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Official Title: A randomized, open-label, parallel-group, active-control study to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of three doses of Leuprolide Oral Tablets (Ovarest™) in comparison to an intramuscular dose of leuprolide acetate (Lupron Depot® 3.75 mg) in healthy female volunteers

NCT number: NCT02807363

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

Statistical Analysis Plan

A RANDOMIZED, OPEN-LABEL, PARALLEL-GROUP, ACTIVE-CONTROL STUDY TO EVALUATE THE PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD) PROFILES OF THREE DOSES OF LEUPROLIDE ORAL TABLETS (OVAREST™) IN COMPARISON TO AN INTRAMUSCULAR DOSE OF LEUPROLIDE ACETATE (LUPRON DEPOT® 3.75 MG) IN HEALTHY FEMALE VOLUNTEERS

Sponsor Protocol No. LOPDT-ENDO-01
inVentiv Health Clinique Inc. Project No. 160218

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Sponsor Protocol No.: LOPDT-ENDO-01

inVentiv Project No.: 160218

Study Title: A Randomized, Open-label, Parallel-group, Active-control Study to Evaluate the Pharmacokinetic (PK) and Pharmacodynamic (PD) Profiles of Three Doses of Leuprolide Oral Tablets (Ovarest™) in Comparison to an Intramuscular Dose of Leuprolide Acetate (Lupron Depot® 3.75 mg) in Healthy Female Volunteers.

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LIST OF ABBREVIATIONS

AE	Adverse event
AUC_{0-24}	Area under the drug concentration versus time curve from 0 hour to 24 hours
AUC_{0-t}	Area under the drug concentration versus time curve from 0 hour to t (time of the last observed non-zero concentration)
AUC_{0-inf}	Area under the drug concentration versus time curve from 0 hour to infinity
bid	Twice daily
BLQ	Below the lower limit of quantitation
BMI	Body mass index
C_{max}	Maximum concentration level
C_{ss_oral}	Steady state concentration level calculated for oral tablets
C_{ss_im}	Steady state concentration level calculated for IM injection
CSR	Clinical study report
C_t	The last observed non-zero concentration
CV	Coefficient of variation (equivalent to C.V.)
df	Degree of freedom
E_2	Estradiol
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
g	Gram
ICF	Informed consent form
IM	Intramuscular
Inc.	Incorporated
IV	Intravenous
K_{el}	The apparent elimination rate constant,
$K_{el\ Lower}$	The time point where $_{Kel}$ calculation begins
$K_{el\ Upper}$	The sampling time of the last non-zero concentration used to estimate the K_{el}
LH	Luteinizing Hormone
LMP	Last menstrual period
ln	Natural logarithm
Max	Maximum (equivalent to max.)
MedDRA®	Medical Dictionary for Regulatory Activities

mg	Milligram
Min	Minimum (equivalent to min.)
mL	Milliliter
n	Number of observations
No.	Number
PD	Pharmacodynamic; Postdosing
pH	Negative logarithm of the activity of H+
PK	Pharmacokinetic
PT	MedDRA® Preferred Term
qd	Once a day
QRS	The QRS complex is a structure on the ECG that corresponds to the depolarization of the ventricles
QT	Time from electrocardiogram Q wave to the end of the T wave corresponding to electrical systole
QTcB	QT corrected with Bazett formula
QTcF	QT corrected with Fridericia formula
RR	Duration of ventricular cardiac cycle
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical analysis system
SD	Standard deviation
SOC	MedDRA® System Organ Class
SOP	Standard Operating Procedure
$T_{1/2\ el}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration level
vs	Versus
WHO DD	World Health Organization Drug Dictionary

1. Introduction

This statistical analysis plan (SAP) is intended to give a detailed description of the summaries and the analyses that will be generated for the present study by inVentiv. Analyses specified in this plan are based on (and/or consistent with) Enteris BioPharma study protocol No. LOPDT-ENDO-01 Amendment 03 dated February 01, 2018 (inVentiv Project No. 160218). Safety, tolerability, pharmacokinetic (PK), and pharmacodynamics (PD) analyses will all be described.

The plan may be revised due to unforeseen circumstances and any changes or modifications made after the plan has been finalized will be documented. If additional or revised analyses are required to supplement the planned analyses described in the SAP, the changes and justification for the changes will be outlined in the clinical study report (CSR). No changes will be made without prior approval of the study sponsor. No formal justifications are required for changes to the SAP which do not affect the statistical analysis methods, definitions, or rules defined in this document.

When applicable, all analyses and related processes will be conducted according to inVentiv's Standard Operating Procedures (SOPs). Protocol deviations occurring during the study will be listed.

2. Study Objectives

The objectives are to determine the safety, PK profile, and PD effects of the three doses of Ovarest™ in healthy female volunteers in comparison to a marketed dose of leuprolide acetate administered intramuscular (IM) (Lupron Depot® 3.75 mg). Note: For the third Ovarest™ dose (Treatment "D"), a complete PK profile will not be evaluated.

This trial will serve as a bridging PK/PD study between the 4 mg Leuprolide Oral Tablet administered over 28 days as daily (qd) or twice daily (bid) regimens and the 10 mg Leuprolide Oral Tablet administered over 28 days as a bid regimen and a marketed IM injection of leuprolide acetate (Lupron Depot® 3.75 mg) designed for one month of therapy. This trial will also be a bridging study to historical PK/PD data for Lupron Depot® 3.75 mg and Lupron Depot® 11.25 mg (3-month) formulations.

The most important objective of this study is to provide adequate PD assessments to support development of the Leuprolide Oral Tablet with E2 suppression similar to those reported for Lupron Depot® and other E2-inhibiting hormonal therapies. Another reason for this trial is to describe the PK/PD dose-proportionality of the 4 mg and 10 mg Leuprolide Oral Tablet administered as qd and bid regimens.

2.1 Primary Objectives

- To determine the safety and to provide comparative evaluation of the PK and PD profiles of the 4 mg Leuprolide Oral Tablets in healthy, premenopausal female volunteers following qd and bid administration and the 10 mg Leuprolide Oral Tablets following bid administration in healthy, premenopausal female volunteers over 28 days vs a marketed formulation of leuprolide acetate administered IM for one month of therapy.
- To evaluate the PK properties of Leuprolide Oral Tablets after multiple dosing (i.e., 28 days of dosing)
- To assess the PK/PD dose-proportionality of the Leuprolide Oral Tablets administered as 4 mg qd, 4 mg bid and 10 mg bid dosing regimens
- To evaluate the PK and/or PD properties of the Leuprolide Oral Tablets (eg, E2 suppression rates) vs other hormonal therapies for the treatment of reproductive disorders, including endometriosis

2.2 Secondary Objectives

- To evaluate safety and tolerability of the long-term administration of leuprolide in healthy female volunteers.

3. Study Design

3.1 General Design

This study will evaluate the safety, PK profile and PD effects of the three Ovarest™ dosing regimens: Leuprolide Oral Tablet, 4 mg, administered qd for 28 consecutive days (Treatment "A"), Leuprolide Oral Tablet, 4 mg, administered bid for 28 consecutive days (Treatment "B"), and Leuprolide Oral Tablet, 10 mg, administered bid for 28 consecutive days (Treatment "D"), in comparison to leuprolide acetate administered IM, Lupron Depot® 3.75 mg (Treatment "C").

This study was originally designed as a randomized, open-label, parallel-group active-control trial. Up to thirty-two (32) subjects (12 subjects in each Ovarest™ treatment group and 8 subjects in the Lupron Depot group) were planned to be randomly assigned to the study drug in a A:B:C ratio of 3:3:2. The randomization schedule was to be balanced by using permuted blocks.

Twenty-three subjects were initially enrolled in this study (9 subjects in each of Ovarest™ treatment groups and 5 subjects in the Lupron Depot group). At the time of the current protocol Amendment, all initially enrolled subjects had completed the study, except for one subject who was withdrawn on post–dose Day 1 (due to vomiting). After interim PK and safety evaluations, it was decided not to enroll any new subjects in Treatment Groups "A", "B" and "C". Instead, up

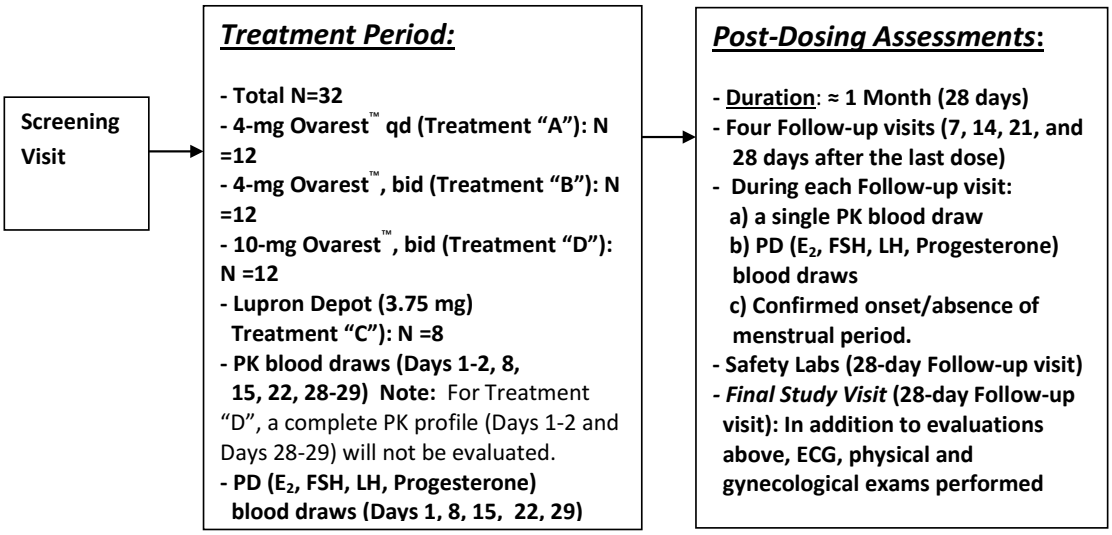
to twelve (12) subjects will be enrolled in a new Treatment Group "D" (Leuprolide Oral Tablet, Ovarest™, 10 mg, administered twice daily (bid), 12 hours apart for 28 consecutive days).

Subjects assigned to the third Ovarest™ dose (Treatment "D") had study drug administered in the same fashion as Treatment "B". Assessments of the PD profile of treatment "D" had to mimic evaluations of Treatment "B". However, unlike other Ovarest™ groups, Treatment "D" does not have comprehensive assessments of the PK profile. The subjects that have already participated in this study could be invited to receive Treatment "D" if they were eligible per the study inclusion and exclusion criteria.

The study consists of two major periods: approximately one month of dosing (either 28 consecutive days of daily oral dosing, or a single IM injection on Treatment Day 1) and approximately 1 month (28 days) of post-dosing PK/PD evaluations. The total study duration from screening to the final study visit will be up to approximately 3.5 months.

Study design schematic is displayed in Figure 1 below.

Figure 1 Study Design Schematic



3.2 Study Procedures

The overall schedule of procedures and assessments is provided in the protocol.

3.3 Treatment Description

The treatments administered in this study are presented in Table 3-1.

Table 3-1 Treatment Description

Treatment	Description
A	Leuprolide Oral Tablet, Ovarest™ 4 mg, administered qd for 28 consecutive days
B	Leuprolide Oral Tablet, Ovarest™ 4 mg, administered bid for 28 consecutive days
C	Leuprolide Acetate IM, Lupron Depot® 3.75 mg, administered for one month of therapy
D	Leuprolide Oral Tablet, Ovarest™ 10 mg, administered bid for 28 consecutive days

Subjects meeting the eligibility criteria were to be initially randomized to receive one of the two doses of Ovarest™ for 28 days or a monthly IM dose of Lupron Depot®. After the protocol amendment, subjects meeting the eligibility criteria were to be enrolled in Treatment "D" The initially randomized subjects had to start dosing (Treatment Day 1) on either days 1-4 or days 18-28 of their menstrual cycle. Subjects enrolled to the third oral dose (Treatment "D") had to start dosing 5-9 days before the anticipated start of their next menstrual cycle, based on their self-reported menstrual cycle length and the day the current menstrual cycle began.

3.4 Subject Withdrawal and Replacement

Every subject has the right to refuse further participation in the study at any time and without providing reasons for this decision and without prejudice to further treatment. A subject's participation is to be terminated immediately upon their request.

The subject may be withdrawn from the study at any time at the discretion of the Investigator. Should the subject, during the course of the study, develop conditions that would prevent the subject from being dosed as per Investigator's judgment (e.g., absolute contraindications, prohibited concomitant medications) or would be considered as potentially dangerous AEs, they must be withdrawn immediately.

A positive alcohol breath test, urine drug screen, or cotinine test will also be grounds for subject withdrawal. If pregnancy occurs or is suspected during study drug treatment, the subject must be discontinued immediately.

The termination of an individual's participation should be considered in case of a serious adverse event (SAE) or considerable worsening of the subject's clinical conditions.

At the discretion of Enteris BioPharma, the entire study or part of the study may be canceled for medical or other reasons. In case of premature termination or suspension of the study or part of the study, the Sponsor will promptly inform the Investigator/institutions, regulatory authorities and IRBs of the termination or suspension and the reason for the measure.

In addition, Enteris BioPharma retains the right to end the study at any time if the study cannot be carried out as agreed upon in the protocol.

The reasons for discontinuation include:

- AE
- Death
- Pregnancy
- Protocol violation
- Lost to follow-up
- Study terminated by Sponsor
- Noncompliance with study drug (to be handled on a case-by-case basis)
- Withdrawal by subject decision (appropriate details must be provided on the CRF)
- Physician decision (appropriate details must be provided on the CRF)
- Other

Subjects discontinued early after having received at least one dose of study drug will not be replaced. Study drug assigned to the withdrawn subject may not be given to another subject.

Data generated from screening failures (subjects not admitted to the study after the screening phase and not assigned a randomization number) may be listed according to main reason for not being admitted into the treatment phase.

4. Changes from the Protocol

Any changes in planned analyses compared to the protocol will be noted in this section.

Primary statistical analyses of the PD endpoints will utilize measurements for Treatment Day 22 and Treatment Day 29 (not Treatment Day 28 as noted in the protocol). This change will ensure consistent methodology across all treatment groups some of which (Treatments "C" and "D") did not have scheduled PD assessments on Treatment Day 28.

Suppression of E_2 ≤50 pg/mL, ≤60 pg/mL, and ≤70 pg/mL may also be assessed, if considered necessary.

The determination of the suppression of E_2 or other PD endpoints across evaluation intervals was clarified.

An additional analysis for the adverse drug reactions (ADR) (excluding the PT "Menstrual Disorder)" was described.

5. Primary and Secondary Parameters

Primary Parameters

- Comparative evaluation of safety and tolerability variables, by treatments (refer to Section 9).
- PK parameters as C_{max}, T_{max}, AUC_{0-24}, AUC_{0-t}, AUC_{0-inf}, C_{ss_oral}, C_{ss_im}, K_{el}, $K_{el\ Lower}$, $K_{el\ Upper}$, and $T_{1/2el}$ for leuprolide (refer to Section 10).
- PD parameters derived from LH, FSH, E_2, and Progesterone levels (refer to Section 11).

Secondary Parameters

- Safety and tolerability variables for long-term administration of leuprolide in healthy female volunteers (refer to Section 9)

6. Analysis Populations

6.1 Safety Population

All subjects who received at least one dose of study medication will be included in the safety population. Subjects will be analyzed based on the actual treatment received.

In addition to the overall safety population, separate safety populations will be identified for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period).

The subjects in Treatment "D" that have already participated in this study (have received Treatments "A", "B", or "C"), will be considered in all listings and summaries as completely new study participants with subject identifiers for the study (SUBJID) unrelated to their previous numbers. Unless otherwise noted, these subjects will not be flagged as previous study participants in any statistical summaries and/or individual data listings.

6.2 Pharmacokinetic Populations

6.2.1 Primary PK Population

The primary PK population is defined as the group of randomized subjects who completed 28 days of dosing without major protocol violations and for whom the PK profile can be adequately

characterized. For Treatment "D", primary PK population is defined as a population of subjects who completed 28 days of dosing without major protocol violations.

6.2.2 Supportive PK Population

The supporting PK population is defined as the group of randomized subjects who received at least one dose of study medication and provided any PK data.

Here are some aspects to be considered (but not to be limited to) when determining subject eligibility for PK population: inclusion and exclusion criteria, acceptable times for visit dates and measurements, compliance with treatment, the nature and quality of the data, withdrawal and any protocol deviation. The final responsibility of deciding which subjects are to be included or excluded lies with the principal investigator and the sponsor.

In addition to the overall PK population, separate PK populations will be identified for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period).

6.3 Pharmacodynamic Populations

6.3.1 Primary PD Population

The primary PD population is defined as the group of randomized subjects who completed 28 days of dosing without major protocol violation.

6.3.2 Supportive PD Population

The supporting PD population is defined as the group of randomized subjects who received at least one dose of study medication and provided any PD data.

In addition to the overall PD population, separate PD populations will be identified for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period).

7. Interim Analyses

No formal interim analysis was planned.

However, there was a preliminary evaluation of the PK and PD results for administrative purposes. The results of the preliminary evaluations triggered a protocol amendment and an introduction of Treatment "D". See section 3.1 for additional details.

8. Study Population and Exposure

Shells for all summary descriptive statistic tables, figures and listings referred to in this section are displayed in separate mock shells document. The shells may be revised as they are presented

to illustrate the general layout of data to be included in the final report. No inferential analyses are planned. No data imputation methods will be utilized i.e. only observed data will be used.

8.1 Subject Disposition

Subject disposition will be summarized by treatment group (frequency and the percentage of subjects). The reason for discontinuation will be also listed.

The subject disposition summaries will be presented for the entire study and separately for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period).

8.2 Protocol Deviations

The protocol deviations will be listed by subject. The protocol deviation criteria have to be endorsed by the sponsor prior to the database lock.

8.3 Demographics and Baseline Characteristics

The descriptive statistics (mean, median, standard deviation [SD], minimum [Min], maximum [Max], and sample size as n) will be reported for continuous variables (age, body mass index [BMI], height, and weight). Frequency counts and percentages will be tabulated for categorical variables (age group, gender, ethnicity, and race). Results will be presented by treatment group. All demographic and baseline characteristics will be listed by subject.

8.4 Medical History

Medical history records will be listed by subject. The Medical Dictionary for Regulatory Activities (MedDRA®) Version 20.1 will be used to classify all medical history findings by System Organ Class (SOC) and Preferred Term (PT).

8.5 Prior and Concomitant Medications

The use of concomitant medications will be monitored throughout the study. The World Health Organization Drug Dictionary (WHO DD) Version Sep2017, format B will be used to classify all medication reported before and during the study.

The prior and concomitant medication summaries will be presented for the entire study and separately for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period).

Prior and concomitant medications (with a study subperiod noted) will be listed by subject.

8.6 Study Drug Administration

The study drug administration details (including duration of dosing period, compliance with the dosing regimen, etc.) will be summarized by treatment group. The compliance rates will be

evaluated for the Ovarest™ groups only as a percentage of days with the protocol-specified dosing during the scheduled 28-dosing interval.

The study drug administration details (including treatment or dose received, date and time of administration, number of pills administered daily, and compliance with the fasting requirements) will be listed by subject.

9. Safety Analyses

Safety data evaluations will be based on adverse events (AEs), laboratory test results, clinical signs and symptoms from physical and gynecological examinations, electrocardiogram (ECG) and vital signs assessments.

Safety parameters will be summarized by treatment group for the entire study and separately for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period).

Shells for all summary descriptive statistic tables and listing referred to in this section are displayed in the document containing the TFL shells; the shells may be revised as they are presented to illustrate the general layout of data to be included in the final report.

9.1 Physical Examination Findings

Physical examinations and gynecological examinations will be performed at screening, end of dosing period (Post-dosing Day 1) and at the Final Visit and also in case of early discontinuation

Any abnormal findings judged to be clinically significant prior to first dose will be documented as medical history and those after first dose will be captures as an AE (treatment emergent AE; [TEAE). Any physical or gynecological examination findings documented as AEs will be included in the AE summaries (overall summaries and summaries for study subperiods).

9.2 Adverse Events

Treatment-emergent AEs (TEAEs) and non-TEAEs (those occurring prior to administration of study medication or those first occurred prior to study drug administration and did not worsen in frequency or severity) will be listed. TEAEs will be defined as AEs that occur on or after the date and time of study drug administration, or those that first occur pre-dose but worsen in frequency or severity after study drug administration. TEAEs will be captured through the end of the entire study including two study sub-periods (a 28-day dosing cycle and a 28-day post-dosing evaluation period) or which occur within 30 days following the final examination. In addition, TEAEs with a start date and time during a particular study sub-period will be attributed to the corresponding subperiod.

Serious adverse events (SAEs), which occur during this study or within 30 days following the final examination, will also be listed separately and described in the study report.

The incidence of TEAEs will be summarized for entire study and separately for the two study sub-periods (a 28-day dosing cycle and a 28-day post-dosing evaluation period) using the safety populations for any particular study subperiods. The MedDRA® dictionary Version 20.1 will be used to classify all TEAEs reported during the study by SOC and PT.

Incidence of subjects who experienced TEAEs will be presented by treatment group, by SOC, PT, by investigator-assessed causality (relationship to study drug) and severity. Each subject may only contribute once to each of the incidence rates, for a TEAE following a given treatment, regardless of the number of occurrences; the highest severity or highest causality will be presented, as appropriate. In each summary table, SOC will be presented in descending order of overall incidence rate in terms of frequency of subjects and then in frequency of events (alphabetical order will be used in case of equal rates). For each SOC, PT will be presented the same way. Incidence of TEAEs (number of events) will also be presented by treatment, SOC, and PT, by investigator-assessed causality and severity.

The causality of TEAEs will be classified according to the study protocol as Unrelated, Possibly Related, Probably Related, or Definitely Related. The severity of TEAEs will be rated as per the protocol as mild, moderate, or severe.

Adverse drug reactions (ADR) are defined in the ICH Guidance for Industry E2A: clinical safety data management: definitions and standards for expedited reporting as follows: “All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADR).” An ADR can therefore be any TEAE judged related to the medicinal product (causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out).

In accordance with the prescribing information for Lupron Depot and other amenorrhea-inducing drugs, one category of ADR (represented by the PT “Menstrual Disorder”), may be analyzed as both TEAE and a metric of the menstrual bleeding pattern (e.g., a number of bleeding days during the dosing interval).

As an additional ADR analysis, incidence of subjects who experienced ADR will be presented by treatment group, by SOC, and PT, excluding the PT “Menstrual Disorder”.

The incidence of ADRs will be summarized for entire study and separately for the two study sub-periods (a 28-day dosing cycle and a 28-day post-dosing evaluation period) using the safety populations for any particular study subperiods. Each subject may only contribute once to each of the incidence rates, for an ADR following a given treatment, regardless of the number of occurrences. In summary table, SOC will be presented in descending order of overall incidence rate in terms of frequency of subjects and then in frequency of events (alphabetical order will be used in case of equal rates). For each SOC, PT will be presented the same way. Incidence of ADR (number of events) will also be presented by treatment, SOC, and PT.

9.3 Laboratory Parameters

Clinical laboratory (hematology and serum chemistry) results will be obtained at screening, end of dosing period (Post-dosing Day 1) and at the Final Visit and also in case of early discontinuation. Urinalysis results will be obtained only at screening and final visit (or early discontinuation).

Listings of all clinical laboratory results will be provided with the abnormal values flagged with "L" for low and "H" for high for continuous parameters, and “A” for abnormal for categorical parameters.

Descriptive statistics (mean, median, SD, Min, Max, and sample size “n”) for each clinical laboratory test (continuous variables) will be presented for screening and final visit, and by treatment for Post-dosing Day 1 timepoint. Change from screening will also be presented. For categorical variable (urinalysis test), the number of subjects (frequency and percentage) will be tabulated by results (e.g. negative, positive, trace). A summary table of shifts from screening to final visit will be provided. The shift tables will include normal, low, and high values relative to the laboratory reference ranges (or normal-abnormal for categorical variables). Results from repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

Note: all analyses described above will be performed by treatment group for the entire study and separately for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period).

In the analyses for the entire study duration, laboratory results from pre-study screening and final study visits will be used. In the analyses for the 28-day dosing cycle, laboratory results from pre-study screening and end-of-dosing study visits will be used. In the analyses for the 28-day postdosing evaluation period, laboratory results from end-of-dosing and final study visits will be used.

9.4 Vital Signs and Body Weight

Vital signs measurements (temperature, heart rate, respiratory rate, systolic and diastolic blood pressure) and body weight will be performed at screening, Days -1, 1, 2, 8, 15, 22, 27, 28 ; PD Days 1, 7, 14, 21 and 28 (Final Visit)) or Early Discontinuation Visit. Note: No evaluations on Days -1, 2, 27, and 28 will be performed for Treatment “D”.

A listing of all vital signs and body weight results will be provided.

Descriptive statistics (mean, median, SD, Min, Max, and sample size) will be presented for screening and final visit (or early discontinuation visit), and by the associated current treatment for other evaluation timepoints, for each vital sign measurement and body weight.

Note: all analyses described above will be performed by treatment group for the entire study and separately for the two study subperiods (a 28-day dosing cycle and a 28-day postdosing evaluation period).

In the analyses for the entire study duration, vital sign and body weight results from pre-study screening and final study visits will be used. In the analyses for the 28-day dosing cycle, vital sign and body weight results from pre-study screening through end-of-dosing study visits will be used. In the analyses for the 28-day postdosing evaluation period, vital sign and body weight results from end-of-dosing through final study visits will be used.

Change from baseline (or change from screening for the final visit) will also be presented. Baseline will be defined as the last results (scheduled or unscheduled) obtained prior to first study drug administration. Results from post-dose repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

9.5 Electrocardiogram

Twelve-lead ECGs will be performed at screening and final visit (or early discontinuation).

A listing of all ECG results will be provided.

Descriptive statistics (mean, median, SD, Min, Max, and sample size "n") will be presented for each timepoint for each ECG measurement as per data availability. Also, change from screening descriptive statistics for final visit will be presented. Results from repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

10. Pharmacokinetic Analyses

Shells for all summary descriptive statistic tables and listings referred to in this section are displayed in the document containing the TFL shells; the shells may be revised as they are presented to illustrate the general layout of data to be included in the final report.

The primary statistical analyses of PK data will be conducted on the primary PK population. Supportive statistical analyses of PK data will be conducted on the supportive PK population.

10.1 Handling of the BLQ and the No Reportable Concentration Values

All concentration values below the lower limit of quantitation (BLQ) and samples with no reportable value occurring prior to dosing (on Day 1 only) will be replaced by "0". For tabulation, graphical representation and calculation purposes, all samples with no reportable value observed after administration of the first dosing will be set to missing.

10.2 Handling of the Difference between the Scheduled and the Actual Sampling Times

The actual clock time for dosing and the actual clock time for each collection time for the PK samples will be recorded using the electronic data capture. For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times expressed in hours and rounded off to three decimal digits will be presented, except for pre-dose samples occurring prior to dosing, which will always be reported as zero (0.000), regardless of the time difference. A listing of the actual times will be provided for PK samples. However, the scheduled sampling times will be used for calculation of the PK parameters. In the PK section of the report, scheduled sampling times will be presented in concentration tables, mean graphs, and the individual graphs.

10.3 Pharmacokinetic Concentration and Parameters

A total of 55 PK blood samples will be taken from subjects in the oral groups (Treatments "A" and "B") for the evaluation of the leuprolide serum concentrations at Dosing period Day 1 and Day 28 immediately prior to dosing (0 time), and at 0.500, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.0, 12.0, 13.0, 14.0, 15.0, 16.0, 17.0, 18.0, 20.0, and 24.0 hours following oral dosing and also in morning prior to dosing on Days 8, 15, and 22. There will be samples taken in Post-dosing Evaluation Period Day 7, 14, 21 and 28.

A total of 16 PK blood samples will be taken from subjects in the Lupron group (Treatment "C") for the evaluation of the leuprolide serum concentrations at Dosing period Day 1 prior to dosing (0 time), at 0.500, 1.00, 2.00, 6.00, 12.0, 18.0, and 24.0 hours post-dosing, Day 8, 15, 22 and Post-dosing Evaluation Period Day 1, 7, 14, 21 and 28.

Subjects enrolled to the third oral dose (Treatment "D") will have a very few PK samples: just prior to the first study drug administration and immediately prior to the first dose of the day on Treatment Days 8, 15, 22, and in the morning of Day 29. The PK samples will also be taken in Post-dosing Evaluation Period Day 7, 14, 21 and 28.

PK parameters will be calculated using the scheduled sample collection timepoints. For each evaluation period (*i.e.*: Treatment Days 1 and 28 for the oral groups and day 1 for the Lupron Depot group), where applicable, serum concentrations from leuprolide acetate will be used to calculate the following parameters by standard non-compartmental methods: Note: these PK parameters will be calculated for each treatment period for Treatment groups "A", "B" and "C only.

AUC_{0-24}	Area under the drug concentration versus time curve calculated using the linear trapezoidal method from 0 hours to 24 hours. In the case where the 24 hours concentration value is missing, AUC_{0-24} will not be calculated.
AUC_{0-t}	Area under the drug concentration versus time curve calculated using the linear

	trapezoidal method from 0 hours to t, where t is the time of the last available observation (C_t)
$AUC_{0\text{-}inf}$	Area under the drug concentration versus time curve from 0 hours to infinity, $AUC_{0\text{-}inf} = AUC_{0\text{-}t} + C_t/K_{el}$
C_{max}	Maximum concentration level
C_{ss_oral}	Steady state concentration level calculated for oral tablets at the end of the fourth treatment week (Treatment Days 28-29) as the 24-hour AUCs divided by the duration of the dosing interval i.e. 24 hours.
C_{ss_im}	Steady state concentration level calculated for IM injection at the fourth treatment week (a mean of leuprolide levels on Days 22 and 29).
T_{max}	Time to maximum concentration level
$T_{½\ el}$	Terminal half-life calculated as $\ln(2)/ K_{el}$
K_{el}	The apparent elimination rate constant, calculated by linear regression of log concentration vs time during the elimination phase

To derive the PK parameters, the serum concentrations below limit of quantification in early timepoints will be treated as zero and serum levels below limit of quantification appearing in the elimination phase will be omitted from the calculations of K_{el}.

Some PK parameters may not be calculated for all or some subjects, at the discretion of the inVentiv pharmacokineticist, if the concentration data is not deemed to be amenable to evaluation. Explanations for PK parameters that could not be estimated will be provided in the CSR report.

10.4 Statistical Analyses

Individual and mean concentration versus time curves will be presented using linear and semi-log scales for leuprolide acetate. Descriptive statistics (mean, standard deviation, coefficient of variation, median, minimum value, maximum value and geometric mean) of the serum concentrations versus time will be presented. Summaries of the leuprolide concentrations will also be reported for each intermediate (within the 28-day dosing interval) and for each follow-up (post-dosing period) visit.

The summaries will be provided for all PK parameters listed above. The most important PK endpoint for the oral groups is C_{ss_oral}. A related primary endpoint for the Lupron group is C_{ss_im}. No formal statistical between-treatment comparisons are planned.

For Treatment “D” leuprolide concentration levels will be summarized for individual sampling timepoints.

11. Pharmacodynamics Analyses

Shells for all summary descriptive statistic tables and listings referred to in this section are displayed in the document containing the TFL shells; the shells may be revised as they are presented to illustrate the general layout of data to be included in the final report.

The primary statistical analyses of PD data will be conducted on the primary PD population. Supportive statistical analyses of PD data will be conducted on the supportive PD population.

11.1 Pharmacodynamic Concentration and Parameters

A total of 11 PD blood samples for Treatments "A" and "B" and 10 PD blood samples for Treatment "C" will be taken for the determination of LH, FSH, E2, and progesterone levels. Serum concentrations of PD endpoints will be measured at screening and in the morning (in the Ovarest™ groups, just prior to oral dosing) on Dosing period Treatment Days 1, 8, 15, 22 and 28 (except for Treatment "C"), and in the morning of Evaluation Period Days 1 (or Day 29), 7, 14, 21 and 28.

A total of 10 PD blood samples for Treatment "D" will be taken for the determination of LH, FSH, E2, and progesterone levels. Serum concentrations of PD endpoints will be measured at screening and in the morning just prior to oral dosing) on Dosing period Treatment Days 1, 8, 15, 22, and in the morning of Evaluation Period Days 1 (or Day 29), 7, 14, 21 and 28.

The primary PD metric - suppression of E_2 level - will be assessed at each on-treatment (28-day dosing) and 28-day post-dosing evaluation timepoint. Treatment dosing Day 22 and Treatment dosing Day 29 evaluations (separately and combined) will be considered as most important primary evaluations.

For the purposes of the statistical analyses, PD measurements for Day 29 will be considered as the last measurements of the 28-day dosing interval. This Day 29 measurement will NOT be included in the post-dosing PD evaluations. The post-dosing PD evaluations will utilize measurements collected on post-dosing days 7, 14, 21, and 28.

Suppression of E_2 levels across various evaluation intervals (e.g., Days 22-29 of the dosing period, entire 28-day dosing period, and 28-day postdosing period) will be evaluated in two ways:

(1) E_2 level is considered suppressed during the evaluation period if a value below pre-specified threshold was reported **at least once** during that period. For example, if a subject had $E_2 \leq 40$ pg/mL at Day 29 and $E_2 > 40$ pg/mL at Day 22, she will be categorized as a subject with a supressed E_2 level during the 22-29 Day evaluation period;

(2) E_2 level is considered suppressed during the evaluation period if a value below pre-specified threshold was reported **at each timepoint of that period**. For example, if a

subject had E_2 ≤40 pg/mL at Day 29 and E_2 > 40 pg/mL at Day 22, she will not be categorized as a subject with a supressed E_2 level during the 22-29 Day evaluation period; To be considered as a subject with a suppressed E_2 level during that period, E_2 must be ≤40 pg/mL on both Days 22 and 29.

The former definition, (1) will be considered as primary.

Note: For Treatments "A" and "B" additional protocol-specified evaluations will be performed for Days 22 and 28 of the dosing period

Similar approach will be utilized for other PD endpoints (e.g., a suppression of ovulation as evidence by progesterone level – see below).

In addition to a primary E_2 suppression threshold (E_2 ≤40 pg/mL), a suppression of E_2 ≤20 pg/mL, ≤50 pg/mL, ≤60 pg/mL, and ≤70 pg/mL may also be assessed, if considered necessary. .

The suppression of ovulation (as evidenced by progesterone levels <3 ng/mL) will be assessed at each on-treatment (28-day dosing) and 28-day post-dosing evaluation timepoint. Treatment dosing Day 22 and Treatment dosing Day 28 (Day 29 for Treatments "C" and "D") evaluations (separately and combined) will be considered as most important (primary) evaluations.

11.2 Statistical Analyses

Individual and mean concentration of hormonal levels versus nominal time curves will be presented by treatment group for each evaluation timepoint. Descriptive statistics (sample size "n", mean, standard deviation, coefficient of variation, median, minimum value and maximum value) of hormonal levels will be presented for each timepoint.

Summaries of the LH, FSH, E_2, and progesterone levels will be reported for each dosing and post-dosing evaluation timepoint, for the dosing days 22 and 28 (Day 29 for Treatments "C" and "D") (combined: i.e. the maximum among the 2 values) and, optionally, for the entire 28-day dosing period and the entire post-dosing Evaluation Period. Changes from pre-dosing baseline in LH, FSH, E_2 and progesterone levels will also be summarized (sample size "n", mean, standard deviation, median, minimum value and maximum value) at each on-treatment evaluation timepoint. Pre-dosing baseline for all PD metrics is the highest value across two observations: (a) screening measurement and (b) measurement taken just prior to the first dose of the study drug. Similar summaries will be provided for the follow-up visits (postdosing Days 7, 14, 21, and 28). In addition, time to return to pre-study baseline hormonal levels could be estimated.

Summaries of PD metrics may be further stratified by the cycle period (days) of the start of dosing. Categorical variables will be summarized by using frequency counts and percentages for each treatment by visits involved. In addition, the number of patients with missing values will be displayed.

Additionally, correlations between leuprolide concentration levels and PD parameters will be examined graphically. PD parameters may include LS, FSH, E_2 and progesterone levels. These evaluations will not be performed for Treatment "D".

Number of vaginal (menstrual) bleeding days will be summarized by treatment group for 28 days of therapy and for 28 days of post-study follow-up. The subject incidence of the onset of menstrual period after completion of therapy will be reported for each treatment group.

The onset of menstrual period is defined as at least three consecutive bleeding/spotting days during the 28-day postdosing period.

Additional PD analyses could be performed if necessary.

12. Datasets Handling

The PK, PD, safety and tolerability data will be received as SAS® datasets from the data management facility. It should be noted that, in the datasets, the subjects in Treatment "D" that have already participated in this study (have received Treatments "A", "B", or "C") will have the same unique subject identifier (USUBJID). However, the link with the different subject identifiers for the study (SUBJID) for those who participated more than once in the study will be provided in a separate dataset (e.g. suppdm).

13. Handling of Missing Data

Only observed data will be used in the data analysis except for concentration values BLQ and samples with no reportable value occurring prior to dosing (on Day 1 only) as described in section 10.1. No attempt will be made to impute (i.e., extrapolate or interpolate) estimates for missing data.

14. Software to be Used

Calculation of the PK parameters for Treatments "A", "B" and "C" will be performed using Phoenix WinNonlin® version 6.4, which are validated for bioequivalence/bioavailability studies by inVentiv. The descriptive statistical analyses, the safety data tables and listings, PK tables and listings, as well as PD tables and listings will be done using SAS®, release 9.2 or a higher version. PK and PD figures will be created using R version 3.2.2 (or higher) or SAS®, release 9.2 or a higher version. The CSR text will be created using Microsoft® Office Word 2010, or a higher version.