed. A gynaecological examination with PAP smear and transvaginal ultrasound will also be performed. Depending on the results of the follow-up assessments, additional visits may be requested at the discretion of the investigator. Subjects should be advised to continue to use a double barrier method of contraception until menses resumes or until another contraceptive method has been established.

**Visit 14 (Anti-FSH Antibody Assessment, Day 28)**

A visit for the collection of a blood sample for assessment of the presence of anti-FSH antibodies will be scheduled on Day 28.

The end of trial is defined as the last visit by the last subject. After this visit the subjects will be contacted once a month until return of normal menstruation.

Subjects with a treatment-induced anti-FSH antibody response on Day 28 (both with and without neutralising capacity) will be asked to return after 1, 2, 3, 6, 9, and 12 months until two consecutive assessments indicate that the anti-FSH antibody level has become negative or has returned to the baseline level.

## Table 1 Trial flow chart

| | Screening | Run-in period | | | Treatment and Assessments | | | | | | | | | | | Follow-up | Anti-FSH ab |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ambulatory visits | | | | Residential stay | | | | Ambulatory visits | | | | | | | | |
| Visit No. | 1 | 2 | 3 | 4 | 5 | | | | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| Day | -63 to -29 | -28 | -10 | -3 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 28 |
| Inclusion/exclusion criteria | X | | | | X | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | |
| Randomisation | | | | | | X | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | |
| Physical examination | X | | | | | | | | | | | | | | | X | |
| Medical history | X | | | | | | | | | | | | | | | | |
| Gynaecological exam. and transvaginal ultrasound | X | | | X[a] | X[a] | | | | | | | | | | | X | |
| Cytology | X[b] | | | | | | | | | | | | | | | X | |
| Serum pregnancy test | X | | | | X | | | | | | | | | | | X | |
| Urine pregnancy test | | X[c] | X[c] | | | | | | | | | | | | | | |
| FSH for eligibility determination (local laboratory) | | | | X | X | | | | | | | | | | | | |
| Blood sampling for PK determination | | | | | | X[d] | X[d] | X[d] | X | X | X | X | X | X | X | | |
| Urine drugs screen | X | | | | X | | | | | | | | | | | | |
| Alcohol breath test | X | | | | X | | | | | | | | | | | | |
| Serology | X | | | | | | | | | | | | | | | | |
| Vital signs[e] | X | | | | X | X[f] | X[f] | X[f] | | | | | | | | X | |
| 12-lead ECG | X | | | | X | X[f] | X[f] | X[f] | | | | | | | | X | |
| Clinical chemistry, haematology, and urinalysis | X | | | | X | | | X | | | | | | | | X | |
| Injection site reactions | | | | | | X[g] | | | | | | | | | | | |
| Blood sampling for anti-FSH antibody analysis | | | | | | X[h] | | | | | | X | | | | | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prior/concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Administration of DECAPEPTYL Depot 3.75 mg | | X | X | | | | | | | | | | | | | | |
| Administration of IMP | | | | | | X | | | | | | | | | | | |

ab: antibody; ECG: electrocardiogram; FSH: follicle-stimulating hormone; IMP: investigational medicinal product; PK: pharmacokinetic;

a) Between Day -3 and Day -1
b) Cytology will be performed at screening if not done within 6 months prior to screening
c) Before the Day -28±1 and Day -10±1 DECAPEPTYL Depot administration
d) –1, –0.5, 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 48 hours post-dose
e) Vital signs include systemic blood pressures, heart rate and body temperature
f) 12, 24 and 48 hours post-dose
g) Immediately, and 30 min and 24 hours after administration
h) Before administration of FE 999049

# 7 TRIAL ASSESSMENTS

A laboratory manual will cover all blood and urine tests and describe sampling and shipment procedures including contact details, storage conditions, equipment, volume, analytical method, reference range, etc. The manual will be provided to the clinical investigational unit before the start of the trial. The total blood volume collected for clinical laboratory assessments and PK measurements will be less than 200 ml. If deemed necessary for safety reasons extra samples may be collected.

## 7.1 Assessments Related to Endpoints

### 7.1.1 Pharmacokinetics

Blood samples for measurement of serum concentration of FSH will be collected 1 and 0.5 hours prior to IMP administration, immediately before administration, and at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 48 hours, and 3, 4, 5, 6, 7, 8, and 9 days after administration. The actual sampling time at the ambulatory visits will be recorded. The serum concentrations of FSH will be analysed under the responsibility of the Department of Bioanalysis at Ferring Pharmaceuticals.

### 7.1.2 Safety Assessments

#### 7.1.2.1 Adverse Events

See Section 8.

#### 7.1.2.2 Vital Signs

Vital signs comprising systolic and diastolic blood pressure, heart rate, and body temperature will be assessed at screening, on Day -1, and 12, 24, and 48 hours after administration of FE 999049, and at the follow-up visit. Systolic and diastolic blood pressure will be measured after the subject has been in supine position for at least 5 minutes. All recordings will be performed using validated standard equipment. Clinically significant abnormal findings will be reported as AEs.

#### 7.1.2.3 Electrocardiography

The 12-lead ECGs will be recorded at screening, Day -1, and 12, 24, and 48 hours after administration of FE 999049, and at the follow-up visit after the subjects have rested for at least 5 min in supine position. The ECG will be recorded with a validated ECG device.

ECG recordings will capture at least four QRS complexes, i.e. 3 evaluable RR intervals. The investigator or a designate will evaluate whether the ECG is normal or abnormal and whether it is clinically significant, if abnormal. Any occurrence of de- or re-polarisation disorders, arrhythmic disorders or other abnormalities will be assessed and any changes compared to the pre-medication record will be commented. ECGs may be repeated for quality reasons and the repeat used for analysis. Clinically significant abnormal findings will be reported as AEs.

#### 7.1.2.4 Laboratory Parameters

Clinical chemistry, haematology, and urinalysis

Blood and urine samples will be collected at screening, on Day -1, Day 3, and at the follow-up visit for safety laboratory evaluations of clinical chemistry, haematology, and urinalysis parameters according to Table 2. The clinical chemistry and haematology analyses will be performed at a local laboratory.

Urinalysis will be performed locally from a sample of mid-stream urine by means of a dip-stick test. In case any result of the dipstick is abnormal, a new urine test will be performed. If the abnormal result is confirmed, further examination may be initiated at the discretion of the investigator. Clinically significant abnormal findings will be reported as AEs.

**Table 2 Safety laboratory parameters**

| Clinical Chemistry | Haematology | Urinalysis |
|---|---|---|
| Alanine aminotransferase | Haematocrit | Protein |
| Albumin | Haemoglobin | Glucose |
| Alkaline phosphatase | Mean cellular volume (MCV) | Bilirubin |
| Aspartate aminotransferase | Mean corpuscular haemoglobin (MCH) | pH |
| Glucose | Mean corpuscular haemoglobin concentration (MCHC) | Nitrite |
| Calcium | Platelet count | Ketone |
| Chloride | Red blood cell count | Urobilinogen |
| Cholesterol | Reticulocytes | Blood |
| Creatinine | White blood cell count with differential count | Leukocytes |
| C-reactive protein | Neutrophils, eosinophils, basophils, lymphocytes | Specific gravity |
| Gamma-glutamyltransferase | Monocytes, large unclassified cells | |
| Phosphate | | |
| Potassium | | |
| Sodium | | |
| Total bilirubin | | |
| Triglycerides | | |
| Urea (blood urea nitrogen) | | |

### 7.1.3 Other Assessments related to Endpoints

#### 7.1.3.1 Injection Site Reactions

Injection site reactions will be assessed by the investigator immediately after injection, 30 minutes, and 24 hours after administration of the IMP. The injection site reactions to be assessed are redness, pain, itching, swelling, and bruising, each to be assessed as none, mild, moderate, or severe. These injection site reactions will not be recorded as AEs.

#### 7.1.3.2 Presence of Anti-FSH Antibodies

Blood for assessment of the presence of anti-FSH antibodies in the serum will be collected on Day 1 before administration of FE 999049, Day 7 and Day 28. The samples will be analysed under the responsibility of the Department of Bioanalysis at Ferring Pharmaceuticals. Confirmed positive samples will subsequently be analysed for neutralising activity by a validated cell-based neutralising antibody assay.

### 7.2 Other Assessments

#### 7.2.1 FSH Determination Day -3 and Day -1

FSH for determination of down-regulation will be analysed on Day -3 and Day -1 using a validated standard method at a local laboratory.

#### 7.2.2 Serology/Virology

Determination of hepatitis B surface-antigen, hepatitis C virus antibodies, HIV antibodies and syphilis bacteria are performed at screening for eligibility purposes.

#### 7.2.3 Pregnancy Test

Serum β-human chorionic gonadotropin (β-hCG) will be determined at screening, and Day -1, and at the follow-up visit using validated standard methods. Urine β-hCG will be determined on Day -28±1 and Day -10±1, prior to administration of DECAPEPTYL Depot 3.75 mg.

#### 7.2.4 Gynaecological Examination and Transvaginal Ultrasound

Gynaecological examination and transvaginal ultrasound will be performed at screening, before dosing (in the period Day -3 to Day -1), and at the follow-up visit. Cytology will be performed at screening if not done within 6 months prior to screening, and at the follow-up visit.

#### 7.2.5 Physical Examination

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

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

At the follow-up visit, potential changes from screening to the follow-up visit will be evaluated for each category. In case of changes, these will be evaluated as normal, abnormal not clinically significant or abnormal clinically significant. Abnormal clinically significant changes from screening to the follow-up visit must be recorded as adverse events.

### 7.2.6 Drug Screen and Alcohol Breath Test

To ensure that drugs are not abused, a urine dip stick drug screen and an alcohol breath test will be performed locally at screening and on Day -1. The drug screening will be performed using fresh mid-stream urine for the determination of amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ecstasy, nortriptyline, opiates, phenacyclidine, and methadone.

## 7.3 Handling of Biological Samples

A detailed description of all sample collections and shipment procedures will be included in a separate laboratory manual. The sponsor or third parties will store the PK and immunogenicity blood samples for a period of up to 2 years after the trial is finalised.

## 7.4 Laboratory Analyses

All laboratory measurements, except for PK, anti-FSH antibodies and those that are assessed bed-side, will be analysed at a local laboratory. The investigator will review the laboratory results and evaluate and document whether the results are clinically significant or non-significant.

# 8 ADVERSE EVENTS

## 8.1 Adverse Events

### 8.1.1 Definitions

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

- Any unfavourable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- Adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital sign or finding from physical or gynaecological examination assessed as clinically significant by the investigator [note: pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not adverse events, but are recorded as medical history].
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.
- Overdoses and medication errors with and without clinical consequences.

**Pre-treatment Adverse Event**

A pre-treatment adverse event is any untoward medical occurrence arising or observed between informed consent and administration of the IMP.

**Treatment Emergent Adverse Event**

A treatment emergent adverse event is any adverse event occurring after the administration of the IMP and within the time of residual drug effect, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of IMP and within the time of residual drug effect.

The time of residual drug effect is the estimated period of time after the administration of the IMP, where the effect of the product is still considered to be present based on pharmacokinetic, pharmacodynamic, or other IMP characteristics. The residual drug effect is generally accepted to be 5 times the terminal half-life. The terminal half-life of FE 999049 after a single administration is expected to be approximately 40-44 hours.[1] Thus, the time from the administration on Day 1 to Visit 13 on Day 11 is likely to cover more than 5 half-lives. All AEs occurring during the treatment and follow-up phase (i.e. including Day 11) are regarded as treatment emergent.

**Post-treatment Adverse Events**

A post-treatment adverse event is any adverse event occurring after the time of residual drug effect of the IMP, i.e. after the visit on Day 11 and until the anti-FSH antibody assessment on Day 28.

## 8.2 Collection and Recording of Adverse Events

### 8.2.1 Collection of Adverse Events

The investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the end-of-trial visit or end of follow-up period as applicable.

The sources of adverse events cover:

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

### 8.2.2 Recording of Adverse Events

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

- Adverse event
- Date and time of onset (time can be omitted, if applicable)
- Intensity
- Causal relationship to the IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome (time can be omitted, if applicable)
- Outcome
- Seriousness

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

#### Adverse Event

Adverse events should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom will 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. However, if an adverse event with onset before the first IMP administration (i.e. a pre-treatment adverse event) changes in intensity, this must be recorded as two separate events. The initial adverse event should be recorded with outcome "not yet recovered" and the date and time of outcome is when the intensity changed. The second adverse event should be recorded with date and time of onset when the intensity changed.

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

**Date and Time of Onset**

The date and time of onset is the date and time 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 and time is the date and time the sample was taken or the examination was performed.

**Intensity**

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

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

Moderate: Event sufficient to affect usual activity (disturbing)

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

**Causal Relationship to the IMP**

The possibility of whether the IMP caused the AE 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 AE. The AE may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

Examples:

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

No reasonable possibility:

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

Examples:

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

**Action Taken to IMP**

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

- No change (medication schedule maintained or no action taken)
- Withdrawn
- Interrupted
- Dose reduced
- Dose increased

**Other Action Taken**

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

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

**Date and Time of Outcome**

The date and time the subject recovers or dies.

**Outcome**

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

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

## 8.3 Adverse Events of Special Interest

Not applicable.

## 8.4 Pregnancy and Pregnancy Outcome

If a pregnancy does occur, the subject will be withdrawn from the trial and Global Pharmacovigilance at Ferring Pharmaceuticals informed, using an SAE Report Form. Note, that pregnancy itself is not an SAE. The mother and the foetus will be followed up at least until the birth of the infant and one month after the birth of the infant. In general, the follow-up will include the course, duration and the outcome of the pregnancy and the health of the infant. If a pregnancy results in an abnormal outcome (birth defect/congenital anomaly) this must be reported as an SAE to Global Pharmacovigilance at Ferring Pharmaceuticals.

## 8.5 Serious Adverse Events

### 8.5.1 Serious Adverse Event Definitions

**Serious Adverse Events during the Trial**

| An event is defined a serious adverse event if it: | Guidance |
|---|---|
| results in **death** | Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within four weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is *per se* not an event, but an outcome. |
| is **life-threatening** | The term life-threatening refers to an AE 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 a **congenital anomaly/birth defect** | Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the IMP. |
| is an **important medical event** | Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse. |

### 8.5.2 Collection, Recording and Reporting of Serious Adverse Events

**SAE Reporting by the Investigator**

All SAEs must be reported **immediately** to Ferring Global Pharmacovigilance as soon as it becomes known to the investigator and not later than within 24 hours of their knowledge of the occurrence of an SAE. The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

SAE Report Form

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

Global Pharmacovigilance, Ferring Pharmaceuticals A/S

E-mail: [redacted]

Fax: [redacted]

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

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

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

**Expedited Reporting by Ferring**

Ferring will report all AEs that are **serious, unexpected and with a reasonable possible causality to the IMP** as judged by either the investigator or Ferring to the relevant parties within the stipulated timelines. The expectedness is assessed by Ferring Pharmaceuticals according to the Investigator's Brochure for FE 999049[11] and the label for DECAPEPTYL.[12]

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

## 8.6 Follow-up of Adverse Events and Serious Adverse Events

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

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

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

### 8.6.2 Collection of Serious Adverse Events with Onset after Last Trial Visit

If an investigator becomes aware of an SAE after the subject's last visit, 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.

# 9 STATISTICAL METHODS

The final statistical analyses will be detailed in a statistical analysis plan (SAP) prepared under the responsibility of Global Biometrics, Ferring Pharmaceuticals. The pharmacokinetic parameters specified will be computed by the Department of Translational Medicine, Ferring Pharmaceuticals. Statistical analysis of PK at end of trial will be performed under the responsibility of Global Biometrics.

## 9.1 Determination of Sample Size

No formal sample size calculation has been performed for this phase 1 trial. Eight subjects receiving active treatment in each dose panel is considered sufficient to provide adequate information about the pharmacokinetic parameters at each dose level for the purposes of this trial.

## 9.2 Subject Disposition

All subjects screened and exposed will be accounted for. The number of subjects screened but not dosed will be stated in the trial report but otherwise not accounted for. All post-dosing discontinuations will be summarised by time of and reason for discontinuation.

## 9.3 Protocol Deviations

Major protocol violations, such as significant non-compliance or other serious unforeseen violations deemed to invalidate the data collected for the purpose of the trial will lead to exclusion of the data from analysis. In case of minor protocol violations, data will not be excluded from the data analysis. The rating of protocol violations in ‘minor’ and ‘major’ will be decided on the basis of a review of the data before declaration of ‘clean file’ and lock of database.

## 9.4 Analysis Sets

### 9.4.1 Full Analysis Dataset

The full analysis data set (FAS) comprises data from all dosed subjects. The FAS will be used for presentation of compliance and all baseline characteristics (demographics, medical history, prior and concomitant medication, and physical examination).

### 9.4.2 Per Protocol Dataset

The per protocol (PP) data set comprises data from all dosed subjects except data excluded as a result of major protocol violations as defined in Section 9.3. The PP analysis set will be used for presentation of PK endpoints.

### 9.4.3 Safety Dataset

The safety analysis dataset comprises data from all dosed subjects and will be used for safety analysis.

## 9.5 Trial Population

### 9.5.1 Demographics and other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented by dose group for the FAS.

### 9.5.2 Medical History, Concomitant Medication and Physical Examination

Medical history and concomitant medication will be presented by descriptive statistics for the FAS by dose group. The results of the physical examination will be listed.

## 9.6 Treatment Compliance

Treatment compliance in terms of the number of subjects that were dosed in each dose group and the individual dose received will be presented for the FAS.

## 9.7 Endpoint Assessments

### 9.7.1 General Considerations

The statistical analyses will include descriptive statistics reflecting the explorative nature of the trial. In general, the data will be presented by dose group.

Continuous data will be summarised by dose using number, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarised by dose using the number and percentage of subjects in each category.

### 9.7.2 Endpoints

#### 9.7.2.1 Pharmacokinetics

The statistical analysis of PK will be performed by Department of Translational Medicine, Ferring Pharmaceuticals. The PK parameters will be calculated for non-corrected as well as baseline corrected data by non-compartmental analysis (NCA) using the software Phoenix WinNonlin® (Certara, US). The baseline value is the mean of the values obtained prior to the administration of the IMP. Actual sampling time points relative to dosing will be used for the NCA and on the individual plots of serum concentration versus time. Serum concentration values below lower limit of quantification (LLQ) and missing values (e.g. no blood sample collected or no value obtained at analysis) will be excluded from the NCA. Values below LLQ will be represented as LLQ/2 in the plots.

PK parameters will be estimated based on measurements from Day 1 to Day 10. From the serum concentration-time data of FE 999049 the following parameters will be estimated, if possible: AUC, $AUC_t$, % Extrap AUC, $C_{max}$, $t_{max}$, $\lambda_z$, $t_{½}$, CL/F, and $V_z$/F.

Selection of data points for calculation of $t_{½}$ via $\lambda_z$ will be based on the following considerations:

- The automatic range selection used in Phoenix WinNonlin® will be used to propose an optimal number of time points to use for the calculation of $\lambda_z$.

- The time range of samples used to estimate $\lambda_z$ should preferably exceed the derived terminal half-life $t_{½}$ (= ln 2/$\lambda_z$).
- All the samples used to calculate $\lambda_z$ should ideally fall in the log-linear elimination phase.
- At least three samples above LLQ obtained during the log-linear elimination phase will if possible be included in the calculation of the $\lambda_z$.
- The final selection of samples for calculation of $\lambda_z$ will be based on visual inspection of log-concentration-time plots of individual profiles.

AUC will be calculated by the linear trapezoidal method. PK parameters will be presented by dose with number of measurements, number of missing data, mean, standard deviation, median, minimum, maximum, geometric mean, and %CV (based on untransformed data) for geometric mean (for AUC and $C_{max}$). For $t_{½}$, the harmonic mean will be listed in addition to the geometric mean. For $t_{max}$ the geometric mean and the %CV will be omitted.

Dose proportionality will be investigated for each of AUC and $C_{max}$ using a multiplicative analysis of variance model with log(dose) as covariate. In this model, a covariate coefficient of 1 would indicate dose proportionality.

### 9.7.3 Safety Assessments

#### 9.7.3.1 Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be presented by time for each parameter and summarised by treatment. Shift tables will be presented for changes from baseline (i.e. the last assessment prior to administration) to the follow-up visit, and will be summarised by dose group.

#### 9.7.3.2 Clinical Chemistry, Haematology, and Urinalysis

Clinical chemistry and haematology parameters will be presented as the vital signs parameters. Urinalysis parameters will be summarised by dose group and visit.

#### 9.7.3.3 ECG

ECGs will be categorised as “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant” (as judged by the investigator) and summarised by treatment.

#### 9.7.3.4 Adverse Events

AEs will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). All data will be listed by subject. Only treatment emergent AEs will be presented in summary tables. Separate data listing will be provided for AEs that are classified as pre-treatment or post-treatment AEs.

#### 9.7.3.4.1 Overview of Treatment Emergent Adverse Events

A treatment emergent AEs summary table will be presented including for each treatment the number of subjects reporting an AE, the percentage of subjects with an AE, and the number of events reported, for the following categories:

- All AEs
- Severe adverse events
- Serious AEs
- Adverse drug reactions
- AEs leading to withdrawal
- Deaths

Adverse drug reactions will be defined as events considered having a reasonable possible relationship to the IMP as judged by the investigator.

#### 9.7.3.4.2 Incidence of Treatment Emergent Adverse Events

Summary tables will be prepared for the incidence of treatment emergent AEs by treatment and MedDRA system organ class (SOC) and preferred term, presenting number of subjects reporting an AE, the percentage of subjects (%) with an AE, and the number of events reported. Summary tables will be prepared for:

- All treatment emergent AEs
- AEs by causality
- AEs by intensity
- ADRs by intensity

Missing values will be treated as missing except for causality, intensity, seriousness, and outcome of an AE, at which occurrence a “worst case” approach will be taken. Thus, if causality is missing the AE will be regarded as related to the IMP, if the intensity is missing the intensity of the AE will be regarded as severe, if seriousness is missing the AE will be regarded as an SAE, and if the outcome is missing and no date of outcome is present the outcome is regarded as “not yet recovered”.

#### 9.7.3.4.3 Serious Adverse Events, Deaths, and other Significant Adverse Events

Separate listings will be provided for SAEs, deaths, and other significant adverse events, if any.

### 9.7.3.5 Injection Site Reactions

Injection site reactions will be summarised by dose group with the number and percentage of subjects experiencing none, mild, moderate, or severe grade of redness, pain, itching, swelling, and bruising immediately after injection, 30 minutes after injection, 24 hours after injection, or at any of these time points.

#### 9.7.3.6 Anti-FSH Antibodies

The proportion of subjects with anti-FSH antibodies as well as the proportion of subjects with anti-FSH antibodies with neutralising capacity will be tabulated for each dose group in total and for each time point.

#### 9.7.3.7 Physical Examination

Physical examination at the screening and the follow-up visits will be listed by subject.

#### 9.7.3.8 Gynaecological Examination, Cytology, and Transvaginal Ultrasound

Results of gynaecological examination, cytology, and transvaginal ultrasound at the screening and the follow-up visit, including changes from baseline, will be listed by subject. Observations categorised as “abnormal” will be flagged.

# 10 DATA HANDLING

## 10.1 Source Data and Records

### 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

Any trial-specific source data and the primary source location of the same will be described in the source data agreement and in the monitoring manual produced for this trial.

## 10.2 Electronic Case Report Form

An electronic CRF (e-CRF) system will be used for data collection. The system is fully validated and access at all levels to the system is granted/revoked following Ferring and vendor procedures, in accordance with regulatory requirements and system requirements.

After the trial database is declared clean and is released to the statistician, a final copy of the database will be stored at Ferring. The investigator will also receive a copy of the site's final and locked data, including audit trail, electronic signature, queries, and management reports, as write-protected PDF-files. The PDF-files will be stored in an electronic format and will be provided to the investigator before access to the e-CRF is revoked. The investigator will approve/authorise the e-CRF entries for each subject with an electronic signature which equals a handwritten signature. The signer must log in with his or her username and password and then re-enter this password on the page(s) requiring a signature. Trial data will be entered into the system in a timely manner, i.e. within 2 working days.

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

## 10.3 Data Management

All data management activities will be specified in a data management plan prepared under the responsibility of Global Biometrics, Ferring Pharmaceuticals. 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. A trial database will be created according to the data management standard operating procedures and data validation programmes will be developed to check for data completion and validity.

Data entry will be performed in accordance with standard operating procedures. For medical coding of AEs, medical history and concomitant medication the most recent versions of MedDRA and WHO Drug will be used. When all data have been processed, queries resolved, medical coding completed and any issues from review of protocol violations and data listings resolved, the database will be locked and any further update will be denied. A final quality assurance audit of the locked database will take place prior to transfer of the final database structured according to Ferring's data transfer specifications.

## 10.4 Provision of Additional Information

On request, the investigator will provide Ferring with additional data relating to the trial, or copies of relevant source records, duly anonymised and protected in accordance with applicable requirements.

# 11 MONITORING PROCEDURES

## 11.1 Periodic Monitoring

Monitoring of the clinical trial will occur both by on-site visits as well as by central (i.e. remote or in-house) review of e-CRF forms and the data management reports.

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Conference of Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of e-CRF entries compared to source data, verification of drug accountability and compliance to safety reporting instructions. The investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The investigator will co-operate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits. A monitoring visit will take place in connection with the first dosing day to ensure that subjects are correctly included and procedures are correctly understood.

## 11.2 Audit and Inspection

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

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

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

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

## 11.3 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the e-CRF or any other documents submitted to Ferring, the subjects will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to Ferring, e.g. the confidential subject identification code and the signed Informed Consent 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 prior to its implementation. Amendments may be submitted for consideration to the approving IEC/IRB and regulatory authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial subjects may be implemented prior to IEC/IRB approval/favourable opinion.

## 12.2 Deviations from the Protocol

If deviations from the protocol occur, the investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented, either as answer to a query in the e-CRF, in a protocol deviation report or a combination of both. A log of protocol deviation reports will be maintained by Ferring. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and in the Trial Master File.

## 12.3 Premature Trial Termination

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

# 13 REPORTING AND PUBLICATION

## 13.1 Clinical Trial Report

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

## 13.2 Confidentiality and Ownership of Trial Data

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

## 13.3 Publication 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 offered authorship and Ferring.

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

### 13.3.2 Public Disclosure Policy

It is the responsibility of Ferring to register the trial in an appropriate registry, i.e. at www.cde.org.cn, which is designated by the China Food and Drug Administration (CFDA).

# 14 ETHICAL AND REGULATORY ASPECTS

## 14.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

An IEC/IRB will review the protocol and any amendments and advertisements used for recruitment. The IEC/IRB will review the Subject Information Sheet and the Informed Consent Form, their updates (if any), and any written materials given to the subjects. The IEC/IRB, to which the protocol has been submitted, and the name of the committee chairman will be denoted in the clinical trial report.

## 14.2 Regulatory Authority Authorisation / Approval / Notification

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

## 14.3 End-of-Trial Notification

End-of-trial notification will be reported according to local regulations. In addition, a summary of the clinical trial report, e.g. the synopsis, will be provided when available and within one year of the trial completion (last subject last visit).

## 14.4 Ethical Conduct of the Trial

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

## 14.5 Subject Information and Consent

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

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

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

## 14.6 Subject Participation Card

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

- That she is participating in a clinical trial

- That she is treated with FE 999049
- The name and phone number of the investigator
- Name and address of Ferring (if required by local regulations)

The subject will be asked to return the Subject Information Card at the last trial visit, if applicable.

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

### 14.7 Compliance Reference Documents

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

# 15 LIABILITIES AND INSURANCE

## 15.1 ICH-GCP Responsibilities

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

## 15.2 Liabilities and Insurance

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

# 16 ARCHIVING

## 16.1 Investigator File

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

The investigator is responsible for the completion and maintenance of the confidential subject identification code which provides the sole link between named subject source records and anonymous e-CRF data for Ferring. The investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Form for at least 15 years after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the investigator and Ferring. Should the investigator elect to assign the trial documents to another party, or move them to another location, the 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 FE 999049 CS01. A randomized, double-blind, placebo controlled, sequential dose escalation trial investigating the safety, tolerability and pharmacokinetics of FE 999049 given as single subcutaneous doses in gonadotrophin down-regulated healthy women. Ferring Pharmaceuticals A/S Report, 12 Feb 2010.

2 FE 999049 CS03. A randomised, double-blind, placebo controlled, sequential dose escalation trial investigating the safety, tolerability and pharmacokinetics of FE 999049 given as single subcutaneous doses in gonadotrophin down-regulated healthy Japanese and Caucasian women. Ferring Pharmaceuticals A/S Report, 23 May 2011.

3 FE 999049 000020. An open-label, randomised, parallel group trial investigating the absolute bioavailability and other pharmacokinetic parameters of FE 999049 and GONAL-F administered as single subcutaneous and intravenous doses in healthy women. Ferring Pharmaceuticals A/S Report, 14 Feb 2013.

4 FE 999049 CS02. A randomized, double-blind, active control, multiple dose study investigating the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity of FE 999049 in comparison to GONAL-F in gonadotrophin down-regulated healthy women. Ferring Pharmaceuticals A/S Report, 31 Mar 2011.

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