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PHARMACEUTICALS

Statistical Analysis Plan

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
NCT number: NCT04150861
Sponsor trial code: 000152
Date: 15 Jan 2020

STATISTICAL ANALYSIS PLAN

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

000152

Investigational 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

Author: [redacted]

Date of issue: 15JAN2020

Version: 1.0

Change log

Version No.	Effective Date	Reason for the Change / Revision	Supersedes
1.0	15JAN2020	First version	None

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1 Introduction

This document describes the planned statistical analyses for trial 000152 and is based on the final protocol version 1.0 dated 20SEP2018. No changes to the analyses described in the trial protocol are introduced, but additional details and descriptions have been added.

1.1 Definitions/ Abbreviations

1.1.1 Definition of Terms

Terms	Definitions
Prior medication	Medication taken prior to treatment (i.e. the stop date is before the first IMP administration)
Concomitant medication	Medication that is not stopped before the first IMP administration, or is started between IMP administration and the follow-up visit (visit 13)
Post-treatment medication	Medication with start date after the follow-up visit (visit 13)
Pre-treatment Adverse Event	An Adverse Event with start time after signing of informed consent and before administration of IMP
Treatment Emergent Adverse Event	An Adverse Event that has start time or worsens in intensity after administration of IMP until the follow-up visit (visit 13)
Post-treatment Adverse Event	An Adverse Event that has start time after the follow-up visit (visit 13)
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
λ_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

1.1.2 Abbreviations

Abbreviations	Meaning of abbreviations in document
AE	Adverse Event
ADR	Adverse Drug Reaction
ATC	Anatomic Therapeutic Chemical
CV	Coefficient of Variation
ECG	Electrocardiogram
FAS	Full Analysis Set
HLGT	High Level Group Term
HLT	High Level Term
IMP	Investigational Medicinal Product

LLQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NIMP	Non-investigational Medicinal Product
PK	Pharmacokinetic
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event

1.2 Presentation of results

1.2.1 Presentation of descriptive results

Categorical data will be summarised using frequency (n) and relative frequency as percentage (i.e. n/N*100).

Continuous data will be summarised using the number of subjects (N), mean and standard deviation (SD), median and range (minimum to maximum). For PK parameters the descriptive statistics will additionally include the geometric mean and the CV. For $t_{½}$, the harmonic mean will be included in addition to the geometric mean. For t_{max} the geometric mean and the CV will be omitted.

1.2.2 Presentation of inferential results

Inferential results will be presented using point estimates, two-sided 95% confidence intervals, and two-sided p-values.

1.2.3 Subject data listings by domain

All subject data will be presented in listings organised in accordance with the ICH E3 guideline.

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

3 Trial design

3.1 General Design Considerations

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

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.

3.1.1 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.

3.1.2 Visits

The trial comprises 14 visits. Visit 1 is a screening visit and visits 2-5 belong to the run-in period. Visit 5 is the end of the run-in period and the start of the treatment period. It starts the day before IMP administration and ends two days after IMP administration. During this time the subjects are residential at the clinic. At visits 6-12 the subjects come to the clinic in the morning for PK serum sampling. Visit 13 is a follow-up visit that takes place the day after the last PK sample was taken (10 days after IMP administration). This visit is regarded as the end of the treatment period. Visit 14 takes place 27 days after IMP administration and has the purpose of collecting blood samples for assessment of the presence of anti-FSH antibodies. The sequence and timing of trial events are shown in Figure 1.

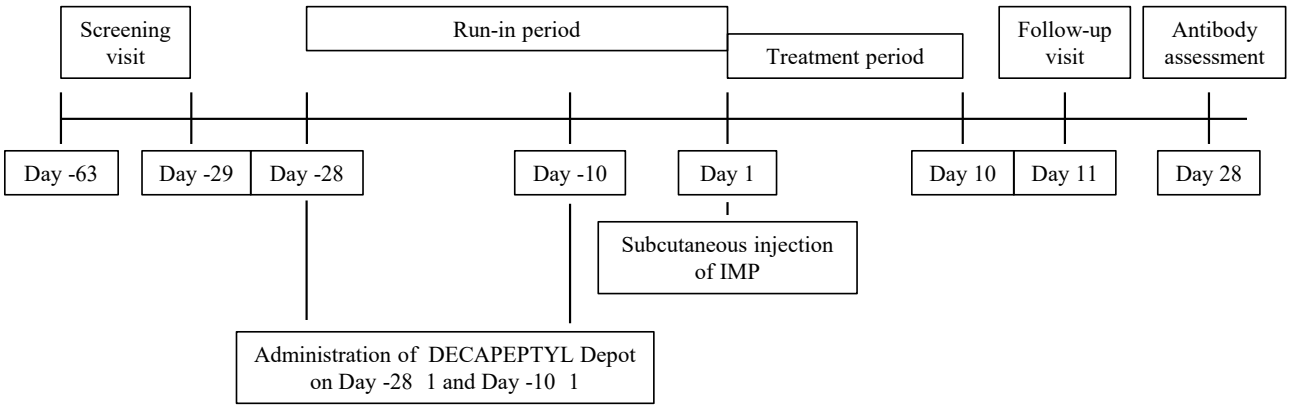

Figure 1 Sequence and timing of trial events

4 Protocol Violations

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 based on a review of the data before declaration of 'clean file' and lock of database.

5 Analysis sets

5.1 Full Analysis Set

The full analysis set (FAS) includes 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). Subjects will be analysed according to the actual treatment received.

5.2 Per Protocol Analysis Set

The per protocol (PP) analysis set includes data from all dosed subjects except data excluded because of major protocol violations as discussed in Section 4. The PP analysis set will be used for presentation of PK data. Subjects will be analysed according to the actual treatment received.

5.3 Safety Analysis Set

The safety analysis set includes data from all dosed subjects and will be used for safety analysis. Subjects will be analysed according to the actual treatment received. The safety analysis set will be identical to the FAS.

6 Trial population

6.1 Demographics and Other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics (e.g. FSH for eligibility determination) will be presented by dose group and in total.

6.2 Medical History

Medical history recorded at the screening visit will be coded using MedDRA and summarised by dose group and in total. The version of MedDRA will be documented.

6.3 Prior and Concomitant medication

Prior and concomitant medication will be summarised by ATC classification (1st and 2nd level). Medications will be tabulated separately for:

- Prior medication; i.e. medication taken exclusively prior to treatment (i.e. the stop date is before the first IMP administration)

- Concomitant medication; i.e. medication that is not stopped before the first IMP administration or is started between IMP administration and the follow-up visit (visit 13). If the timing of the dose of a concomitant medication cannot be established in relation to the administration of IMP, it will be considered as concomitant medication.

- Post-treatment medication; i.e. medication with start date after the follow-up visit (visit 13).

7 Subject Disposition

All post randomisation discontinuations will be summarised by time of and reason for discontinuation. The number of subjects screened but not found eligible will be stated in the trial report, and the reason for screening failure will be summarised.

8 Exposure and Treatment Compliance

Times for administration of NIMP and IMP will be listed. Potential non-compliances with NIMP or IMP administration will be listed.

9 Pharmacokinetics

9.1 General considerations

All individual concentration data (both baseline adjusted and unadjusted) and PK parameters will be listed by treatment and summarised by treatment with descriptive statistics. Individual and mean serum concentration (both baseline adjusted and unadjusted) vs. time curves will be presented for each treatment both on linear and logarithmic concentration axes.

For serum concentrations the descriptive statistics will include number of subjects, arithmetic mean, standard deviation, median, minimal value and maximal value. For PK parameters the descriptive statistics will additionally include the geometric mean and the between-subject CV (i.e. the coefficient of variation based on the total variability, calculated as $100 \cdot \sqrt{e^{s^2} - 1}$, where s is the standard deviation calculated for the log-transformed data).

9.1.1 Pharmacokinetic Endpoints

The calculation of PK parameters 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 three values obtained prior to the administration of the IMP (-1h, -30 min, 0 min). Baseline corrected values below LLQ will be set to zero. 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 estimation of λ_z. Values below LLQ will be represented as LLQ/2 in the plots and in descriptive statistics.

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: AUC, AUC_t, % Extrap AUC, C_{max}, t_{max}, λ_z, $t_{½}$, CL/F, and V_z/F.

Selection of data points for calculation of $t_{½}$ via λ_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 λ_z.
- The time range of samples used to estimate λ_z should preferably exceed the derived terminal half-life $t_{½}$ (= ln 2/λ_z).
- All the samples used to calculate λ_z should ideally fall in the log-linear terminal phase.
- At least three samples above LLQ obtained during the log-linear terminal phase will if possible be included in the calculation of the λ_z.

- The final selection of samples for calculation of λ_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 summarised by treatment (i.e. dose group) using descriptive statistics.

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

10 Safety

10.1 Vital Signs

Vital signs (blood pressure, heart rate, and body temperature) will be presented by time and treatment. Values at screening (visit 1), pre-administration (visit 5, day -1), post-administration (visit 5: 12, 24 and 48h post-administration), changes from pre-administration to 12, 24 and 48h post-administration, and at follow-up (visit 13) will be summarised for each variable by treatment.

Individual and mean values for the six measurements will be plotted for all variables.

Changes relative to normal ranges will be presented in shift tables with total number of subjects, and number and percent of subjects who experienced a shift from pre-administration (visit 5, day -1), to post-administration (visit 5: 12, 24 and 48h post-administration). The following categories are defined for these shift tables:

- Low: Values which are below the lower reference range limit;
- Normal: Values which are within the lower and upper reference range;
- High: Values which are above the upper reference range limit.

The reference limits for vital signs will be 90-180 mmHg for systolic blood pressure, 50-105 mmHg for diastolic blood pressure, 50-120 bpm for pulse, and <38.3°C for body temperature.

10.2 Clinical Chemistry, Haematology, and Urinalysis

Clinical chemistry, haematology and urinalysis parameters will be presented by time and treatment. Values at screening (visit 1), pre-administration (visit 5, day -1), post-administration (visit 5, day 3), the change from pre- to post-administration, and follow-up (visit 13) will be summarised for each laboratory variable by treatment.

Individual and mean values for the four measurements will be plotted for all numerical lab variables.

Changes relative to normal ranges will be presented in shift tables with total number of subjects, and number and percent of subjects who experienced a shift from pre-administration (visit 5, day -1), to post-administration (visit 5, day 3). The following categories are defined for these shift tables:

- Low: Values which are below the lower reference range limit;
- Normal: Values which are within the lower and upper reference range;
- High: Values which are above the upper reference range limit.
- Absent: No value for measured variable (for urinalysis)
- Present: Any value obtained for measured variable (for urinalysis)

The reference range limits will be the ones used by the analysing lab.

10.3 ECG

12-lead ECGs are categorised as “normal”, “abnormal, not clinically significant” or “abnormal clinically significant”. Data will be summarised by treatment. Shift tables will be presented for changes from pre-administration (visit 5, day -1) to 12, 24 and 48h post-administration (visit 5, day 1, 2, and 3).

10.4 Adverse Events

AEs will be coded according to the latest version of the MedDRA. All data will be listed by subject. For treatment emergent AEs, the listings will include the number of days from administration of IMP until the start of the AE. Only treatment emergent AEs (TEAEs) will be presented in summary tables. All summary tables will include columns for each treatment and a total column. Separate data listing will be provided for AEs that are defined as pre-treatment or post-treatment. The following definitions will be used:

- A pre-treatment Adverse Event is an Adverse Event with start time after signing of informed consent and before administration of IMP
- A Treatment Emergent Adverse Event (TEAE) is an Adverse Event that has start time or worsens in intensity after administration of IMP and until the follow-up visit (visit 13)
- A post-treatment Adverse Event is an Adverse Event that has start time after the follow-up visit (visit 13)

If the start date of an AE is completely or partially missing, the AE will be considered treatment emergent unless it can be excluded that it was treatment emergent based on the incomplete date.

10.4.1 Overview of Treatment Emergent Adverse Events

The summary table for treatment emergent adverse events will include the number of subjects reporting an AE, the percentage of subjects (%) with an AE and the number of events reported, for each treatment and in total, for the following categories:

- All TEAEs
- Deaths
- Serious TEAEs
- Non-serious TEAEs
- Severe TEAEs
- Moderate TEAEs
- Mild TEAEs
- Adverse drug reactions (ADRs, i.e. TEAEs with reasonable possible causal relationship to IMP)
- AEs leading to withdrawal
- Other significant AEs

10.4.2 Incidence of Treatment Emergent Adverse Events

Summary tables will be prepared for the incidence of treatment emergent adverse events per treatment and in total by MedDRA system organ class (SOC) and preferred term (PT), 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 TEAEs
- SAEs
- TEAEs by causality (reasonable possibility/no reasonable possibility)
- TEAEs by intensity (mild/moderate/severe)
- ADRs by intensity

Supporting data listings will be provided for:

- All adverse events
- Serious adverse events
- ADRs
- Adverse events leading to death
- Adverse events leading to withdrawal
- Pre-treatment adverse events
- Post-treatment adverse events

Missing values will be treated as missing except for causality, intensity, and seriousness 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”.

10.4.3 Serious Adverse Events, Deaths and Other Significant Adverse Events

Separate listings will be provided for SAEs, deaths and other significant AEs if any such event occurs.

Written narratives will be issued for all serious AEs (including deaths) and AEs leading to withdrawal.

10.5 Injection Site Reactions

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

10.6 Malfunctions of the Administration Device

The frequency of malfunctions of the administration device will be tabulated and the details of each malfunction will be listed.

10.7 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.

10.8 Physical Examination

Physical examination at the screening (visit 1) and the follow-up visit (visit 13) will be listed by subject. Shift tables will be presented for changes from screening to follow-up.

10.9 Gynaecological Examination, Cytology, and Transvaginal Ultrasound

Results of gynaecological examination, cytology, and transvaginal ultrasound at the screening (visit 1), pre-administration (visit 5), and the follow-up visit (visit 13) will be listed by subject. Shift tables will be presented for changes from screening to follow-up.

11 Interim analyses

There will be no interim analyses.

12 Deviations from the protocol

No changes to the analyses described in the trial protocol are introduced, but additional details and descriptions have been added.