FERRING
PHARMACEUTICALS

Protocol

Title of trial: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating Three Doses of Subcutaneous Pulsatile GnRH Administered via OmniPod Pump for Ovulation Induction in Female Subjects with Primary Amenorrhea with Hypogonadotropic Hypogonadism
NCT number: NCT01976728
Sponsor trial code: 000070
Date: 06 Dec 2017

CLINICAL TRIAL PROTOCOL

A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating Three Doses of Subcutaneous Pulsatile GnRH Administered via OmniPod Pump for Ovulation Induction in Female Subjects with Primary Amenorrhea with Hypogonadotropic Hypogonadism

Trial Code 000070

Consolidated Protocol Incorporating Amendments 1-7

IND Number:	22,278
Investigational Medicinal Product:	LutrePulse OmniPod
Indication:	Primary Hypothalamic Amenorrhea
Phase:	III
Name and Address of Sponsor:	Ferring International Pharmascience Center U.S., Inc. 100 Interpace Parkway Parsippany, NJ 07054 P: 973-796-1600 F: 973-796-1660
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study Evaluating Three Doses of Subcutaneous Pulsatile GnRH Administered via OmniPod Pump for Ovulation Induction in Female Subjects with Primary Amenorrhea with Hypogonadotropic Hypogonadism

TRIAL SITES

The study will be conducted at approximately 50 sites in the United States and Canada.

PLANNED TRIAL PERIOD	**CLINICAL PHASE**
First subject first visit (FSFV) March 2014 Last subject last visit (LSLV) June 2019	III

OBJECTIVES

Primary objective

- To compare the ovulation rate in women with primary amenorrhea with hypogonadotropic hypogonadism (HH) following each of three doses (10 μg, 15 μg, and 20 μg per pulse) of subcutaneous (SC) pulsatile gonadotropin-releasing hormone (GnRH) administered with the LutrePulse OmniPod Pump versus placebo

Secondary objectives

- To evaluate clinical pregnancy rate
- To evaluate biochemical pregnancy rate
- To evaluate LH surge rate
- To evaluate ovarian follicular development
- To evaluate luteal phase support with GnRH
- To evaluate pharmacodynamic parameters
- To evaluate the safety of LutrePulse OmniPod SC

ENDPOINTS

Primary endpoint

- Ovulation rate, calculated as a proportion of subjects with at least 1 post-baseline progesterone (P_4) level ≥ 6 ng/mL or a confirmed positive serum β-hCG (i.e., 2 positive results) or presence of a gestational sac documented by transvaginal ultrasound (TVUS)

Secondary endpoints

Progesterone levels:

- Proportion of subjects with at least 1 post-baseline P_4 level ≥ 10 ng/mL

Pregnancy:

Clinical pregnancy rate:

- Proportion of subjects with presence of gestational sac and fetal heart movement (FHM) on transvaginal ultrasound (TVUS) at approximately 2 to 4 weeks after a second positive serum beta human chorionic gonadotropin (β-hCG) test

Biochemical pregnancy rate:

- Proportion of subjects with a confirmed positive serum β-hCG (i.e., 2 positive results) 14 + 4 days post luteinizing hormone (LH) surge

LH Surge Detection:

- Proportion of subjects with a positive detection of LH surge on a Clearblue test

Ovarian Follicular Development:

- Number of follicles with a mean diameter ≥ 14 mm
- Number of dominant follicles with a mean diameter ≥ 18 mm

Luteal Phase Support:

- Maximum P_4 levels from Days 19, 21, 23, 25, and 27
- Mean P_4 levels from Days 19, 21, 23, 25, and 27

Pharmacodynamic Endpoints:

- Follicle-stimulating hormone (FSH) and LH change from baseline in relation to the first GnRH pulse on Day 1 and Day 10
- Mean serum FSH and LH levels on Day 1 and Day 10

- Estradiol (E_2) serum levels on Day 1 and Day 10

Safety Endpoints:

- Adverse events (type, frequency, intensity, and seriousness)
- Clinical chemistry, hematology, urinalysis
- Frequency and severity of ovarian hyperstimulation syndrome (OHSS)

METHODOLOGY

This multicenter, randomized, double-blind, placebo-controlled study will be performed in approximately 60 women with primary amenorrhea with HH who desire pregnancy. The treatment duration with LutrePulse OmniPod SC or placebo can be approximately 7 weeks. It is expected that the response to treatment will occur within 2 to 3 weeks after therapy initiation. When LH surge is detected by LH urine kit test, therapy should be continued for approximately another 2 weeks to maintain corpus luteum function (continue until confirmatory serum pregnancy test). Subjects will discontinue treatment either at the onset of menses or after having two (2) negative or two (2) positive confirmatory serum pregnancy tests. Subjects will be required to return to the study site for pharmacodynamic blood draws, TVUS, serum pregnancy tests, and safety follow-up assessments.

The study will consist of 3 periods: Screening (includes progestin challenge test), Treatment (includes pituitary priming and treatment phase), and Follow-up.

Screening (Day -60 to Day -1): Only subjects with diagnosed primary amenorrhea with HH should be screened. Only subjects who desire pregnancy will be eligible to participate in the trial.

The site will obtain written informed consent before any study-related procedures begin. Upon signing the Informed Consent Form, subjects will be screened based on inclusion/exclusion criteria. The assessments during the screening period will include medical/gynecologic history, safety laboratory tests (chemistry, hematology, urinalysis), other laboratory tests (serum pregnancy, LH, FSH, E_2, P_4, prolactin [PRL], and thyroid-stimulating hormone [TSH] levels), vital signs (blood pressure, heart rate, body temperature), Papanicolaou (PAP) smear (if not done within the last 24 months; PAP smear may be performed at Screening and for every patient if warranted, per investigator discretion), TVUS documenting normal uterus and adnexa, and a physical/gynecological examination. A normal or stable computed tomography (CT) scan or magnetic resonance imaging (MRI) scan of the hypothalamic pituitary region must be on file to exclude other causes for the disease. The male partner should have a recent normal semen analysis (within 1 year). A progestin challenge test will also be initiated to confirm HH.

Rescreening will be allowed at the investigators' discretion for subjects who exhibit laboratory tests outside of the normal or required range. No subject may be rescreened more than once. Rescreening for the progestin challenge test is not allowed.

> **Progestin challenge test**: After confirmed negative serum pregnancy test, subjects will be dispensed 10 mg of medroxyprogesterone acetate (Provera®) once daily for 10 days. Subjects who do not have uterine bleeding 5 days after the last dose of progestin will continue to the treatment period. Per investigator's discretion, occasional spotting is not considered withdrawal bleeding. Subjects with uterine bleeding are considered screen failures and will be ineligible for study participation. Rescreening for the progestin challenge test is not allowed.

Treatment (Day 1 to approximately Day 37): Subjects who do not have uterine bleeding within 5 days after the last dose of progestin will return to the clinic; a negative urine pregnancy test result is required and then the subject will be randomly assigned to 1 of 4 treatment arms: LutrePulse OmniPod SC 10 µg/pulse, 15 µg/pulse, 20 µg/pulse, or placebo (10, 15, or 20 µg/pulse delivery setting) every 90 minutes.

Subjects will be instructed on the application of the OmniPod pump. The first OmniPod pump will be applied on Day 1. Each OmniPod pump will be worn for 3 days (Days 1-3, 4-6, 7-9, etc. to approximately Day 37). The subject will apply subsequent OmniPod pumps every 4th day at approximately the same time as the 1st application (±1 hour).

> **Pharmacodynamic assessments**: A blood sample for E_2, LH and FSH will be taken on Day 1 (pre-treatment baseline) prior to dosing. Additional blood samples for only LH and FSH will be taken 5, 15, 30, 60, and 90 minutes after the first dose is administered.
>
> A blood sample for E_2, LH and FSH will be taken on Day 10 at the same time as the Day 1 initial sample (±1 hour) and before the first dose is administered by the Day 10 pump. Additional blood samples for only LH and FSH will be taken 5, 15, 30, 60, and 90 minutes after the first dose is administered.

Follicular and endometrial development: Follow-up will begin on Day 10 of treatment. Follicular and endometrial development will be monitored by TVUS every other day or per the investigator's discretion (minimum of 3 TVUS), until a dominant follicle of ≥ 18 mm mean diameter and normal endometrium (thickness and pattern) are confirmed. If a dominant follicle ≥ 18 mm mean diameter is not observed after 21 full days of treatment, the therapy will be discontinued. However, the treatment may be continued for a maximum of 39 days at the discretion of the investigator if the patient has growing follicle(s). After Day 10, a single blood sample for E_2 assessment will be collected each time the subject returns for TVUS. A subject who has an increased risk of developing multiple gestation/OHSS (4 or more follicles with a mean diameter ≥ 15 mm by TVUS and E_2 levels ≥ 1200 pg/mL) will be discontinued from treatment.

LH surge detection: Clearblue® digital ovulation urine test will begin when follicles with a mean diameter ≥ 14 mm are documented on TVUS. The subject will administer a Clearblue test daily, between 8 and 11 AM at approximately the same time each morning, until a positive test result occurs. Subjects should document the date of their first Clearblue test and the date of their first positive test result on the subject diary card (Appendix II). The subject should notify the site immediately once the surge has been detected to schedule a visit within 72 hours for a confirmatory TVUS. Subjects will be advised to engage in sexual intercourse on the day of LH surge, the day following LH surge, and per investigator's discretion thereafter. The subject should also document the date(s) of sexual intercourse on the subject diary card.

If LH surge is not detected after 21 full treatment days, the subject will be discontinued. However, the treatment may be continued for a maximum of 39 days at the discretion of the investigator if the patient has growing follicle(s).The subject will be instructed to visit the site to return all study drug and the OmniPod System.

Blood samples for progesterone (P_4) levels: A single blood sample for P_4 will be taken on Day 1 (pre-treatment baseline) prior to dosing. Blood samples will also be obtained on Day 19, Day 21, Day 23, Day 25 and Day 27. For subjects who have discontinued the study early and ended treatment on or after Day 14, a blood sample will also be taken at the End-of-Study Visit.

Menses Onset: Subjects who begin menstruating after treatment was initiated will be instructed to stop the treatment and to visit the site to return all study drug and the OmniPod System. The site will record the first day of menses and duration of menses for all non-pregnant subjects.

Serum pregnancy tests (β-hCG): will be performed 14 days (+ 4 days) after LH surge and 3 days thereafter. Two positive pregnancy tests are required to confirm biochemical pregnancy. If only one of the 2 tests is positive, the subject will return within 5 days (unscheduled visit) to confirm pregnancy with another test.

After obtaining two (2) negative or two (2) positive confirmed serum pregnancy test results, the treatment will complete.

All subjects will be assessed for an End-of-Study visit and return all study drug and the OmniPod System.

Follow-up: TVUS for pregnancy outcome: Subjects who achieve pregnancy (2 positive serum pregnancy tests) will be followed up for clinical pregnancy (gestational sac and fetal heart movement) 2 to 4 weeks after second positive pregnancy test and will complete an End-of-Study visit the day of documented fetal heart movement on TVUS. If the fetal heartbeat is not detected, the subject will return within 7 days for a follow-up ultrasound to confirm fetal heartbeat. Sites will contact these subjects to collect data for ongoing pregnancy rate (fetal heart movement at gestational Week 11 or Week 12), including safety follow-up of the subjects for miscarriage, fetal anomalies and live birth rate.

NUMBER OF SUBJECTS

Approximately 60 female subjects will be randomized.

MAIN CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria:

1 Signed written informed consent prior to any study-related procedure

2 Women 18 - 40 years old

3 Body mass index (BMI) between 18 and 38 kg/m^2

4 Documented clinical history or recently diagnosed with primary amenorrhea with hypogonadotropic hypogonadism

5 Hormonal values in a centrally analyzed fasting blood sample: FSH < 5 IU/L and mean LH < 5 IU/L

6 Desire to become pregnant

7 Discontinued estrogen-progesterone replacement therapy at least 1 month before screening

8 Negative progestin challenge test performed during screening

9 Normal PAP smear within 24 months of the initial visit (PAP smear can be performed at Screening, per investigator discretion and standard of practice if warranted, even if results within 24 months are available)

10 Normal or stable CT scan or MRI scan of the hypothalamic pituitary region on file

11 Prolactin and TSH within normal limits for the clinical laboratory at the Screening Visit

12 Male partner with normal semen analysis, including volume, liquefaction time, sperm count, and motility, according to the local laboratory normal criteria, within the past year

13 Normal TVUS at Screening with respect to uterus and adnexa (presence of both ovaries and tubes, without evidence of clinically significant abnormality) and with normal uterine cavity, normal cervix

14 Tube patency on saline tubal perfusion, hysterosalpingography or laparoscopy on file within the past 2 years

15 Willing and able to comply with the protocol for the duration of the study

Exclusion Criteria:

1 Any medical condition that, in the judgment of the investigator, may interfere with the absorption, distribution, metabolism, or excretion of the drug

2 A history of or currently diagnosed with clinically important cardiovascular, pulmonary (e.g., serious corticosteroid-dependent asthma), gastrointestinal, hepatic, metabolic, renal, endocrinological (e.g., insulin-dependent diabetes mellitus), or neurological (e.g., epilepsy, serious migraine, central nervous system [CNS] lesions [in cases where HH is secondary to a CNS lesion or its treatment]) abnormality

3 A history of adrenal or uncontrolled thyroid disorders, or hyperprolactinemia

4 Prior treatment cycle with gonadotropins or GnRH within the last 2 months

5 Known allergy to study drug or its components

6	Infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C
7	Ovarian enlargement or cyst of unknown etiology
8	Abnormal gynecological bleeding of undetermined origin
9	Previous or current hormone-dependent tumor
10	Known active substance abuse
11	Planning to undergo in vitro fertilization procedure in the course of a study treatment cycle
12	Currently undergoing treatment with gonadotropin hormones (FSH and LH), psychotropic medication, sex hormones, or any other medication known to interfere with normal reproductive function or that can affect GnRH secretion (e.g., neuroleptics, dopamine antagonists, spironolactone, levodopa, phenothiazine, digoxin)
13	Ongoing pregnancy or lactation
14	Participation in any experimental drug study within 30 days prior to screening
15	Previously randomized in this study
16	The patient is considered by the investigator to be unsuitable to participate in the trial for any other reason
17	The patient has a mental incapacity or language barrier precluding adequate understanding or cooperation.

MEDICINAL PRODUCTS

LutrePulse (gonadorelin acetate) for subcutaneous (SC) pulsatile injection via OmniPod System, delivering 10 µg, 15 µg, or 20 µg of GnRH or placebo per pulse every 90 minutes.

Investigational Medicinal Product (IMP):

- Lutrelef 3.2 mg, lyophilized powder for reconstitution
- Solvent in vials of 10 ml for reconstitution of Lutrelef 3.2 mg, or to serve as placebo

Non- Investigational Medicinal Product (NIMP):

- Provera® (medroxyprogesterone acetate tablets, USP) 10 mg

Device:

- Delivery pump (OmniPod) for administration of IMP
- Managers for programming of the delivery pump
- Syringes, needles and adaptors used for reconstitution and loading of delivery pump

DURATION OF TREATMENT

LutrePulse (gonadorelin acetate) delivered via pulsatile injection every 90 minutes (1-minute delivery followed by an 89-minute gap) for a total of approximately 16 administrations over a 24-hour period for up to approximately 7 weeks. Duration of treatment depends on subject response; it is expected that follicular response to LutrePulse will occur within 2 to 3 weeks after therapy initiation. However, the treatment may be continued for a maximum of 39 days at the discretion of the investigator if the patient has growing follicle(s). Additionally, when ovulation occurs, therapy should be continued for approximately another 2 weeks to maintain corpus luteum function (continue until confirmatory serum pregnancy test).

STATISTICAL METHODS

Sample size:
The sample size was determined based on the original fixed parallel group study design. The true ovulation rate for LutrePulse OmniPod SC 20 µg, 15 µg, 10 µg, and placebo was assumed to be 70%, 65%, 60%, and 1%, respectively. Under these assumptions, a sample size of 14 subjects per group (total 56 subjects) will provide at least 80% power to detect differences between LutrePulse OmniPod SC 20 µg and placebo, 15 µg and placebo, and 10 µg and placebo in ovulation rate separately using stratified one-sided Fisher's exact tests[19] at an overall one-sided significance level of 0.025 with the closed testing procedure (Kong et al., 2005)[18] to be used for the primary efficacy analysis.

Approximately 60 subjects will be randomized, assuming up to 4 subjects may be ineligible for the full analysis set (FAS).

Efficacy:
The primary efficacy analysis will be based on all randomized subjects who received at least 14 days of study drug for pituitary priming (i.e., FAS).

The primary efficacy endpoint will be ovulation rate calculated as the proportion of subjects who had at least 1 post-baseline value of P_4 level $\geq$ 6 ng/mL or pregnancy confirmed by a positive serum β-hCG (i.e., 2 positive results) or presence of a gestational sac documented by transvaginal ultrasound (TVUS). A Bayesian adaptive design is adopted to address the following objectives:

1. Demonstrate superiority of the pooled middle and high doses over placebo in the ovulation rate
2. Evaluate the dose-response relationship

The adaptive design includes two interim analyses, conducted after approximately 9 and 12 patients per arm enrolling in the study, respectively. The interim analysis provides an opportunity for stopping the trial early due to efficacy success utilizing the group sequential strategy or due to efficacy futility through Bayesian predictive probability of success. Furthermore, it allows the

low dose to be dropped following the interim look if it shows a much lower response rate compared with the middle and high doses.

Each interim analysis will result in one of the following possible outcomes:

1. Continue the trial with all arms
2. Continue the trial without the low dose
3. Declare early success, but continue the trial without placebo
4. Declare early success and stop the trial (both placebo and low dose dropped)
5. Stop the trial for futility

When the primary efficacy analysis is not successful at the interim analysis, and if the ovulation rate in the low-dose arm is sufficiently low, satisfying

$$R_{low} < (R_{high+middle}) - 0.2, \quad (1)$$

then the trial will continue without the low dose, resulting in outcome #2 listed above. Note that R_{low} and $R_{high+middle}$ in inequality (1) are the observed ovulation rates in the low dose arm and the combined middle- and high-dose arms, respectively. However, if inequality (1) is not satisfied, then the trial will continue with all arms (outcome #1 listed above).

Conversely, when success on the primary efficacy analysis is declared at an interim analysis, if the response rate in the low-dose arm meets the condition in inequality (1), then the trial is completed at this point (outcome #4 listed above) with dose selection using the ED80 rule (see below).

In the case the primary efficacy analysis is successful, but the response rate in the low-dose arm is within 20% from the combined low- and high-dose success rate, the trial is not stopped immediately. Rather, the trial will continue to enroll additional patients into the low-, middle- and high-dose arms to further assess dose responses.

Finally, the trial may terminate (outcome #5 listed above) as a result of a low predictive probability of success (<0.05) given the data collected at the interim analysis.

At the end of the study, for a trial that achieves efficacy success, the dose to be selected as the lowest effective dose is the ED80 dose, defined as the lowest dose that retains at least 80% of the largest treatment effect, i.e.

$$(R_{ED80} - R_{placebo}) \geq (R_{maximum} - R_{placebo}) \times 0.8, \quad (2)$$

where $R_{maximum}$ is the observed ovulation rate in the most effective dose arm, $R_{placebo}$ is the observed ovulation rate in the placebo arm, and R_{ED80} is the observed ovulation rate in the selected dose arm.

The primary efficacy analysis will compare the pooled ovulation rate of LutrePulse OmniPod SC 20 µg and 15 µg to placebo. Let $P_{high+middle}$ and $P_{placebo}$ be the underlying ovulation rates in the combined middle- and high-dose arms and the placebo arm, respectively. The hypotheses for the one-sided statistical testing are:

$$H_0: P_{high+middle} \leq P_{placebo},$$

vs.

$$H_0: P_{high+middle} > P_{placebo.}$$

The hypotheses are tested using a stratified one-sided Fisher's exact test (Jung et al., 2014) in the FAS including the randomization scheme as the stratification factor. The SAS PROC FREQ with permutation-based Cochran-Mantel-Haenszel test with exact p-value derived from all possible permutations will be employed for the calculation of p-value for the stratified Fisher's exact test.

To account for the multiplicities introduced by early success interim analyses, Pocock boundaries are used. Thus, the success threshold at each analysis corresponds to a nominal p-value < 0.0131 to maintain an overall one-sided type I error rate of 0.025.

Sensitivity analysis:

- will be performed on the PPS
- will be performed on the mITT

For the secondary efficacy analyses, clinical and biochemical pregnancy rates will be compared between the pooled middle- and high-dose arms vs. the placebo arm using the same statistical method to be applied to the primary efficacy analysis. Numbers of follicles with a mean diameter ≥ 14 mm and dominant follicles with a mean diameter ≥18 mm will be compared using Wilcoxon's rank sum test by stratifying based on the randomization scheme. The maximum P_4 level and the mean P_4 level from Days 19, 21, 23, 25, and 27 values will be compared using an analysis of covariance (ANCOVA) model including the treatment group and randomization scheme as factors and mean baseline value as covariate. The proportion of subjects with at least 1 post-baseline progesterone (P_4) level ≥ 10 ng/mL will be compared to placebo using the same statistical method to be applied to the primary efficacy analysis. The mean FSH and LH on Day 10, as well as the change from baseline, will be compared using ANCOVA model including the treatment group and randomization scheme as factors and mean baseline value as covariate. The E_2 levels on Day 10, as well as the change from baseline, will be compared using a similar ANCOVA model. The change in the maximum value of FSH, LH, and E_2 levels on Day 1 and Day 10 from the first value taken on Day 1 and Day 10, respectively, will be presented with descriptive statistics by treatment group. The FSH, LH, and E_2 levels on Day 1 and Day 10 will be presented graphically by treatment group.

Safety:
Safety parameters will be summarized by treatment group for all subjects who received at least 1 pulsatile injection delivery of study drug.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations	Meaning of abbreviations in document
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical-therapeutic-chemical
β-hCG	beta human chorionic gonadotropin
BMI	body mass index
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CT	computed tomography
E_2	estradiol
ECG	electrocardiogram
eCRF	electronic case report form
FAS	Full Analysis Set
FDA	Food and Drug Administration
FHM	fetal heart movement
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HCP	Healthcare Professional
HH	hypogonadotropic hypogonadism
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ICMA	immunochemiluminometric assay
IEC	Independent Ethics Committee
IFU	Instructions for Use
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	intravenous
LSLV	last subject last visit
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NIMP	Non-Investigational Medicinal Product
OHSS	ovarian hyperstimulation syndrome
P_4	progesterone
PAP	Papanicolaou
PD	pharmacodynamic
PPS	Per Protocol Set

Abbreviations	Meaning of abbreviations in document
PRL	prolactin
PT	preferred term
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
TVUS	transvaginal ultrasound
UADE	unanticipated adverse device effect
US	United States

1 INTRODUCTION

1.1 Background

Pulsatile gonadotropin-releasing hormone (GnRH) has been widely used in the United States (US) and Europe for over 25 years, with an estimated 12,000 cases treated annually. It has an excellent safety record and a high degree of effectiveness in treating primary hypothalamic amenorrhea and in inducing ovulation and pregnancy in a variety of infertile patients. Pulsatile GnRH is safer than other parenteral preparations and has a much lower incidence of inducing multiple pregnancies or ovarian hyperstimulation than other therapies such as anti-estrogens or gonadotropins.[1,2] Hypogonadotropic hypogonadism (HH), characterized by inappropriately low serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the setting of hypogonadism, may be amenable to treatment with GnRH.

Several investigations utilizing subcutaneous (SC) administration of GnRH, including pharmacokinetic studies conducted by Ferring, showed favorable GnRH and LH profiles and ovulation and pregnancy rates comparable to intravenous (IV) regimens.[3,4,5,6,7] Favorable results were obtained in women with hypothalamic amenorrhea, with pregnancy rates comparable to those achieved with exogenous gonadotropins, with a much lower risk of ovarian hyperstimulation and multiple pregnancy. When a physiological replacement regimen of pulsatile GnRH is used, a high rate of ovulation and conception can be anticipated in women with complete GnRH deficiency and hypothalamic amenorrhea.[8]

Gonadorelin acetate is a synthetic decapeptide that is identical in amino acid sequence to endogenous GnRH synthesized in the human hypothalamus and in various neurons terminating in the hypothalamus. Therapeutic pulsatile GnRH for treatment of primary hypothalamic amenorrhea was first approved in Europe as Lutrelef® in 1983 and as LutrePulse™ in the US in 1989 and in Canada in 1993 with different pumps.

LutrePulse (gonadorelin acetate) was approved in the US for use in patients with primary hypothalamic amenorrhea administered IV via the Zyklomat® pump, but was later withdrawn from the market for commercial reasons. Therefore, no approved GnRH product is currently available for ovulation induction and treatment of primary hypothalamic amenorrhea patients in the US. LutrePulse (known as Lutrelef) with OmniPod for subcutaneous use was approved in France (2009), Netherlands (2010) and Germany (2011) to treat both men and women with GnRH deficiency or GnRH impairment. In 2012, LutrePulse (gonadorelin acetate) with the OmniPod device for subcutaneous administration was also approved and re-introduced in Canada for ovulation induction in patients with primary hypothalamic amenorrhea.

The OmniPod® pump is a disposable SC delivery pump for LutrePulse with a hand-held wireless controller (the Manager).[9] The OmniPod has been demonstrated to provide similar volume and similar bolus/pulse accuracy as the Zyklomat IV pump (data on file). In addition, the stability of

LutrePulse solution over the intended period of use was demonstrated for the OmniPod pump (data on file). Compared to the IV pumps, the OmniPod SC pump with LutrePulse (Gonadorelin Acetate) represents a technologically advanced and more patient-friendly solution for pulsatile drug delivery. If a successful efficacy and safety profile is established for GnRH with the OmniPod, this will address the current unmet need in the very rare population of patients with HH in the US.

1.2 Scientific Justification for Conducting the Study

There is an unmet medical need for a replacement GnRH treatment of patients with primary hypothalamic amenorrhea in the US. Good results for ovulation induction, with similar ovulation results, have been previously reported in the literature for two IV doses of pulsatile GnRH administered to GnRH-deficient women: 75 ng/kg (~3-4 µg/pulse) and 100 ng/kg (~5 µg/pulse).[8] The recommended GnRH dose for primary hypothalamic amenorrhea women in the previously approved label for LutrePulse with IV pump was 5 µg IV every 90 minutes, which could be increased up to 20 µg in stepwise fashion if there was no response. The efficacy and safety of 10 and 20 µg/pulse administered SC in terms of ovulation induction were studied and published in literature in the past (See Section 5.5 for more details) but there is currently a need for a well-powered and well-controlled, randomized clinical trial to confirm the efficacy and safety profile of LutrePulse with OmniPod subcutaneous delivery pump.

In addition to the 10 and 20 µg/pulse doses, an intermediate dose of 15 µg/pulse has been added to better understand the dose range. This study is expected to provide much needed efficacy and safety information in this very rare HH population of patients.

2 STUDY OBJECTIVES AND ENDPOINTS

Primary Objective

- To compare the ovulation rate in women with primary amenorrhea with hypogonadotropic hypogonadism (HH) following each of three doses (10 μg, 15 μg, and 20 μg per pulse) of subcutaneous pulsatile gonadotropin-releasing hormone (GnRH) administered with the LutrePulse OmniPod Pump versus placebo

Secondary Objectives

- To evaluate clinical pregnancy rate
- To evaluate biochemical pregnancy rate
- To evaluate LH surge rate
- To evaluate ovarian follicular development
- To evaluate luteal phase support with GnRH
- To evaluate pharmacodynamic parameters
- To evaluate the safety of LutrePulse OmniPod SC

Primary Endpoint

- Ovulation rate, calculated as a proportion of subjects with at least 1 post-baseline progesterone (P_4) level ≥ 6 ng/mL or a confirmed positive serum β-hCG (i.e., 2 positive results) or presence of a gestational sac documented by transvaginal ultrasound (TVUS)

Secondary Endpoints

Progesterone levels:

- Proportion of subjects with at least 1 post-baseline P_4 level ≥ 10 ng/mL

Pregnancy:

Clinical pregnancy rate:

- Proportion of subjects with presence of gestational sac and fetal heart movement (FHM) on transvaginal ultrasound (TVUS) at approximately 2 to 4 weeks after second positive serum beta human chorionic gonadotropin (β-hCG) test

Biochemical pregnancy rate:

- Proportion of subjects with a confirmed positive (i.e., 2 positive results) serum β-hCG 14 + 4 days post LH surge

LH Surge Detection:

- Proportion of subjects with a positive detection of LH surge on a Clearblue test

Ovarian Follicular Development:

- Number of follicles with a mean diameter ≥ 14 mm
- Number of dominant follicles with a mean diameter ≥ 18 mm

Luteal Phase Support:

- Maximum P_4 levels from Days 19, 21, 23, 25, and 27
- Mean P_4 levels from Days 19, 21, 23, 25, and 27

Pharmacodynamic (PD) Endpoints:

- FSH and LH change from baseline in relation to the first GnRH pulse on Day 1 and Day 10
- Mean serum FSH and LH levels on Day 1 and Day 10
- Estradiol (E_2) serum levels on Day 1 and Day 10

Safety Endpoints:

- Adverse events (type, frequency, intensity, and seriousness)
- Clinical chemistry, hematology, urinalysis
- Frequency and severity of ovarian hyperstimulation syndrome (OHSS)

3 INVESTIGATIONAL PLAN AND STUDY DESIGN

3.1 Overall Design and Plan – Description

This multicenter, randomized, double-blind, placebo-controlled study will be performed in approximately 60 women with primary amenorrhea with HH who desire pregnancy. The treatment duration with LutrePulse OmniPod SC or placebo can be approximately 7 weeks. It is expected that the response to treatment will occur within 2 to 3 weeks after therapy initiation. When LH surge is detected by LH urine kit test, therapy should be continued for approximately another 2 weeks to maintain corpus luteum function (continue until confirmatory serum pregnancy test). Subjects will discontinue treatment either at the onset of menses or after having two (2) negative or two (2) positive confirmatory serum pregnancy tests. Subjects will be required to return to the study site for pharmacodynamic blood draws, TVUS, serum pregnancy tests, and safety follow-up assessments.

The study will consist of 3 periods: Screening (includes progestin challenge test), Treatment (includes pituitary priming up to 14 days and treatment phase), and Follow-up.

Screening (Day -60 to Day -1): Only subjects with diagnosed primary amenorrhea with HH should be screened for this trial. Only subjects who desire pregnancy will be eligible to participate in this trial.

The site will obtain written informed consent before any study-related procedures begin. Upon signing the Informed Consent Form, subjects will be screened based on inclusion/exclusion criteria. The assessments during the screening period will include medical/gynecologic history, safety laboratory tests (chemistry, hematology, urinalysis), other laboratory tests (serum pregnancy, LH, FSH, E_2, P_4, prolactin [PRL], and thyroid-stimulating hormone [TSH] levels), vital signs (blood pressure, heart rate, body temperature), Papanicolaou (PAP) smear (if not done within the last 24 months; PAP smear may be performed at Screening and for every patient if warranted, per investigator discretion), TVUS documenting normal uterus and adnexa, and a physical/gynecological examination. A normal or stable computed tomography (CT) scan or magnetic resonance imaging (MRI) scan of the hypothalamic pituitary region must be on file to exclude other causes for the disease. The male partner should have a documented recent normal semen analysis (within 1 year). A progestin challenge test will be initiated to confirm HH.

Rescreening will be allowed at the investigators' discretion for subjects who exhibit laboratory tests outside of the normal or required range. No subject may be rescreened more than once. Rescreening for the progestin challenge test is not allowed.

Progestin challenge test: After confirmed negative serum pregnancy test, subjects will be dispensed 10 mg of medroxyprogesterone acetate (Provera®)[10] once daily for 10 days. Subjects who do not have uterine bleeding 5 days after the last dose of progestin will continue to the treatment period. Per investigator's discretion, occasional spotting is not considered withdrawal bleeding. Subjects with uterine bleeding are considered screen failures and will be ineligible for study participation. Rescreening for the progestin challenge test is not allowed.

Treatment (Day 1 to approximately Day 37): Subject who do not have uterine bleeding within 5 days after the last dose of progestin will return to the clinic; a negative urine pregnancy test result is required and then the subject will be randomly assigned to 1 of 4 treatment arms: LutrePulse OmniPod SC 10 µg/pulse, 15 µg/pulse, 20 µg/pulse, or placebo (10, 15, and 20 µg/pulse delivery setting) every 90 minutes.

Subjects will be instructed on the application of the OmniPod pump (See Instructions for Use [IFU]).[11,12] The first OmniPod pump will be applied on Day 1. Each OmniPod pump will be worn for 3 days (Days 1-3, 4-6, 7-9, etc. to approximately Day 37). The subject will apply subsequent OmniPod pumps every 4th day at approximately the same time as the first application (±1 hour).

Pharmacodynamic (PD) assessments: A blood sample for E_2, LH and FSH will be taken on Day 1 (pretreatment baseline) prior to dosing. Additional blood samples for only LH and FSH will be taken 5, 15, 30, 60, and 90 minutes after the first dose is administered.

A blood sample for E_2, LH and FSH will be taken on Day 10 at the same time as the Day 1 initial sample (±1 hour) and before the first dose is administered by the Day 10 pump. Additional blood samples for only LH and FSH will be taken 5, 15, 30, 60, and 90 minutes after the first dose is administered.

Follicular and endometrial development: Follow-up will begin on Day 10 of treatment. Follicular and endometrial development will be monitored by TVUS every other day or per the investigator's discretion (minimum of 3 TVUS), until a dominant follicle of ≥ 18 mm mean diameter and normal endometrium (thickness and pattern) are confirmed. If a dominant follicle ≥ 18 mm mean diameter is not observed after 21 full days of treatment, the therapy will be discontinued. However, the treatment may be continued for a maximum of 39 days at the discretion of the investigator if the patient has growing follicle(s). After Day 10, a single blood sample for E_2 assessment will be collected each time the subject returns for TVUS. A subject who has an increased risk of developing multiple gestation/OHSS (4 or more follicles with a mean diameter ≥ 15 mm by TVUS and E_2 levels ≥ 1200 pg/mL) will be discontinued from treatment.

LH surge detection with Clearblue® digital ovulation urine test [13] will begin when follicles with a mean diameter ≥ 14 mm are documented on TVUS. The Clearblue test will be administered daily, between 8 and 11 AM at approximately the same time each morning, until a positive test result occurs. Subjects should document the date of their first Clearblue test and the date of their first positive test result on the subject diary card (Appendix II). The subject should notify the site immediately once the surge has been detected to schedule a visit within 72 hours for confirmatory TVUS. Subjects will be advised to engage in sexual intercourse on the day of LH surge, the day following LH surge, and per investigator's discretion thereafter. The subject should also document the date(s) of sexual intercourse on the subject diary card.

If LH surge is not detected after 21 full treatment days, the subject will be discontinued. However, the treatment may be continued for a maximum of 39 days at the discretion of the investigator if the patient has growing follicle(s). The subject will be instructed to visit the site to return all study drug and the OmniPod System.

Blood samples for progesterone (P_4) levels: A single blood sample for P_4 will be taken on Day 1 (pre-treatment baseline) prior to dosing. Blood samples will also be obtained on Day 19, Day 21, Day 23, Day 25, and Day 27 after initiation of study drug. For subjects who have discontinued the study early and ended treatment on or after Day 14, a blood sample will also be taken at the End-of-Study Visit.

Menses Onset: Subjects who begin menstruating after treatment was initiated will be instructed to stop the treatment and to visit the site to return all study drug and the OmniPod System. The site will record the first day of menses and duration of menses for all non-pregnant subjects.

Serum pregnancy tests (β-hCG): will be performed 14 days (+ 4 days) after LH surge and 3 days thereafter. Two positive pregnancy tests are required to confirm biochemical pregnancy. If only one of the 2 tests is positive, the subject will return within 5 days (unscheduled visit) to confirm pregnancy with another test.

After obtaining two (2) negative or two (2) positive confirmed serum pregnancy test results, the treatment will complete.

All subjects will be assessed for an End-of-Study visit and return all study drug and the OmniPod System.

Follow-up:

TVUS for pregnancy outcome: Subjects who achieve pregnancy (2 positive serum pregnancy tests) will be followed up for clinical pregnancy (gestational sac and fetal heart movement) 2 to 4 weeks after second positive pregnancy test and will complete an End-of-Study visit the day of documented fetal heart movement on TVUS. If the fetal heartbeat is not detected, the subject will return within 7 days for a follow-up ultrasound to confirm fetal heartbeat. Sites will contact these subjects to collect data for ongoing pregnancy rate (fetal heart movement at gestational Week 11 or Week 12), including safety follow-up of the subjects for miscarriage, fetal anomalies and live birth rate.

3.2 Number of Centers and Subjects

The study will be conducted in approximately 50 sites in the United States and Canada. Approximately 60 female subjects will be randomized.

3.3 Discussion of Study Design and Choice of Control Groups

This is a multicenter, randomized, double-blind, placebo-controlled trial. Subjects with primary amenorrhea with HH will be treated with 1 of 3 doses of pulsatile GnRH, or placebo, administered SC via the OmniPod pump manufactured by Insulet.

The three active dose regimens of GnRH and placebo will be administered using indistinguishable vials to maintain the blind. Insulet is a leader in wearable insulin pump technology with its OmniPod Insulin Management System. The OmniPod Insulin Management System, a revolutionary, discreet and easy-to-use insulin infusion system, features 2 easy-to-use parts with no tubing and fully automated cannula insertion. Insulet worked with Ferring Pharmaceuticals to develop a system for the delivery of gonadorelin acetate. A custom version of the OmniPod's Personal Diabetes Manager was developed, which was the first non-diabetes drug delivery application for the OmniPod System. The OmniPod System is expected to be an effective platform technology for the delivery of various drugs that require continuous or frequent infusions, including GnRH.

4 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

Subjects who meet all of the following criteria will be eligible for the study:

1. Signed written informed consent prior to any study-related procedure
2. Women 18 - 40 years old
3. Body mass index (BMI) between 18 and 38 kg/m^2
4. Documented clinical history or recently diagnosed with primary amenorrhea with hypogonadotropic hypogonadism
5. Hormonal values in a centrally analyzed fasting blood sample: FSH < 5 IU/L and mean LH < 5 IU/L
6. Desire to become pregnant
7. Discontinued estrogen-progesterone replacement therapy at least 1 month before screening
8. Negative progestin challenge test performed during screening
9. Normal PAP smear within 24 months of the initial visit (PAP smear can be performed at Screening, per investigator discretion and standard of practice if warranted, even if results within 24 months are available)
10. Normal or stable CT scan or MRI scan of the hypothalamic pituitary region on file
11. Prolactin and TSH within normal limits for the clinical laboratory at the Screening Visit
12. Male partner with normal semen analysis, including volume, liquefaction time, sperm count, and motility, according to the local laboratory normal criteria, within the past year
13. Normal TVUS at Screening with respect to uterus and adnexa (presence of both ovaries and tubes, without evidence of clinically significant abnormality) and with normal uterine cavity, normal cervix
14. Tube patency on saline tubal perfusion, hysterosalpingography or laparoscopy on file within the past 2 years
15. Willing and able to comply with the protocol for the duration of the study

4.2 Exclusion Criteria

The presence of any of the following excludes a subject from study enrollment:

1. Any medical condition that, in the judgment of the investigator, may interfere with the absorption, distribution, metabolism, or excretion of the drug
2. A history of or currently diagnosed with clinically important cardiovascular, pulmonary (e.g., serious corticosteroid-dependent asthma), gastrointestinal, hepatic, metabolic, renal, endocrinological (e.g., insulin-dependent diabetes mellitus), or neurological (e.g., epilepsy, serious migraine, CNS lesions [in cases where HH is secondary to a CNS lesion or its treatment]) abnormality
3. A history of adrenal or uncontrolled thyroid disorders or hyperprolactinemia
4. Prior treatment cycles with gonadotropins or GnRH within the last 2 months
5. Known allergy to study drug or its components
6. Infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C
7. Ovarian enlargement or cyst of unknown etiology
8. Abnormal gynecological bleeding of undetermined origin
9. Previous or current hormone-dependent tumor
10. Known active substance abuse
11. Planning to undergo in vitro fertilization procedure in the course of a study treatment cycle
12. Currently undergoing treatment with gonadotropin hormones (FSH and LH), psychotropic medication, sex hormones, or any other medication known to interfere with normal reproductive function or that can affect GnRH secretion (e.g., neuroleptics, dopamine antagonists, spironolactone, levodopa, phenothiazine, digoxin)
13. Ongoing pregnancy or lactation
14. Participation in any experimental drug study within 30 days prior to screening
15. Previously randomized in this study
16. The patient is considered by the investigator to be unsuitable to participate in the trial for any other reason
17. The patient has a mental incapacity or language barrier precluding adequate understanding or cooperation.

4.3 Prior and Concomitant Therapies

Use of any medication other than study medication provided for this study should be avoided from the Screening/Pre-treatment Period until the completion of the study.

Details of all concomitant medications (and other therapies) including the main reason for their prescription must be recorded in the medical source data and the electronic case report form (eCRF) for all eligible patients within 14 days of the Screening Visit until the completion of the study. This information should include name of the drug, route of administration, indication, and duration of treatment. Any changes (including new therapies) must be recorded at each subsequent trial visit.

4.4 Withdrawal Criteria

Every subject has the right to refuse further participation in the study at any time and without providing a reason(s). A subject's participation is to terminate immediately upon her request. The investigator should seek to obtain the reason(s) if possible and record this in the eCRF.

If, at the time of refusal, a dose of the investigational product has already been administered, the subject must be advised to agree to follow-up safety investigations, which will include all procedures outlined in the End-of-Study Visit. Any early term subjects should complete this visit within 3 days of discontinuation.

A subject may be withdrawn from the study at any time at the discretion of the investigator; the reason should be discussed with the sponsor prior to discontinuing the subject and the reason fully documented in the eCRF. Should the subject, during the course of the study, develop conditions that would have prevented her entry into the study according to the exclusion criteria, she must be withdrawn immediately.

A subject who has an increased risk of developing multiple gestation/OHSS (4 or more follicles with a mean diameter $\geq$ 15 mm by TVUS and E_2 levels $\geq$ 1200 pg/mL) will be discontinued from treatment.

In addition, any clinically important adverse physical or symptomatic findings/events and/or abnormal laboratory findings that are above the pre-specified critical values defined in the laboratory manual will be grounds for discontinuation from the study.

Subjects who do not become pregnant following treatment (2 negative serum pregnancy tests) will be discontinued from the study and must complete an End-of-Study Visit on the day of the second negative serum pregnancy test.

4.5 Subject Replacement

Subjects discontinued from the study will not be replaced.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Product (IMP)

Subjects will be randomly assigned to 1 of 4 treatment arms:

- LutrePulse OmniPod SC 10 µg/pulse as a fixed dose (Test Product)
- LutrePulse OmniPod SC 15 µg/pulse as a fixed dose (Test Product)
- LutrePulse OmniPod SC 20 µg/pulse as a fixed dose (Test Product)
- Placebo (10, 15, or 20 µg/pulse as a fixed "dose")

Subjects will receive consecutive pulses of GnRH or placebo, each delivered at 90-minute intervals, for approximately 37 days of treatment. Each OmniPod will be worn for 3 full days (Days 1-3, 4-6, 7-9, etc. to approximately Day 37) and will be replaced every 4th day (i.e., Day 4, Day 7, Day 10, etc.). New OmniPod pumps should be applied at approximately the same time as the first pump (±1 hour).

Test Product - LutrePulse (gonadorelin acetate)

LutrePulse is a white lyophilized powder that is highly soluble in water and is intended for SC pulsatile injection with the OmniPod pump after reconstitution. LutrePulse is manufactured by the sponsor. Each vial with 13.2 mg powder contains 3.2 mg of lyophilized gonadorelin acetate, equivalent to 2.91 mg gonadorelin; each vial with 10 mL solvent (pH 4.0 – 5.0) contains sodium chloride, water for injection, and hydrochloric acid 10%. Randomized fixed doses of either 10 µg, 15 µg, or 20 µg will be programmed into the OmniPod Manager and subcutaneously delivered to the subject. For every 10 µg, 15 µg, or 20 µg dose, the subject will receive 10 µL, 15 µL, or 20 µL amount of volume with the same concentration of drug per pulsatile injection.

Test Product – Placebo

The placebo product is a vial with solvent (pH 4.0 – 5.0) containing sodium chloride, water for injection, and hydrochloric acid 10%. Placebo is manufactured by the sponsor. Each vial of placebo will appear similar to the LutrePulse 3.2 mg reconstituted vials. Randomized fixed doses to match 10 µg, 15 µg, or 20 µg will be programmed into the OmniPod Manager and subcutaneously delivered to the subject. Placebo doses will be the same amount of volume respectively, either 10, 15 µg, or 20 µg/pulse, as the LutrePulse OmniPod dose without active drug substance.

Drug Delivery System

The OmniPod Drug Delivery system is a disposable delivery pump (OmniPod) with a handheld wireless controller (the Manager) for SC drug delivery (see Figure 1). The OmniPod is a discreet and easy-to-use delivery pump featuring two parts, with no tubing and fully automated cannula insertion manufactured by Insulet Corporation (located at 9 Oak Park Dr., Bedford, MA, US). A custom version of the originally developed OmniPod's Manager (wireless controller for insulin delivery) was subsequently modified for use with LutrePulse.

The OmniPod is a small (1.530" wide × 2.055" long × 0.575" high), lightweight (< 1.1 oz.), self-adhesive device filled with LutrePulse or placebo and worn directly on the body. The OmniPod delivers precise doses of LutrePulse or placebo through a small flexible subcutaneous cannula, based on instructions programmed into its wireless controller, the Drug Delivery Manager. The deliverable reservoir volume is 2000 µL. The cannula insertion depth is between 6 and 7 mm at ≤ 50° insertion angle when measured from the perpendicular axis to the skin, and the cannula is inserted only once with each OmniPod.

The OmniPod's adhesive keeps it securely in place for up to 3 days. Body lotion, creams, or oils should not be used near the infusion site, as these products may loosen the adhesive. The infusion site should be changed each time a new OmniPod is applied; the new site should be at least 1 inch away from the last site. To avoid infusion-site infection, subjects will be instructed to use an aseptic technique such as an alcohol swab to prepare the infusion site before applying an OmniPod.

The Manager is a wireless, handheld device that programs the OmniPod with the subject's LutrePulse or placebo delivery instructions and wirelessly monitors the OmniPod's operation. The Manager is 2.5" wide × 4.5" long × 1.0" high, and it weighs 4.4 oz. with batteries. The Manager is powered by 2 AAA alkaline batteries that have a battery life of approximately 3 weeks. Additional batteries will be supplied in order to cover the entire trial length.

With its two parts, OmniPod provides all the functionality and benefits of continuous pulsatile drug delivery. In addition, OmniPod provides safety, convenience, and freedom, with no tubing, no record keeping, and automated cannula insertion.

The OmniPod is applied to the skin with an adhesive backing, similar to an adhesive bandage.	The Manager

Figure 1: The OmniPod Drug Delivery System

More detailed characteristics of the investigational product, dosage and administration can be found in the Investigator's Brochure.[14] An abbreviated version of the LutrePulse User Guide for the OmniPod Pump[9] is provided in the LutrePulse™ Healthcare Professional (HCP) Quick Reference Guide and LutrePulse™ Guide for the Patient.[11, 12]

5.1.2 Non-Investigational Medicinal Product (NIMP)

During the progestin challenge, subjects will be dispensed 10 mg medroxyprogesterone acetate (Provera®) for oral administration, a derivative of progesterone used to induce menstrual onset. Provera 10 mg tablets will be dispensed via prescription in the US. For Canada, Provera will be provided by Ferring as either 5 mg (×2) tablets or 10 mg tablets.

More detailed characteristics can be found in the package insert for medroxyprogesterone acetate.[10]

5.2 Packaging and Labeling

Packaging and labelling of the medicinal products will be performed under the responsibility of the IMP Department at Ferring Pharmaceuticals A/S in accordance with GMP and national regulatory requirements.

5.2.1 Investigational Medicinal Product

Reconstituted vials, SC pumps, and accessories will be supplied in subject kits on Treatment Day 1, Treatment Day 10, and Treatment Day 25 (if applicable). Subjects will receive a sharps container for safe disposal of needles. The OmniPod Managers will also be supplied to the subjects on Treatment Day 1.

The active and placebo study drug will be identical in appearance and labeling. The IMP will be packaged and distributed using a secure system assuring full traceability from production to site. The unblinded coordinator will program the Manager to deliver the assigned dose, according to the randomization schedule (but will remain blinded to assigned study drug, whether active or placebo).

Each subject study kit will contain the following:

- OmniPod Manager (initial shipment only)
- Replacement batteries for Manager (initial shipment only)
- OmniPod pump(s) (2 mL syringe and needle included)
- Vial adapter(s)
- Vial(s) of LutrePulse or Placebo
- One (1) sharps container
- Alcohol swab(s)

Each subject study kit will have a study specific label uniquely numbered assuring traceability with one self-adhesive tear-off portion to be affixed to the source document form and maintained at the trial site.

5.2.2 Non-Investigational Medicinal Product

Provera® will have a study specific label uniquely numbered assuring traceability. No modification will be made from the usual commercial state, other than application of trial specific labelling.

5.3 Conditions for Storage and Use

The investigator or designee will ensure that the investigational product and Non-Investigational medicinal product is stored in appropriate conditions in a reasonably secure, substantially constructed locked cabinet with controlled access. The temperature in the storage compartment shall be constantly monitored with a minimum/maximum thermometer and the values shall be controlled regularly and documented. Deviations in storage temperature must be reported to the sponsor without delay and the IMP cannot be used until acceptance from the sponsor is received. The investigator or designee will also ensure the subject has an understanding of the proper storage conditions for IMP at home.

All LutrePulse products and supplies (including unopened pumps) should be stored in a cool, dry place. Medication vials should not be stored above 25°C (77°F). The OmniPod's operating temperature is 5-40°C (40-104°F). Extreme heat or cold can damage the OmniPod and the Manager, causing them to malfunction. The OmniPod should not be exposed to direct sunlight for long periods of time and should be removed prior to using hot tubs, whirlpools, or saunas. The Manager should not be left inside a car or other places where it could be exposed to extreme temperatures. If Pods are exposed to extreme temperatures, they should first be returned to room temperature and inspected carefully before they are used. During storage, the batteries should remain in the Manager. See the User Manual for details regarding OmniPod pump use and storage.[9]

Provera® should be stored according to the commercial pack.

The investigator or designee will dispense the medication only to the identified subjects of this study, following the procedures described in this study protocol and documented in the subject dispensing log. Drug inventory/dispensing will be documented in the source documents for each subject and the drug accountability binder. Subjects will be given a diary card on Treatment Day 1 to document time of replacing pods every 4th day. The investigator is responsible for all drug supplies. Written documentation is mandatory. After completion of the study, all unused investigational Medicinal product and Non-investigational medicinal product will be returned to the sponsor.

5.4 Blinding / Unblinding

5.4.1 Blinding

To ensure blinding, subjects assigned to placebo will be randomized to 1 of 3 placebo "dose" groups – 10 µg, 15 µg, or 20 µg according to a computer-generated randomization list prepared for all trial sites. Study personnel involved in the conduct of the study will be blinded to the assigned drug product (active or placebo) regardless of dose. The OmniPod Manager will display the dose once it has been programmed for a subject, regardless of active or placebo assignment.

All eligible subjects will be randomly assigned at least 5 days before Treatment Day 1 (7 days for sites in Canada), based on the computer-generated randomization list. The first 15 eligible subjects will be randomly assigned to 1 of 3 treatment arms: LutrePulse OmniPod SC 10 µg, LutrePulse OmniPod SC 20 µg, or OmniPod SC placebo in a 1:1:1 ratio. The subsequent 25 eligible subjects will be randomly assigned to LutrePulse OmniPod SC 10 µg, LutrePulse OmniPod SC 15 µg, LutrePulse OmniPod SC 20 µg, or OmniPod SC placebo in a 1:2:1:1 ratio. The rest of the eligible subjects will be randomly assigned to LutrePulse OmniPod SC 10 µg, LutrePulse OmniPod SC 15 µg, LutrePulse OmniPod SC 20 µg, or OmniPod SC placebo in a 1:1:1:1 ratio. To maintain blinding for subjects and the unblinded coordinator to the assigned drug product, the placebo subjects will be randomly assigned to the equivalent dosing setting in the Manager for 10 µg /pulse or 20 µg /pulse for the first 15 eligible subjects and 10 µg /pulse, 15 µg /pulse, or 20 µg /pulse for

the other randomization schemes. The randomization dose assignment (dose only) will be available to the OmniPod Manager programmer (unblinded coordinator), but not to any other site personnel involved in the conduct and evaluation of the study until the study database is declared clean and is released to the statistician.

Prior to the start of the study, the investigator will assign a coordinator to act as the unblinded coordinator. This person will be the only person unblinded to the subject's study drug dose and will be responsible for the set-up of the Manager, distribution and accountability of the drug. Although the unblinded coordinator will be aware of the dose assigned, the unblinded coordinator will not be aware of whether the subject is receiving active drug or placebo. The unblinded coordinator will instruct each subject as to the proper administration and the timing of administration of the study drug. This person will be available to answer the subject's questions regarding study drug and its administration.

The integrity of the blind will be further preserved by requiring each subject and the unblinded coordinator to sign a nondisclosure affidavit form (Appendix I) instructing subjects and the unblinded coordinator not to disclose the study drug dosage.

5.4.2 Unblinding of Individual Subject Treatment

An emergency decoding possibility (either a code envelope or another system) will be available to the investigator and designated persons at Ferring. Breaking of the blind for individual subjects in emergency situations is only permitted in case of an important adverse event where the knowledge of the IMP in question is required for therapeutic decisions for the management of the subject.

As far as the emergency permits, the need to break the blind will be agreed by the investigator and Ferring. The person who opens a code envelope must record on it the reason and the date of opening, and then sign and date the opened envelope if a code envelope is prepared. If the randomization is done via an electronic system, the system will record the access for this unblinding. It should be recorded in the eCRF that the code is broken, why, when, and by whom. The investigator must record the event of unblinding in the subject's medical record, including the reason for unblinding, but not the treatment allocation if this can be avoided.

In case of accidental unblinding to the dose (e.g., the subject tells the investigator), the same documentation as for emergency unblinding must be obtained, i.e., why, when and by whom must be noted in the eCRF, and the event must also be recorded in the subject's medical record.

It may be necessary to unblind an individual subject's treatment for the purposes of expedited reporting to the authorities and/or IECs/IRBs. In that situation, every effort will be made to maintain blinding of sponsor personnel involved in data analysis and interpretation. Pharmacovigilance/Safety personnel may be unblinded for purposes of reporting suspected unexpected serious adverse reactions (SUSARs). Regulatory Affairs personnel submit SUSARs to the FDA. A US Regulatory Affairs person not involved with the conduct of the study will be designated to submit SUSARs to the IND.

Information on whether the blind has been broken for any subjects must be collected before the database is declared clean and is released to the statistician.

5.5 Selection of Doses in the Study

The selected GnRH dose per pulse will be either 10 µg, 15 µg, or 20 µg delivered at 90-minute intervals.

The SC GnRH doses proposed in this study are based on existing Ferring data and previously published research. The 20 µg dose has been used successfully in clinical studies in the US and Europe.[3]

In a pharmacokinetic study conducted in a small group of women with hypothalamic amenorrhea, SC GnRH administration resulted in pulsatile plasma GnRH and gonadotropin responses resembling those seen after IV GnRH.[15] No significant differences were found between peak LH responses to 10 µg/pulse of IV and SC doses of GnRH administered at 90-minute intervals.

In Ferring Study 2005-06, the SC route was associated with a slightly lower rise to peak and a slower disappearance of GnRH from the circulation; however, SC and IV dosing produced similar peak concentrations and total exposures (area under the concentration-time curve, AUC).[5] The study showed 25% bioavailability with SC compared to IV administration of GnRH. Thus, if the most commonly used initiating dose of the IV route is 5 µg /pulse, the SC dose needed to achieve approximately the same blood concentration GnRH levels is expected to be 4-fold higher, namely, 20 µg /pulse.

Ferring Study 000010 demonstrated favorable GnRH and LH profiles following SC administration of 20 µg/pulse doses every 90 minutes of LutrePulse with the OmniPod device.[7] Martin (1990) reported that 10 to 20 µg of GnRH per bolus yielded satisfactory ovulatory rates.[16]

The frequency of GnRH administration is best based on the GnRH pulse frequency in normal women. The literature to date supports a follicular-phase pulse frequency of 90 minutes or less to achieve maximum spontaneous ovulation rates.

Taken together, these results confirm the suitability of the SC route and the selected 10, 15, and 20 µg doses in a study with fixed 90-minute interpulse frequency for GnRH ovulation induction therapy.

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

The IMP will be dispensed only to subjects who meet the eligibility criteria. A drug-dispensing log will be maintained at the site detailing the date and quantity of IMP administered to each subject, as well as the batch number. The monitor will verify drug accountability during the study. The drug accountability binder will be managed by the study coordinator or designee. Subject Diary Cards (Appendix II) documenting date and time of replacement pods will also be monitored. Any unused investigational product and Non-Investigational Medicinal products will be accounted for and returned to the sponsor. The used vials, pumps, and Managers must be returned to the trial site by the subject and will be destroyed at the site and/or returned to the sponsor.

5.6.2 Assessment of Compliance

The OmniPod will be applied at the study site on Treatment Day 1, Treatment Day 10, and Treatment Day 25 (if applicable). All other OmniPods can be applied by the subject either at home or at the study site. Subjects will be provided training and an instruction manual.

On Day 1 and at each study visit during treatment, the subjects will be monitored closely by the unblinded coordinator to ensure the medication is being delivered and the pump is functioning properly. The Manager records drug delivery data that may also be analyzed. The data in the Manager may be collected and recorded by the unblinded coordinator when the subject returns the Manager to the site.

5.7 Auxiliary Supplies

All subject auxiliary items and devices are described in Section 5.1.1 and Section 5.1.2. These will be provided by the sponsor and packaged into blinded subject kits. These kits will be distributed to the sites together with the IMP for Treatment Days 1, 10, and 25 (if applicable).

5.8 Return and Destruction of Medicinal Products and Auxiliary Supplies

All unused IMP and NIMP will be returned to the sponsor, as instructed by Ferring IMP Department, after the drug accountability has been finalized, verified by the monitor, and signed off by the investigator or designee.

The used vials, pumps, and Managers must be returned to the trial site by the subject and will be destroyed at the site and/or returned to the sponsor. Used syringes and needles must be discarded in the sharps container and returned to the site.

The trial medication delegate at the site should ensure that the destruction of used medicinal products is done in accordance with local legislation/national requirements after the drug accountability has been finalized, verified by the monitor, and signed off by the investigator or designee.

6 STUDY FLOW CHART AND STUDY PROCEDURES

6.1 Schedule of Activities

The schedule of activities for the study is presented in Table 1.

Table 1 Schedule of Activities

Procedure	Screening (Day -60 to Day -1)	Treatment Day 1	Treatment Day 10	Follicle ≥ 18 mm and LH surge	Days 19, 21, 23, 25 and 27	14 (+4) days post LH surge and 3 days later	2 to 4 weeks from 2nd positive serum ß-hCG test	End-of-Study Visit
Informed consent	X							
Inclusion/exclusion	X							
Medical/gynecologic history	X							
Physical examination	X							X
Gynecological exam	X							X
Vital signs	X							X
Safety laboratory tests	X							X
Hepatitis B, C, & HIV screen	X							
Hormones: PRL, TSH	X							
TVUS	X		X – X[a]				X[b]	
Semen analysis	X							
Progestin challenge test[c]	X							
Serum pregnancy test	X					X		
Concomitant medications	X	X	X	X	X	X	X	X
Urine pregnancy test		X						X[d]
Blood samples for E_2	X	X	X[a]	X[a]				
Hormones: LH, FSH	X	X[e]	X[e]					

Procedure	Screening (Day -60 to Day -1)	Treatment Day 1	Treatment Day 10	Follicle ≥ 18 mm and LH surge	Days 19, 21, 23, 25 and 27	14 (+4) days post LH surge and 3 days later	2 to 4 weeks from 2nd positive serum ß-hCG test	End-of-Study Visit
Blood samples for P_4	X	X			X			X[f]
Randomization		X[g]						
OmniPod application[h]		X						
Clearblue testing[i]			X					
Begin sexual intercourse[j]				X				
Adverse events		X	X	X	X	X	X	X
Follow-up phone call[k]								X

a. Follicular size will be monitored every other day (minimum of 3 times) starting at Day 10 until a follicle ≥ 18 mm or LH surge is detected. E_2 samples will be taken each time a TVUS is performed.

b. If fetal heartbeat is not documented, the subject may return within 7 days for another TVUS.

c. Subjects with uterine bleeding within 5 days of the last dose of medroxyprogesterone acetate will be considered screen failures. Rescreening for the progestin challenge test is not allowed.

d. A urine pregnancy test should be performed at the End-of-Study visit for all except those with documented fetal heart movement.

e. On Day 1 (pre-treatment baseline) and Day 10 (post-treatment), LH and FSH samples will be collected at 0 hour (first sample taken prior to dosing) and 5, 15, 30, 60, and 90 minutes after the first dose is administered.

f. Only for subjects who have discontinued the study early and ended treatment on or after Day 14

g. Randomization will occur at least 5 days before Treatment Day 1 (7 days for sites in Canada).

h. The first OmniPod applied will remain on the subject until Day 4, when the second OmniPod will be applied at approximately the same time (±1 hour); each OmniPod will be worn for 3 full days.

i. When follicles ≥ 14 mm are detected on TVUS, Clearblue tests are dispensed to the subject to be administered each day at approximately the same time between 8 AM and 11 AM until a positive test result occurs.

j. Intercourse to begin at confirmed Clearblue LH surge.

k. For subjects who achieve biochemical pregnancy – collect ongoing pregnancy rate and birth data.

6.2 Study Procedures

6.2.1 Screening/Pre-treatment

Screening procedures are to be performed between Days -60 and -1. Note: The diagnosis of primary amenorrhea with HH should be known by the investigator.

Screening (Days -60 to -1)

At the Screening Visit, the subject should receive a detailed explanation of the study and, after having sufficient time to consider her participation in the study, sign the Informed Consent Form. After the subject has signed the Informed Consent Form, the following will be collected/performed:

- Inclusion/exclusion criteria
- Medical/gynecologic history and demographic data
- Physical examination, including height and weight
- Vital signs (blood pressure, heart rate, and oral temperature)
- Clinical safety laboratory assessment: chemistry, hematology, urinalysis
- Other laboratory assessment: hepatitis B, hepatitis C, HIV screen
- Hormone assessments: E_2, P_4, FSH, LH, prolactin, and TSH
- Serum pregnancy test
- Gynecological examination (including breast exam) and Pap smear (unless Pap smear results within the past 24 months are provided)
- TVUS
- Documentation of normal semen analysis within past year for male partners
- Prior/concomitant medication use up to 14 days prior to the Screening Visit
- Progestin Challenge Test during Screening:
  - Medroxyprogesterone acetate 10 mg oral tablet once daily for 10 days

- If uterine bleeding occurs within 5 days of the last dose of progestin, the subject is considered a screen failure and ineligible for study participation. Rescreening for the progestin challenge test is not allowed. Per investigator's discretion, occasional spotting is not considered withdrawal bleeding.

- If uterine bleeding does not occur 5 days after the last dose of progestin, the subject will return to the study site for initiation of treatment.

6.2.2 Treatment Day 1 through Day 10

Randomization is to occur at least 5 days before Treatment Day 1 (7 days for sites in Canada).

Treatment Day 1

- Urine pregnancy test
- Blood samples for baseline E_2 and P_4 collected prior to first dose. Blood samples for baseline LH and FSH collected prior to first dose and 5, 15, 30, 60, and 90 minutes after the first dose is administered.
- Instruction and application of OmniPod
- Distribution of LutrePulse subject study kit and Subject Diary Card
- Concomitant medication use
- Adverse event and unanticipated adverse device effect (UADE) assessment post treatment
- 12-lead electrocardiogram (ECG) (for subjects who report chest pain or are symptomatic of chest pain)

Treatment Day 10

Subjects will return to the study site at approximately the same time as Day 1 for pharmacodynamic (PD) assessments and monitoring of follicular development and endometrial thickness. They will remove their current pod and apply their Day 10 pod at the study site.

- Concomitant medication use
- A single blood sample for E_2
- Blood samples for LH and FSH collected at the same time as Day 1 first sample (± 1 hour), before the first dose is administered by the Day 10 pod and 5, 15, 30, 60, and 90 minutes after the dose is administered.

- TVUS to monitor size and number of follicles and endometrial thickness
- Adverse event and unanticipated adverse device effect assessment
- 12-lead ECG (for subjects who report chest pain or are symptomatic of chest pain)

OmniPod Application Days

Subjects remove the OmniPod and apply a new OmniPod at approximately the same time as the first OmniPod was applied (±1 hour) every fourth day. This occurs on Treatment Days 4, 7, 10, 13, 16, 19, and onwards if deemed necessary by the investigator.

After confirmed LH surge, treatment will continue for approximately another 2 weeks to maintain corpus luteum function (continue until confirmatory serum pregnancy test).

6.2.3 Treatment Day 11 until LH Surge

Subjects will return to the study site every other day (or at the investigator's discretion [minimum of 3 times]) to monitor follicular development and endometrial thickness, until a dominant follicle of ≥ 18 mm mean diameter and LH surge are confirmed. If LH surge is not detected after 21 full treatment days, the subject will be discontinued. However, the treatment may be continued for a maximum of 39 days at the discretion of the investigator if the patient has growing follicle(s).

- TVUS
- Blood collection for E_2 (each time TVUS is performed)
- When follicles ≥ 14 mm are detected on TVUS, Clearblue tests will be dispensed to subject to begin testing
    - Clearblue digital urine ovulation test is to be performed every day at approximately the same time between 8 and 11 AM
    - When a positive test result occurs, the subject should notify the site immediately to schedule a visit within 72 hours for confirmatory TVUS and will be advised to engage in sexual intercourse on the day of LH surge, the day following LH surge, and per investigator's discretion thereafter
    - Subjects should document the date of their first Clearblue test and the date of their first positive test result on the subject diary card (Appendix II)
    - The subject should also document the date(s) of sexual intercourse on the subject diary card.

- Concomitant medication use
- Adverse event and unanticipated adverse device effect assessment
- 12-lead ECG (for subjects who report chest pain or are symptomatic of chest pain)

Up to 72 hours after LH surge

- Confirmatory TVUS
- Concomitant medication use
- Adverse event and unanticipated adverse device effect assessment
- 12-lead ECG (for subjects who report chest pain or are symptomatic of chest pain)

6.2.4 Progesterone and Pregnancy Monitoring

Treatment Days 19, 21, 23, 25, and 27

- Blood collection for P_4
- Concomitant medication use
- Adverse event and unanticipated adverse device effect assessment
- 12-lead ECG (for subjects who report chest pain or are symptomatic of chest pain)
- LutrePulse Omnipod treatment continues for luteal phase support for subjects with confirmed LH surge

Interview and study drug return

Non-pregnant subjects will visit the site to return used and unused study drug product, their subject diary card and the OmniPod delivery system and report the day menstruation began and duration of menses, if applicable. Gonadotropins for one treatment cycle as well as compensation toward a future IVF cycle could be offered to all non-pregnant subjects who participated in and completed the study (had at least 14 days of study medication) and completed an End-of-Study visit. No study-related follow-up will be conducted regarding such cycles.

14 (+ 4) days after LH surge and 3 days thereafter

Two positive serum pregnancy tests are required to confirm biochemical pregnancy 14 (+ 4) days after LH surge and 3 days thereafter. If only one of the 2 tests is positive, the subject will return within 5 days (unscheduled visit) to confirm pregnancy with another serum pregnancy test. Subjects with 2 negative pregnancy tests will complete an End-of-Study Visit on the day of the second negative pregnancy test.

- Serum pregnancy test
- Concomitant medication use
- Adverse event and unanticipated adverse device effect assessment
- 12-lead ECG (for subjects who report chest pain or are symptomatic of chest pain)

2 to 4 weeks after second positive serum pregnancy test

- TVUS to detect gestational sac and fetal heartbeat
- If fetal heartbeat is not documented, the subject may return within 7 days for another TVUS
- Concomitant medication use
- Adverse event and unanticipated adverse device effect assessment
- 12-lead ECG (for subjects who report chest pain or are symptomatic of chest pain)

End-of-Study Visit

The End-of-Study Visit is performed in conjunction with the final TVUS visit 2 to 4 weeks after the second positive serum pregnancy test or on the day of the second negative serum pregnancy test for subjects who do not become pregnant (2 negative serum pregnancy tests).

- Gynecological examination, including breast exam
- Physical examination, including weight
- Vital signs (blood pressure, heart rate, and oral temperature)
- 12-lead ECG (for subjects who report chest pain or are symptomatic of chest pain)
- Clinical safety laboratory assessment: chemistry, hematology, urinalysis

- Urine pregnancy test (for all except those with documented fetal heart movement)
- Blood collection for P_4 (only for subjects who have discontinued the study and ended treatment on or after Day 14)
- Concomitant medication use
- Adverse event and unanticipated adverse device effect assessment

After the End-of-Study Visit, the site will be asked to provide follow-up information on subjects with a biochemical pregnancy regarding ongoing pregnancy rate and birth data. The follow up will be conducted via telephone or mail. The site will also document miscarriage/pregnancy loss (spontaneous and/or induced), date of live birth, number of deliveries, fetal anomalies, and birth defects.

7 STUDY ASSESSMENTS

7.1 Pharmacodynamic Assessments

Hormone assays will be performed by a central laboratory service. LH will be measured by automated LH two-site sandwich immunoassay using direct chemiluminometric technology (ICMA). Estradiol, progesterone and FSH will also be assayed by a central laboratory service.

A blood sample for E_2, LH and FSH will be taken on Day 1 (pre-treatment baseline) prior to dosing. Additional blood samples for LH and FSH will be taken 5, 15, 30, 60, and 90 minutes after the first dose is administered. The trial site should prepare the subject for at least a 2 to 3-hour office visit.

A blood sample for E_2, LH and FSH will be taken on Day 10 at the same time as the Day 1 first sample (± 1 hour) before the first dose is administered by the Day 10 pod. Additional blood samples for LH and FSH will be taken 5, 15, 30, 60, and 90 minutes after the first dose is administered. Samples for measurement of E_2 will also be obtained each time the subject has a TVUS to monitor follicular development and endometrial thickness.

PD blood samples of 10 mL (for LH, FSH, and E_2 levels) will be collected.

Serum samples will be obtained following centrifugation of clotted samples. All serum samples should be clearly labeled before freezing to ensure label adherence to the container and to avoid sample mix up.

All samples will be kept frozen at -20°C and shipped on dry ice. No more than 45 minutes is to elapse between collecting the blood and freezing the serum sample. The subject's number and initials, actual 24-hour clock and date time of each sample collection, sample identification number, and other appropriate information will be recorded on the label and in the eCRF. Any deviations either from the scheduled time of sample collection or from the instructions for handling and processing of samples should be documented in the study records.

Specific instructions for blood collection will be provided in a laboratory manual to the study center.

7.2 Transvaginal Ultrasound

A transvaginal ultrasound, including ovaries, uterus, endometrium, and adnexa, will be performed at Screening (to determine eligibility) and beginning at Day 10 of treatment to monitor number and size of follicles and endometrial thickness. Subjects will return every other day (or based on investigator judgment) for additional TVUS (at least 3 TVUS are to be performed). For subjects that become pregnant, a TVUS will be performed 2 to 4 weeks after the 2nd positive serum pregnancy test.

7.3 Detection of LH Surge

When follicles ≥ 14 mm in mean diameter are detected on TVUS, subjects will begin monitoring LH surge using a Clearblue test. The test will be administered each morning at approximately the same time between 8 and 11 AM. When a positive test result occurs, subjects are to notify the site and will be advised to engage in sexual intercourse on the day of LH surge, the day following LH surge, and per investigator's discretion thereafter.

7.4 Progesterone Evaluations

Blood samples (10 mL) for measurement of progesterone levels will be obtained by venipuncture on Days 19, 21, 23, 25, and 27. A blood sample will also be obtained at the End-of-Study visit for any subject that discontinues the study early and ends treatment on or after Day 14. A P_4 level ≥ 6 ng/mL as measured by a central laboratory indicates ovulation.

7.5 Pregnancy Assessments

7.5.1 Serum Pregnancy Tests

Serum pregnancy tests (β-hCG) will be performed at Screening, and negative pregnancy test results are required for study admission and/or administration of pulsatile GnRH (urine pregnancy tests are performed prior to initial study drug administration for all subjects and at the End-of-Study visit for all subjects except those with documented fetal heart movement). To confirm biochemical pregnancy, a serum pregnancy test will be performed 14 days (+ 4 days) after LH surge and 3 days thereafter. Two positive serum pregnancy tests are required to confirm biochemical pregnancy. If only one of the 2 tests is positive, the subject will return within 5 days (unscheduled visit) to confirm pregnancy with another test. Subjects who have 2 negative serum pregnancy test results will complete their End-of-Study Visit on the day of the second negative serum pregnancy test.

7.5.2 Pregnancy and Pregnancy Outcome

Subjects who achieve pregnancy (2 positive serum pregnancy tests) will be followed up for clinical pregnancy (gestational sac and fetal heart movement) and will complete their final visit (End-of-Study Visit) on the day of documented fetal heart movement on TVUS (2 to 4 weeks after second positive serum pregnancy test).

7.6 Safety Assessments

7.6.1 Medical History

A complete medical/gynecologic history will be obtained at Screening and will include a review of prior medical history and female reproductive status. Documentation of the diagnosis of primary amenorrhea with HH should be provided, including normal or unchanged CT scan or MRI scan of the hypothalamic pituitary region on file and blood samples indicating FSH < 5 IU/L and LH < 5 IU/L. Medical history findings will be recorded in the eCRF.

7.6.2 Physical and Gynecological Examination

A complete physical examination including height, weight and BMI calculation will be performed at Screening. A gynecological exam including pelvic and breast exam will be performed at Screening. In addition, a Pap smear (or other cervical cancer screening) will also be performed at Screening if not done in the previous 24 months (PAP smear can be performed at Screening, per investigator discretion, even if results within 24 months are available). If done in the previous 24 months, a copy of the report is needed and must be filed in the subject's chart. At the End-of-Study Visit (or at the time of early termination), another physical and gynecological examination including vital signs will be performed. Any clinically significant deterioration from baseline will be recorded as an adverse event.

7.6.3 Vital Signs

At Screening and the End-of-Study Visit, blood pressure, heart rate, and oral body temperature will be measured under resting conditions. All blood pressure measurements should be made using the same arm and prior to any scheduled blood draws.

7.6.4 ECG Evaluation

Subjects who report chest pain or are symptomatic of chest pain should have an ECG evaluation any time during the study when chest pain or symptoms occur.

7.6.5 Clinical Laboratory Tests

7.6.5.1 Hematology, Serum Chemistry, and Urinalysis

A standard panel, as well as the following safety laboratory tests, will be performed at Screening and at the End-of-Study Visit (or at the time of early termination). A 10 hour overnight fast is required prior to collecting the blood samples. The total amount of blood required for safety assessments is approximately 80 mL.

Hematology: red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count, and differential count.

Serum Chemistry: fasting glucose, blood urea nitrogen, creatinine, potassium, sodium, chloride, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase.

Urinalysis: leukocyte esterase, blood, pH, specific gravity, protein, glucose, urobilinogen, and microscopic if positive for blood or protein.

7.6.5.2 Serological Testing

Serological testing for hepatitis B, hepatitis C, and HIV I and II will be performed at Screening.

7.6.5.3 Hormone Testing

Prolactin (PRL) and TSH will be measured only at Screening. P_4 levels will be measured at Screening and Treatment Days 19, 21, 23, 25, and 27. P_4 levels will also be measured at the End-of-Study visit for any subject that discontinues the study early and ends treatment on or after Day 14. E_2 levels will be measured at Screening, Treatment Days 1 and 10, and each time a TVUS is performed. LH and FSH levels will be measured at Screening and again on Treatment Days 1 and 10 (prior to first dose and 5, 15, 30, 60, and 90 minutes after first dose is administered).

7.6.6 Ovarian Hyperstimulation Syndrome Monitoring

In women undergoing controlled ovarian hyperstimulation, an excessive response to follicular stimulating agents may lead to the development of ovarian hyperstimulation syndrome (OHSS). OHSS represents a spectrum that can be categorized as mild, moderate or severe.

The following table will be used in assessing and classifying the severity of OHSS.

Table 2 Classification of Mild, Moderate and Severe OHSS[17]

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

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

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

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

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

All cases of OHSS will be considered adverse events and will be recorded in the source documents for that subject and on the Adverse Event page in the eCRF. Severe OHSS that requires medical or surgical intervention (i.e., paracentesis, hospitalization, dopamine administration) is considered a serious adverse event (see Section 8.3).

7.7 Concomitant Medications

At each study visit, subjects will be queried for use of any medication other than the study drug since the last visit. Any use of prior medication or concomitant medication, including vitamin or dietary supplements or oral herbal preparations, will be recorded in the source documents and the eCRF and include the following information: name of medication, total daily dose, route of administration, start and stop dates, and reason for use. If the reason for the use of concomitant medication meets the definition of an adverse event, the adverse event should be recorded in the source documents for that subject and on the Adverse Event page of the eCRF.

8 ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

8.1 Adverse Event Definition

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

- Any unfavorable 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 gynecological examination assessed as clinically significant by the investigator [note: findings from assessments and examinations done during screening 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.

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

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

The sources of adverse events cover:

- The subject's response to questions about 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., hospitalization).

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 IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome (time can be omitted, if applicable)
- Outcome
- Seriousness (see 8.3.1 for definition)
- Each of the items in the Adverse Event Log is described in detail in the following sections.

Adverse Event

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

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

[a] Exception: 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 the following: A procedure is not an adverse event; the reason for conducting the procedure is. Hospitalization is not an adverse event; the reason for hospitalization is. Death is not an adverse event, but the cause of death is (an exception is sudden death of unknown cause, which is an adverse event).

Date and Time of Onset

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

Intensity

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

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

Moderate: Event sufficient to affect usual activity (disturbing).

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

Causal Relationship to IMP

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

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

Examples:

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

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

Examples:

- known consequences of the underlying disease or condition under investigation.

- adverse events common in the trial population, which are also anticipated to occur with some frequency during the course of the trial, regardless of IMP exposure.

Action Taken to IMP

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

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

Other Action Taken

Adverse events requiring therapy must be treated with recognized 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 (time can be deleted/omitted, if not applicable) the subject recovered or died.

Outcome

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

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

8.3 Serious Adverse Events

8.3.1 Serious Adverse Event Definition

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 4 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 that may have caused death if it were more severe.
requires inpatient **hospitalization** or prolongation of existing hospitalization	The term hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Overnight stay for observation, stay at emergency room or treatment on an outpatient basis do not constitute a hospitalization. However, medical judgment must always be exercised and, when in doubt, the case should be considered serious (i.e., if case fulfills the criterion for a medically important event). Hospitalizations 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.

An event is defined a serious adverse event if it:	Guidance
is an **important medical event**	Important medical events are events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include AEs that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgement should be exercised in deciding whether events qualify as medically important. Important medical events include any suspected transmission of an infectious agent via a medicinal product. Any organism virus or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a subject exposed to a medicinal product.

8.3.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

An SAE must be reported **immediately** to Ferring Pharmaceuticals as soon as it becomes known to the investigator and not later than within 24 hours of the investigator's knowledge of the occurrence of an SAE.

The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details to the local safety officer at Ferring Pharmaceuticals, Inc. by fax **within 24 hours** of his/her knowledge of the SAE **and submit all related follow-up information no later than 3 calendar days** using the contact details below:

Safety Fax: [redacted]

Safety E-mail: [redacted]

For questions contact: Medical Monitor, [redacted]
E-mail: [redacted]

Contact Number: [redacted]

Completion of the Demographics, Adverse Events Log, Medical History Log and Concomitant Medication Log is **mandatory** for initial reports and for follow-up reports if any changes have been made since the initial report.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g., laboratory parameters (that are not already uploaded in the eCRF), invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring 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 identification 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 adverse events 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 according to the Investigator's Brochure.[14]

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.

8.4 Follow-up of Adverse Events and Serious Adverse Events

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

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

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

8.4.2 Collection of Serious Adverse Events with Onset after Last 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 of how long after the end of the trial this takes place.

8.5 Unanticipated Adverse Device Effects

The definition of an Unanticipated Adverse Device Effect per FDA regulations is as follows:

Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. Adverse device effects should be collected and assessed as for adverse events above.

The investigator should collect, record, and assess any UADE similar to the directions for adverse events above. The investigator must report the adverse device effect to Ferring as described in Section 8.3.2 above on the device report form. In the circumstance that a serious adverse event and an UADE occur together, the SAE form should be completed and the device information also included.

9 STATISTICAL METHODS

Details of the statistical methodology will be provided in a separate Statistical Analysis Plan.

9.1 Determination of Sample Size

The sample size was determined based on the original fixed parallel group study design. The true ovulation rate for LutrePulse OmniPod SC 20 µg, 15 µg, 10 µg, and placebo was assumed to be 70%, 65%, 60%, and 1%, respectively. Under these assumptions, a sample size of 14 subjects per group (total 56 subjects) will provide at least 80% power to detect differences between LutrePulse OmniPod SC 20 µg and placebo, 15 µg and placebo, and 10 µg and placebo in ovulation rate separately using the stratified one-sided Fisher's exact tests [19] at an overall one-sided significance level of 0.025 with the closed testing procedure (Kong et al., 2005)[18] to be used for the primary efficacy analysis.

Approximately 60 subjects will be randomized, assuming up to 4 subjects may be ineligible for the full analysis set (FAS).

9.2 Subject Disposition

The number and percentage of randomized subjects treated with IMP, prematurely discontinued, and completing the study will be summarized. All post-baseline discontinuations will be summarized by reason for discontinuation. The number of subjects screened and not randomized will be presented.

9.3 Protocol Deviations

The criteria for protocol deviations considered major with the implication of data exclusions from the per-protocol analysis set will be determined before database lock.

9.4 Analysis Sets

9.4.1 Intent-to-Treat (ITT) Analysis Set

All randomized subjects will be included in the ITT analysis set.

9.4.2 Full Analysis Set (FAS)

All randomized subjects who are included in the ITT analysis set and received at least 14 days of study drug for pituitary priming will be included in the FAS.

9.4.3 Modified Intent-to-Treat (mITT) Analysis Set

All randomized subjects who received at least one (1) pulsatile injection delivery of study drug will be included in the mITT Population.

9.4.4 Per Protocol Set (PPS)

All subjects who are included in the FAS and did not have major protocol deviations will be included in the PPS.

9.4.5 Safety Population

All subjects who received at least one (1) pulsatile injection delivery of study drug will be included in the Safety Population.

9.5 Trial Population

9.5.1 Demographic and Baseline Characteristics

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

9.5.2 Medical History and Concomitant Medications

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be summarized by anatomical-therapeutic-chemical (ATC) classification 1st level (alphabetically) and ATC classification 2nd level (in decreasing order of frequency).

9.6 Efficacy Endpoint Assessments

9.6.1 General Considerations

A Bayesian adaptive design is adopted to address the following objectives:

1. Demonstrate superiority of the pooled middle and high doses over placebo in the ovulation rate
2. Evaluate the dose-response relationship

The adaptive design includes two interim analyses, conducted after approximately 9 and 12 patients per arm enrolling in the study, respectively. The interim analysis provides an opportunity for stopping the trial early due to efficacy success utilizing the group sequential strategy or due to efficacy futility through Bayesian predictive probability of success. Furthermore, it allows the low dose to be dropped following the interim look if it shows a much lower response rate compared with the middle and high doses.

Each interim analysis will result in one of the following possible outcomes:

1. Continue the trial with all arms
2. Continue the trial without the low dose
3. Declare early success, but continue the trial without placebo
4. Declare early success and stop the trial (both placebo and low dose dropped)
5. Stop the trial for futility

When the primary efficacy analysis is not successful at the interim analysis, and if the ovulation rate in the low-dose arm is sufficiently low, satisfying

$$R_{low} < (R_{high+middle}) - 0.2, \quad (1)$$

then the trial will continue without the low dose, resulting in outcome #2 listed above. Note that R_{low} and $R_{high+middle}$ in inequality (1) are the observed ovulation rates in the low dose arm and the combined middle- and high-dose arms, respectively. However, if inequality (1) is not satisfied, then the trial will continue with all arms (outcome #1 listed above).

Conversely, when success on the primary efficacy analysis is declared at an interim analysis, if the response rate in the low-dose arm meets the condition in inequality (1), then the trial is completed at this point (outcome #4 listed above) with dose selection performed using the ED80 rule (see below).

In the case the primary efficacy analysis is successful, but the response rate in the low-dose arm is within 20% from the combined low- and high-dose success rate, the trial is not stopped immediately. Rather, the trial will continue to enroll additional patients into the low-, middle- and high-dose arms to further assess dose responses.

Finally, the trial may terminate (outcome #5 listed above) as a result of a low predictive probability of success (<0.05) given the data collected at the interim analysis.

At the end of the study, for a trial that achieves efficacy success, the dose to be selected as the lowest effective dose is the ED80 dose, defined as the lowest dose that retains at least 80% of the largest treatment effect, i.e.

$$(R_{ED80} - R_{placebo}) \geq (R_{maximum} - R_{placebo}) \times 0.8, \quad (2)$$

where $R_{maximum}$ is the observed ovulation rate in the most effective dose arm, $R_{placebo}$ is the observed ovulation rate in the placebo arm, and R_{ED80} is the observed ovulation rate in the selected dose arm.

9.6.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the ovulation rate calculated as the proportion of subjects who had at least one post-baseline P_4 level $\geq$ 6 ng/mL or pregnancy confirmed by a positive serum β-hCG (i.e., 2 positive results) or presence of a gestational sac documented by transvaginal ultrasound (TVUS). The denominator will be based on all subjects in the FAS. Subjects who do not have a confirmed pregnancy or at least one P_4 level $\geq$ 6 ng/mL due to the P_4 levels never reaching this threshold, missing data, early withdrawal, or any other reason will be counted as not having ovulation (treatment failure).

The primary efficacy analysis will compare the pooled ovulation rate of LutrePulse OmniPod SC 20 µg and 15 µg to placebo. Let $P_{high+middle}$ and $P_{placebo}$ be the underlying ovulation rates in the combined middle- and high-dose arms and the placebo arm, respectively. The hypotheses for the one-sided statistical testing are:

$$H_0: P_{high+middle} \leq P_{placebo},$$

vs.

$$H_0: P_{high+middle} > P_{placebo.}$$

The hypotheses are tested using a stratified one-sided Fisher's exact test (Jung et al., 2014) in the FAS including the randomization scheme as the stratification factor. The SAS PROC FREQ with permutation-based Cochran-Mantel-Haenszel test with exact p-value derived from all possible permutations will be employed for the calculation of p-value for the stratified Fisher's exact test. Jung has shown that the stratified Fisher's exact test is equivalent to the exact stratified Mantel-Haenszel test when exact p-value is derived from all possible permutations.

To account for the multiplicities introduced by early success interim analyses, Pocock boundaries are used. Thus, the success threshold at each analysis corresponds to a nominal p-value < 0.0131 to maintain an overall one-sided type I error rate of 0.025.

Further details on the Bayesian adaptive method, including simulation studies assessing design operating characteristics, will be provided in the Statistical Analysis Plan (SAP).

9.6.2.1 Sensitivity Analyses

The primary comparison between the pooled middle- and high-dose arms vs. the placebo arm for the primary variable will be conducted on the following analysis sets as sensitivity analyses:

- PPS
- mITT

9.6.3 Secondary Efficacy Endpoints

Clinical and biochemical pregnancy rates, as well as rates of LH surge, will be compared between the pooled middle- and high-dose arms vs. the placebo arm using the same method to be applied to the primary efficacy analysis.

Numbers of follicles with a mean diameter ≥ 14 mm and dominant follicles with a mean diameter ≥ 18 mm in LutrePulse OmniPod SC 20 µg, 15 µg, and 10 µg groups will be compared to those in the placebo group using Wilcoxon's rank sum test by stratifying based on the randomization scheme.

The maximum P_4 level and the mean P_4 level from Days 19, 21, 23, 25, and 27 values in LutrePulse OmniPod SC 20 µg, 15 µg, and 10 µg groups will be compared to those in placebo group using an analysis of covariance (ANCOVA) model including the treatment group and randomization scheme as factors and mean baseline value as covariate.

The proportion of subjects with at least one (1) post-baseline P_4 level ≥ 10 ng/mL will be compared to placebo using the same statistical method to be applied to the primary efficacy analysis.

The mean FSH and LH on Day 10 calculated from all time points on a day as well as the change from baseline in LutrePulse OmniPod SC 20 µg, 15 µg, and 10 µg groups will be compared to those in the placebo group using an ANCOVA model including the treatment group and randomization scheme as factors and mean baseline value as covariate. The E_2 levels on Day 10 as well as the change from baseline in LutrePulse OmniPod SC 20 µg, 15 µg, and 10 µg groups will be compared to those in the placebo group using a similar ANCOVA model. The change in the maximum value of FSH, LH, and E_2 levels on Day 1 and Day 10 from the first value taken on Day 1 and Day 10, respectively, will be presented with descriptive statistics by treatment group. The FSH, LH, and E_2 levels on Day 1 and Day 10 will be presented graphically by treatment group.

9.7 Extent of Exposure

The total study treatment exposure, measured by total duration (calculated by treatment start and stop dates/times), will be summarized and listed for the Safety Population by treatment group.

9.8 Safety Analysis

9.8.1 General Considerations

Complete listings and summary tables for all safety information, including adverse events, clinical laboratory safety data, physical examination, and vital signs, will be presented for subjects who are included in the Safety Population. No formal statistical analysis will be performed.

9.8.2 Adverse Events

Treatment-emergent adverse events (TEAEs) will be tabulated by System Organ Class (SOC) and Preferred Term (PT) using MedDRA for each treatment group. The total number of subjects reporting a TEAE, the percentage of subjects (%) with a TEAE, and the number of TEAEs reported will be presented. A TEAE will be any adverse event occurring after the start of IMP and within 2 days after the last dose, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after the start of IMP and within 2 days after the last dose. All adverse events occurring after 2 days from the last dose will be categorized as post-treatment adverse events.

In addition, TEAEs will be presented by causality (relationship to the study medication) and intensity (severity). Deaths, serious adverse events, and adverse events leading to discontinuation will be listed.

9.8.3 Clinical Laboratory Variables

Baseline and end-of-study laboratory values for each subject will be listed by test, and all values outside the normal range will be identified. Mean changes from baseline to the end of study will be summarized by treatment group using descriptive statistics.

9.9 Interim Analyses

Two interim analyses are planned after approximately 9 and 12 patients per arm complete the study. The details of the interim analysis strategy are described in Section 9.6 and SAP.

An independent data monitoring committee consisting of two unblinded clinicians and one unblinded statistician will be set up to review the interim analysis study results and make recommendations for the direction of the study, in accordance with the adaptive design decision-making rules specified in Section 9.6. In addition, an independent statistician and programmer will be identified to generate the data analysis output. Individuals involved in the first and second interim analysis of the study will not be involved in the conduct of the study afterwards; individual patient identification will not be released to anyone who is directly involved in the conduct of the study.

The interim analysis process, the measures used to protect the blind and the integrity of the study, the communication plan, and the confidentiality agreement will be described in a separate document.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – ICH Definition

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

Source Documents - ICH Definition

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

Trial-Specific Source Data Requirements – Ferring

For each subject allocated to treatment, the investigator will indicate in the hospital/medical source records that the subject participates in this trial and the date of obtaining the informed consent. The records should document data on the condition of the subject at the time the subject is enrolled in the trial to enable verification of eligibility. Signed and dated Informed Consent Forms will be stored and archived according to local requirements. In addition, the following information, at the minimum, will also be recorded in the hospital/medical source records for each subject:

- Documentation of signed and dated informed consent
- Subject's name and date of birth
- Screening/randomization number
- Trial identification
- Eligibility of participation in the trial (inclusion/exclusion)
- Body weight and height
- Dosing of IMP/NIMP–date of first and last dose
- Occurrence of any AEs/SAEs (including description and duration)

- Medical history
- Date of each visit
- Any assessment performed
- Any concomitant therapy
- Status of the subject at the end of trial
- Reason for discontinuation/withdrawal, if applicable

The following documents collected during the trial should be stored and archived together with the subject's hospital/medical records or in the Investigator File as agreed upon prior to the trial start at each trial site:

- Laboratory print-outs from central and local laboratory – evaluated, signed, and dated by the investigator or a delegated sub-investigator
- Patient dispensing logs of IMP
- Evaluations of physical examinations
- Collection of laboratory samples
- Demographics
- Known substance abuse

10.2 eCRF

An eCRF system provided by an independent third-party contract research organization (CRO) will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Ferring and vendor procedures, in accordance with regulatory and system requirements.

Data should be entered into the system within 5 working days after the subject has attended a visit or after the data become available, as applicable.

The investigator will approve/authorize the eCRF entries for each subject with an electronic signature that is equivalent to a handwritten signature.

The eCRF system and the database will be hosted at the independent third party CRO. After the trial database is declared clean and released to the statistician, a final copy of the database will be stored at Ferring. The investigator will also receive a copy of the trial site's final and locked data (including audit trail, electronic signature and queries) as write-protected PDF-files produced by the independent third party CRO. The PDF-files will be stored on a CD and will be provided to the investigator before access to the eCRF is revoked.

Errors occurring in the eCRF 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.

For each subject enrolled, an eCRF will be completed and signed by the investigator.

10.3 Data Management

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

The data management plan will describe captured methods, who is authorized to enter the data, decisions about ownership of data, source data storage, which data will be transferred (including timing of transfers), the origin and destination of the data, and who will have access to the data at all times.

10.4 Provision of Additional Information

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

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the investigator periodically to ensure adherence to the protocol, International Conference of Harmonisation-Good Clinical Practice (ICH-GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy and verifiability of eCRF 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 cooperate with the monitor to ensure that any discrepancies that may be identified are resolved. The investigator is expected to be able to meet the monitor during these visits. When the first subject is randomized at the trial site, a monitoring visit will take place shortly afterwards. For this trial, the frequency of the interim monitoring visits will be determined by the enrollment rate and will be detailed in the Monitoring Plan.

11.2 Audit and Inspection

The investigator will make all the trial-related source data and records available at any time to quality-assurance auditor(s) mandated by Ferring, or to domestic/foreign regulatory inspectors or representatives from IECs/IRBs who may audit/inspect the trial. The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP including the Declaration of Helsinki and all other relevant regulations.

The subjects must be informed by the investigator and in the Informed Consent Documents that authorized 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/randomization 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 eCRF or any other documents submitted to Ferring, the subjects will not be identified by their names, but by an identification system that 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 Documents, will be maintained by the investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment, issued by Ferring, and agreed upon by the investigator and Ferring prior to its implementation. Amendments may be submitted for consideration to the approving IEC(s)/IRB(s) and Regulatory Authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial subjects may be implemented prior to IEC(s)/IRB(s) approval/favorable 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 eCRF, 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 2 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 IECs/IRBs will be informed.

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

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring. The final report may be used for the further development of the investigational product as considered necessary by Ferring.

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 Pharmaceuticals, Inc.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

Submission of data for journal publication and/or presentation of data to scientific audiences may be considered by Ferring Pharmaceuticals Inc. and the investigator(s). Submission of a manuscript for publication will be considered based on the merits of the study results. The details of specific journal authorship will be discussed by the investigator(s) and the sponsor, with the final decision at the discretion of the sponsor. The investigator(s) agrees the sponsor will have the opportunity to review (at least 30 days) all manuscripts and abstracts related to this study prior to any submission for presentation or publication. Likewise, if the sponsor prepares a publication based on the results of this study, a copy of the manuscript will be provided to the investigator(s) prior to publication.

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

13.3.2 Public Disclosure Policy

The International Committee of Medical Journal Editors member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public, clinical trials registry. Thus, it is the responsibility of Ferring to register the trial in an appropriate registry (i.e., www.ClinicalTrials.gov) that is sponsored by the National Institutes of Health.

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. A list of all IECs/IRBs to which the protocol has been submitted and the name of the committee chairmen will be included in the Clinical Trial Report.

14.2 Regulatory Authorities Authorization / Approval / Notification

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

14.3 End-of-Trial and End-of-Trial Notification

The trial will end on the date of the last visit of the last subject (LSLV) ongoing in the trial.

For public disclosure purposes, **FDA** uses the 'primary completion date' as a baseline point in time from which disclosure reporting of results is required. The primary completion date is defined as the date of the final data collection specifically regarding the Primary Outcome Measure of a trial. (This could be the date the last subject was examined [e.g., LSLV] or the date the subject received intervention for the purpose of the final collection of data for the primary outcome).

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 Documents 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 completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for her further care and without the need to justify her decision. The subject will receive a copy of the Subject Information and her signed Informed Consent Form.

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

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

For subjects not qualified to give their legal consent, the written informed consent must be obtained from the legal parent or guardian in accordance with national/local regulations. If such subjects can understand the risks and benefits of the trial, they should also be informed and provide their written assent.

14.6 Compliance Reference Documents

The Helsinki Declaration, the consolidated ICH-GCP, and other national laws in the countries where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor and the investigator 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

In case of any damage or injury occurring to a subject in association with the IMP or the participation in the trial, Ferring has contracted an insurance that covers the liability of Ferring, the investigator and other persons involved in the trial in compliance with the laws in the countries involved.

16 ARCHIVING

16.1 Investigator File

The investigator is responsible for maintaining all the records that enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the investigator for at least 15 years (or longer if so required by local law) 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 that provides the sole link between named subject source records and anonymous CRF data for Ferring. The investigator must arrange for the retention of this Subject Identification Log and signed Informed Consent Documents for at least 15 years (or longer if so required by local law) after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the investigator and Ferring. Should the investigator elect to assign the trial documents to another party, or move them to another location, Ferring must be notified. Documents may be transferred to Ferring Global Quality Assurance, for example, if the investigator retires and the documents no longer can be archived by the site.

16.2 Trial Master File

Ferring will archive the trial master file in accordance with ICH-GCP and applicable regulatory requirements.

17 REFERENCES

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18 APPENDICES

Appendix I – Subject's Confidential Non-Disclosure Affidavit

CONFIDENTIAL NON-DISCLOSURE AFFIDAVIT

I, _____, agree to keep confidential my study medication assignment provided to me by: _____, Study Coordinator.

On this date: _____, I agree not to discuss or to disclose the dose of my study medication assigned to me with the study doctor and anyone other than the above Study Coordinator in order to protect the integrity of the data being collected for this clinical research study. I understand that the study doctor will not know my study medication assignment and will not be allowed to ask me questions about my study medication assignment. If I have questions concerning my study medication assignment, I agree to use the following contact information.

Study Contact: _____

Study Contact Number: _____

SIGNATURES
I have read this affidavit and understand the above information. The content and meaning of this information has been explained to me.

_____	_____	_____
Date/Time	Print Subject Name	Subject Signature
_____	_____	_____
Date/Time	Name of Person conducting Discussion	Signature of Person conducting Discussion

Copy of signed/dated confidential non-disclosure affidavit given to subject on (date) _____ by _____ (initials)

Appendix II – Subject Diary Card

Front of card

FERRING PHARMACEUTICALS

Site Number: ___ ___ ___

Subject Initials: ___ ___ ___

Subject Number: ___ ___ ___ ___

If you have any questions regarding your appointment, please contact the study site.

Coordinator: _____

Phone: _____

BRING THIS CARD WITH YOU TO ALL OF YOUR APPOINTMENTS AT THE STUDY SITE.
Start completing this diary card on your first day of treatment.

- Your OmniPod will be applied at the site on Treatment Days 1 and 10.
- Change your OmniPod every 4th day at the same time of day +/- one (1) hour.
- Record each Omnipod change on this card on the corresponding day even if the change is unscheduled.
- Record any unscheduled changes, pod malfunctions, application errors or other issues/concerns in the Notes/Comments field. There is also a field for Additional Notes.

Day	Date	Time of OmniPod Application		Notes/Comments
Day 1	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min*	☐ AM ☐ PM	
Day 4	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min*	☐ AM ☐ PM	
Day 7	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min*	☐ AM ☐ PM	
Day 10	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min*	☐ AM ☐ PM	*Were you instructed to start LH testing? If so, don't forget to enter your testing information on the back of the card!*
Day 13	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min*	☐ AM ☐ PM	*Were you instructed to start LH testing? If so, don't forget to enter your testing information on the back of the card!*
Day 16	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min*	☐ AM ☐ PM	*Were you instructed to start LH testing? If so, don't forget to enter your testing information on the back of the card!*
Day 19	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min*	☐ AM ☐ PM	*Were you instructed to start LH testing? If so, don't forget to enter your testing information on the back of the card!*

ADDITIONAL NOTES:

_____
_____
_____
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_____
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_____

Back of card

- Bring this card with you to all of your appointments.
- Change your OmniPod every 4th day at the same time of day +/- one (1) hour.
- Record each Omnipod change on this card on the corresponding day even if the change is unscheduled.
- Record any unscheduled changes, pod malfunctions, application errors or other issues/concerns in the Notes/Comments field. There is also a field for Additional Notes.

Day	Date	Time of OmniPod Application	Notes/Comments
Day 22	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min* ☐ AM ☐ PM	
Day 25	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min* ☐ AM ☐ PM	
Day 28	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min* ☐ AM ☐ PM	
Day 31	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min* ☐ AM ☐ PM	
Day 34	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min* ☐ AM ☐ PM	
Day 37	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min* ☐ AM ☐ PM	*Day 37 can be included if applicable.*
Day _____	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min* ☐ AM ☐ PM	*This is an unspecified day. It can be included if applicable.*
Day _____	_____/_____/_____ *mm dd yyyy*	_____:_____ *hr min* ☐ AM ☐ PM	*This is an unspecified day. It can be included if applicable.*

LH Surge Testing and Detection with Clearblue® Ovulation Kit

Date Clearblue testing began: _____/_____/_____ mm dd yyyy

Date Clearblue testing is positive: _____/_____/_____ mm dd yyyy

Sexual Intercourse: You must engage in sexual intercourse on the day that your Clearblue test is positive, on the day following your positive test, and per your doctor's instruction after that. Enter the date(s) of sexual intercourse below for each day that applies.

Day	Date	Did you have sexual intercourse on this day?
Day of positive Clearblue test	_____/_____/_____ mm dd yyyy	☐ Yes ☐ No
1 day after positive Clearblue test	_____/_____/_____ mm dd yyyy	☐ Yes ☐ No
2 days after positive Clearblue test	_____/_____/_____ mm dd yyyy	☐ Yes ☐ No
3 days after positive Clearblue test	_____/_____/_____ mm dd yyyy	☐ Yes ☐ No

ADDITIONAL NOTES: _____

_____

_____

_____

_____